Results From a Phase 2, Randomized, Placebo-Controlled Trial of CRISPR-Based Therapy NTLA-2002 for Hereditary Angioedema

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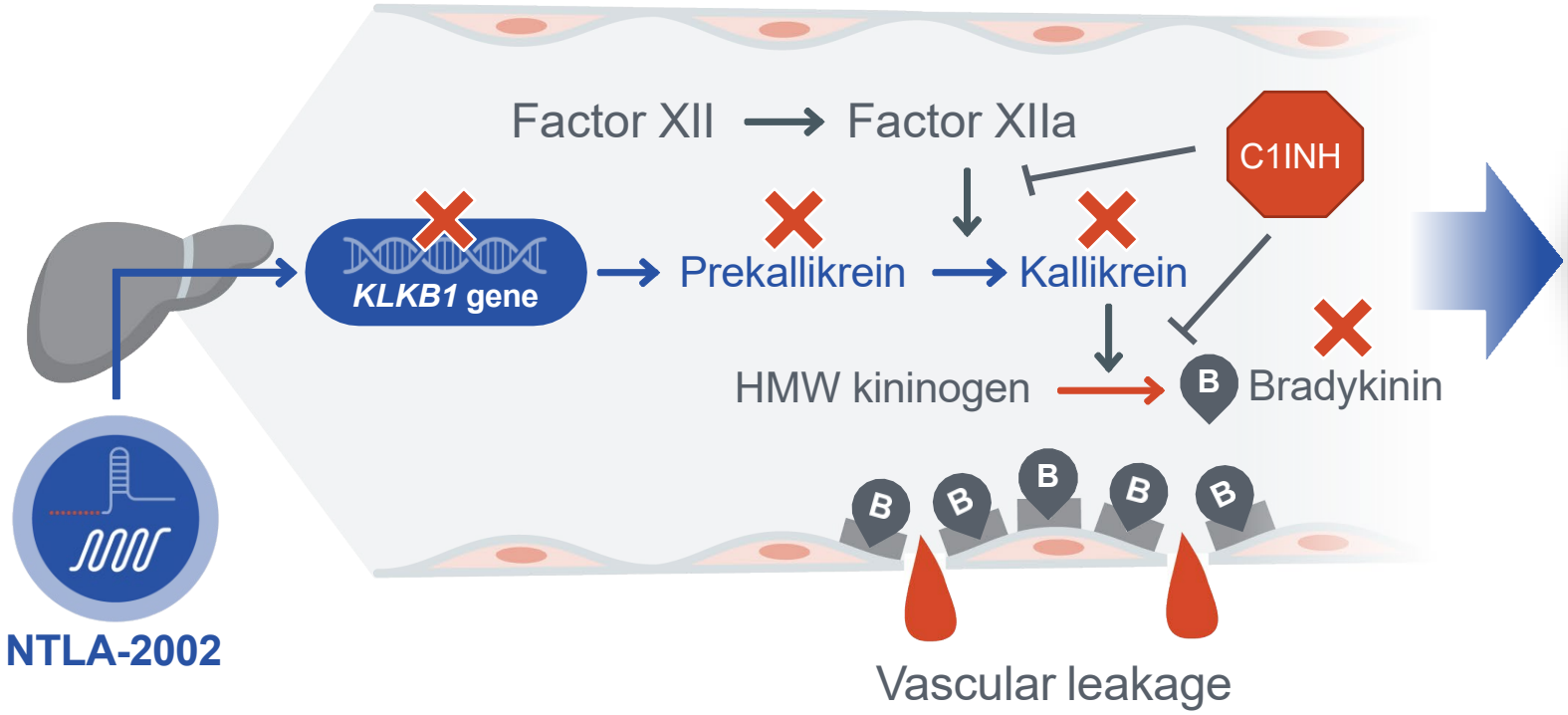
- Dr. Cohn has acted as a consultant or speaker for or participated in research with Astria, BioCryst, CSL Behring, Intellia Therapeutics, Ionis Pharmaceuticals, KalVista, Pharming, Pharvaris, and Takeda

This presentation is dedicated to our friend and colleague Marcus Maurer, who has inspired and brought together many people in the field of angioedema research over the last 25 years. We have lost a unique and extraordinary person; we will remember him as a bubbling source of ideas, experienced advisor, inspiring speaker, gifted organizer, and enthusiastic networker. May he rest in peace.

