# Cost-Effectiveness Model for On-Demand Treatment of HAE Attacks


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## BACKGROUND

- Hereditary angioedema (HAE) is a rare C1-inhibitor (C1-INH) deficiency characterized by recurrent episodes of painful and often disabling swelling in subcutaneous and/or submucosal tissues[1].
- Therapeutic agents targeting the specific physiological pathway of HAE attacks can offer improved outcomes with limited side-effects compared to non-specific therapies[2].
- HAE attacks can be unpredictable and the need to treat sudden attacks promptly and effectively is critical to minimize risk of hospitalization or death[1].
- Dependent on frequency and severity of attacks, on-demand treatment may remain a suitable option for many patients; even patients receiving prophylaxis therapy can experience "break-through" attacks for which on-demand rescue medication is required.
- Expensive HAE therapies can become even more costly due to frequent re-dosing and downstream costs associated with administration and hospitalization[3].

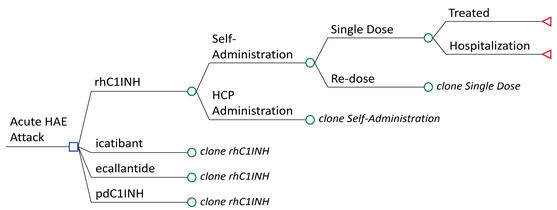
## OBJECTIVE

- Cost and utility estimates for on-demand treatment of HAE attacks that take into account re-dosing rates, administration costs, and associated effects will help to better clarify and control disease management expenses.

## METHODS

- TreeAge Pro software was used to develop a decision tree model to evaluate costs and utilities associated with on-demand treatment of HAE attacks (FIGURE 1).
- Four comparators were included: Berinert® (pdC1INH)[4], Firazyr® (icatibant)[5], Kalbitor® (ecallantide)[6], and Ruconest® (rhC1INH)[7].

### FIGURE 1. DECISION TREE MODEL DIAGRAM




- Variables specific to each therapy included drug cost as Wholesale Acquisition Cost (WAC), proportion of self-administration, re-dosing rate, and time to attack resolution (TABLE 1).
- Global variables applying to all therapies included hospitalization risk, utilities, and general healthcare administration costs (TABLE 2).
- Baseline costs and utilities per attack were calculated from the model.
- Baseline results were then used to extrapolate to annualized costs, QALYs, and cost-per-QALY.
- A budget impact model was developed using baseline results and assumptions of 1M covered lives, a prevalence of 1 in 50000 [18], and a mean attack rate of 26.9 per year[3].

### TABLE 1. THERAPY-SPECIFIC INPUT VALUES

| | Dosing | Unit | Unit Cost (WAC) | Re-Dosing Rate | Self-Admin Rate | Time to Resolution |
|---|---|---|---|---|---|---|
| pdC1INH | 20 U/kg [4] | 500U vial [4] | $2815 | 0.19 [8] | 0.95 [12] | 8.4 [2] |
| icatibant | 30 mg [5] | 3mL 10mg/mL [5] | $10823 | 0.29 [9] | 1 [5] | 6 [2] |
| ecallantide | 30 mg [6] | 1mL 10mg/mL [6] | $4779 | 0.12 [10] | 0 [6] | 3.1 [2] |
| rhC1INH | 50 U/kg [7] | 2100U vial [7] | $5708 | 0.03 [11] | 0.95 [12] | 4.4 [2] |

### TABLE 2. GLOBAL INPUT VALUES

| | |
|---|---|
| Bodyweight | 81kg |
| Non-attack Utility | 0.83 [13] |
| Attack Utility | 0.51 [13] |
| Hospitalization Risk (Self-Administer) | 0.036 [14] |
| Hospitalization Risk (HCP Administer) | 0.228 [14] |
| Home nurse, cost | $177 [15] |
| Outpatient admin, cost | $262 [15] |
| Emergency department admin, cost | $1479 [16] |
| Hospitalization, cost | $11309 [17] |

- Sensitivity analyses to assess the robustness of the model were performed by assigning value ranges to each variable in the model and creating a triangular distribution for each where the range maximum and minimum form the upper and lower bounds of the distribution while the peak of the distribution is the baseline value.
- Upper and lower range limits were drawn from published literature such as peer-review journals, conference proceedings and abstracts when possible.
- One-way tornado diagrams were used to assess the influence of each variable on the overall cost estimates of the model.
- A 5000-trial probabilistic sensitivity analysis (PSA) was performed to evaluate ranges of cost-effectiveness for each therapy for simultaneous variability across all model values, with a cost-effectiveness scatter plot used to establish variance for the therapies.

