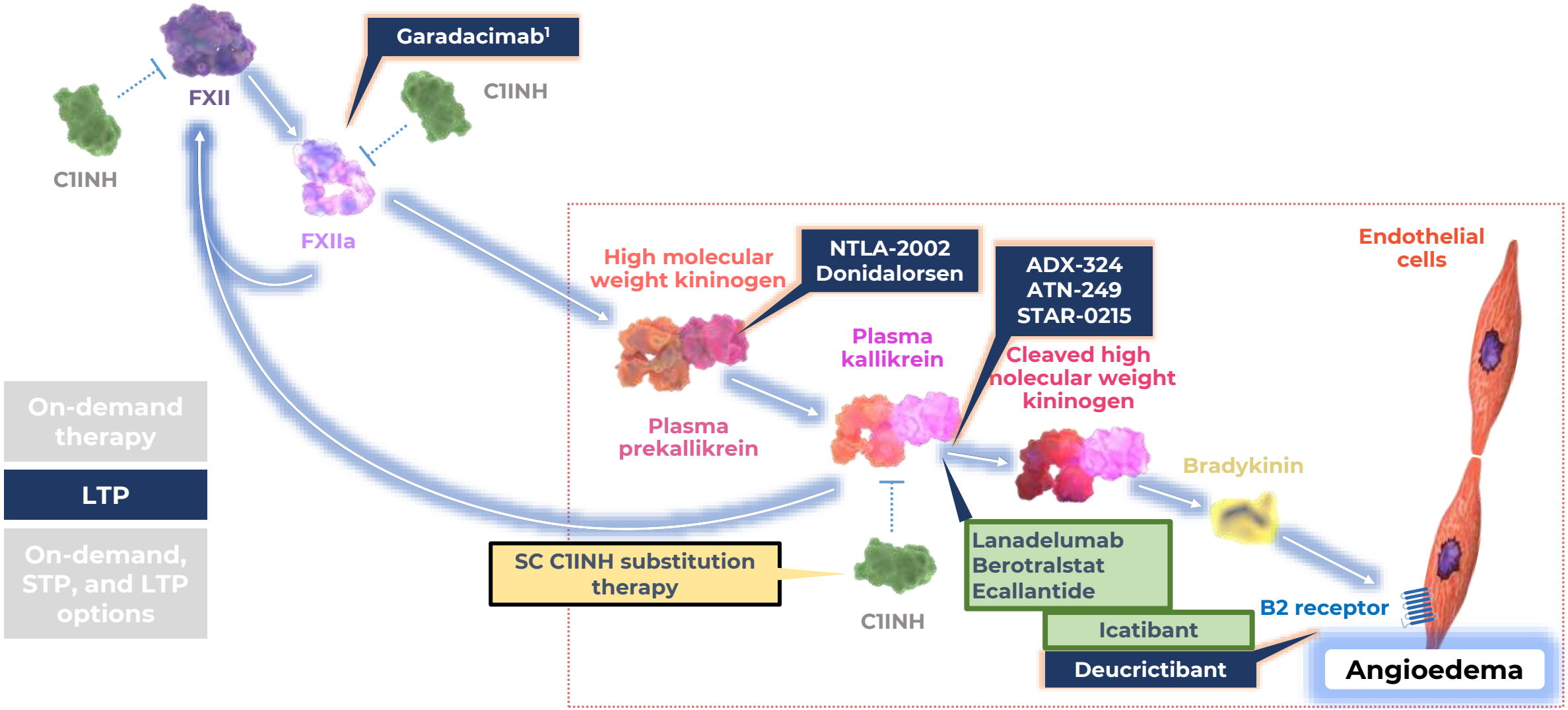
HAE treatment landscape

BSACI SpR training day – Cambridge

05.02.2026

Novel HAE LTP therapies target different parts of the contact activation pathway



Figures adapted from Lera AL et al. 2021 and Kaplan AP et al. 2022.[5,6]
C1INH, C1-esterase inhibitor; FXII, coagulation factor XII; FXIIa, activated factor XII; HAE, hereditary angioedema; LTP, long-term prophylaxis; SC, subcutaneous.

1. Craig TJ et al. *Lancet* 2023;401:1079–1090; 2. Fijen LM et al. *N Engl J Med* 2022;386:1026–1033; 3. Riedl M et al. *J Allergy Clin Immunol* 2024;153;AB11; 4. Longhurst HJ et al. *N Engl J Med* 2024;390:432–441; 5. Lera A. *Balkan Med J* 2021;38:82–88; 6. Kaplan AP. *Blood* 2022;139:2732–2733; 7. Maurer M et al. *Allergy* 2022;77:1961–1990; 8. Reshef A et al. *J Allergy Clin Immunol* 2024:S0091-6749(24)00407-X; 8. Smith et al. *Ann Asth Immunol* 2023;131:S27; 9. Bedian et al.. *J Pharmacol Exp Ther*. 2023;387(2):214-225; 10. Busse P, Kaplan A. *J Allergy Clin Immunol Pract*. 2022;10(3):716–722.

2

HAE Treatment options

- On demand therapy
- Short term prophylaxis
- Long term prophylaxis
- Cure

On demand therapy for HAE

- C1 inhibitor concentrates
- Icatibant
- Sebetralstat
- Deucrictibant

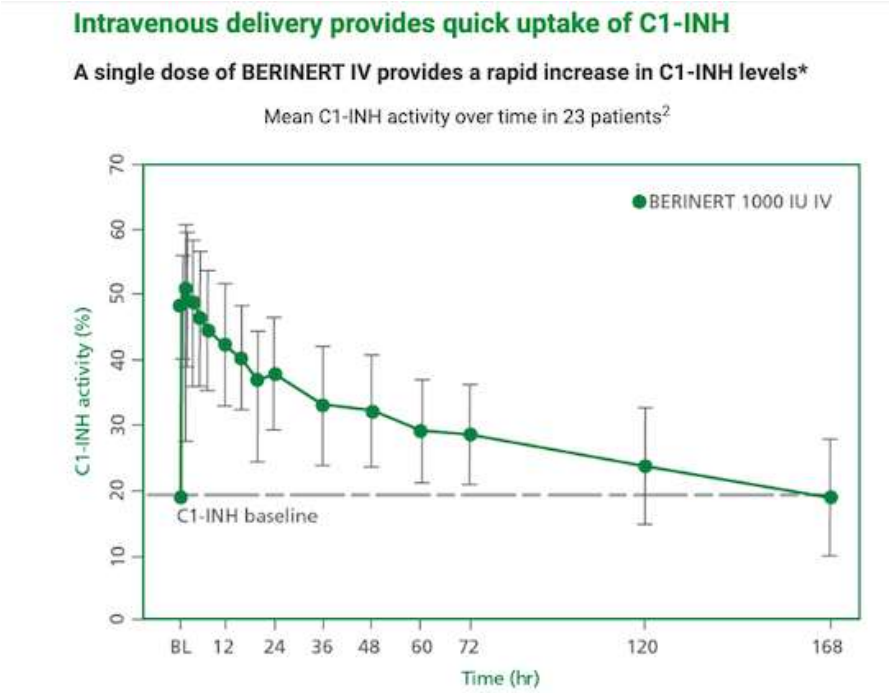
STP

- C1 inhibitor concentrates
- Sebetralstat

LTP

- C1 inhibitor concentrates
- Oral KKI
- Subcutaneous KKI - monoclonal
- Long acting KKI – monoclonal
- Factor XII inhibitor - monoclonal
- Anti sense RNA
- Small interfering RNA

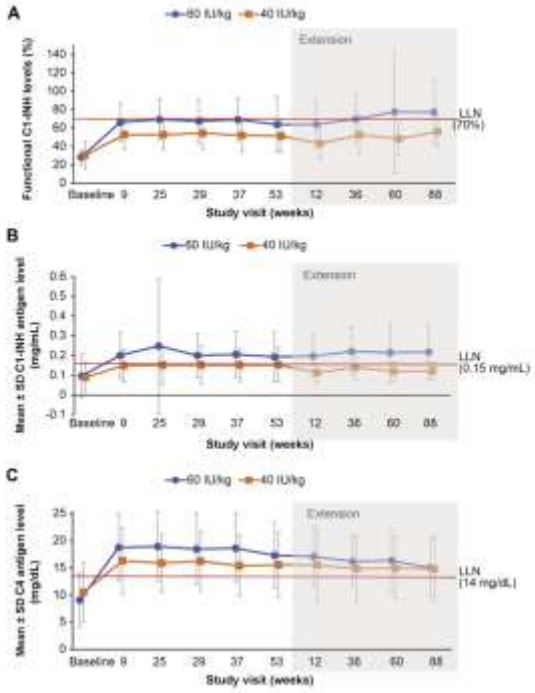
Plasma derived C1 inhibitor concentrates – IV route

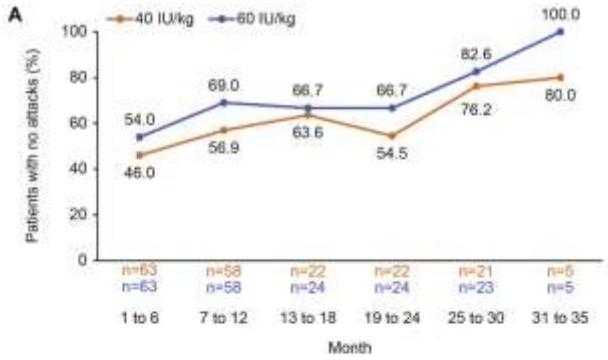


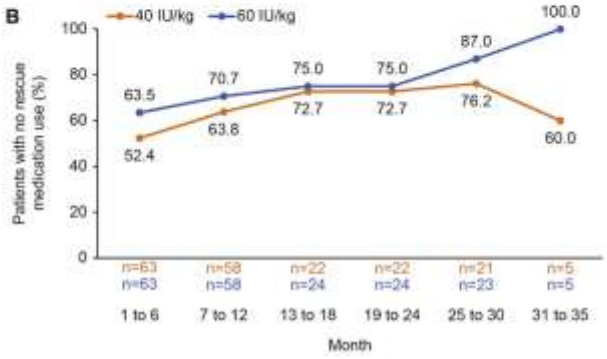
20U per KG

Plasma derived Sub cutaneous C1 inhibitor for LTP – Haegarda

Every 4 weeks







With HAEGARDA, HAE attacks were reduced by

95%†

As a preventive therapy, HAEGARDA can effectively reduce the number of HAE attacks you experience.

†In the clinical trial, the median reduction in number of attacks in people receiving HAEGARDA 60 IU/kg vs. placebo.

Use of rescue medication was nearly eliminated by

>99%‡

You should always have HAE rescue medication available at all times in case of a breakthrough attack.

‡In the clinical trial, the median reduction in rescue medication use in people receiving HAEGARDA 60 IU/kg vs. placebo.

