CME

Hereditary Angioedema (HAE) Research Highlights:
2022 AAAAI Annual Meeting

Paula Busse, MD

Associate Professor, Medicine, Division of Clinical Immunology

Icahn School of Medicine at Mount Sinai

Disclosures

What is Hereditary Angioedema (HAE)?

- Rare autosomal dominant disease
  - Recurrent and unpredictable episodes of angioedema
  - Airway swelling can be life threatening
  - Significant impact on QoL
- Subtypes
  - HAE-I and –II due to dysfunction of C1-inhibitor protein (C1-INH)
  - HAE-nl-C1INH
  - Impact contact pathway to excessive bradykinin production and in some HAE-nl-C1INH endothelial dysfunction
- Significant improvement over past 10 years for both treatment of attacks and prophylaxis

2022 AAAAI Annual Meeting

- **American Academy of Allergy, Asthma, & Immunology**
- February 25-28, 2022 in Phoenix, AZ (option to attend the event virtually)
- Abstracts published in the *Journal of Allergy and Clinical Immunology*
  - *Updates on recently approved therapies*
  - *Pipeline therapies*
  - *Monitoring of HAE (predicting severity and HAE as cause of angioedema)*

Updates: Newly Approved Medications

Lanadelumab

- 4 abstracts at AAAAI 2022
  - 3 -EMPOWER observational study
  - 1 -Open label extension of original HELP phase 3 study

Lanadelumab: Background

- SC PK inhibitor for prophylaxis of attacks
- Approved by the FDA based upon the HELP Phase 3 (DBPC) study
  - Patients randomized 2:1 lanadelumab (n = 84) to placebo (n = 41); lanadelumab group further randomized to receive 1 of 3 dose regimens
  - Primary outcome: monthly attack rate

Dosing Regimen	Monthly Attack Rate
150mg Q4W	0.48
300mg Q4W	0.53
300mg Q2W	0.26
Placebo	1.97

- Approved 300mg Q2W with option to extend to Q4W

Banerji A, Riedl MA, Bernstein JA, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. *JAMA*. 2018;320(20):2108-2121.

EMPOWER observational study: Background

- 93 participants (U.S. and Canada)
  - HAE type I, II
- Two patient populations prescribed lanadelumab
  - ‘New users’ (<4 doses at enrollment, n=15)
  - ‘Established users’ (>4 doses at enrollment, n=78)
- Outcomes collected every 6 months
  - Attack rates, AE-QoL, Treatment satisfaction
  - Patient characteristics of co-morbidities
- Abstracts reported interim data (12 month period)

1. Goodyear D, et al. Treatment Patterns Among Patients with HAE-C1- INH: Interim Analysis Findings from US and Canada Participants in the EMPOWER Study. *J Allergy Clin Immunol* 2022; 149(2): Abstract #502

EMPOWER observational study: Results

- Treatment patterns in the ‘real world’[1]
  - Prior to starting Lanadelumab
    - pd C1INH for prophylaxis used by 46.7% of new users and 11.5% established users
    - 2.6% of established users used androgens
  - Treatment intervals
    - 100% of new users and 81.8% of established users administer q 2 weeks
    - Remainder of established users administer q 4 weeks
    - 6 of established users discontinued Lanadelumab – none to AE

1. Goodyear D, et al. Treatment Patterns Among Patients with HAE-C1- INH: Interim Analysis Findings from US and Canada Participants in the EMPOWER Study. *J Allergy Clin Immunol* 2022; 149(2): Abstract #502

EMPOWER observational study: Results

- Real-world efficacy and safety similar to HELP study[1]
  - Most common AE were infections
  - 2% of patients reported serious AEs (none. related to lanadelumab)
  - Mean attack rate 83.3%

- Real-world Patient Reported Outcomes in new users[2]
  - Better QoL (AE-QOL)- scores decreased
  - Improved angioedema control (AECT)
  - Improved treatment satisfaction (TSQM-9)

