Prophylaxis of Hereditary Angioedema with Lanadelumab and C1 Inhibitors: Effectiveness and Value

Modeling Analysis Plan

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1. Approach

The primary aim of this analysis is to estimate the cost-effectiveness of lanadelumab and three C1 inhibitors (Haegarda®, CSL Behring; Cinryze®, Shire; and Ruconest®, Pharming) for long-term prophylaxis against acute attacks in patients with hereditary angioedema (HAE). The model structure for this assessment is described below. The model will be developed in Microsoft Excel.

2. Methods

2.1 Overview and Model Structure

We will develop a Markov model with two health states: "alive with HAE" and "dead" (Figure 2.1). The model will use one-month cycles over a lifetime time horizon. Transition from the "alive with HAE" state to "dead" will be based on background mortality from US life tables and HAE-specific mortality. Within the "alive with HAE" health state, we will track health-related quality of life, number of acute attacks and time spent in acute attack. For each attack, we will track the severity of attack, anatomical location of the attack for severe attacks (i.e., laryngeal and non-laryngeal), mortality from asphyxiation due to laryngeal attack, and attack-specific disutility, as well as treatment patterns (setting and drugs), emergency department (ED) visits, hospitalizations and associated costs (Figure 2). These outcomes will be tracked over time for persons receiving long-term prophylaxis with lanadelumab and the C1 inhibitors, and those not receiving long-term prophylaxis.

We will use both a US health care system perspective (i.e., focus on direct medical care costs only) and a societal perspective (i.e., includes indirect costs) with a 3% discount rate for costs and health outcomes.

Figure 2.1. Model Framework

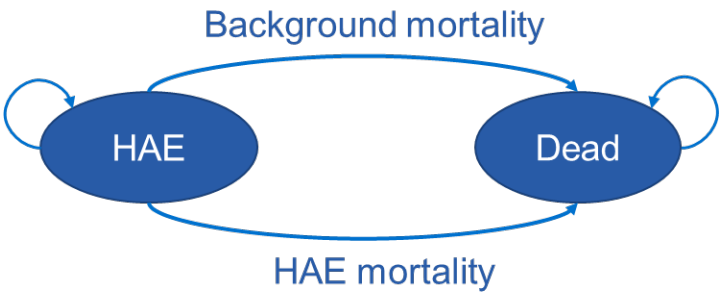
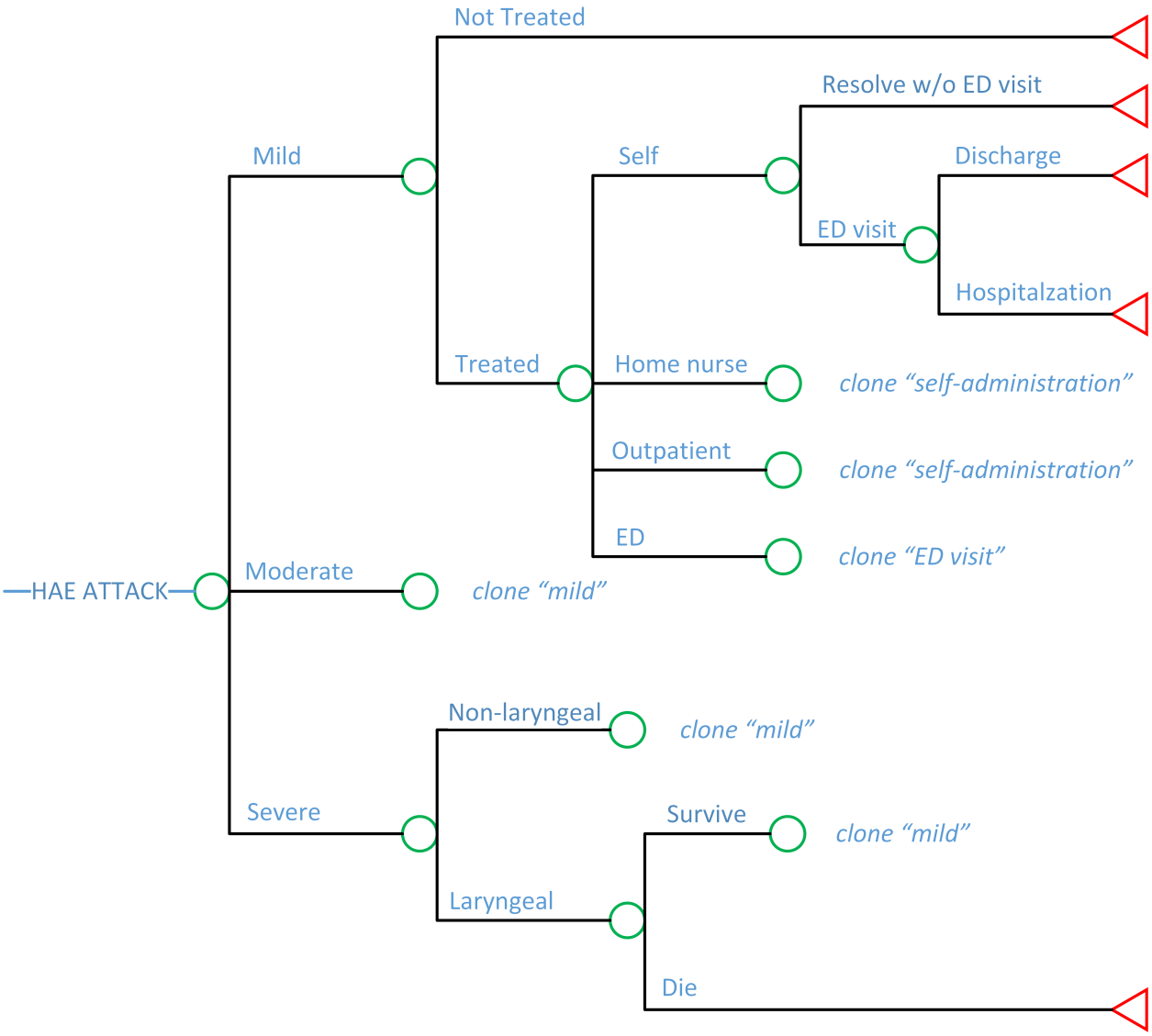