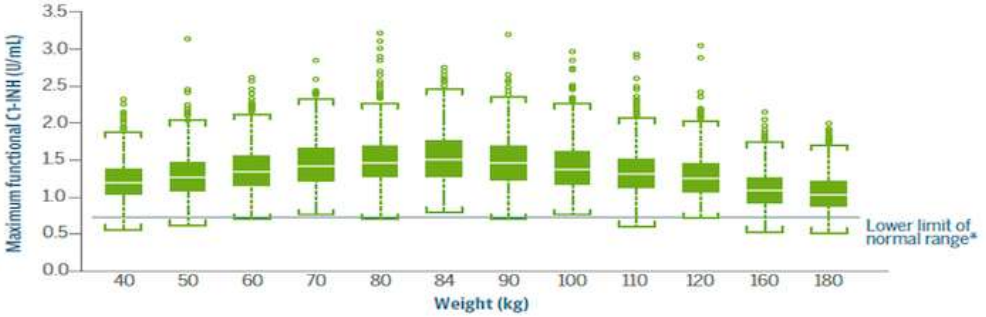
FDA approved 2017
NICE – due in June 2025

Recombinant C1 inhibitor concentrates – IV route

- Genetically engineered and is extracted from rabbit milk

RUCONEST® raised C1-INH plasma levels back to normal

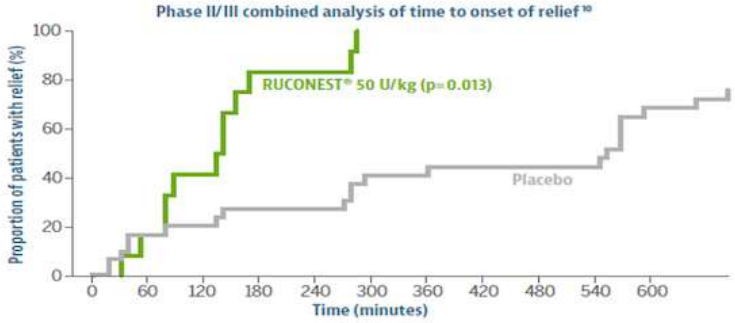
- One dose of RUCONEST®** raises human C1-INH plasma levels back into the normal range* in 94% of patients, regardless of body weight[6]



50U per KG

RUCONEST® provided rapid symptom relief

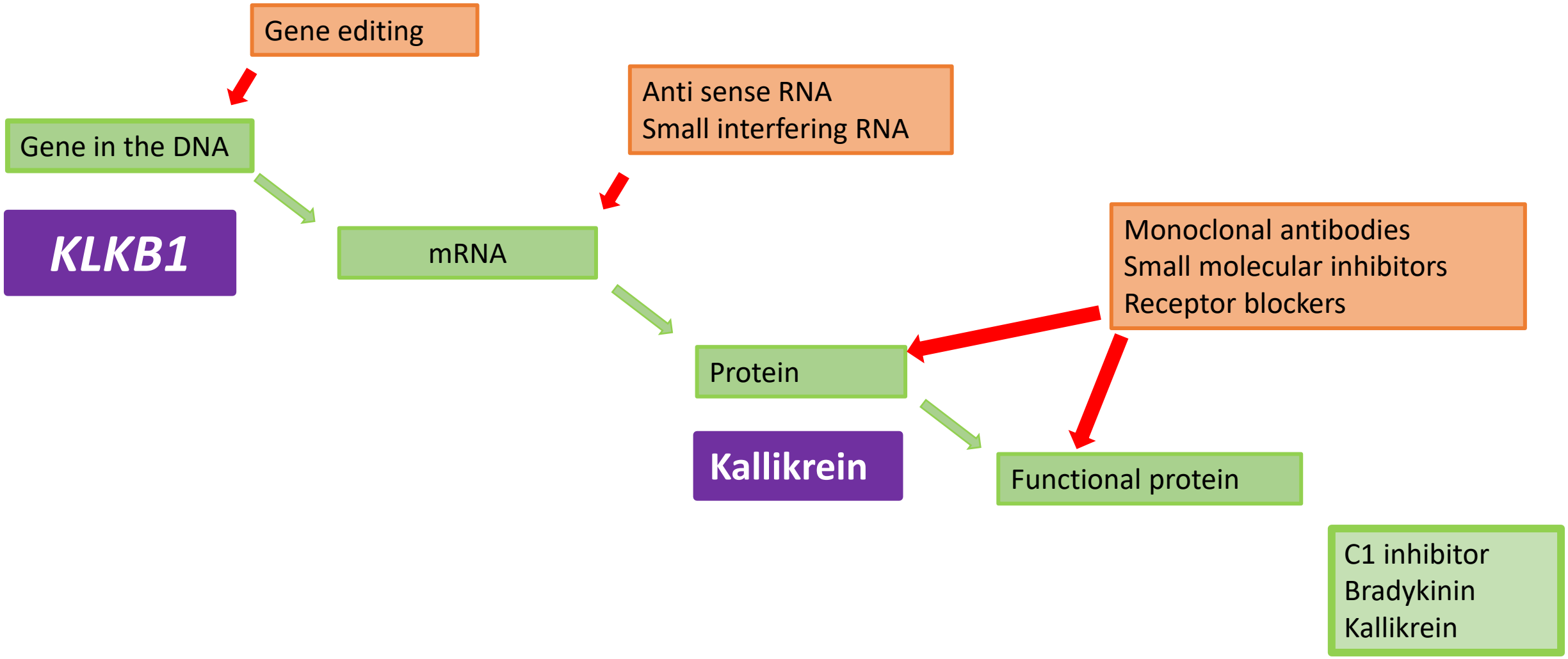
WAO guidelines[1] state that HAE patients experienced earlier relief from symptoms when treated early in the course of an attack



- A single dose of RUCONEST® worked rapidly to help patients get control of their symptoms fast*[10,11]

Phase III RCT[11] – TEQ: 90 vs. 152 minutes (p=0.031); VAS: 75 vs. 303 minutes (p<0.003)
Phase II/III RCTs combined analysis[10] – VAS: 122 vs. 495 minutes (p=0.013). TEQ – Treatment Effect Questionnaire; VAS – Visual Analogue Scale

Gene to functional protein and therapeutic targets

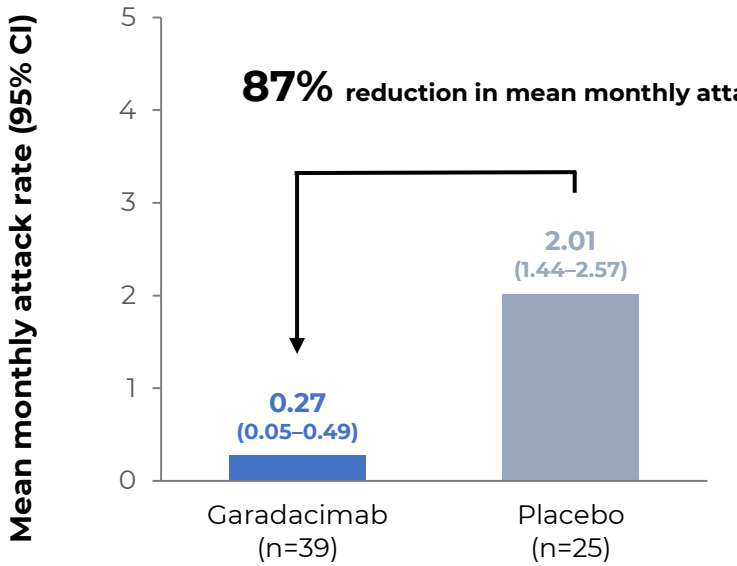


Garadacimab: Pivotal Phase 3 (VANGUARD) study

Patients aged ≥12 years with HAE-C1INH were randomized 3:2 to receive garadacimab (400 mg loading dose, then 200 mg SC once monthly; n=39) or placebo (n=25) for 6 months

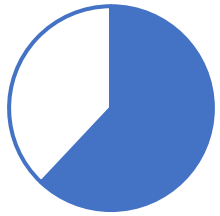
Efficacy: All patients on garadacimab achieved substantial reduction in HAE attacks

Primary endpoint: Mean monthly HAE attack rate

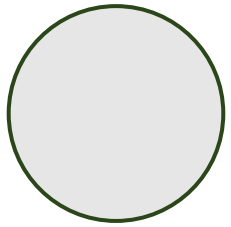


FDA approved December2023
NICE – due in June 2025

Secondary endpoint: HAE attack-free patients



62%
HAE attack-free
Garadacimab



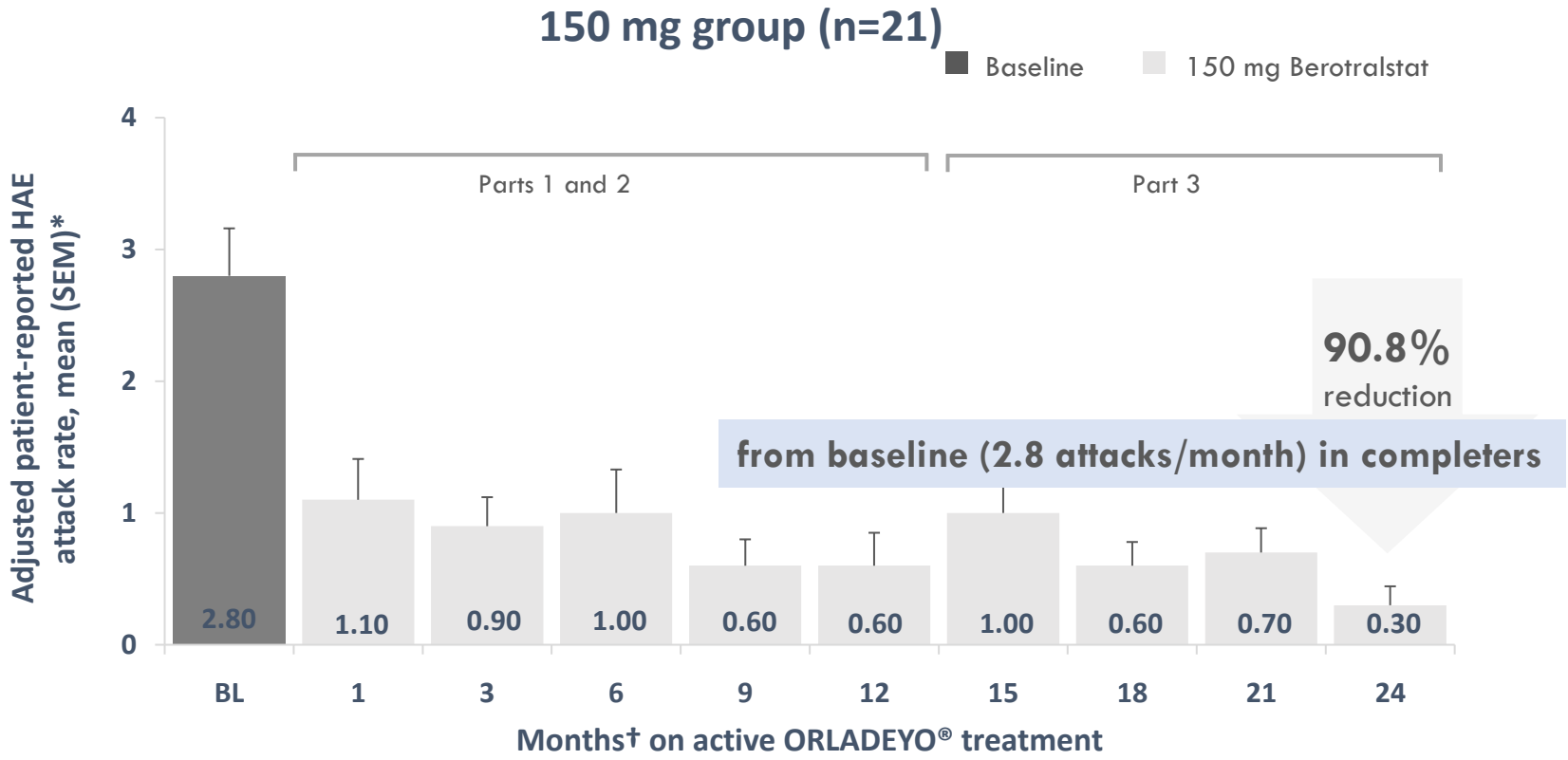
0%
HAE attack-free
Placebo

Garadacimab is not approved for use by any regulatory authorities. CSL Behring recommends the use of its products only as directed in the approved product label.
*Other secondary endpoints included additional clinical efficacy outcomes and SGART; †One severe SAE (laryngeal attack) was assessed as not related to garadacimab; the patient made a full recovery and was kept under hospital observation overnight; ‡Severe hypersensitivity including anaphylaxis, thromboembolic events, and abnormal bleeding events; §Patients provided ratings based on the question: "Considering all the ways HAE affects you, please rate your response to the study medication you were given to prevent HAE attacks during this treatment period."
AESI, adverse event of special interest; CI, confidence interval; HAE, hereditary angioedema; HAE-C1INH, HAE with C1INH deficiency or dysfunction; SC, subcutaneous; SGART, Subject's Global Assessment Response Treatment; TEAE, treatment-emergent adverse event.
1. Craig TJ et al. *Lancet* 2023;401:1079–1090 and supplementary appendix.