## RESULTS

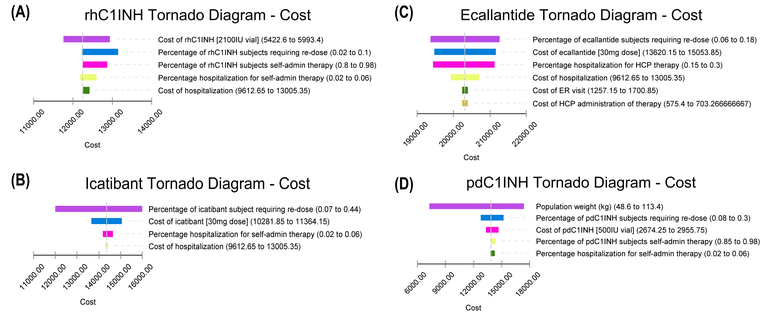
- Base-case scenario results are shown in TABLE 3.
- Cost per attack is inclusive of re-dosing, healthcare-provider administration, drug price mark-up, and potential hospitalization.
- Quality-adjusted-life-hours (QALH) are out of 72 hour attack period.
- Derived effectiveness compares to attack-free HAE utility of 0.83.
- Budget impact model results (TABLE 3) show annual treatment costs ranging from $6.64M (rhC1INH) up to $10.93M (ecallantide).
- The model indicates that rhC1INH is the dominant therapy in the base case analysis; rhC1INH is both less expensive and more effective than other therapeutic options.
- Ecallantide is highly effective but also the most expensive, resulting in the least cost-effective therapy in the model.
- Driven by higher re-dosing rates, icatibant suffers from comparatively poor effectiveness measures.

### TABLE 3. BASE-CASE AND BUDGET IMPACT MODEL RESULTS

| | | rhC1INH | icatibant | ecallantide | pdC1INH |
|---|---|---|---|---|---|
| Base Case Results | Cost per Attack | $12342 | $14369 | $20315 | $13993 |
| | QALH (per 72hr) | 57.91 | 53.94 | 56.62 | 54.64 |
| | Effectiveness | 0.804 | 0.749 | 0.786 | 0.759 |
| Annualized Extrapolation | *Mean Attacks per Year* | *26.9* [3] | | | |
| | Cost per Year | $332010 | $386526 | $546484 | $376421 |
| | QALYs per Year | 0.824 | 0.812 | 0.820 | 0.814 |
| | Cost per QALY | $402769 | $475942 | $666153 | $462275 |
| Budget Impact Model | *Covered Lives* | *1,000,000* | | | |
| | *Prevalence* | *1/50,000* [18] | | | |
| | *HAE Patients* | *20* | | | |
| | Overall Cost to Plan | $6.64M | $7.73M | $10.93M | $7.53M |
| | Cost PMPM | $0.55 | $0.64 | $0.91 | $0.63 |

- Tornado diagrams (FIGURE 2) indicate that costs are widely influenced by re-dosing rates (1st or 2nd most influential in all therapies) and the ability to self-administer (pdC1INH, icatibant, and rhC1INH are all labeled for self-administration).
- Population weight appears in tornado diagram for pdC1INH, but not rhC1INH even though both are weight-based dosing; because rhC1INH is distributed as 2100u, subjects over 42kg will use 2 vials, while pdC1INH is distributed as 500u vials so number of vials used is more varied.
- PSA scatter-plot (FIGURE 3) shows each of 5000 trials as pale dots, while mean cost-effectiveness is shown by large diamonds.
- Mean cost and effectiveness from PSA: $12390 and 0.786 for rhC1INH, $14132 and 0.738 for icatibant, $13050 and 0.746 for pdC1INH, $20286 and 0.785 for ecallantide.
- Re-dosing rates as high as 44% [19] for icatibant could lead to mean treatment cost approaching $16000 in spite of fixed self-administration rate and fixed dose volume.
- Weight-based dosing of pdC1INH and rhC1INH with different vial utilization appears in PSA scatter-plot as point groups stratified by cost.
- Ecallantide is tightly controlled in both cost and effectiveness.
- Large variance in cost for pdC1INH and rhC1INH results from weight-based dosing, while self-administration and re-dosing rates influence both cost and effectiveness.