Targeting *KLKB1* Gene Expression for Long-Term Prophylaxis 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

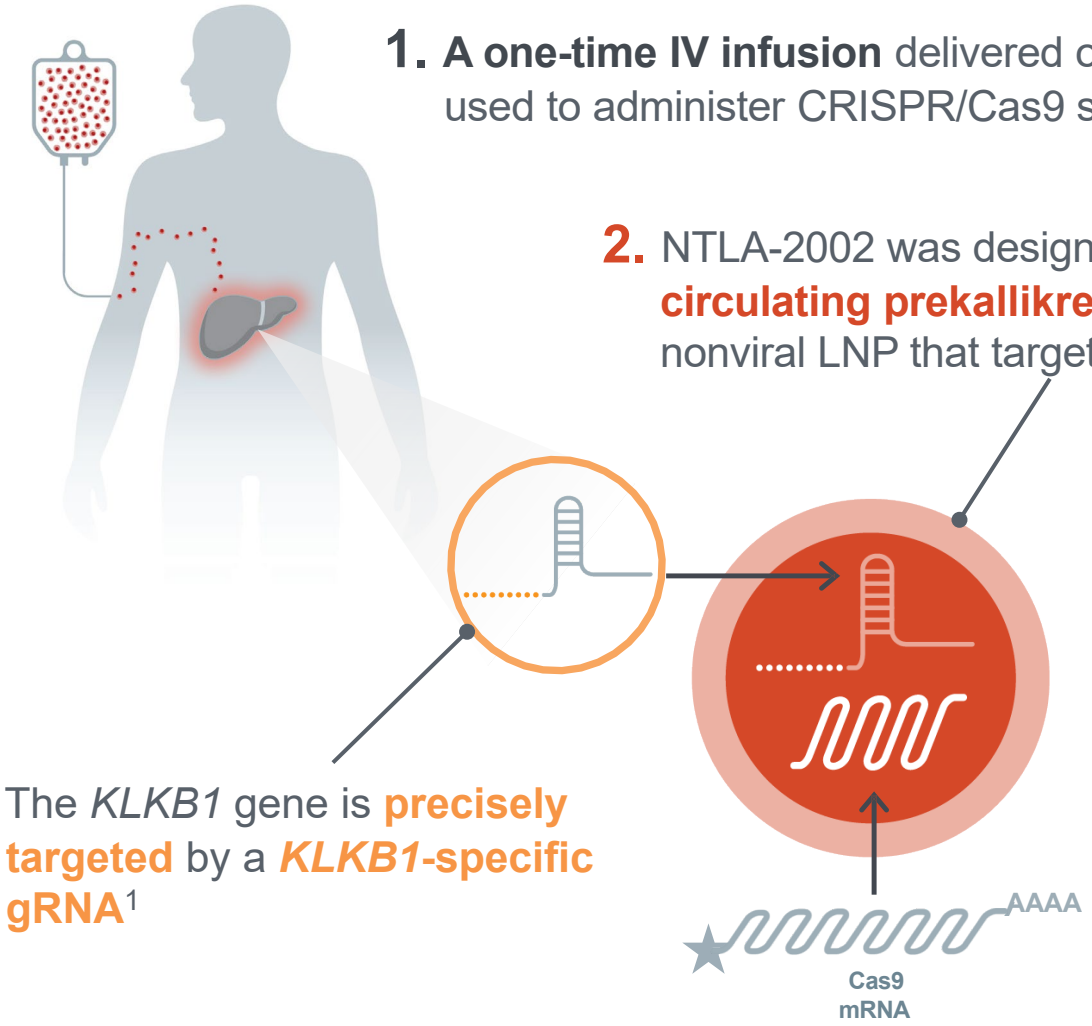
C1INH, C1 inhibitor; HAE, hereditary angioedema; HMW, high-molecular weight.
Adapted from Zuraw BL. *N Engl J Med.* 2008;359(10):1027-1036.