Figure 2.2. HAE Attack Pathway



Legend: This reflects how payoffs (i.e., costs and utilities) associated with the different HAE attack events and outcomes will be weighted. Green circles are chance nodes. Red triangles are terminal nodes. "Clone" refers to structural replication of a previously described branch of the decision tree (i.e., not replication of probabilities). "ED" refers to emergency department.

2.2 Target Populations

The population for this analysis will be patients in the US with types I and II HAE who are considered to be candidates for prophylactic treatment. The baseline characteristics used in the model will reflect the weighted average of the baseline characteristics across the four pivotal clinical trials for the interventions (Table 2.1).

Table 2.1. Baseline Values for Patient Population

Variable	Value	Source
Age in years (mean)	40.5	Banerji et al. 2017, Longhurst et al. 2017, Riedl et al. 2017, Zuraw et al. 2010[1-4]
Gender (% female)	70.0%	Banerji et al. 2017, Longhurst et al. 2017, Riedl et al. 2017, Zuraw et al. 2010[1-4]
Weight (kg)	80.6	Banerji et al. 2017, Longhurst et al. 2017, Riedl et al. 2017, Zuraw et al. 2010[1-4]
Baseline attack frequency (per month)	3.8	Banerji et al. 2017, Longhurst et al. 2017, Riedl et al. 2017, Zuraw et al. 2010[1-4]

2.3 Interventions

The interventions assessed in this model are:

- Lanadelumab
- Ruconest (C1 inhibitor, intravenous injection [recombinant])
- Cinryze (C1 inhibitor, intravenous injection [human])
- Haegarda (C1 inhibitor, subcutaneous injection [human])

Comparators

The comparator will be no long-term prophylaxis. Patients in all intervention and comparator groups can receive on-demand treatment for acute attacks