Mean Attack Rates in Established vs New Patients

Established Patients (n = 78)		New Patients (n = 15)	
Before LAN	After LAN	Before LAN	After LAN
N/A	0.2 attack/month	1.2 attack/month	0.2 attack/month

83.3% reduction

Quality of Life Scores in New Patients

Mean AE-QoL Score		Mean AECT Score		Mean TSQM-9 Score	
Baseline	Month 12	Baseline	Month 12	Baseline	Month 12
36.0	30.0	9.3	11.7	72.5	81.7

1. Johnston D, et al. Long-term Effectiveness and Safety of Lanadelumab in the US and Canada: Findings from the EMPOWER Study. *J Allergy Clin Immunol* 2022; 149(2): Abstract #495
2. Busse P, et al. Impact of Lanadelumab on Patient-Reported Outcomes in Hereditary Angioedema in the US and Canada: Interim Findings from the EMPOWER Study. *J Allergy Clin Immunol* 2022; 149(2): Abstract #496

HELP and HELP-OLE: Post-hoc analysis results

- Lanadelumab has a similar efficacy and safety profile in patients who had previously only used androgens for prophylaxis compared to the larger study population

HELP (n=3)		HELP OLE (n=9)	
Placebo (n=1) (attack/month)	Lanadelumab (n=2) (attack/month)	Baseline (attack/month)	Lanadelumab (attack/month)
3.26	0.08	1.47	0.15

92.2% mean reduction

Lumry W, et al. Lanadelumab Efficacy and Safety After Switching from Androgens: Analysis of the Phase 3 HELP and HELP OLE Studies for Hereditary Angioedema. *J Allergy Clin Immunol* 2022; 149(2): Abstract #498

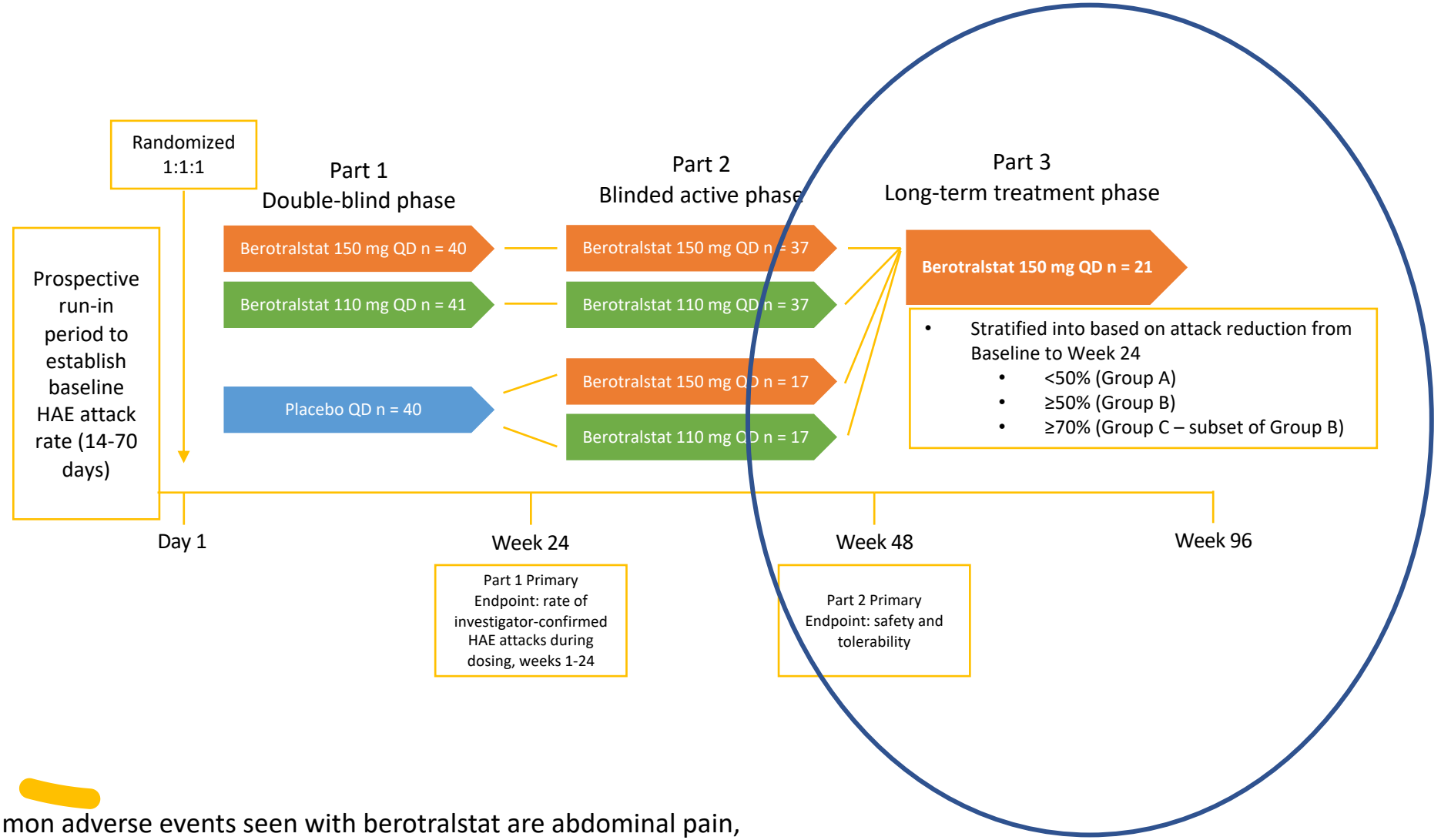
Berotralstat: Background (1)