Ecallantide

- Not licensed in thee UK The first selective kallikrein inhibitor approved in the United States
- The first subcutaneous, reversible inhibitor of plasma kallikrein, KALBITOR (ecallantide)
- A recombinant protein produced by *Pichia pastoris* yeast
- Ecallantide (DX-88) binds directly to plasma kallikrein to prevent cleavage to HMWK and the generation of bradykinin

Patient-reported HAE attack rates decreased, then sustained or further decreased over 24 months of treatment with Berotralstat



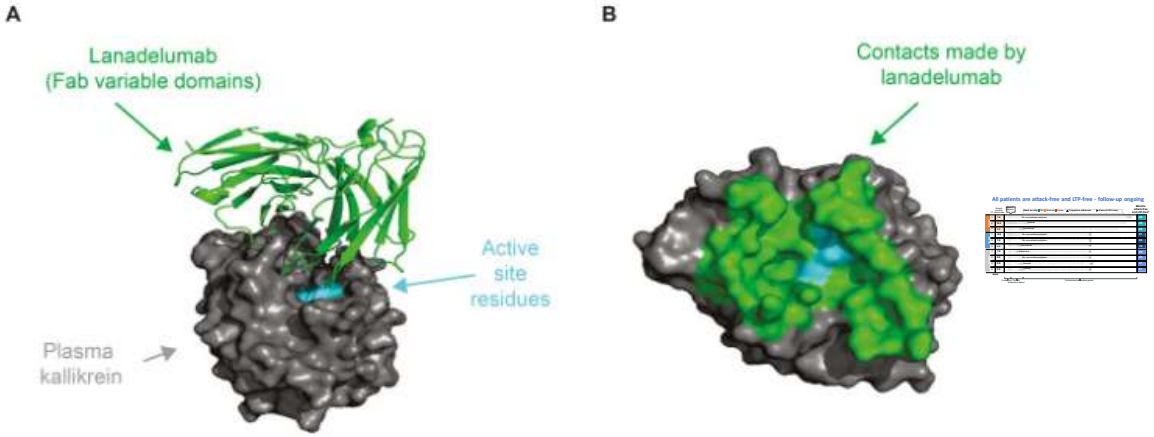
Across all treatment groups, **patient-reported HAE attack rates decreased** within the first 4 weeks of initiating berotralstat treatment

Figure adapted from: Kiani-Alikhan S, et al. 2024.

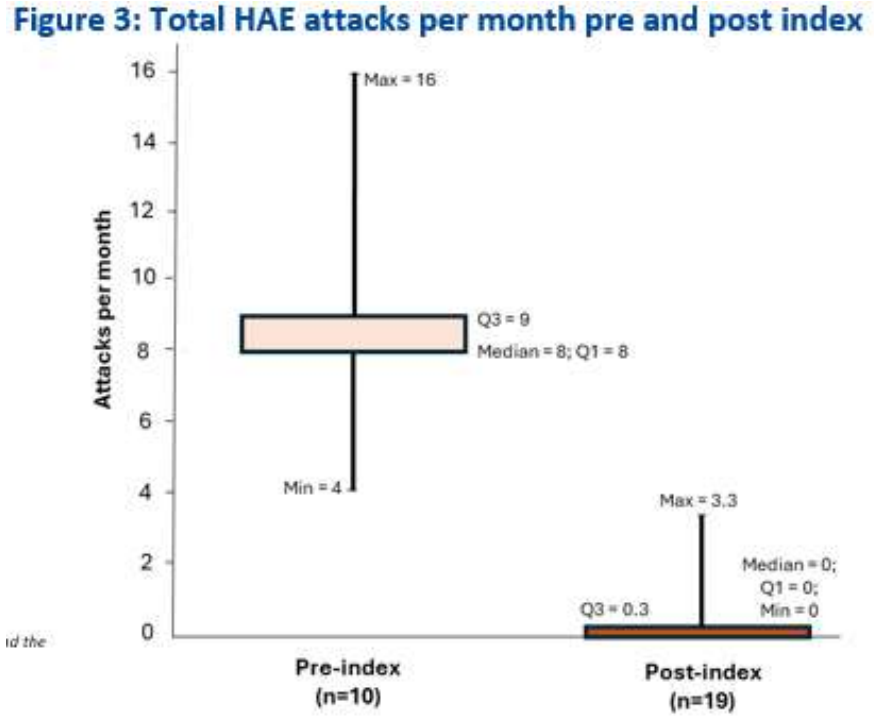
*Mean adjusted patient-reported HAE attacks rates for patients who entered Part 3 of APeX-2 and completed 96 weeks of ORLADEYO® treatment from baseline to 96 weeks of treatment for the 96-week completers from the 150 mg group. Five patients discontinued 150 mg ORLADEYO® treatment during Part 3 (one due to illness/condition, one due to perceived lack of efficacy, two due to withdrawn consent and one due to a lab abnormality of TEAE). Baseline-adjusted subject-reported HAE attack rates are based on the number of HAE attacks experienced between screening and the start of Part 1 (i.e. the run-in period). †A month is defined as 28 days. **Abbreviations:** HAE, hereditary angioedema; SEM, standard error of the mean; TEAE, treatment-emergent adverse event.

Reference: Kiani-Alikhan S, et al. *J Allergy Clin Immunol Pract*. 2024;12:733–743.

Lanadelumab – sub cutaneous Kallikrein inhibitor - Mabs

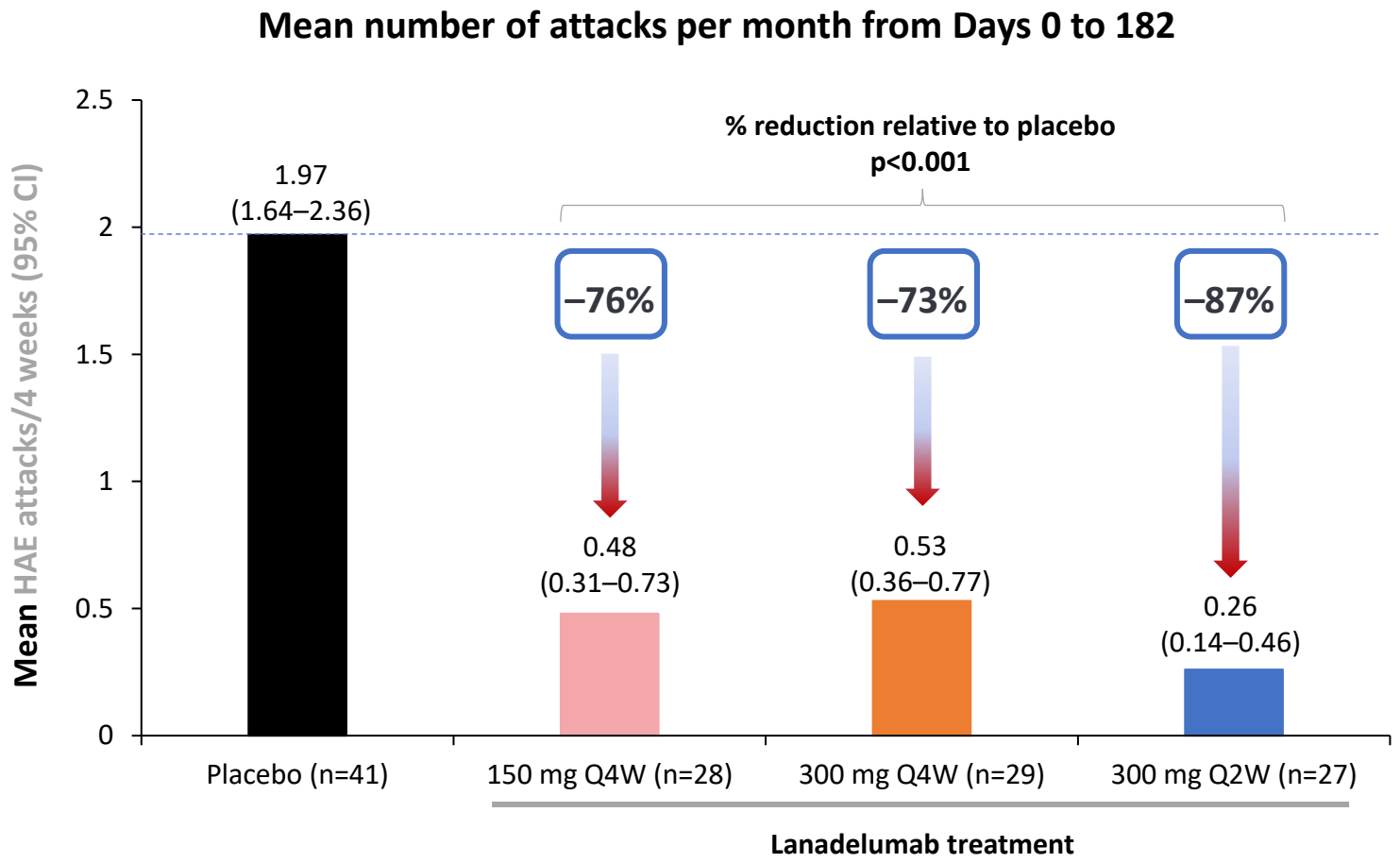


- Given every 2-4 weeks



Reduction in Mean HAE Attack Rate (Primary Endpoint)

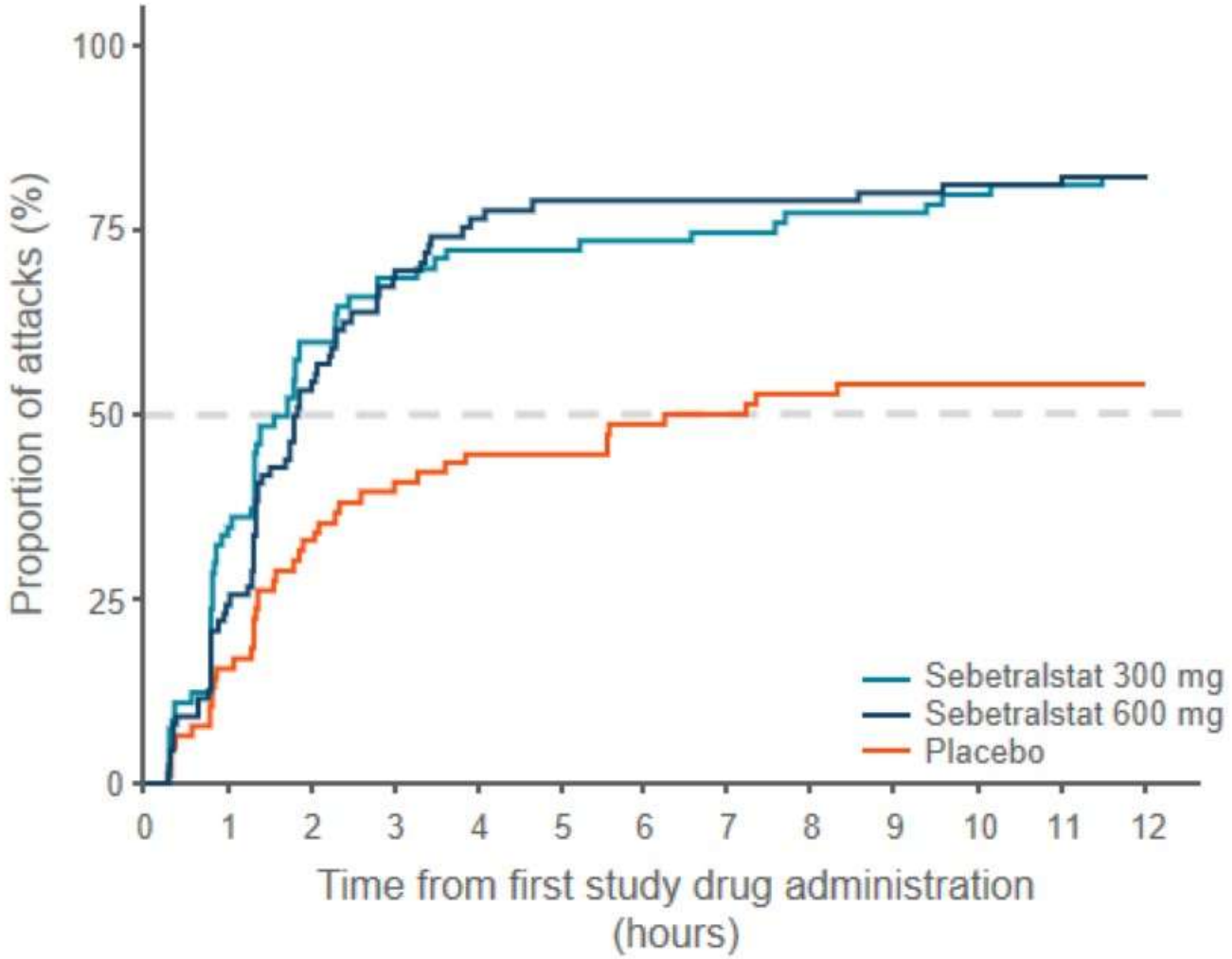
125 patients



- Lanadelumab significantly reduced mean attack rates by 73–87% overall when compared to placebo

Results are from a Poisson regression model; treatment group and normalized baseline attack rate were fixed effects, and the logarithm of time (days) each patient was observed during the treatment period was an offset variable. Adjusted p values are shown.
CI, confidence interval; HAE, hereditary angioedema; Q2W, every 2 weeks; Q4W, every 4 weeks.
Banerji A, et al. *JAMA* 2018;320:2108–2121.