2.4 Key Model Choices and Assumptions

Table 2.2. Key Model Assumptions

Assumption	Rationale
HAE-specific mortality results only from asphyxiation following a laryngeal attack; other anatomical locations for acute attacks do not result in death.	Death from HAE attacks primarily results from asphyxiation following a laryngeal attack.[5]
Death due to asphyxiation following a laryngeal attack occurs quickly following the attack; we will assume that these persons do not receive on demand treatment.	The mean (standard deviation) duration of a fatal laryngeal attack is 4.5 (3.6) hours.[5] In Bork et al., 2008,[5] whether on-demand therapy had been administered to persons who died following a laryngeal attack was unclear.
The one-year fatality rate from laryngeal attack is 0.3% (i.e., 3 in 1000 attacks observed over a one-year period result in a death).	Data on the fatality rate due to a laryngeal attack are limited.
All non-fatal moderate and severe acute attacks are treated (varied in sensitivity analysis).	Treatment guidelines and empirical data suggest that moderate and severe attacks are treated.[6]

Only (and all) severe attacks are treated in the ED.	Treatment guidelines and empirical data suggest that severe attacks are typically treated in the ED.[6]
Non-severe attacks do not result in ED visits or hospitalizations.	Treatment guidelines and empirical data suggest that non-severe attacks are not typically treated in the ED nor do they result in hospitalizations.[6]
The durations of mild, moderate, and severe attacks are one, three, and five days respectively. Untreated attacks last an extra day.	Data on the duration of attacks by severity is limited but attacks generally last between two-five days.[6]
Patients do not discontinue prophylactic therapies over their lifetime.	There is no indication that attack rate declines with age.
We will not model adverse events (AEs).	There were no serious/treatment-related AEs attributable to the prophylactic therapies in the clinical trials.

2.5 Input Parameters

Clinical Inputs

Severity and Anatomical Location of Acute Attacks

Data on the severity and anatomical location of acute attacks were drawn from the Berinert® (CSL Behring) Patient Registry (Table 2 in Riedl 2016[7]), ignoring the attacks of unknown intensity. The Berinert Patient Registry, a multicenter, observational study, was conducted between 2010 and 2014 at 30 US and seven European sites to obtain both prospective and retrospective safety and usage data on subjects receiving plasma-derived, highly purified, pasteurized, nanofiltered C1-inhibitor concentrate (pnfC1-INH, Berinert). We back-calculated the probability of a laryngeal attack conditional on it being severe as 11.5%, in order to match the overall proportion of laryngeal attacks in the Berinert Patient Registry, which was 2.0%.

Table 2.3. Baseline Values for Attack Characteristics

Variable	Value	Source
Severity of attack (%)		Reidl 2016[7]
Mild	36.6%	
Moderate	46.2%	
Severe	17.2%	
Severe attacks that are laryngeal (%)	11.5%	Reidl 2016[7]

Mortality Due to HAE Attacks

We will assume that only laryngeal attacks could be fatal. The current model assumes that over one year, the fatality rate from a laryngeal attack is 0.3%.

Treatment Patterns, ED Visits, and Hospitalizations for Acute Attacks

We derived the treatment patterns for acute HAE attacks using data from a survey of US physicians (Figure 7 in Reidl et al., 2015 excluding EDs and hospitals).[8] Specifically, we estimate that 21%, 65% and 14% of non-severe acute attacks are treated at the physician's office/outpatient urgent care center, self-administered at home, and home nurse administered, respectively. We will assume that all severe attacks will be treated in the ED setting, and that 40.9% of emergency department visits will result in a hospitalization.[9]

Duration of Acute Attacks

The model assumes that the durations of mild, moderate, and severe attacks are one, three, and five days respectively. Untreated attacks will last an extra day. We applied a mean (standard deviation) duration of a fatal laryngeal attack of 4.5 (3.6) hours.[5]

Treatment Effects

Prophylactic therapies reduce the frequency of acute attacks. We obtained treatment effects, measured as the percent reduction in the number of attacks, from the pivotal trials of each of the prophylactic therapies.