- **APeX-2 Study**
  - Oral PK inhibitor, berotralstat, for HAE prophylaxis
  - Study design
    - Week 0-24 (110mg, 150mg, or placebo) QD
    - Week 24-48 (placebo participants randomized to 110mg or 150mg study drug)
  - Approved Dec 2020 based on study at 150mg po QD
- Three abstracts on extension of APEX-2 study at 96-week

*Most common adverse events seen with berotralstat are abdominal pain, vomiting, diarrhea, back pain, and gastroesophateal reflux disese

1. Wedner HJ, et al. Sustained Reductions in Hereditary Angioedema (HAE) Attack Rates Observed over 96 Weeks of Oral Berotralstat Treatment Regardless of Initial Response. *J Allergy Clin Immunol* 2022; 149(2): Abstract #490
2. Aygoren-Pursun E, et al. Oral Berotralstat Treatment for 96 Weeks Consistently Reduces Hereditary Angioedema (HAE) Attack Rates Regardless of Baseline Attack Rate. *J Allergy Clin Immunol* 2022; 149(2): Abstract #491
3. Gower R, et al. Sustained Improvement Observed in Patient- Reported Quality of Life (QoL) with 96 Weeks of Oral Berotralstat Treatment. *J Allergy Clin Immunol* 2022; 149(2): Abstract #492