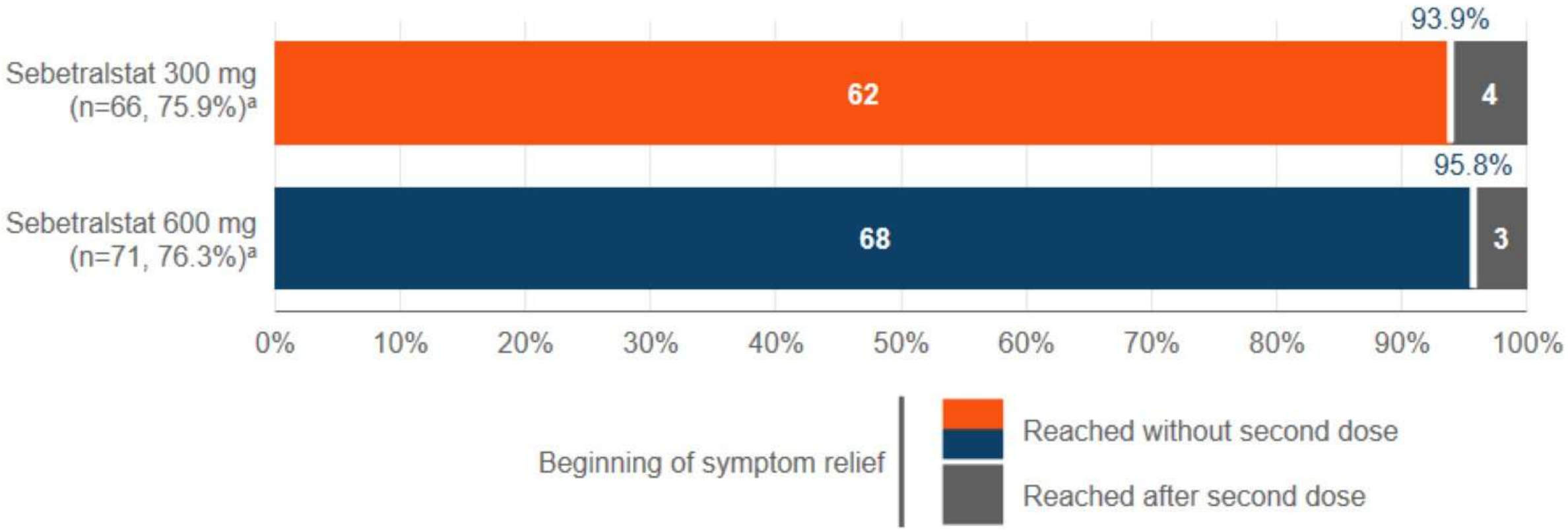
Primary Endpoint: Sebetralstat
Time to Beginning of Symptom Relief (PGI-C)



- Time to beginning of symptom relief was significantly faster vs placebo for
  - 300 mg ($p<0.0001$)
  - 600 mg ($p=0.0013$)
- Median time (95% CI) to beginning of symptom relief was
  - 1.61 h (1.28, 2.27) for 300 mg
  - 1.79 h (1.33, 2.27) for 600 mg
  - 6.72 h (2.33, >12) for placebo

Endpoint definition: time to beginning of symptom relief defined as a PGI-C rating of at least "A Little Better" for 2 time points in a row within 12 hours of the first dose of study drug administration.

Primary Endpoint: Proportion of Attacks Reaching Beginning of Symptom Relief (PGI-C) With 1 vs 2 Doses



FDA and NICE applications are in progress

Navenibart – long acting KKI - sucutaneous

PROGRAM	DISCOVERY	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	RECENT & EXPECTED MILESTONES
NAVENIBART (STAR-0215) *Anti-plasma kallikrein half-life extended mAb*	**Hereditary Angioedema**					✓ **Q4 2024:** Final results from Phase1b/2 ALPHA-STAR trial ◆ **Q1 2025:** Phase 3 trial initiation ◆ **Mid-2025:** Initial results from ALPHA-SOLAR ◆ **Early 2027:** Phase 3 ALPHA-ORBIT top-line results

Every 3-6 months injections

The NEW ENGLAND JOURNAL of MEDICINE

Donidalorsen for Hereditary Angioedema

A PLAIN LANGUAGE SUMMARY

Based on the NEJM publication: Efficacy and Safety of Donidalorsen for Hereditary Angioedema by M.A. Riedl et al. (published May 31, 2024)

In this trial, researchers assessed the efficacy and safety of donidalorsen, given subcutaneously every 4 or 8 weeks, in preventing hereditary angioedema attacks.

Hereditary angioedema is a rare, chronic disease characterized by potentially life-threatening and sudden tissue swelling caused by increased flux through the kallikrein–kinin system.

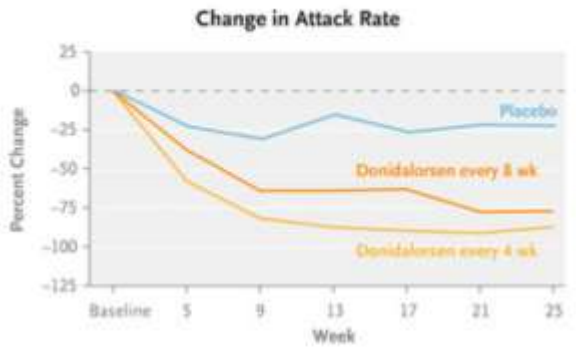
Phase 3 OASIS study

>90% reduction in monthly attack rate

Anti sense RNA is a single stranded RNA molecule that binds to mRNA and often uses RNases to promote mRNA degradation or inhibits translation

RNA-targeted prophylactic medicine designed to precisely target and silence the production of prekallikrein (PKK), interrupting the pathway that leads to HAE attacks.

NICE application is due this year



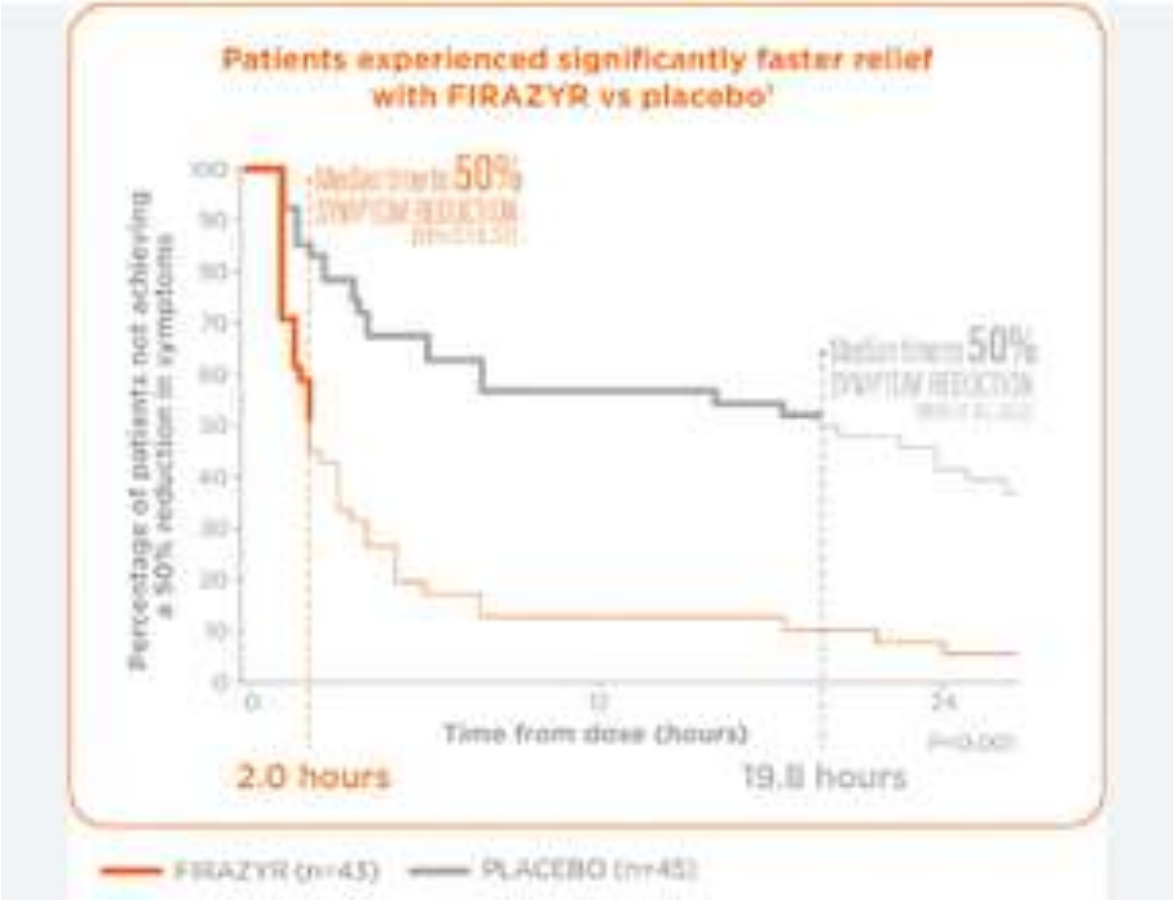
ADX-324

- Small interfering RNA is a double stranded RNA that uses an RNA induced silencing complex (RISC) that cleaves complementary mRNA
- ADX-324 is a short-interfering RNA (siRNA) designed to reduce the production of pre kallikrein.
- for possible a bi-annual, and possibly annual, low volume subcutaneous dose regimen
- We will be recruiting patients soon

Icatibant

Icatibant Injection

Icatibant Injection from Fresenius Kabi

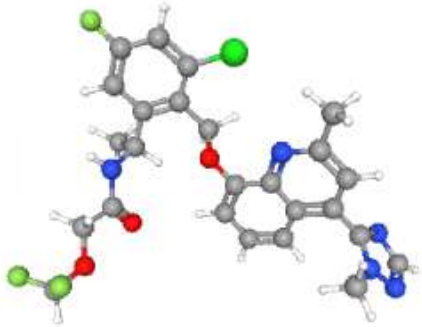


Two investigational oral therapies utilizing the same active ingredient for on-demand and prophylactic treatment of HAE

Deucrictibant
Immediate-release capsule

Rapid absorption

Aims to provide rapid and reliable symptom relief, through rapid exposure of attack-mitigating therapy in a convenient, small oral dosage form[a]

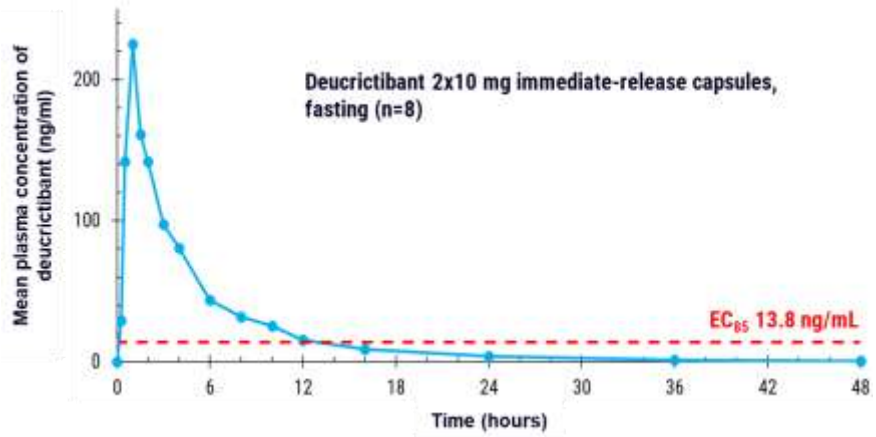


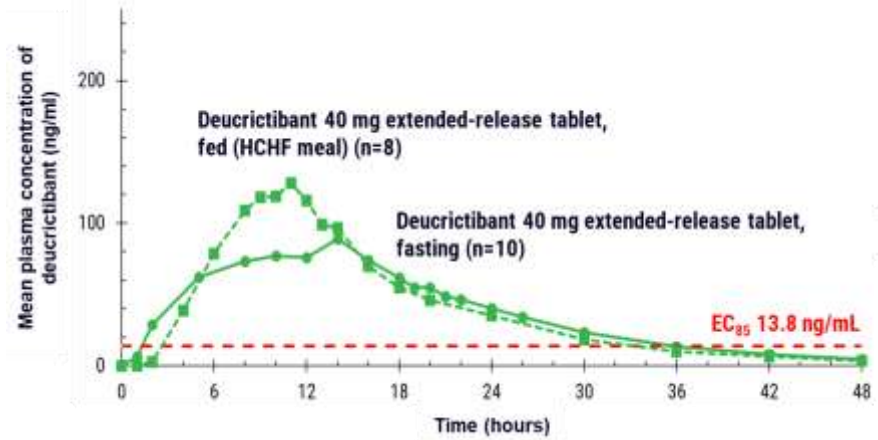
Deucrictibant
Extended-release tablet

Sustained absorption

Aims to provide sustained exposure of attack-preventing therapy in a convenient, small oral dosage form[a]

