CRISPR-Based NTLA-2002 Improves Quality of Life in Patients With Hereditary Angioedema

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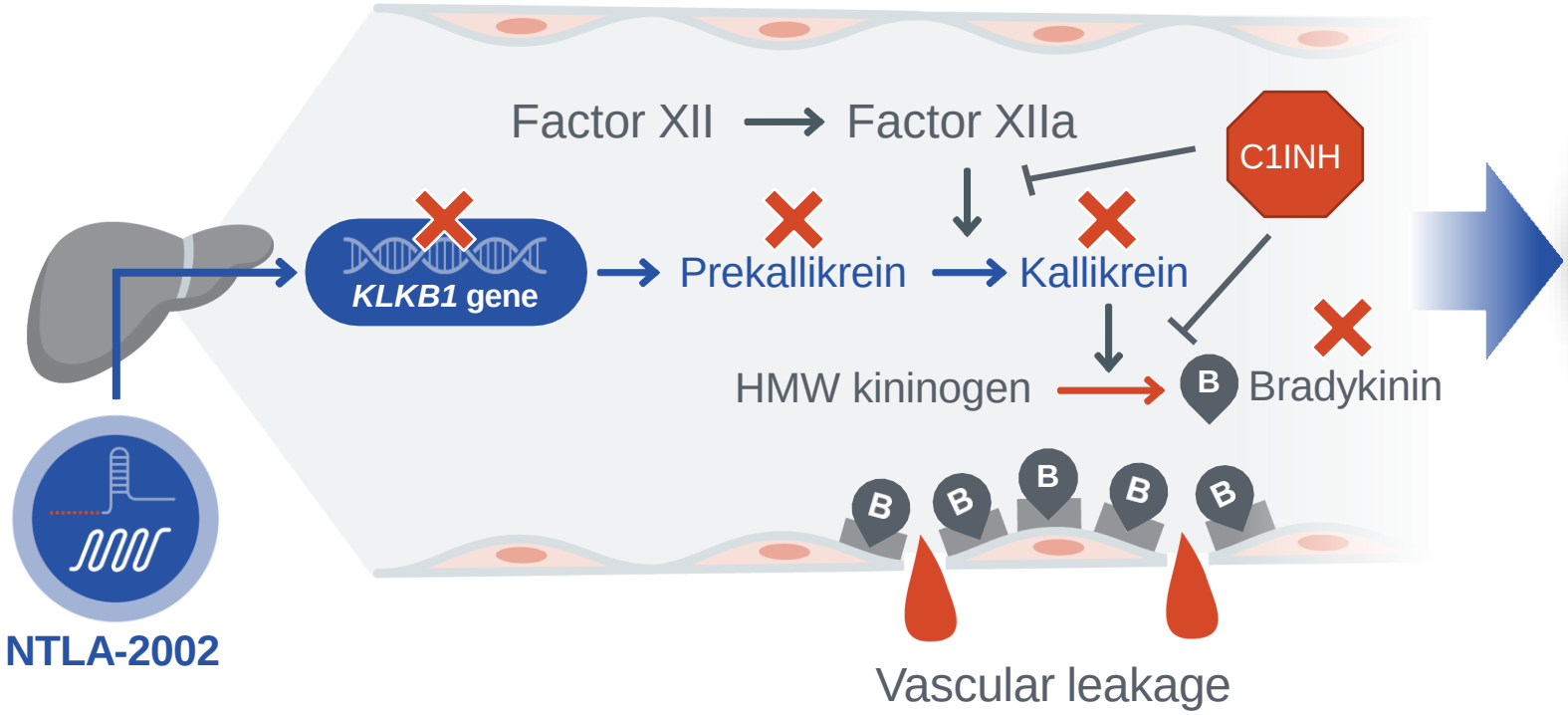
Targeting *KLKB1* Gene Expression for Long-Term Prophylaxis of HAE Attacks