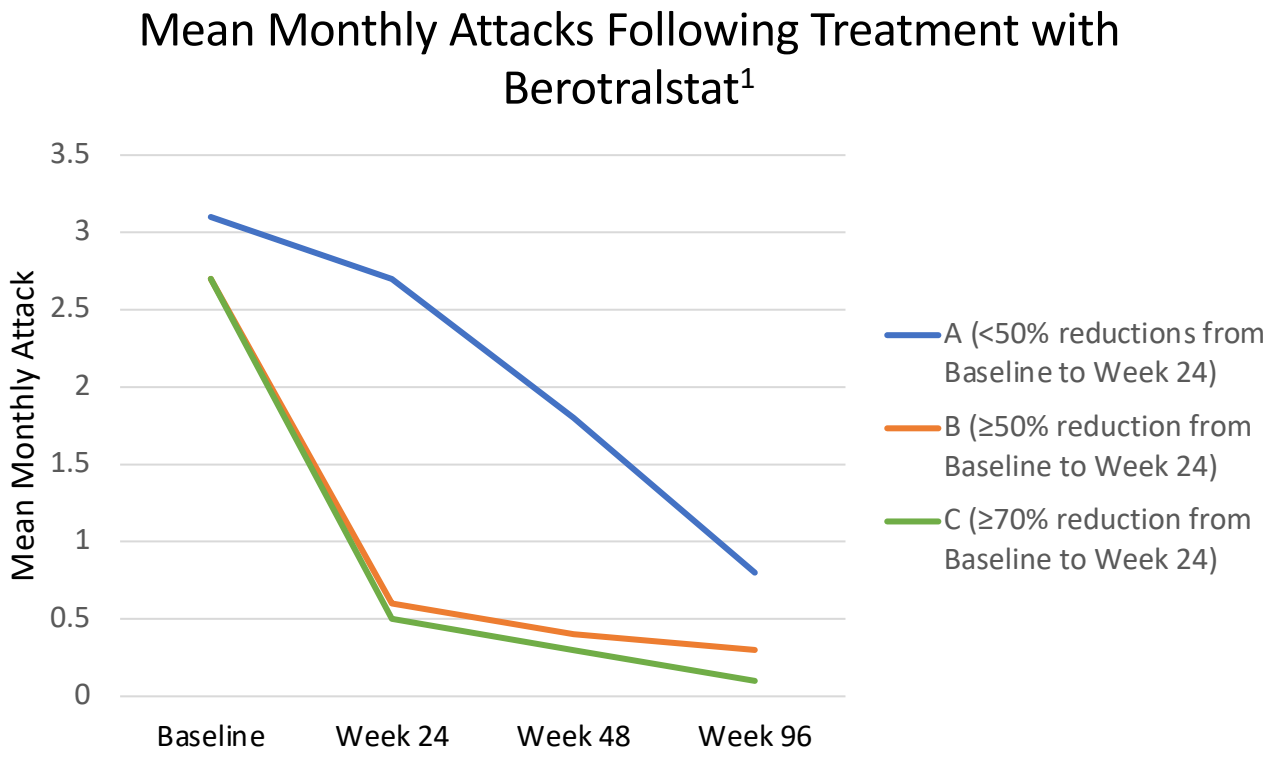
Berotralstat: Background (2)



*Most common adverse events seen with berotralstat are abdominal pain, vomiting, diarrhea, back pain, and gastroesophateal reflux disese

Berotralstat 96 Weeks: Results

- Participants had continued decreased attacks at 96 weeks
  - Even if had an initial slower attack rate reduction (Group A-Figure)[1]
  - Regardless of baseline attack frequency[2]
- Long-term treatment with berotralstat continued to improve QoL[3]



*Most common adverse events seen with berotralstat are abdominal pain, vomiting, diarrhea, back pain, and gastroesophageal reflux disease

1. Wedner HJ, et al. Sustained Reductions in Hereditary Angioedema (HAE) Attack Rates Observed over 96 Weeks of Oral Berotralstat Treatment Regardless of Initial Response. *J Allergy Clin Immunol* 2022; 149(2): Abstract #490
2. Aygoren-Pursun E, et al. Oral Berotralstat Treatment for 96 Weeks Consistently Reduces Hereditary Angioedema (HAE) Attack Rates Regardless of Baseline Attack Rate. *J Allergy Clin Immunol* 2022; 149(2): Abstract #491
3. Gower R, et al. Sustained Improvement Observed in Patient- Reported Quality of Life (QoL) with 96 Weeks of Oral Berotralstat Treatment. *J Allergy Clin Immunol* 2022; 149(2): Abstract #492