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

NTLA-2002 Is an Investigational CRISPR/Cas9-based Therapy Designed to Disrupt the *KLKB1* Gene and Permanently Rebalance the Kallikrein-Kinin System With a One-Time IV Infusion[1]

HAE:

- The kallikrein-kinin system is imbalanced in HAE and **kallikrein is a clinically validated target for the prevention of angioedema attacks**[1,2]
- **The majority of circulating kallikrein protein is synthesized in the liver**—a single location targetable by LNP[1]
- Ideal application to investigate CRISPR/Cas9 gene editing therapy[1]



Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; gRNA, guide RNA; HAE, hereditary angioedema; IV, intravenous; LNP, lipid nanoparticle; mRNA, messenger RNA.

1. Longhurst HJ, et al. *N Engl J Med*. 2024;390(5):432-441. 2. De Maat S, et al. *J Thromb Haemost*. 2018;16(9):1674-1685.

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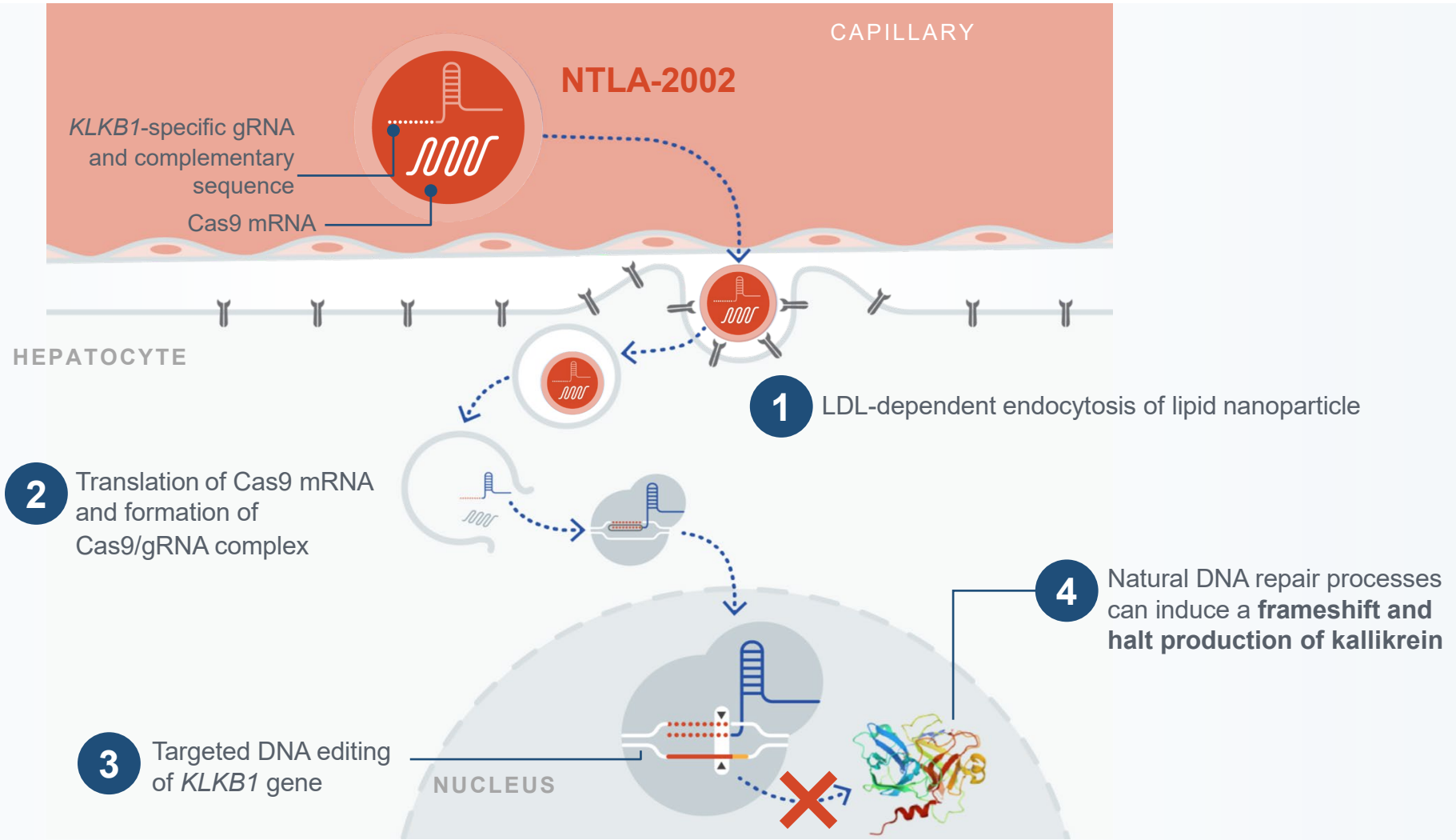
Mechanism of Action of NTLA-2002



NTLA-2002 aims to disrupt *KLKB1* to permanently rebalance the disease pathway and resolve angioedema attacks in patients

Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; gRNA, guide RNA; LDL, low-density lipoprotein; mRNA, messenger RNA.