Deucrictibant





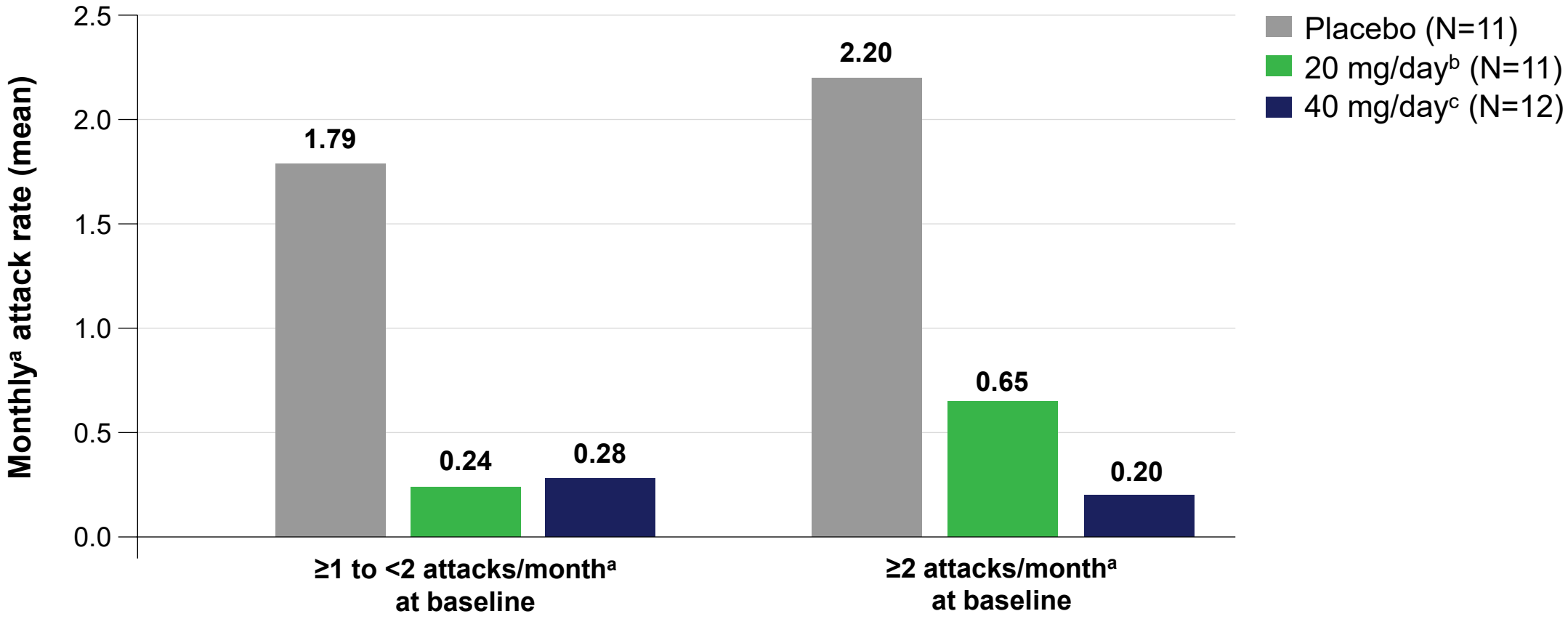
Adapted from: Groen K, et al. Presented at ACAAI 2022; November 10–14, 2022; Louisville, KY, USA. EC_{85}, concentration at which 85% of the maximum inhibitory effect is observed; HAE, hereditary angioedema; HCHF, high-calorie high-fat. [a]Aspirational; to be confirmed with clinical data.

This presentation includes data for an investigational product not yet approved by regulatory authorities.

Deucrictibant trials

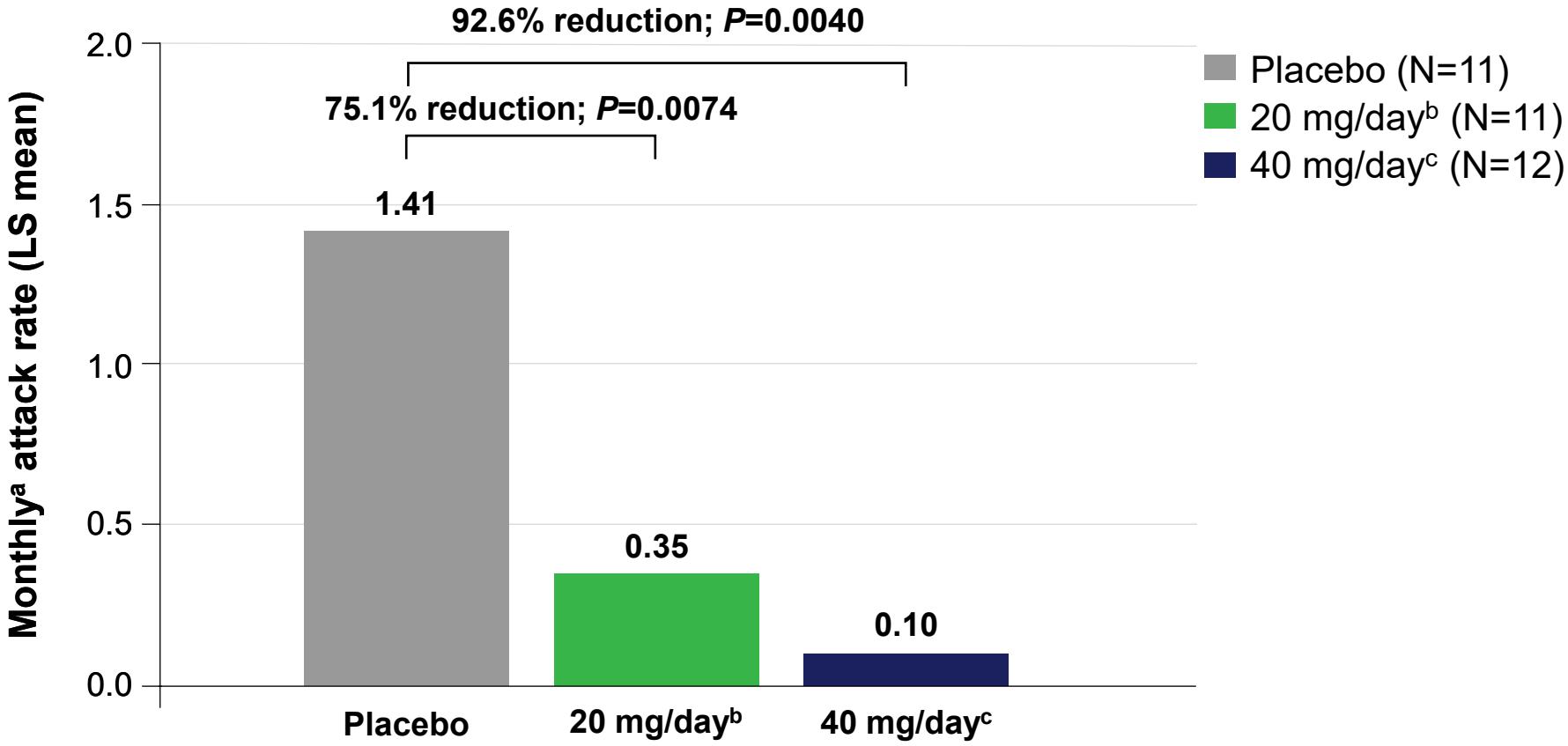
- CHAPTER – 1, 3 and 4 - slow-release tablet
- RAPIDe – 1,2 and 3 - rapid release capsule

Deucrictibant reduced monthly attack rate regardless of baseline attack rate



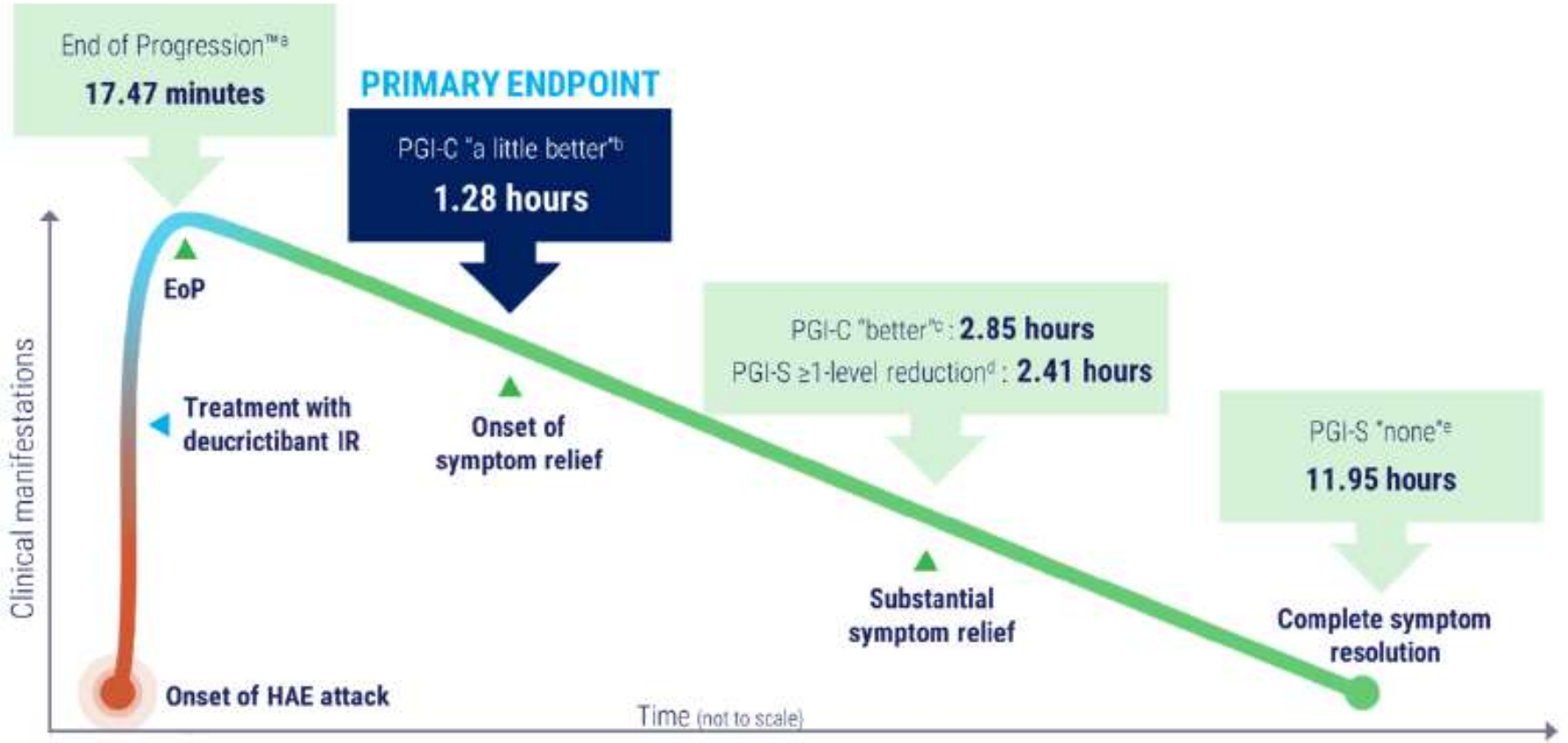
IR, immediate-release; N, number of randomized participants. [a]1 month = 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.
This presentation includes data for an investigational product not yet approved by regulatory authorities.