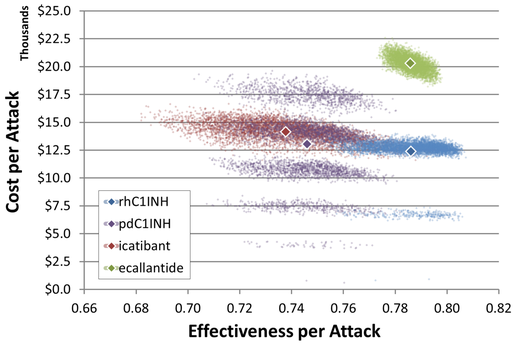
### FIGURE 2. ONE-WAY SENSITIVITY ANALYSIS - TORNADO DIAGRAMS




## CONCLUSIONS

- Accounting for associated downstream costs of on-demand treatment for HAE attacks presents a more complete picture of disease management expenses than drug costs alone.
- Cost-effectiveness is significantly influenced by re-dosing rates and the ability to self-administer.
- This model indicates that rhC1INH is most cost-effective in many scenarios while ecallantide is the least cost-effective.
- Although a rare disease, appropriate selection of on-demand therapy could represent substantial savings to the health system.

### FIGURE 3. PROBABILISTIC SENSITIVITY ANALYSIS COST-EFFECTIVENESS SCATTER PLOT





### References

**[1]** Zuraw BL, Bernstein JA, Lang DM. *J Allergy Clin Immunol.* 2013;131(6):1491-1493. **[2]** Bork K, Bernstein JA, Machnig T, Craig TJ. *J Emerg Med.* 2016 Apr;50(4):567-80.e1. **[3]** Lumry WR. *Front Med (Lausanne).* 2018 Feb 16;5:22. **[4]** Berinert [*Prescribing Information*]. Marburg, Germany: CSL Behring; 2018. **[5]** Firazyr [*Prescribing Information*]. Lexington, MA, USA: Shire Pharmaceuticals US Inc; 2018. **[6]** Kalbitor [*Prescribing Information*]. Lexington, MA, USA: Shire Pharmaceuticals US Inc; 2018. **[7]** Ruconest [*Prescribing Information*]. Leiden, Netherlands: Pharming Group; 2018. **[8]** Craig TJ, Levy RJ, Wasserman RL, et al. *J Allergy Clin Immunol.* 2009 Oct;124(4):801-8. **[9]** Zuraw BL. *J Manag Care Spec Pharm.* 2019 Feb;25(2):148-151. **[10]** Li HH, Campion M, Craig TJ, et al. *Ann Allergy Asthma Immunol.* 2013 Mar;110(3):168-72 **[11]** Bernstein JA, Relan A, Harper JR, Riedl M. *Ann Allergy Asthma Immunol.* 2017 Apr;118(4):452-455 **[12]** Riedl MA, Bygum A, Lumry W, et al. *J Allergy Clin Immunol Pract.* 2016 Sep-Oct;4(5):963-71. **[13]** Nordenfelt P, Dawson S, Wahlgren CF, et al. *Allergy Asthma Proc.* 2014 Mar-Apr;35(2):185-90 **[14]** Bygum A. *Acta Derm Venereol.* 2014 Jul;94(4):436-41 **[15]** Graham C, Supina D, Knox H, Krishnarajah S. *J Manag Care Spec Pharm.* 2017 Oct;23(10-a):S33. **[16]** Zilberberg MD, Nathanson BH, Jacobsen T, Tillotson G. *Allergy Asthma Proc.* 2011a Sep-Oct;32(5):390-4 **[17]** Zilberberg MD, Nathanson BH, Jacobsen T, Tillotson G. *Allergy Asthma Proc.* 2011b May-Jun;32(3):248-54 **[18]** Li HH. *Patient Prefer Adherence.* 2016 Sep 7;10:1727-37 **[19]** Magerl M, Zampeli V, Buttgereit T, Maurer M. *Observations on real-world on-demand therapy use and outcome in patients with HAE due to C1-INH deficiency.* Presented to 4th Global Urticaria Forum, Berlin, Germany. 5-6 December 2018.


### Disclosures

CT: employee of AHRM Inc. AR: employee of Pharming Healthcare Inc. PA: employee of Pharming Healthcare Inc. RM: employee of AHRM Inc.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