Longhurst HJ, et al. *N Engl J Med*. 2024;390:432-441.

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

Intervention
Single dose administered via an 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 2:2:1

N=25

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

KEY PH2 INCLUSION CRITERIA

- ✓ Documented diagnosis of HAE-C1INH-Type1 or HAE-C1INH-Type2
- ✓ At least 3 investigator-confirmed HAE attacks during the 90 days prior to screening, and at least 2 investigator-confirmed HAE attacks during the screening period
- ✓ Access to acute therapies to treat HAE attacks

KEY PH2 EXCLUSION CRITERIA

- × Concomitant use of LTP within 5 half-lives prior to the start of screening and through the end of the 16-week primary observation period

PRETREATMENT REGIMEN

Day -1: Oral glucocorticoid[a]

Day 1: Glucocorticoid,[b] H1 blocker, and H2 blocker; C1INH at bedside

PRIMARY PH2 ENDPOINT

- Number of angioedema attacks per month during primary observation period (Weeks 1-16)
  - Primary analysis occurred when the 25th patient reached Week 16

REPORTED SECONDARY PH2 ENDPOINTS

- Safety
- Number of angioedema attacks per month (Weeks 5-16)
- Change from baseline in total plasma kallikrein level

[a]Oral dexamethasone 8 mg or equivalent, 8-24 hours prior to study drug administration. [b]IV steroid (eg, dexamethasone, 10 mg or equivalent).
C1INH, C1 inhibitor; H1, histamine receptor 1; H2, histamine receptor 2; HAE, hereditary angioedema; IV, intravenous; LTP, long-term prophylaxis.

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Patient Demographics and Characteristics

Characteristic		NTLA-2002 25 mg (n=10)	NTLA-2002 50 mg (n=11)	Placebo (n=6)
Median age (range), years		48.5 (34-62)	44.0 (18-61)	47.0 (31-76)
Sex, n (%)	Male	7 (70.0)	5 (45.5)	2 (33.3)
Median weight (range), kg		89 (58-133)	78 (56-107)	79 (50-92)
HAE type, n (%)	HAE-C1INH-Type1 HAE-C1INH-Type2	8 (80.0) 2 (20.0)	10 (90.9) 1 (9.1)	5 (83.3) 1 (16.7)
Prior use of long-term prophylaxis, n (%)		6 (60.0)	6 (54.5)	5 (83.3)
Long-term prophylaxis prior to study entry, n (%)	Lanadelumab Attenuated androgens Berotralstat C1INH Tranexamic acid	2 (20.0) 2 (20.0) 1 (10.0) 1 (10.0) 0	2 (18.2) 1 (9.1) 2 (18.2) 0 1 (9.1)	1 (16.7) 2 (33.3) 1 (16.7) 1 (16.7) 0
Median no. of angioedema attacks during the historical attack period (range)[a]		6.5 (3-24)	4.0 (3-11)	5.5 (3-9)
Typical attack severity, n (%)	Mild Moderate Severe	1 (10.0) 6 (60.0) 3 (30.0)	0 9 (81.8) 2 (18.2)	1 (16.7) 4 (66.7) 1 (16.7)
Mean baseline monthly attack rate, n		3.6	3.6	3.7

[a]The historical attack period is defined as the 90 days before the screening period, which coincided with washout of any long-term prophylaxis by a patient prior to study entry.
C1INH, C1 inhibitor; HAE, hereditary angioedema.

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Data cutoff date: 04 Apr 2024.

