Hereditary Angioedema Prophylaxis With Plasma Kallikrein Inhibitors: Role of Target Binding Kinetics, Pharmacokinetics, and Treatment Adherence

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Rationale

- Hereditary angioedema (HAE) is a rare inherited disorder characterized by recurrent episodes (also called attacks) of severe swelling of the skin and mucous membranes.
- Unopposed contact system activation leads to excess plasma kallikrein (PKa) activity and, subsequently, increased bradykinin, a key mediator of HAE attacks.
- PKa inhibitors reduce contact system activation and have been approved or are in development for HAE.
- Lanadelumab, a fully human monoclonal antibody inhibitor of PKa (half-life of ~14 days) approved for HAE prophylaxis in several regions,* reduced attack rates at 300 mg administered every 2 weeks (q2wks) for 26 weeks by ~87% compared with placebo in the phase 3 HELP Study (NCT02586805).[1]
- We sought to understand the impact of target binding kinetics, pharmacokinetics, and treatment adherence on maintaining HAE disease control with lanadelumab versus small molecule PKa inhibitors (half-life of 20 hours) in development for HAE prophylaxis via a quantitative systems pharmacology (QSP) approach.[2-5]

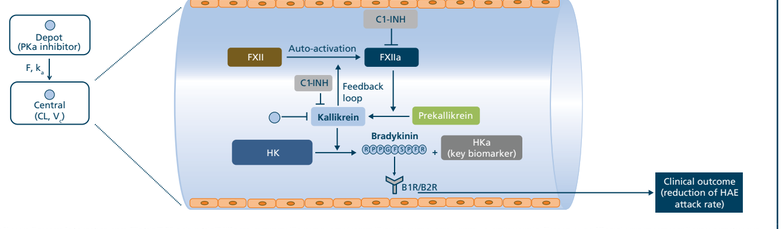
Methods

- A mechanistic biological model of HAE was developed using QSP that incorporated critical components of the contact system and a virtual HAE patient population (**Figures 1 and 2**).
- Cleaved high molecular weight kininogen pharmacodynamic biomarker data and clinical outcomes from lanadelumab clinical studies were used to verify the model within an acceptable range (**Figures 3–5**).
- The verified model was used to evaluate the impact of various drug-related factors on HAE disease outcome, including binding potency, treatment adherence (assessed via virtual patient populations by QSP modeling), and half-life (**Figures 6–9**).

Results

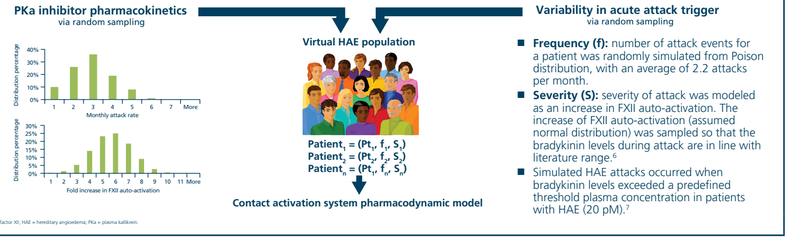
Model development

Figure 1: QSP model of in vivo contact system activation



C1-INH = C1-inhibitor; CL = clearance; F = fraction of dose absorbed; FXII = factor XII; FXIIa = activated factor XII; HAE = hereditary angioedema; HK = high molecular weight kininogen; HKa = cleaved high molecular weight kininogen; k_a = absorption rate constant; PKa = plasma kallikrein; QSP = quantitative systems pharmacology; V_c = central volume of distribution.

Figure 2: Representation of the HAE virtual patient population capturing patient variability in the propensity for acute attacks represented by frequency and severity

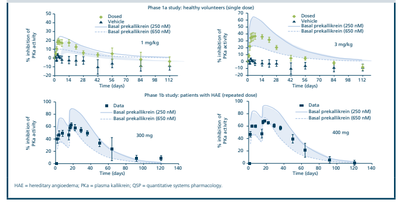


- **Frequency (f):** number of attack events for a patient was randomly simulated from Poison distribution, with an average of 2.2 attacks per month.
- **Severity (S):** severity of attack was modeled as an increase in FXII auto-activation. The increase of FXII auto-activation (assumed normal distribution) was sampled so that the bradykinin levels during attack are in line with literature range.[6]
- Simulated HAE attacks occurred when bradykinin levels exceeded a predefined threshold plasma concentration in patients with HAE (20 pM).[7]

FXII = factor XII; HAE = hereditary angioedema; PKa = plasma kallikrein.