Table 2.4. Treatment Effect Estimates

Drug	Treatment effect (% reduction in number of attacks)	Source
Lanadelumab	86.9%	Banerji et al., 2017[1]
Ruconest	63.3%	Riedl et al., 2017[3]
Cinryze	50.4%	Zuraw et al., 2010[10]
Haegarda	84.0%	Longhurst et al., 2017[2]

Health State Utilities

Our utility estimates were derived from a study in Sweden that utilized the EuroQoL 5D (EQ-5D) for valuing health-related quality of life among HAE patients.[11] Patients completed EQ-5D-5L (five-level) for both the attack-free state (EQ-5D today), and the last HAE attack (EQ-5D attack), and collected data on age, sex, and other variables such as attack location and severity. The estimated mean $\pm$ standard error EQ-5D today (i.e., "attack free") utility score was 0.825 $\pm$ 0.207. We will use this as the baseline utility of HAE. The difference between the EQ-5D today and EQ-5D attack scores of the latest attack were 0.07 for mild, 0.369 for moderate, and 0.486 for severe attacks (Figure 2 in Nordenfelt et al., 2014[11]). We will use these as the disutilities associated with mild, moderate, and severe attacks, respectively. The authors also found that older age was associated with reduced

quality of life (-0.02205 per 10-year increase in age). We will apply this age adjustment to the baseline HAE utility.

Drug/Therapy Utilization

We will assume that prophylactic therapies are taken on a life-long basis. The dosing regimens, schedules, and dose intensity adjustment factors for each therapy are shown in Table 2.5.

Table 2.5. Drug Utilization Parameters

Drug	Dosing
Lanadelumab	300 mg every 2 weeks
Ruconest	50 U/kg, max. 4,200 U twice a week
Cinryze	1,000 U twice a week
Haegarda	60 IU/kg twice a week

Adverse Events

There were no serious or clinically relevant adverse events attributable to any of the prophylactic therapies in clinical trials.

Cost Inputs

Where necessary, all costs will be inflated to 2018 US dollars. Healthcare costs will be inflated using the Personal Health Care (PHC) index up to 2016,[12] and the Personal Consumption Expenditure (PCE) price index up to 2018.[13] Non-healthcare costs will be inflated using the general consumer price index.[14]

Prophylactic Drug Acquisition Costs

Prophylactic drug cost inputs are shown in Table 2.6. We will use the Federal Supply Schedule (FSS) price per dose unit for subcutaneously administered drugs and self-administered doses of intravenously administered drugs. For non-self-administered doses of intravenously administered drugs, because the drug is not being dispensed directly to the patient, we will use the average sales price (ASP) plus a 9% markup representing the mean markup for physicians' offices, home infusion, and hospital outpatient administered dose units (Table 2.6).

Table 2.6. Prophylactic Drug Cost Inputs

Intervention	Administration	Unit	FSS per Unit/Dose*	ASP per Unit/Dose†
Lanadelumab	SC	300 mg	-	-
Haegarda	SC	2,000 IU	$1,393	-
Haegarda	SC	3,000 IU	$2,090	-
Cinryze	IV	500 U	$2,752	$3,049
Ruconest	IV	2,100 U	$4,231	$6,344

*FSS (Federal Supply Schedule) price as of June 1, 2018.

†ASP (Average Selling Price) as of June 13, 2018 plus 9% markup for physicians' offices, home infusion, and hospital outpatient administered dose units

Administration and Monitoring Costs for Prophylactic Drugs

For lanadelumab and Haegarda, which are administered subcutaneously, only the first dose administration was assumed to be performed in a clinic. We will apply the cost of a physician office visit of $80 (CPT 99214) and the cost of subcutaneous administration of $20.88 (CPT code 96372). Subsequent doses will be self-administered.

For Cinryze and Ruconest, which are administered intravenously, training for self-administration occurs over the first five physician office visits.[15] Therefore, we will apply the cost of five physician office visits, and a cost of IV drug administration of $47.16 (CPT code 96374). Based on data from the Berinert registry, we estimate that 95% of patients will self-administer their IV therapies.[7] For the 5% who cannot or choose not to self-administer, we will apply physician visit and drug administration costs in each cycle of the model.