A Single Dose of NTLA-2002 Led to a Reduction in Monthly Angioedema Attack Rate Compared With Placebo

Variable	NTLA-2002 25 mg (n=10)	NTLA-2002 50 mg (n=11)	Placebo (n=6)
Median follow-up (range), month	8.2 (4.4-11.8)	5.6 (2.9-11.5)	6.9 (1.9-12.5)
Weeks 1-16			
Mean no. of angioedema attacks per month (95% CI)[a]	0.7 (0.3, 2.0)	0.7 (0.2, 1.8)	2.8 (0.8, 9.9)
Percentage difference vs. placebo (95% CI)	**−75% (-95%, 27%)**	**−77% (-95%, 15%)**	
Weeks 5-16			
Mean no. of angioedema attacks per month (95% CI)[a]	0.6 (0.2, 1.9)	0.6 (0.2, 1.7)	3.1 (0.8, 11.8)
Percentage difference vs. placebo (95% CI)	**-80% (-96%, 14%)**	**-81% (-97%, 3%)**	

[a]The mean number of angioedema attacks per month was estimated using a negative binomial model with treatment arm and baseline attack rate as independent variables. Baseline is defined as the time from date of informed consent to randomization. A month is defined as 28 days.

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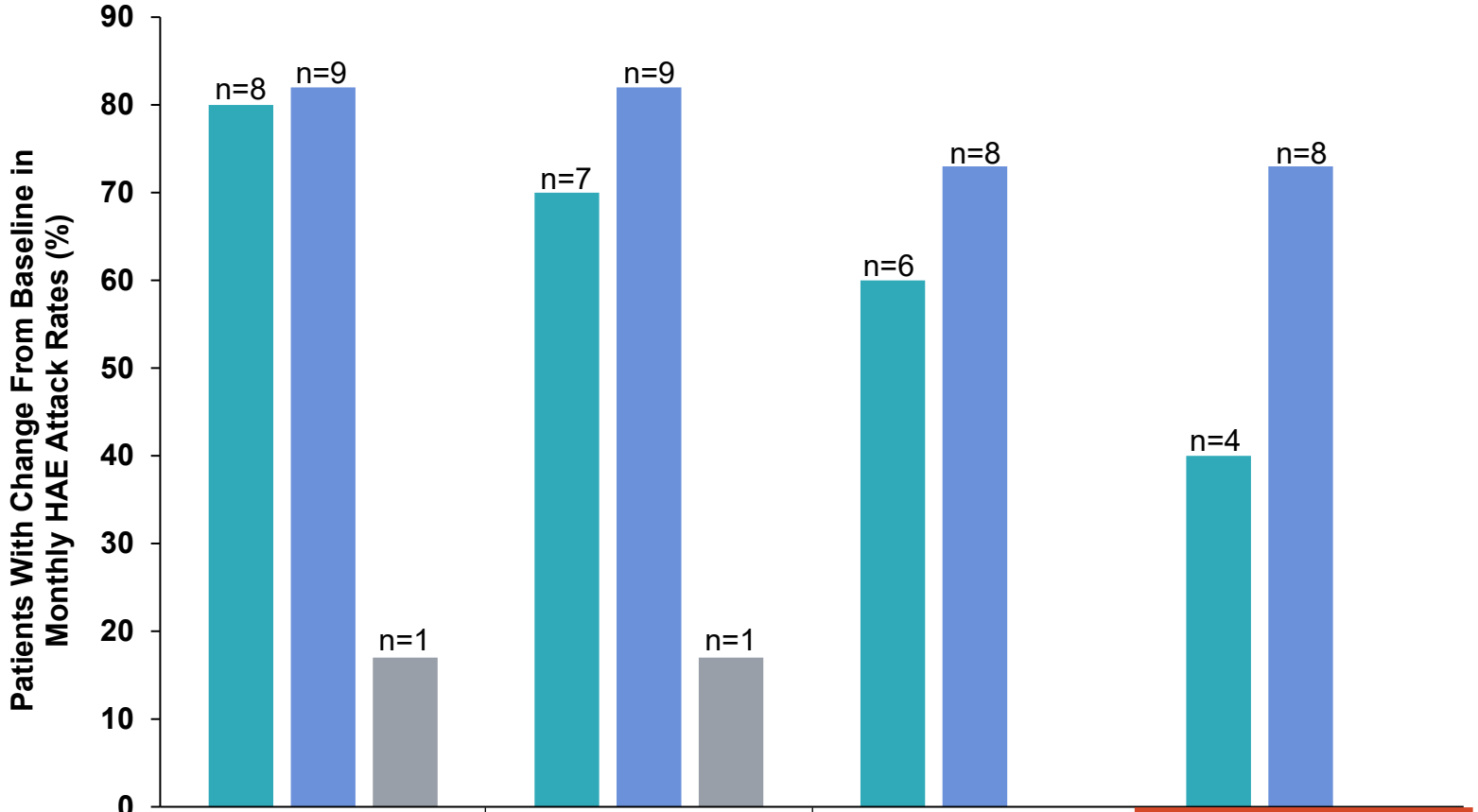
The Majority of Patients Receiving NTLA-2002 50 mg Experienced a Complete Response – Attack-Free and No Subsequent Treatment Required