Deucrictibant reduced occurrence of attacks treated with on-demand medication



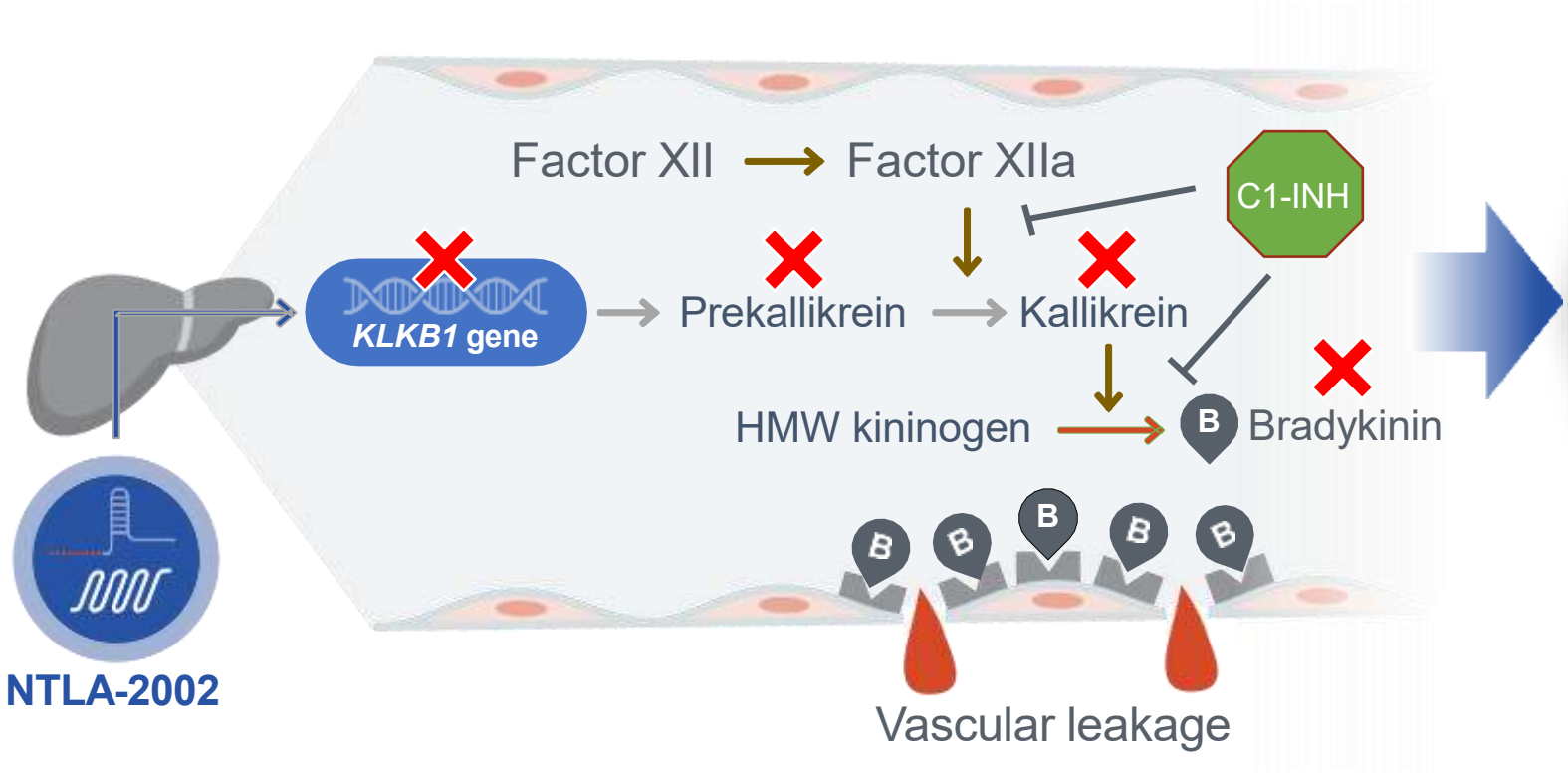
IR, immediate-release; LS, least squares; N, number of randomized participants. [a]1 month = 4 weeks. [b]Deucrictibant IR capsule, 10 mg twice daily. [c]Deucrictibant IR capsule, 20 mg twice daily.
This presentation includes data for an investigational product not yet approved by regulatory authorities.

RAPIDe – 3 – topline data



RAPIDe-3 study outcomes (primary and select secondary endpoints) from deucrictibant immediate-release (IR) capsule-treated attacks, median time to event. Outcomes of placebo-treated attacks (not visualized) refer to data on file. a. End of Progression (EoP): defined as the earliest post-treatment timepoint after which all subsequent PGI-C ratings are stable or improved within 12 hours post-treatment. The term End of Progression is a registered trademark of Pharvaris GmbH. b. PGI-C "a little better": Primary endpoint as time to onset of symptom relief, defined as PGI-C rating of at least "a little better" for 2 consecutive timepoints within 12 hours post-treatment. c. PGI-C "better": Time to substantial symptom relief, defined as achieving PGI-C rating of at least "better" for 2 consecutive timepoints within 12 hours post-treatment. d. PGI-S ≥1-level improvement: Time to substantial symptom relief by Patient Global Impression of Severity (PGI-S), defined as achieving ≥1-level improvement in PGI-S from pre-treatment for 2 consecutive timepoints within 12 hours post-treatment. e. PGI-S "none": Time to complete symptom resolution, defined as achieving PGI-S rating of "none" within 48 hours post-treatment.

Targeting *KLKB1* Gene Expression for LTP of HAE Attacks



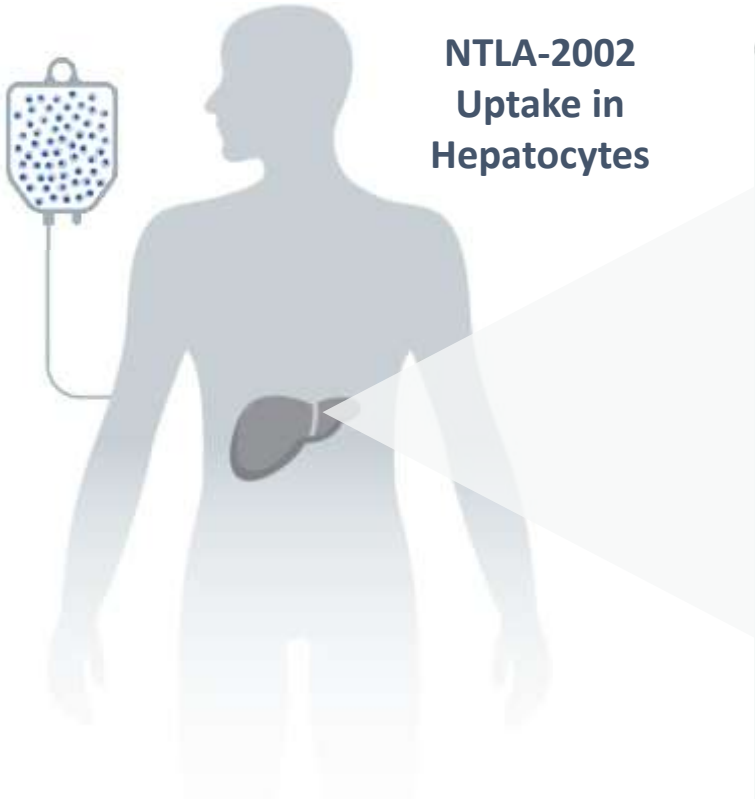
1. Knocking out *KLKB1* gene is intended to prevent production of kallikrein
2. Decreasing kallikrein rebalances pathway by reducing bradykinin production
3. Reducing bradykinin is intended to prevent HAE attacks

Kallikrein is a clinically validated therapeutic target for preventing HAE attacks

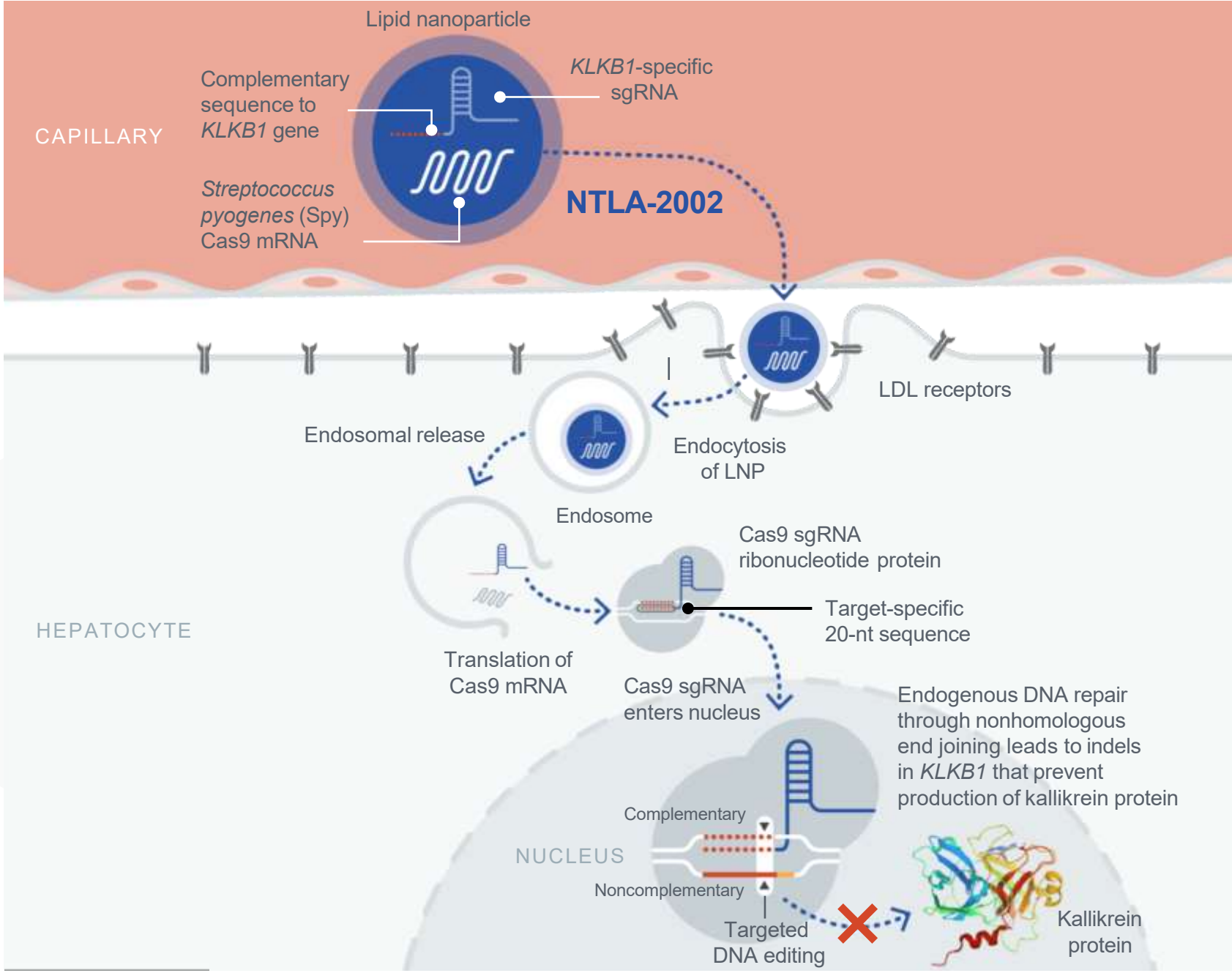
C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; HMW, high-molecular weight.
Adapted from Zuraw BL. *N Engl J Med*. 2008;359(10):1027-1036.

This presentation includes data for an investigational product not yet approved by regulatory authorities.