Health Care Utilization Costs for On-Demand Treatment

Direct costs of acute attacks will include the drug costs, costs of home nurse ($177) and physician office ($262) administration of on-demand treatment from Graham et al., 2017[16], and costs of ED visits ($1,479, 95% confidence interval [CI]: $1,028-$1,929) and hospitalizations ($4,760, 95% CI: $3,612-$5,907) from Zilberberg et al.[9,17]

Therapeutic options for on-demand treatment of acute attacks are Cinryze® (20 U/kg), Berinert (20 U/kg), ecallantide (Kalbitor® 30 mg, Shire), icatibant (Firazyr® 30 mg, Shire) and Ruconest (50 U/kg). We computed the average costs per attack in each treatment setting as the cost of these drugs weighted by the proportion of attacks treated with each drug in each treatment setting. We assumed equal proportions of attacks treated with each drug in each treatment setting (Table 2.8). We note that Kalbitor is not approved for home or self-administration.

Table 2.7. Parameters for Costs of on-Demand Treatment for Acute Attacks

	Cinryze	Berinert	Kalbitor	Firazyr	Ruconest
Dose schedule	20 units/kg	20 units/kg	30 mg	30 mg	50 units/kg
FSS per dose*	$11,008	$4,541	$11,174	$21,533	$8,461
ASP per dose	$12,195	$10,668	$14,306	$21,533	$12,688
% requiring extra dose	10%	10%	10%	15%	10%

*FSS (Federal Supply Schedule) price as of June 1, 2018.
§ ASP (Average Selling Price) as of June 13, 2018 plus 9% markup for physicians' offices, home infusion, and hospital outpatient administered dose units

Table 2.8. Proportion of attacks treated by different drugs and setting of administration

	Cinryze	Berinert	Kalbitor*	Firazyr	Ruconest
Self	25%	25%	0	25%	25%
Home nurse	25%	25%	0	25%	25%
Physician office	20%	20%	20%	20%	20%
ED	20%	20%	20%	20%	20%

*Not approved for self- or home-nurse administration

In Bork et al., 2012[5], 31% of patients with fatal laryngeal attacks did not receive any emergency life-saving care. We will assume that these patients died before making it to the ED. Of the remainder (69%), 40% received an emergency cricothyrotomy and intubation was attempted in the rest. Artificial respiration was attempted in 40% of patients following a cricothyrotomy (50% for more than 96 hours) and 27% of those who were intubated (25% for more than 96 hours). Based on these proportions, in addition to the cost of an ED visit, we will apply costs of a cricothyrotomy of $347 (CPT 31605), costs of intubation of $146 (CPT 31500), and artificial respiration costs of $14,809 for less than 96 hours (DRG 208).

Adverse Event Costs

There were no serious or clinically-relevant AEs attributable to any of the prophylactic therapies in the clinical trials.

Productivity Costs

Indirect costs (including missed work, child care, and travel) for acute attacks (by severity) will be obtained from Wilson et al., 2010[18]: $959, $4,048, and $6,656, adjusted for the mean number of attacks (26.9).

2.6 Model Outcomes

Model outcomes of interest will include:

- By intervention:
    - Total health care costs (undiscounted and discounted)
    - Direct health care costs (undiscounted and discounted)
    - Indirect health care costs (undiscounted and discounted)
    - Number of attacks
    - Life years (undiscounted and discounted)
    - QALYs (undiscounted and discounted)
- Pairwise comparisons:
    - Incremental cost-effectiveness ratios (cost per attack avoided, cost per life-year, and cost per QALY) of each prophylactic therapy versus no long-term prophylaxis

2.7 Analysis

We will estimate the expected direct and indirect costs for each attack, expected disutility for each attack, expected probability of death per attack, and the expected duration with symptoms per attack.

Each model cycle lasts one month. For each intervention, we will calculate the probability of death given the number of attacks in each cycle, patient survival, the number of attacks, time spent in the "attack free" state, quality-adjusted survival, and health care costs. Outcomes will be summed over a lifetime time horizon for each intervention. Differences in survival, quality-adjusted survival and costs between each treatment and comparator will be used to calculate incremental cost-effectiveness ratios.