Pipeline therapies

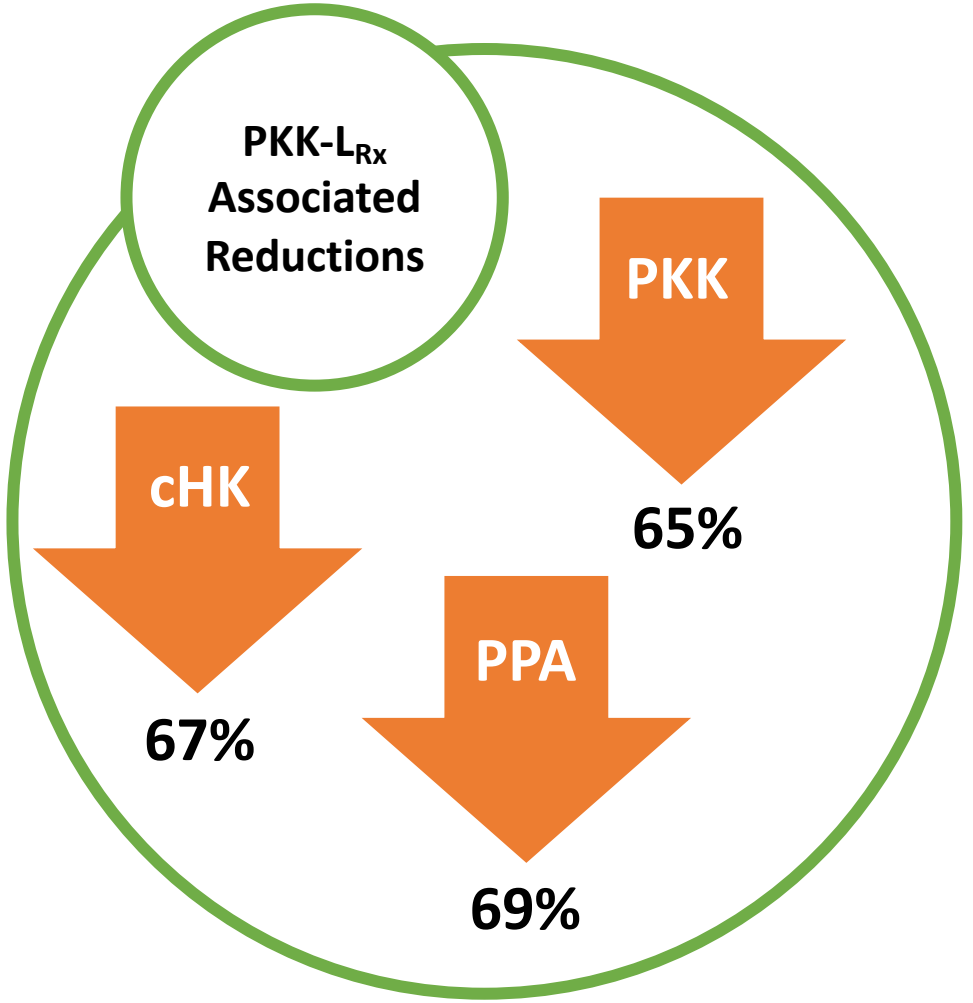
Donidalorsen (PKK-L_{Rx}): Background

- Antisense oligonucleotide targeted at reduction of hepatic prekallikrein (PKK), precursor to bradykinin
- Two abstracts presented phase 2 study results (recently published in NEJM)
- Study design
  - DBPC 2:1 SQ 80mg PKK-LRx (n=14) or placebo (n=6) q4 wks (12 weeks)
  - Participants with HAE-C1-INH

Fijen LM, et al. Inhibition of prekallikrein for hereditary angioedema. *New Engl J Med* 2022; 386: 1026-1033.

Donidalorsen (PKK-L_{Rx}): Results HAE-C1-INH

- Rapidly absorbed into systemic circulation
- Reduced plasma bradykinin expression
  - Significant reduction by 2 weeks
  - Peak: 65% PKK, 69% PPA, and 67% cHMWK at day 85)
- From Day 85 - no HAE attacks reported[1]
- Significantly improved validated angioedema qualify of life tool (AE-QoL)[2]



1. Bordone L, et al. Pharmacodynamics and Pharmacokinetics of PKK-LRx in Patients with Hereditary Angioedema. *J Allergy Clin Immunol* 2022; 149(2): Abstract #493
2. Fijen L, et al. The Impact on Quality of Life Following Treatment with Plasma Prekallikrein Targeted Oligonucleotide Antisense Therapy in Hereditary Angioedema Patients. *J Allergy Clin Immunol* 2022; 149(2): Abstract #506.