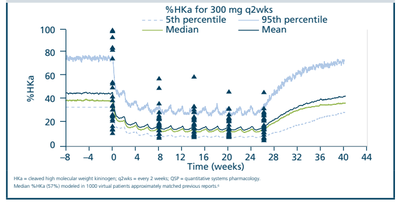
Model qualification

Figure 3: QSP model approximated observed %PKa inhibition data from phase 1a (NCT01923207) and phase 1b (NCT02093923) lanadelumab studies



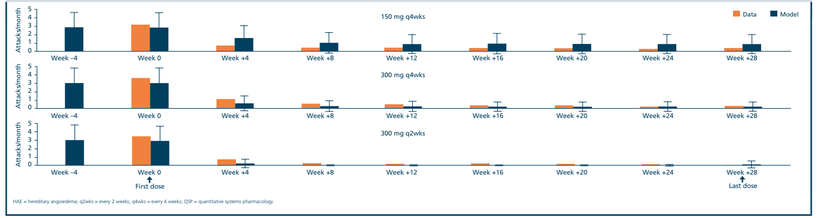
HAE = hereditary angioedema; PKa = plasma kallikrein; QSP = quantitative systems pharmacology.

Figure 4: QSP model approximated observed %HKa levels from the phase 3 lanadelumab study (NCT02586805)



HKa = cleaved high molecular weight kininogen; q2wks = every 2 weeks; QSP = quantitative systems pharmacology.
Median %HKa (57%) modeled in 1000 virtual patients approximately matched previous reports.[1]

Figure 5: QSP model prediction of monthly HAE attack rates in 1000 virtual patients approximated observed attack rates from the phase 3 lanadelumab study (NCT02586805)

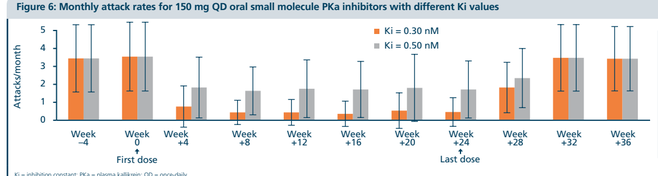


HAE = hereditary angioedema; q2wks = every 2 weeks; q4wks = every 4 weeks; QSP = quantitative systems pharmacology.

Model application

Role of target binding kinetics and pharmacokinetics

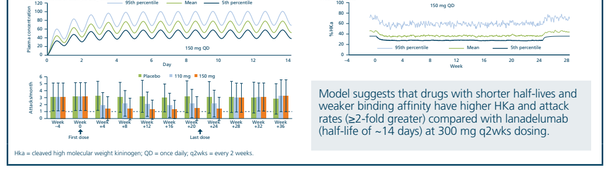
Figure 6: Monthly attack rates for 150 mg QD oral small molecule PKa inhibitors with different Ki values



In the absence of plasma protein binding, for a 150 mg QD dose, the binding affinity needs to be strong enough (eg, <0.3 nM) to effectively suppress attacks.

Ki = inhibition constant; PKa = plasma kallikrein; QD = once-daily.

Figure 7: Efficacy of drugs with shorter half-lives (20 hours)



Model suggests that drugs with shorter half-lives and weaker binding affinity have higher HKa and attack rates (≥2-fold greater) compared with lanadelumab (half-life of ~14 days) at 300 mg q2wks dosing.

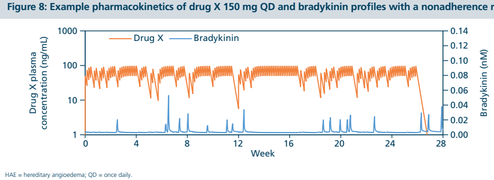
HKa = cleaved high molecular weight kininogen; QD = once daily; q2wks = every 2 weeks.

Impact of treatment nonadherence in patients

- Pharmacology adherence rates to daily oral therapy in the real-world setting report an 80% mean adherence, with a range of ~65–90%.[8]
- Nonadherence was studied for drugs with shorter half-lives (drug X) using population simulations with an assumed average of occurrence of nonadherences (random missing dose) of 20% for a virtual patient population (ie, 6 missed doses in a 30-day month).

Impact of treatment nonadherence in patients

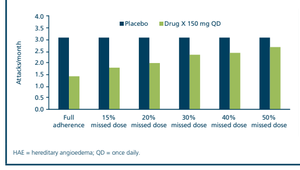
Figure 8: Example pharmacokinetics of drug X 150 mg QD and bradykinin profiles with a nonadherence rate of 20%



Nonadherence for daily dosing of drug X could negatively impact the suppression of HAE attacks because each missed dose would reduce drug coverage and make the patient more prone to HAE attacks.

HAE = hereditary angioedema; QD = once daily.

Figure 9: Simulated numbers of monthly attacks during treatment of drug X 150 mg QD with different nonadherence rates



	% reduction of attack rates compared with placebo					
	Full adherence	15% missed dose	20% missed dose	30% missed dose	40% missed dose	50% missed dose
Drug X 150 mg QD	**53.9**	**41.9**	**35.5**	**23.9**	**21.3**	**13.2**

The monthly attack profiles showed that the more missed doses, the higher the HAE attack occurrence. Simulations showed 6–8 days of randomly missed doses out of 4 weeks daily dosing could translate to a ~2-fold efficacy decline. At ≥50% missed dose scenario, treatment with drug results in marginal efficacy.