Sensitivity Analyses

We will conduct one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analysis will also be performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results.

Scenario Analyses

We may conduct relevant scenario analyses, including variations in duration of treatment effect, baseline attack rate, probability of treatment for acute attacks, and variations in the mean age of patients. Additionally, we will perform threshold analyses by systematically altering the price of the

interventions to estimate the maximum prices that would correspond to given willingness-to-pay (WTP) thresholds.

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using internal reviewers. Finally, we will compare results to other cost-effectiveness models of long-term prophylaxis against acute HAE attacks.

References

1. Banerji A, Busse P, Shennak M, et al. Inhibiting Plasma Kallikrein for Hereditary Angioedema Prophylaxis. *The New England journal of medicine.* 2017;376(8):717-728.
2. Longhurst H, Cicardi M, Craig T, et al. Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor. Paper presented at: New England journal of medicine2017.
3. Riedl MA, Grivcheva-Panovska V, Moldovan D, et al. Recombinant human C1 esterase inhibitor for prophylaxis of hereditary angio-oedema: a phase 2, multicentre, randomised, double-blind, placebo-controlled crossover trial. *The Lancet.* 2017;390(10102):1595-1602.
4. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *New England Journal of Medicine.* 2010;363(6):513-522.
5. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol.* 2012;130(3):692-697.
6. Cicardi M, Zuraw B. Hereditary angioedema: Treatment of acute attacks. *Uptodate.* 2018. https://www.uptodate.com/contents/hereditary-angioedema-treatment-of-acute-attacks. Accessed June 28 2018.
7. Riedl MA, Bygum A, Lumry W, et al. Safety and Usage of C1-Inhibitor in Hereditary Angioedema: Berinert Registry Data. *J Allergy Clin Immunol Pract.* 2016;4(5):963-971.
8. Riedl MA, Banerji A, Gower R. Current medical management of hereditary angioedema: follow-up survey of US physicians. *J Allergy Clin Immunol Pract.* 2015;3(2):220-227.
9. Zilberberg MD, Nathanson BH, Jacobsen T, Tillotson G. Descriptive epidemiology of hereditary angioedema emergency department visits in the United States, 2006-2007. *Allergy Asthma Proc.* 2011;32(5):390-394.
10. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *The New England journal of medicine.* 2010;363(6):513-522.
11. Nordenfelt P, Dawson S, Wahlgren CF, Lindfors A, Mallbris L, Bjorkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. *Allergy Asthma Proc.* 2014;35(2):185-190.
12. Personal Health Care (PHC) indices for all services (Table 23). http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/Tables.zip. Accessed June 28 2018.
13. Price Indexes for Personal Consumption Expenditures. https://www.bea.gov/iTable/iTable.cfm?reqid=19&step=2#reqid=19&step=3&isuri=1&1921=survey&1903=64. Accessed June 28 2018.
14. Consumer Price Index: Medical Care. https://data.bls.gov/cgi-bin/surveymost. Accessed June 10 2018.
15. Gregory C, Landmesser LM, Corrigan L, Mariano D. Feasibility of home infusion and self-administration of nanofiltered C1 esterase inhibitor for routine prophylaxis in patients with hereditary angioedema and characterization of a training and support program. *J Infus Nurs.* 2014;37(1):29-34.
16. Graham C, Supina D, Knox H, Krishnarajah S. Cost Savings Associated With Subcutaneous C1-Inhibitor (Human) Long-Term Prophylaxis for Hereditary Angioedema. *Academy of Managed Care Pharmacy, Dallas, TX, US, October 16-19, 2017.* 2017.
17. Zilberberg MD, Nathanson BH, Jacobsen T, Tillotson G. Descriptive epidemiology of hereditary angioedema hospitalizations in the United States, 2004-2007. *Allergy Asthma Proc.* 2011;32(3):248-254.

18. Wilson DA, Bork K, Shea EP, Rentz AM, Blaustein MB, Pullman WE. Economic costs associated with acute attacks and long-term management of hereditary angioedema. *Ann Allergy Asthma Immunol.* 2010;104(4):314-320.