Donidalorsen (PKK-L_{Rx}): Results HAE-nl-C1INH

- Open-label study of 3 participants with HAE-nl-C1-INH
  - Four doses 80mg SC PKK-L_{Rx} q4 weeks
  - Mean decrease in monthly attack rate from baseline to treatment period (-76%)
  - PKK-L_{Rx} was well tolerated without severe adverse events

Patients (n = 3)	
Baseline	During Treatment
4.23 attack/month	1.5 attack/month

76% reduction

Cohn D, et al. An Open-label Trial With Plasma Prekallikrein Oligonucleotide Antisense Therapy To Control Angioedema Attacks In HAE Patients With Normal C1-inhibitor. *J Allergy Clin Immunol* 2022; 149(2): Abstract #494.

KVD900: Background

- Two abstracts on Phase 2 clinical trial HAE-C1-INH
- KVD900 - oral plasma kallikrein inhibitor for treatment of acute attacks
- Study design
  - Part I: Single dose 600mg open label in clinic
  - Part II: DBPC cross-over

KVD900: Results

- Rapid absorption of 600mg KVD900
  - Plasma PKa activity inhibited >50% within 15 minutes
  - Nearly completely inhibited (≥ 95%) within 1 hour
  - PKa inhibition was maintained for ≥ 4 hours after dosing
- KVD900 treatment significantly (P<0.0001) reduced time to symptom relief (Part 2), measured by Patient Global Impression of Change (PGI-C)[1]
- PGI-C score effectively reported outcome similar to reduction of symptom relief by VAS for complete attack resolution

Median Time to Symptom Relief

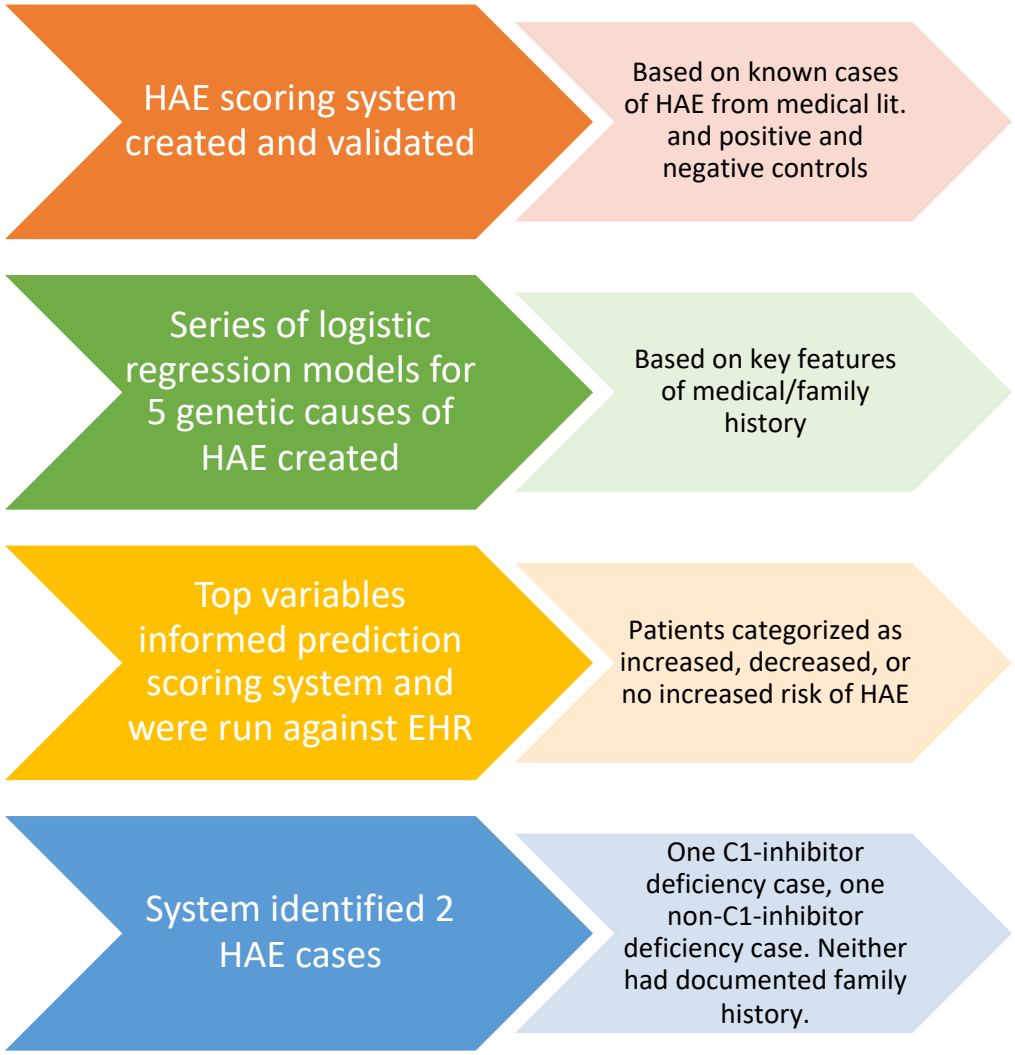
KVD900 Cohort	Placebo Cohort
1.6 hours	9.0 hours