HAE = hereditary angioedema; QD = once daily.

Conclusions

- **A QSP model of excess contact system activation coupled with virtual population of patients with HAE was developed to quantitatively describe the dynamic interactions of the contact factors and PKa inhibitors. The model successfully captures the clinical outcomes of lanadelumab in virtual patients with HAE.**
- **The model was applied to investigate the role of target binding and pharmacokinetics and showed that drugs with long half-lives (>2 weeks) had ≥2-fold improved efficacy versus those with short half-lives (20 hours).**
- **For small molecules with short half-lives, the model suggested that the more missed doses, the higher the HAE attack occurrence.**
- **Drug development programs address noncompliance and nonpersistence via the development of drugs that require less frequent dosing and demonstrate longer half-lives.**

Presented at the American Academy of Asthma, Allergy & Immunology Annual Meeting, March 13–16, 2020, Philadelphia, PA

Lanadelumab is approved as prophylaxis to prevent attacks of HAE in patients ≥12 years of age in the United States and for the routine prevention of attacks in patients ≥12 years of age in Canada.[9,10] Lanadelumab also was approved in the European Union, Australia, and Brazil for the routine prevention of recurrent attacks of HAE in patients ≥12 years of age,[11,12] and in Switzerland for the long-term prevention of attacks of HAE in patients ≥12 years of age.[13]

References: 1. Banerji A, et al. *JAMA* 2018;320:2108-2121. **2.** Aygören-Pürsün E, et al. *N Engl J Med* 2018;379:352-362. **3.** Kalfus I, et al. Presented at the Annual Scientific Session of the Western Society of Allergy, Asthma and Immunology; January 20–4, 2019; Maui, HI. **4.** Hampton SL, et al. *J Allergy Clin Immunol* 2019;143:A839. **5.** van der Graaf PH, Benson N. *Pharma Res* 2011;28:1460-1464. **6.** Nussberger J, et al. *Lancet* 1998;351:1693-1697. **7.** Suffritti C, et al. *Clin Exp Allergy* 2014;44:1503-1514. **8.** Osterberg L, Blaschke T. *N Engl J Med* 2005;353:487-497. **9.** Shire. Highlights of prescribing information. Takhzyro™ (lanadelumab-flyo) injection, for subcutaneous use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761090s000lbl.pdf. Accessed January 6, 2020. **10.** Shire Pharma Canada. Product monograph including patient medication information. Takhzyro™ (lanadelumab injection). https://www.shirecanada.com/-/media/shire/shirecglobal/shirecanada/pdf/files/product%20information/takhzyro-pm-en.pdf. Accessed January 6, 2020. **11.** European Medicines Agency Takhzyro 300 mg solution for injection. Summary of product characteristics. http://ec.europa.eu/health/documents/community-register/2018/20181122143033/anx_143033_en.pdf. Accessed January 6, 2020. **12.** Takhzyro Australian product information. https://www.tga.gov.au/prescription-medicines-registration-new-chemical-entities-australia. Accessed January 6, 2020. **13.** Takhzyro Brazilian product information. http://portal.anvisa.gov.br/resultado-de-busca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=5076578&_101_type=content&_101_groupId=219201&_101_urlTitle=takhzyro-novo-registro&redirect=http%3A%2F%2Fportal.anvisa.gov.br%2Fresultado-de-busca%3Fp_p_id%3D101%26p_p_lifecycle%3D0%26p_p_state%3Dmaximized%26p_p_mode%3Dview%26p_p_col_id%3Dcolumn-1%26p_p_col_count%3D1%26_3_groupId%3D0%26_3_keywords%3Dlanadelumab%26_3_cur%3D1%26_3_struts_action%3D%252Fsearch%26_3_format%3D%26_3_formDate%3D1441824476958. Accessed January 6, 2020. **14.** Swissmedic. Takhzyro, solution for injection. https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisation/authorised-medicinal-products-with-new-active-substances/takhzyro_injektionsloesung_lanadelumabum.html. Accessed January 6, 2020.

Funding and acknowledgments: We thank all patients, investigators, and their study staff. This study was sponsored by Shire Human Genetic Therapies, Inc., a Takeda company. Under the direction of the authors, Hoa Q. Nguyen, employee of Takeda, provided writing assistance for this poster. Editorial assistance in formatting, proofreading, copyediting, and fact-checking also was provided by Excel Medical Affairs. Shire Human Genetic Therapies, Inc., a Takeda company, provided funding to Excel Medical Affairs for support in writing and editing this poster. The interpretation of the data was made by the authors independently.

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