NTLA-2002 Mechanism of Action

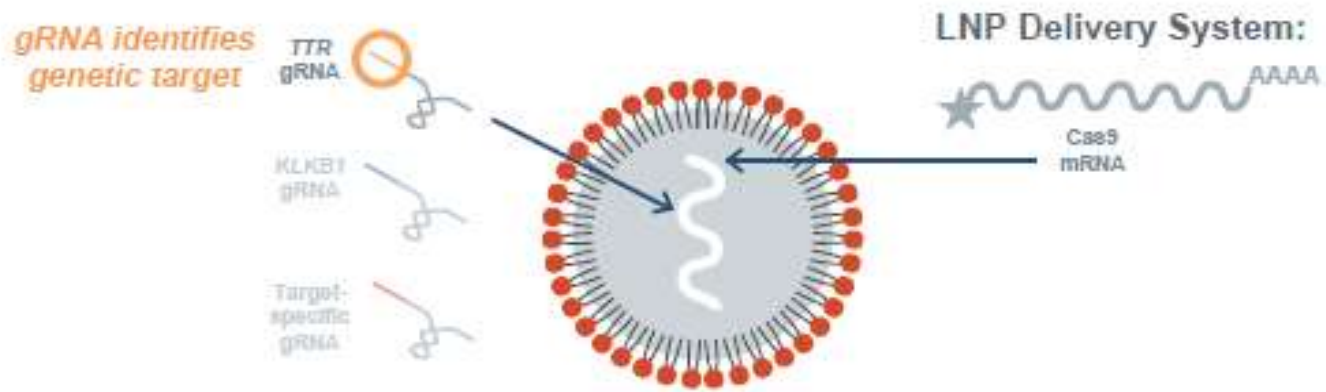


NTLA-2002 Uptake in Hepatocytes



indel, insertion-deletion; LDL, low-density lipoprotein; LNP, lipid nanoparticle; mRNA, messenger RNA; nucleotide; sgRNA, single-guide RNA. Longhurst HJ, et al. *N Engl J Med*. 2024;390:432-441

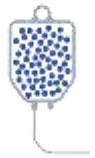
Modular Delivery Platform Enables Rapid and Reproducible Path to Clinical Development



Key Advantages of LNP Delivery

- Clinically-proven delivery to liver
- Large cargo capacity
- Transient expression
- Biodegradable
- Low immunogenicity
- Well-tolerated
- Redosing capability
- Scalable synthetic manufacturing
- Tunable to other tissues

NTLA-2002 Global Phase 1/2 Study Design and Eligibility Criteria: Two-Part, Multicenter Study in Adults With HAE Types I and II



Intervention
Single dose administered via an intravenous (IV) infusion

PHASE 1
Open-label, single-ascending dose

- 25 mg (n=3)
- 50 mg (n=4)
- 75 mg (n=3)

PHASE 2
Expansion study to confirm recommended dose

Randomized

- 25 mg (n=10)
- 50 mg (n=10)
- Placebo arm (n=5)

PRETREATMENT REGIMEN

Day -1: Oral dexamethasone 8 mg (or equivalent)

Day 1: IV dexamethasone 10 mg (or equivalent), IV or oral H1 and H2 blocker, C1-INH

PRIMARY OBJECTIVES

Evaluate safety and tolerability

OTHER OBJECTIVES

PK, PD, clinical efficacy (attacks)

PRIMARY OBJECTIVES

Clinical efficacy (attacks through Week 16)

OTHER OBJECTIVES

PD, safety and tolerability, PK, QOL

KEY INCLUSION CRITERIA

- ✓ Documented diagnosis of Type I or Type II HAE
- ✓ At least 3 investigator-confirmed HAE attacks within 90 days prior to screening
- ✓ Access to acute therapies to treat HAE attacks
- ✓ Concurrent therapy with standard of care, long-term prophylaxis allowed

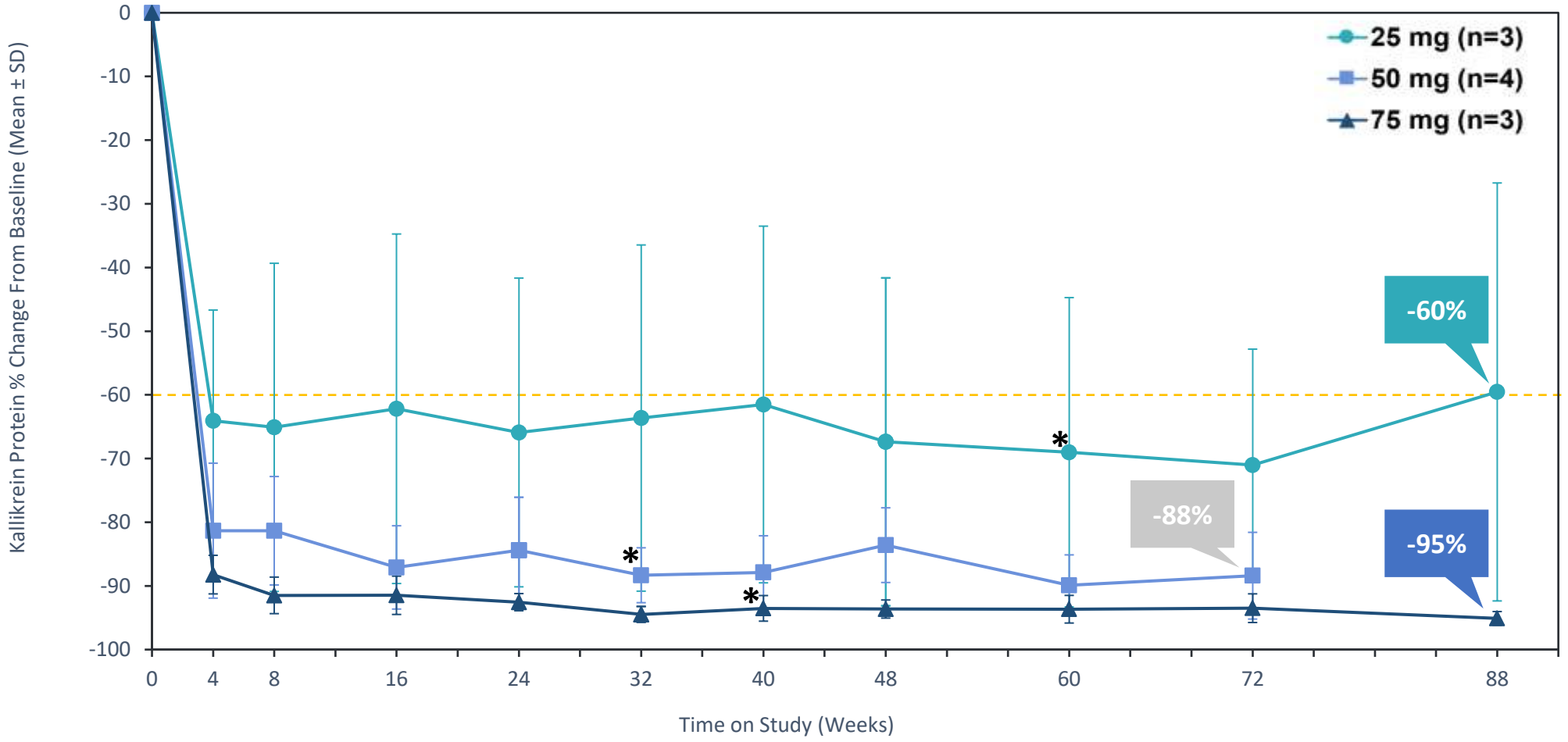
KEY EXCLUSION CRITERIA

- × Concomitant use of ecallantide or lanadelumab or berotralstat
- × Known hypersensitivity or prior infusion-related reaction to LNP components
- × History of cirrhosis, hepatitis B, hepatitis C, or HIV

C1-INH, C1 esterase inhibitor; H1, histamine receptor 1; H2, histamine receptor 2; HAE, hereditary angioedema; LNP, lipid nanoparticle; PD, pharmacodynamics; PK, pharmacokinetics; QOL, quality of life.

This presentation includes data for an investigational product not yet approved by regulatory authorities.

A Single Dose of NTLA-2002 Continues to Show Dose-Dependent and Durable Reductions in Plasma Kallikrein Protein Over Time



Baseline value is the average of 2 samples on separate days during the screening period and 1 predose on study Day 1. Only visits completed by all patients within a cohort are presented.
Dashed line represents targeted minimum reduction.
Asterisks indicate the start of additional ongoing follow-up since the previous datacut of 17Feb2023.
SD, standard deviation.
This presentation includes data for an investigational product not yet approved by regulatory authorities.

Data cutoff date: 12Feb2024.

A Single Dose of NTLA-2002 Led to a 98% Mean Reduction in Monthly HAE Attack Rate Through the Latest Follow-up

	Percentage Change from Baseline[a] Mean (SD)		
	All Attacks	Attacks Requiring On-Demand Treatment	Moderate-to-Severe Attacks
Weeks 1-16 (Primary observation period)	-90% (17%)	-82% (22%)	-95% (8.2%)
Weeks 5-16	-92% (16%)	-86% (28%)	-96% (7.7%)
Post-primary observation period[b]	-99% (1.4%)	-100% (0.49%)	-100% (0)
On-study period[c]	**-98% (2.7%)**	**-97% (3.5%)**	**-99% (1.3%)**

Mean (SD) monthly attack rate post-primary observation period is 0.01 (0.02)

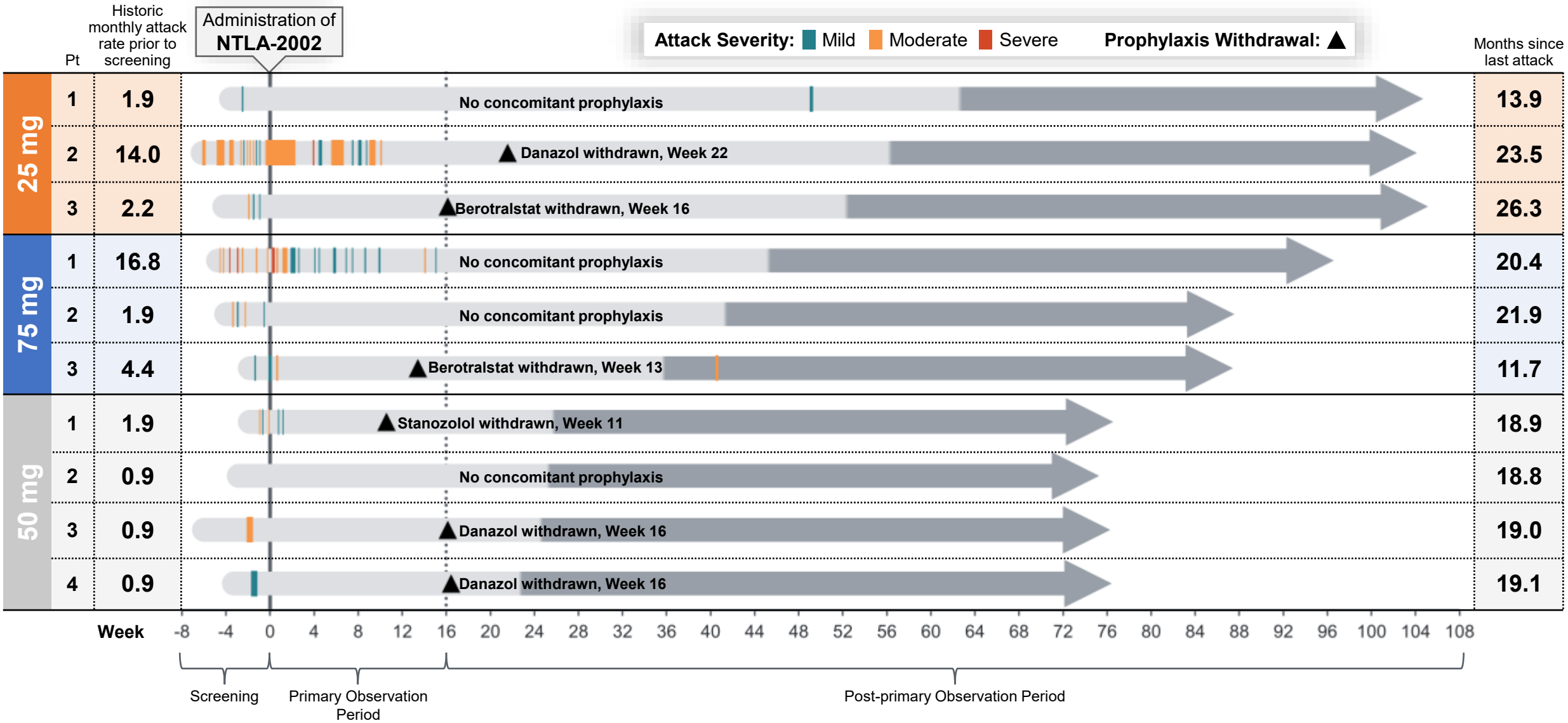
[a]Patients without the indicated type of attack at baseline are not included in percentage change calculations.
[b]Post-primary observation period is defined as Week 16 through the last HAE attack assessment as of the data cutoff date.
[c]On-study period is defined as the time from the administration of NTLA-2002 through the last HAE attack assessment as of the data cutoff date.
A month is defined as 28 days.