1. Duckworth E, et al. Rapid Plasma Kallikrein Inhibition Following Oral KVD900 is Associated With Early Symptom Relief in Patients With Hereditary Angioedema. *J Allergy Clin Immunol* 2022; 149(2): Abstract #500.
2. Audhya U, et al. Agreement of Patient Global Impression of Change With Attack Resolution or Use of Rescue Medication in Patients With Hereditary Angioedema . *J Allergy Clin Immunol* 2022; 149(2): Abstract #509

Monitoring

Detecting HAE From Electronic Health Records

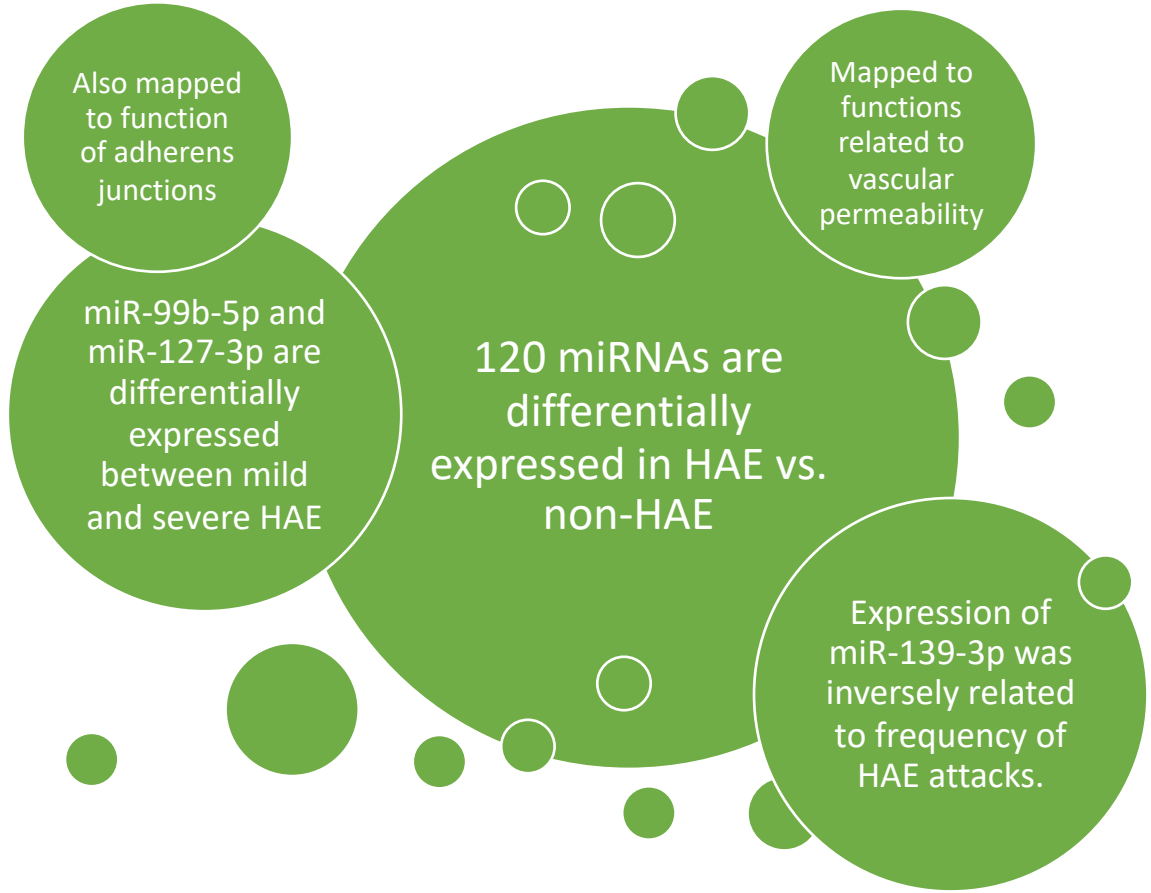
- Automated prediction scoring system to identify patients with increased likelihood of HAE (prior to laboratory confirmation)
- Prediction score based upon key medical and family history variables
- Logistic regression models created to identify variables with known participants with HAE-C1-INH
- Created a scoring system with 25 variables with reached 100% sensitivity/specificity for HAE0-C1-INH diagnosis
- In a general population, identified 26 at-risk patients