	≥50%	≥70%	≥90%	100% (attack-free)
NTLA-2002 25 mg (n=10)	80%	70%	60%	40%
NTLA-2002 50 mg (n=11)	82%	82%	73%	73%
Placebo (n=6)	17%	17%	0%	0%

Investigator-confirmed angioedema attack response status for the 16-week primary observation period. Response status is defined as the patients' monthly attack rate reduction from baseline of at least 50%, 70%, 90%, and 100% (attack-free). HAE, hereditary angioedema.

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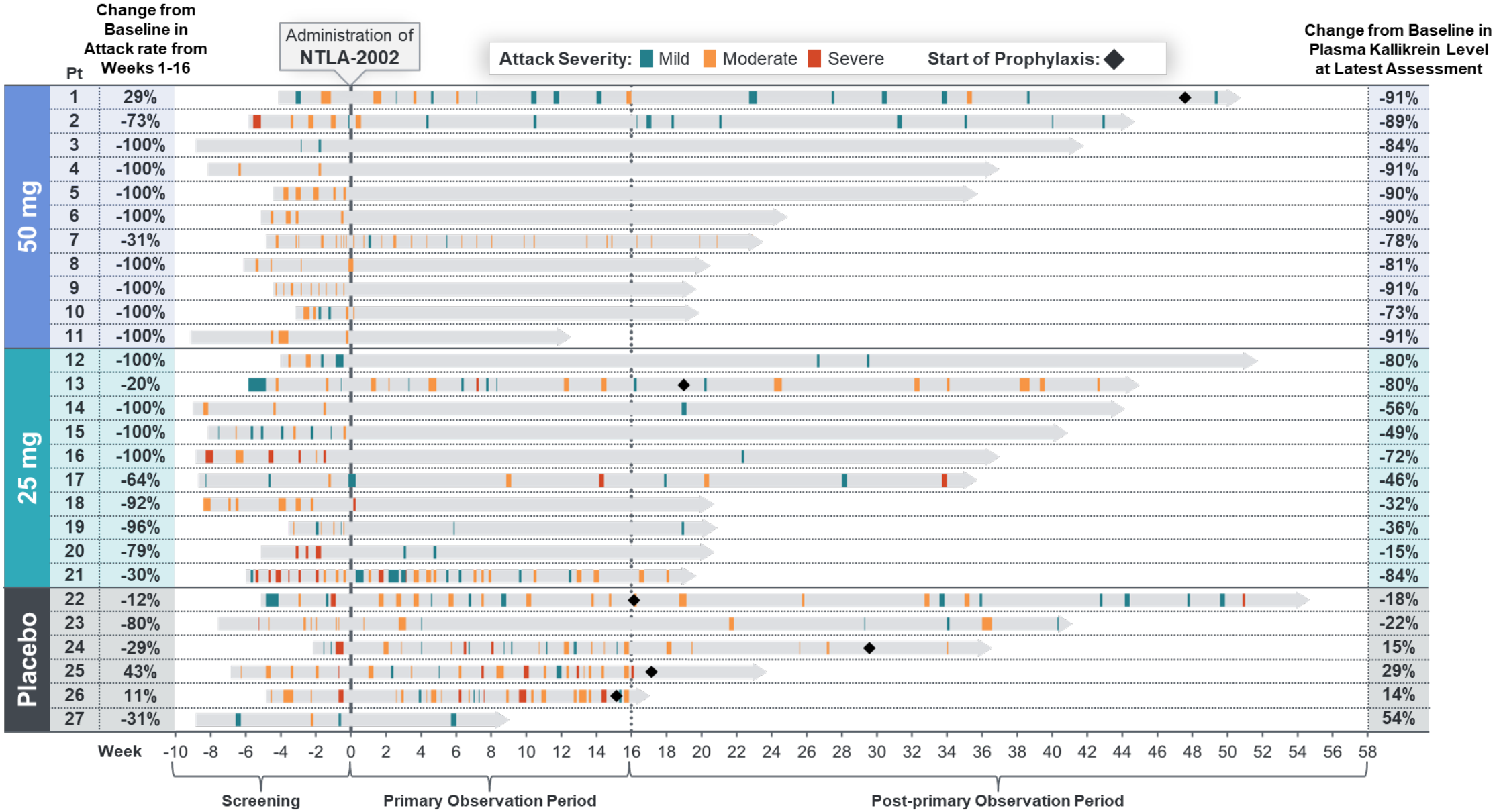
Angioedema Attacks Before and After Administration of NTLA-2002



