People Living with Hereditary Angioedema (HAE) Prioritize Attack-Free Status as a Target for Therapeutic Efficacy

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Background

In a clinical trial, endpoints are the specific measurements used to evaluate the effectiveness or safety of an investigational treatment. Endpoints fall into 3 categories: *primary*, *secondary*, and *exploratory*. A *primary endpoint* is the outcome or event that most accurately measures the benefit of the investigational treatment. It needs to be recognized by regulatory agencies, such as the Food and Drug Administration (FDA), as being clinically meaningful or conferring clinical benefit and it should reflect the accepted norms and standards in the relevant field of research. A clinical trial is considered successful if the primary endpoint(s) meet the statistical threshold for significance; these data are subsequently used as the primary basis for regulatory evaluation.

Secondary endpoints may provide supportive information about an investigational treatment's effect on the primary endpoint or demonstrate additional effects on the disease or condition. *Exploratory endpoints* are included to explore new hypotheses.

To evaluate the effectiveness of an investigational treatment designed to prevent HAE attacks, efficacy endpoints can measure effect on attack occurrence, severity, and duration. In this study, we conducted a literature review of all *registrational trials* (clinical trials designed for evaluation by regulatory agencies to support a treatment's approval) of HAE preventative treatments to identify the frequency with which these efficacy endpoints were used. We also obtained patient feedback on which efficacy endpoints matter most when considering starting or switching to a new HAE preventative treatment.

Methods

To identify the efficacy endpoints used in HAE preventative treatment registrational trials for the four FDA-approved preventative therapies (IV plasma derived C1-INH, subcutaneous plasma derived C1-INH, lanadelumab, and berotralstat) and the two therapies in Phase 3 development (garadacimab and donidalorsen), trials were identified using clinicaltrials.gov.[1,2,3,4,5,6] The endpoints for each trial were further validated with a literature review of the publications corresponding to each of the registrational trials for the four FDA-approved preventative therapies and garadacimab (the registrational trial for donidalorsen is not yet completed and published).[7,8,9,10, 11]

People with HAE were recruited by the U.S. Hereditary Angioedema Association (HAEA) to complete a self-reported online survey conducted by The NemetzGroup LLC, an independent life sciences consultancy. The survey was designed to explore participants' perspectives and preferences on a variety of topics and took approximately 20-25 minutes to complete. The survey was conducted using a double-blind approach, ensuring that both the identity of the respondents was concealed from the sponsor and the identity of the sponsor was masked. Survey participants met the following criteria:

Participation Criteria
Adults (ages 18+)
Formal diagnosis of HAE Types I or II
Living in the United States of America
Diagnosis of HAE made by a physician at least 1 year ago
Ability to complete a web-based, self-completed survey
Currently on one of the following HAE treatments: IV plasma derived C1-INH, subcutaneous plasma derived C1-INH, lanadelumab, or berotralstat ***or*** not on the above treatments but have at least one attack during a typical 3-month period.

The survey was fielded in November 2022 and was completed by 101 participants.

Included in this survey was a question that asked participants to rank characteristics of a potential new treatment, including efficacy endpoints used in HAE clinical trials, according to their importance for considering starting or switching to a new preventative treatment. This question was intended to obtain directional information; no statistical testing was planned. To aid participants' understanding, efficacy endpoints were translated into lay terminology.

Efficacy endpoints as described in literature	Efficacy endpoints as presented in survey (lay terminology)
Time-normalized number/rate of attacks for participants	Fewer number of attacks in 6-month study period, whether requiring on-demand treatment or not
Number of attack-free days	More attack-free days (days without swelling) in a 6-month study period
Number/rate of HAE attacks requiring acute treatment	Fewer attacks that need acute (on-demand) treatment
Proportion of attack-free participants (i.e., patients having 0 attacks during the treatment period)	Increased likelihood of having zero (0) attacks in a 6-month study period
Number/rate of moderate or severe HAE attacks	Fewer moderate or severe attacks in a 6-month study period

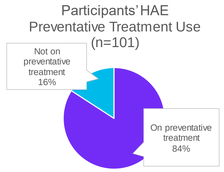
Question: Imagine that a new treatment were available for routine prophylaxis to prevent HAE attacks. Please rank order the listed characteristics from the most important to least important reasons for you to consider switching to or starting this new medicine. While some of these statements may seem similar or overlapping, please rank based on how you best interpret the statement.