1. Laney D, et al. Implementation of an automated prediction scoring system to identify patients at possible increased risk for Hereditary Angioedema. *J Allergy Clin Immunol* 2022; 149(2): Abstract #124

Can MicroRNA Profiles Predict HAE Severity?

- Plasma samples from healthy controls (n=15), patients with mild (<6 attacks/year, n=11) or severe HAE (≥2 attacks/month, n=19)
- miRNA analysis form NextSeq 500 (depth 10 million reads/sample)
- 120 miRNAs differentially expressed in HAE vs. non-HAE
  - Pathway analysis revealed functions related to vascular permeability.
  - Two miRNAs were differentially expressed between mild and severe HAE. These miRNAs also mapped to adherens junctions function.
  - Expression of miR-139-3p was inversely related to frequency of HAE attacks (R=0.42, p=0.019).



1. Ishmael F, et al. Can Plasma MicroRNA Expression Patterns Predict Who May Develop Severe Hereditary Angioedema (HAE)? *J Allergy Clin Immunol* 2022; 149(2): Abstract #670.

Clinical Pearls

Clinical Pearls

- Lanadelumab:
  - SC prophylactic treatment
  - Mean decrease in attack rate similar among new patients as established ones
  - Quality of life improved with treatment
  - Has similar efficacy and safety profile in patients who had previously only used androgens compared to the larger study population
- Berotralstat:
  - Oral prophylactic treatment
  - Shows significant benefit in HAE patients at 96 weeks regardless of initial decrease in symptoms or baseline monthly attacks
  - Long-term prophylactic treatment with berotralstat continues to improve QoL in HAE patients

Clinical Pearls cont.

- Donidalorsen (PKK-L_{Rx})
  - Phase 2 study
  - Novel prophylactic SC antisense oligonucleotide to inhibit prekallikrein
  - Administered q 4 weeks
  - Significantly reduced bradykinin expression (PKK, PPA, and cHMWK)
  - By day 85, no HAE attacks reported in patients with HAE-C1-INH
  - Significant improved angioedema associated QoL
  - Open label study of 3 participants with HAE-nl-C1INH demonstrated 76% reduction in attacks, well tolerated
- KVD900
  - Phase 2 study
  - An investigational oral plasma kallikrein inhibitor for acute attacks
  - Rapid PK inhibition
  - Associated with early symptom relief of attacks (Patient Global Impression of Change, VAS)
  - PGI-C effective monitoring tool to predict response

Clinical Pearls cont.

- Development of an automated prediction scoring systems can be useful identifying patients with undiagnosed HAE
- A subset of miRNAs may also be able to predict HAE severity or disease control