The length of the gray bars indicates the interval from the start of the screening period to the last assessment as of the data cutoff date. Arrows indicate the patient is still on study.
The width of the colored bars indicates the duration of the attack. Black diamonds indicate when a patient resumed long-term prophylaxis, which was permitted after Week 16. Pt, patient.
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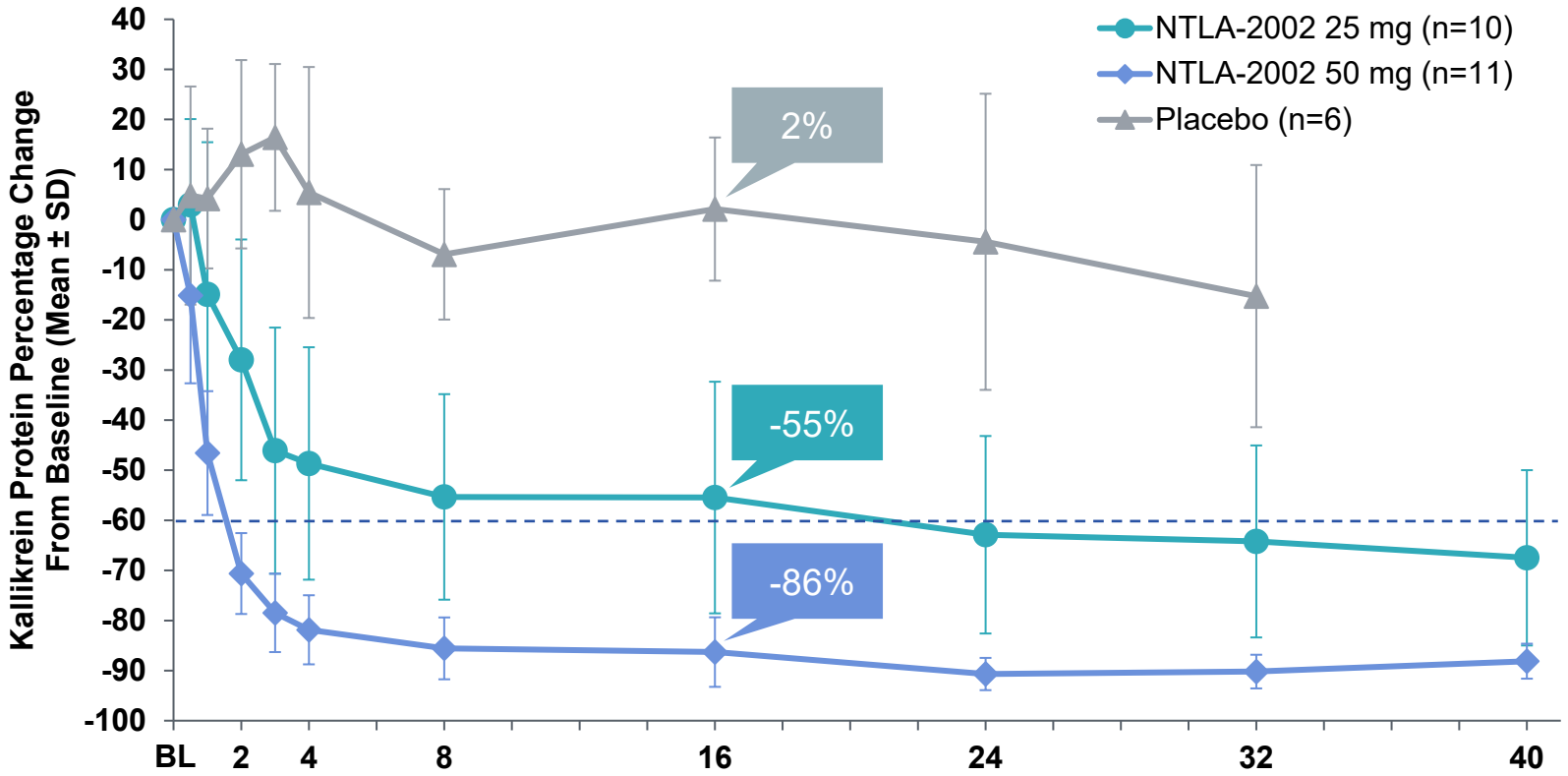
A Single Dose of NTLA-2002 Showed Dose-Dependent and Durable Reductions in Plasma Kallikrein Protein Over Time