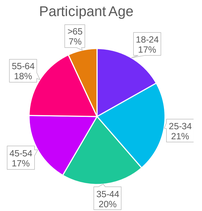
Survey Question	
Treatment Characteristic	**Rank Order (1-8)**
Fewer number of attacks in 6-month study period, whether requiring on-demand treatment or not	
More attack-free days (days without swelling) in a 6-month study period	
Fewer attacks that need acute (on-demand) treatment	
Increased likelihood of having zero (0) attacks in a 6-month study period	
Fewer moderate or severe attacks in a 6-month study period	
Note: These 5 options were part of a larger set of 8 options but are the only ones related to efficacy, and thus relevant for this analysis.	

Efficacy endpoints

Results

Participant Demographics





Participants' Ranking of Efficacy Measures According to Their Importance for Considering Starting or Switching to a New Preventative Drug

Averaged across all 101 survey participants, the likelihood of having zero (0) attacks in a 6-month study period was the most important efficacy endpoint when considering starting or switching to a new preventative treatment. Following this, in order of reported importance, were: 1) More attack-free days over 6 months; 2) Fewer moderate-to-severe attacks over 6 months; 3) Fewer attacks of any severity over 6 months; and 4) Fewer attacks that require acute treatment. Average rankings of importance of efficacy endpoints were similar regardless of whether participants were taking preventative treatment or not.

	Average Forced Rank		
Efficacy Endpoint	**All Participants (n=101)**	**Participants On Preventative Treatment (n=85)**	**Participants Not On Preventative Treatment (n=16)**
Increased likelihood of having zero (0) attacks in a 6-month study period	1	1	1.5
More attack-free days (days without swelling) in a 6-month study period	2	2	1.5
Fewer moderate or severe attacks in a 6-month study period	3	3	3
Fewer number of attacks in 6-month study period, whether requiring on-demand treatment or not	4	4	4
Fewer attacks that need acute (on-demand) treatment	5	5	5

Use of Efficacy Endpoints in HAE Preventative Drug Registrational Trials

- "Time-normalized number/rate of attacks for participants" was the primary endpoint used for all six registrational trials for HAE preventative treatments. This result is consistent with findings from a broader literature search across all randomized controlled trials for HAE preventative treatment.[12]
  - The most commonly-used secondary endpoint was "number of attacks requiring acute or on-demand treatment."
  - Among the four most recent clinical trials initiated since 2016 (lanadelumab, berotralstat, garadacimab, and donidalorsen), "proportion of attack-free participants" was the only other measure used by all, suggesting that this endpoint is increasingly being recognized as important in conveying the clinical benefit of an HAE preventative treatment.

Efficacy Endpoint Characteristic	Primary Endpoint	Secondary Endpoints	Exploratory Endpoints	Participants' Ranking
Time-normalized number/rate of attacks for participants	6			4
Number/rate of HAE attacks requiring acute treatment	0	5	1	5
Number/rate of moderate or severe HAE attacks	0	3	0	3
Number of attack-free days	0	2	2	2
Proportion of attack-free participants (i.e., patients having 0 attacks during the treatment period)	0	2	2	1

Conclusions

The survey participants' prioritization of "increased likelihood of having zero (0) attacks in a 6-month study period" aligns with the position of both the advocacy and physician communities: the goals of HAE treatments should be to achieve complete control of the disease and to normalize patients' lives.[13,14,15]

The FDA, across all its Centers of Research, encourages stakeholders to engage with patients and other appropriate subject matter experts when designing and implementing studies to evaluate the burden of disease and treatment, and perspectives on treatment benefits and risks. Thus, it is important to continue engaging people with HAE to ensure their needs and burdens of disease are being considered and incorporated into the development of new HAE treatments.

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