HAE, hereditary angioedema; SD, standard deviation.

This presentation includes data for an investigational product not yet approved by regulatory authorities.

Data cutoff date: 12Feb2024.

8 of 10 Patients Have Been Attack-Free post Primary Observation Period



Pt, patient. A month is defined as 28 days.

Dark gray arrows indicate additional ongoing follow-up since the previous data cut of 17Feb2023.

This presentation includes data for an investigational product not yet approved by regulatory authorities.

Data cutoff date: 12Feb2024.

Review

Congenital prekallikrein deficiency

Antonio Girolami, Pamela Scarparo, Nicole Candeo & Anna Maria Lombardi

Pages 685-695 | Published online: 10 Jan 2014

Download citation https://doi.org/10.1586/ehm.10.69

- Fletcher Factor syndrome
- Rare disease with AR inheritance - approximately 80 cases reported
- Severe in vitro defect without bleeding
- Diagnosis is based – prolonged APTT, normal prothrombin time and thrombin time
- Most cases go undetected or, if detected, go unreported
- Occasional bleeding or thrombosis have been reported in a few patients but this was only due to the presence of associated risk factors

nC1-INH-HAE with *FXII mutations*

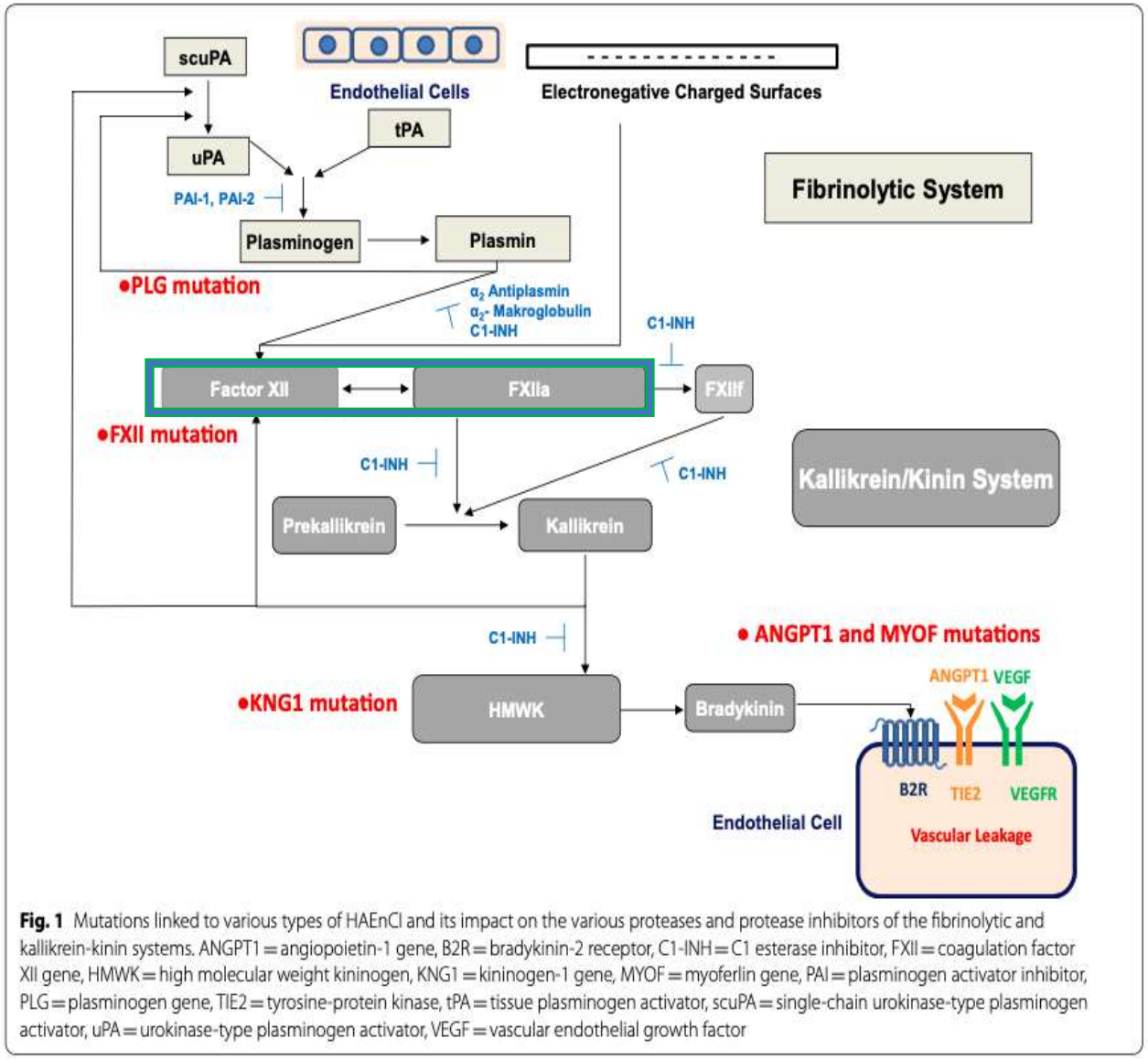


Fig. 1 Mutations linked to various types of HAEnCI and its impact on the various proteases and protease inhibitors of the fibrinolytic and kallikrein-kinin systems. ANGPT1 = angiopoietin-1 gene, B2R = bradykinin-2 receptor, C1-INH = C1 esterase inhibitor, FXII = coagulation factor XII gene, HMWK = high molecular weight kininogen, KNG1 = kininogen-1 gene, MYOF = myoferlin gene, PAI = plasminogen activator inhibitor, PLG = plasminogen gene, TIE2 = tyrosine-protein kinase, tPA = tissue plasminogen activator, scuPA = single-chain urokinase-type plasminogen activator, uPA = urokinase-type plasminogen activator, VEGF = vascular endothelial growth factor

- AD GOF
- Over 400 patients to date
- Acts via kallikrein and plasmin
- Effect of anti-fibrinolytic medications in this type of HAE – tranexamic acid
- The promoters of *FXII* and oestrogen responsive element (*ERE*) genes are similar but not identical
- Oestrogen precipitates attacks by enhancing FXII in plasma
- Female predominance, aggravation in pregnancy and oestrogen dependency

Bork *et al. Orphanet J Rare Dis (2020) 15:289* :11 of 14

nC1-INH-HAE with *PLG mutations*

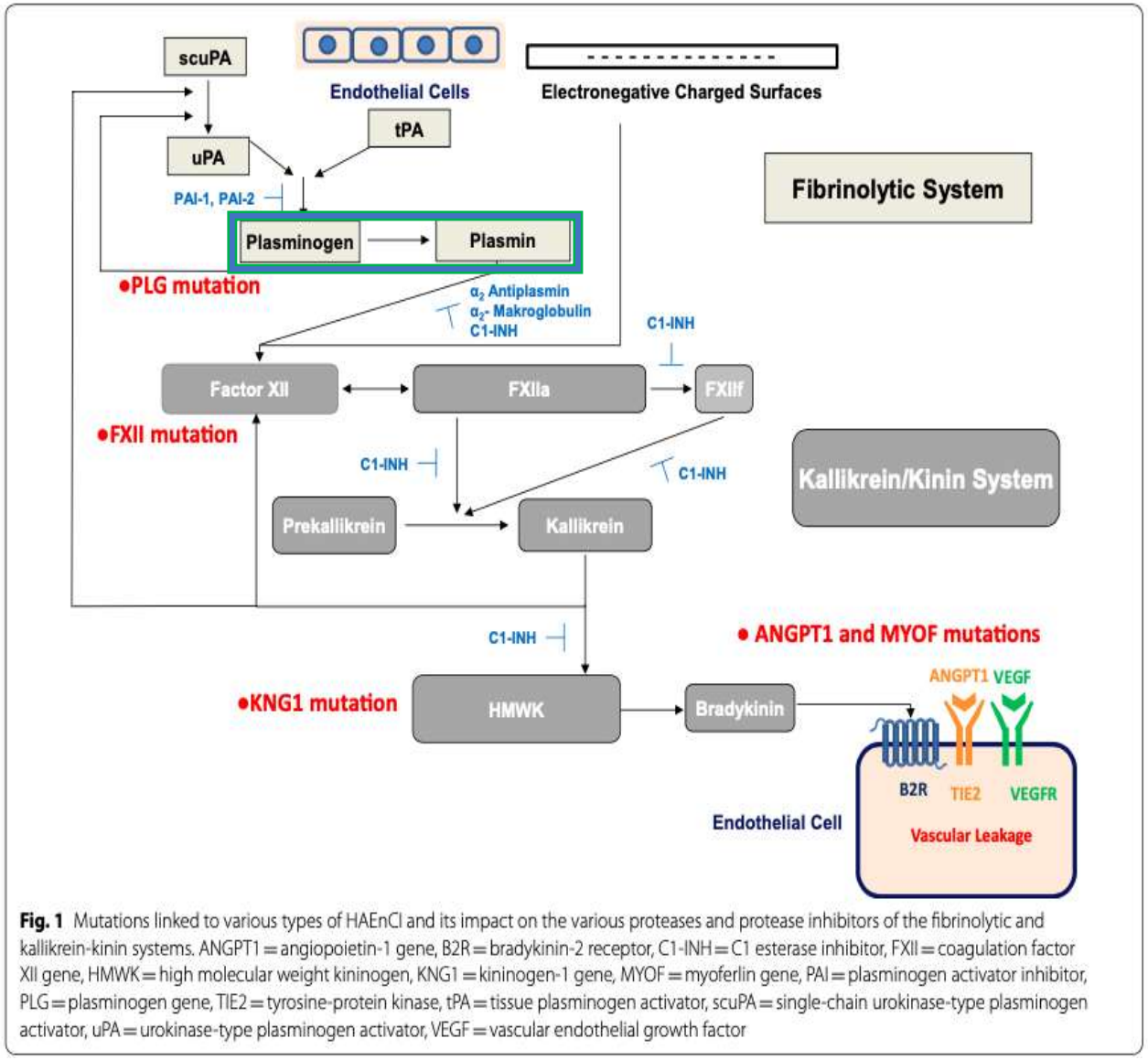


Fig. 1 Mutations linked to various types of HAEnCI and its impact on the various proteases and protease inhibitors of the fibrinolytic and kallikrein-kinin systems. ANGPT1 = angiopoietin-1 gene, B2R = bradykinin-2 receptor, C1-INH = C1 esterase inhibitor, FXII = coagulation factor XII gene, HMWK = high molecular weight kininogen, KNG1 = kininogen-1 gene, MYOF = myoferlin gene, PAI = plasminogen activator inhibitor, PLG = plasminogen gene, TIE2 = tyrosine-protein kinase, tPA = tissue plasminogen activator, scuPA = single-chain urokinase-type plasminogen activator, uPA = urokinase-type plasminogen activator, VEGF = vascular endothelial growth factor

- AD GOF missense mutation in exon 9 of *PLG*, c.988A>G; (p.Lys330Glu)
- 146 patients from 33 families
- Present usually in adulthood as compared to paediatric in C1-INH deficiency HAE

- High - tongue, face, laryngeal oedema
- low - peripheral or abdominal or genital swelling

- ACE inhibitors tend to precipitate attacks

Bork *et al. Orphanet J Rare Dis (2020) 15:289* :11 of 14

Why SERPING1 is overlooked in this project?

- Highly heterogenous mutation profile with similar clinical phenotype
- Highly conserved group of proteins with similar structure that inhibits multiple enzyme pathways
- The chance of creating functional SERPIN with unintended target
- Lessons from Alpha 1 AT – Pittsburgh
- Single substitution of M358R (methionine to arginine) – change the target specificity
  - No longer inhibits neutrophil elastase but
  - Strong inhibitor of PKa, FXIIa, thrombin, plasmin and activated protein C
- There are ongoing trials to create SERPINs with narrow specificity