Number of patients								
NTLA-2002 25 mg	10	10	10	10	10	6	6	4
NTLA-2002 50 mg	11	11	11	11	10	5	5	3
Placebo	6	6	6	5	5	4	3	

For postbaseline assessments, only scheduled visits completed by at least 3 patients in each arm are presented. Dashed line represents targeted minimum reduction.
BL, baseline; SD, standard deviation.

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NTLA-2002 Continues to Be Well Tolerated Across All Dose Levels

TEAEs in ≥2 Patients After NTLA-2002 Administration (pooled), n (%)	NTLA-2002 25 mg (n=10)	NTLA-2002 50 mg (n=11)	Placebo (n=6)
Any TEAE	10 (100)	11 (100)	6 (100)
Headache	4 (40)	4 (36)	1 (17)
Fatigue	3 (30)	3 (27)	2 (33)
Nasopharyngitis	3 (30)	3 (27)	2 (33)
Back pain	3 (30)	2 (18)	0
Upper respiratory tract infection	3 (30)	2 (18)	1 (17)
Cough	3 (30)	1 (9)	0
Infusion-related reaction	1 (10)	3 (27)	1 (17)
COVID-19	2 (20)	1 (9)	1 (17)
Ear infection	2 (20)	0 (0.0)	0
Epistaxis	0	2 (18)	1 (17)
Influenza-like illness	1 (10)	1 (9)	0
Oropharyngeal pain	1 (10)	1 (9)	1 (17)
Pyrexia	0	2 (18)	0
Sinusitis	1 (10)	1 (9)	0

- All TEAEs were Grade 1 or 2 in severity[a]
- No SAEs in patients treated with NTLA-2002
- 4 IRRs with NTLA-2002; 2 led to temporary interruption of study drug
  - Each instance resolved without sequelae and both patients received the full dose
- No clinically significant laboratory abnormalities
  - 1 patient had transient Grade 2 increase in ALT on Day 22

[a]Grading per Common Terminology Criteria for Adverse Events (CTCAE).
ALT, alanine aminotransferase; IRR, infusion-related reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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Phase 2 Data Continue to Reinforce the Potential of a Single Dose of NTLA-2002 to Be a Functional Cure for Patients With HAE

- Robust and durable attack reductions continue to be observed in all patients following NTLA-2002 treatment, with reduced frequencies of angioedema attacks compared with placebo
  - All 11 patients receiving NTLA-2002 50 mg achieved a clinically meaningful response
    - 8 of 11 were attack-free during Weeks 1-16, and remained attack-free without additional treatment at the latest assessment
- NTLA-2002 resulted in deep, dose-dependent, and durable reductions in plasma kallikrein protein, which have remained stable for the duration of follow-up
- Safety was consistent with what was observed in Phase 1, with no unexpected findings observed in Phase 2
  - In Phase 2, all AEs in patients treated with NTLA-2002 were Grade 1 or 2

NTLA-2002 50 mg was selected as the optimal dose to assess in the randomized, double-blind, placebo-controlled Phase 3 HAELO trial

AE, adverse event; HAE, hereditary angioedema.

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HAELO Clinical Trial

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ORIGINAL ARTICLE

CRISPR-Based Therapy for Hereditary Angioedema

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