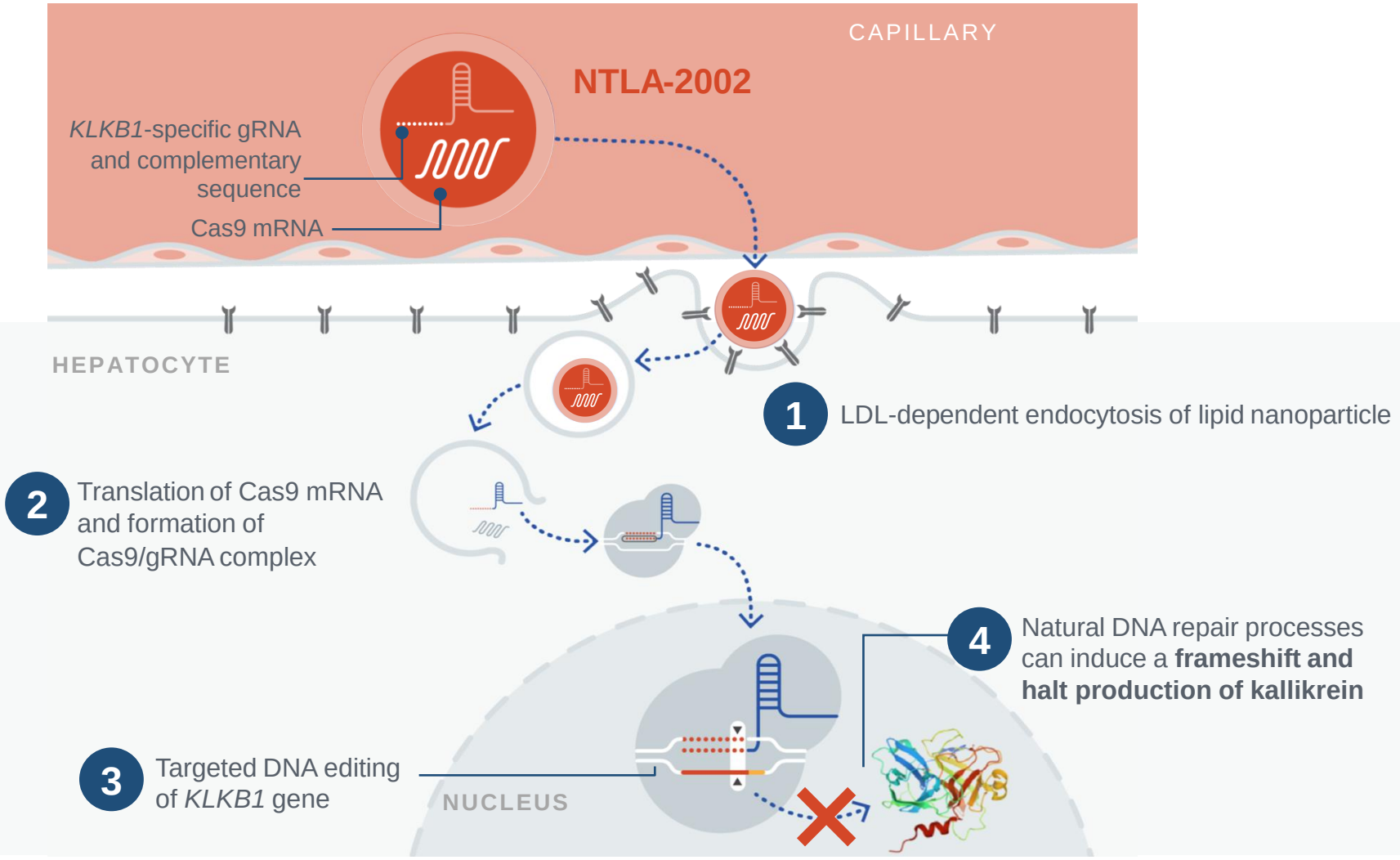
1. Knocking out *KLKB1* gene is intended to prevent production of kallikrein
2. Decreasing kallikrein rebalances pathway by reducing bradykinin production
3. Reducing bradykinin is intended to prevent HAE attacks

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.

Mechanism of Action of NTLA-2002



NTLA-2002 aims to disrupt *KLKB1* to permanently rebalance the disease pathway and prevent 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(5):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 (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

EXPLORATORY ENDPOINTS

- Change from baseline in QoL parameters, as measured by MOXIE AE-QoL and WPAI-GH

[a]Oral dexamethasone 8 mg or equivalent, 8-24 hours prior to study drug administration. [b]IV steroid (eg, dexamethasone, 10 mg or equivalent).

AE-QoL, angioedema quality of life questionnaire; C1INH, C1 inhibitor; H1, histamine receptor 1; H2, histamine receptor 2; HAE, hereditary angioedema; IV, intravenous; LTP, long-term prophylaxis; QoL, quality of life; WPAI-GH, Work Productivity and Activity Impairment General Health questionnaire.

Cohn DM, et al. *N Engl J Med.* 2025;392:458-467.

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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	8 (80.0)	10 (90.9)	5 (83.3)
	HAE-C1INH-Type2	2 (20.0)	1 (9.1)	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	2 (20.0)	2 (18.2)	1 (16.7)
	Attenuated androgens	2 (20.0)	1 (9.1)	2 (33.3)
	Berotralstat	1 (10.0)	2 (18.2)	1 (16.7)
	C1INH	1 (10.0)	0	1 (16.7)
	Tranexamic acid	0	1 (9.1)	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	1 (10.0)	0	1 (16.7)
	Moderate	6 (60.0)	9 (81.8)	4 (66.7)
	Severe	3 (30.0)	2 (18.2)	1 (16.7)
Mean baseline monthly attack rate, n		3.6	3.6	3.7

As of April 4, 2024, median (range) follow-up was 8.2 months (4.4-11.8) in the 25-mg group, 5.6 months (2.9-11.5) in the 50-mg group, and 6.9 months (1.9-12.5) in the placebo group

[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.
Cohn DM, et al. *N Engl J Med.* 2025;392:458-467.

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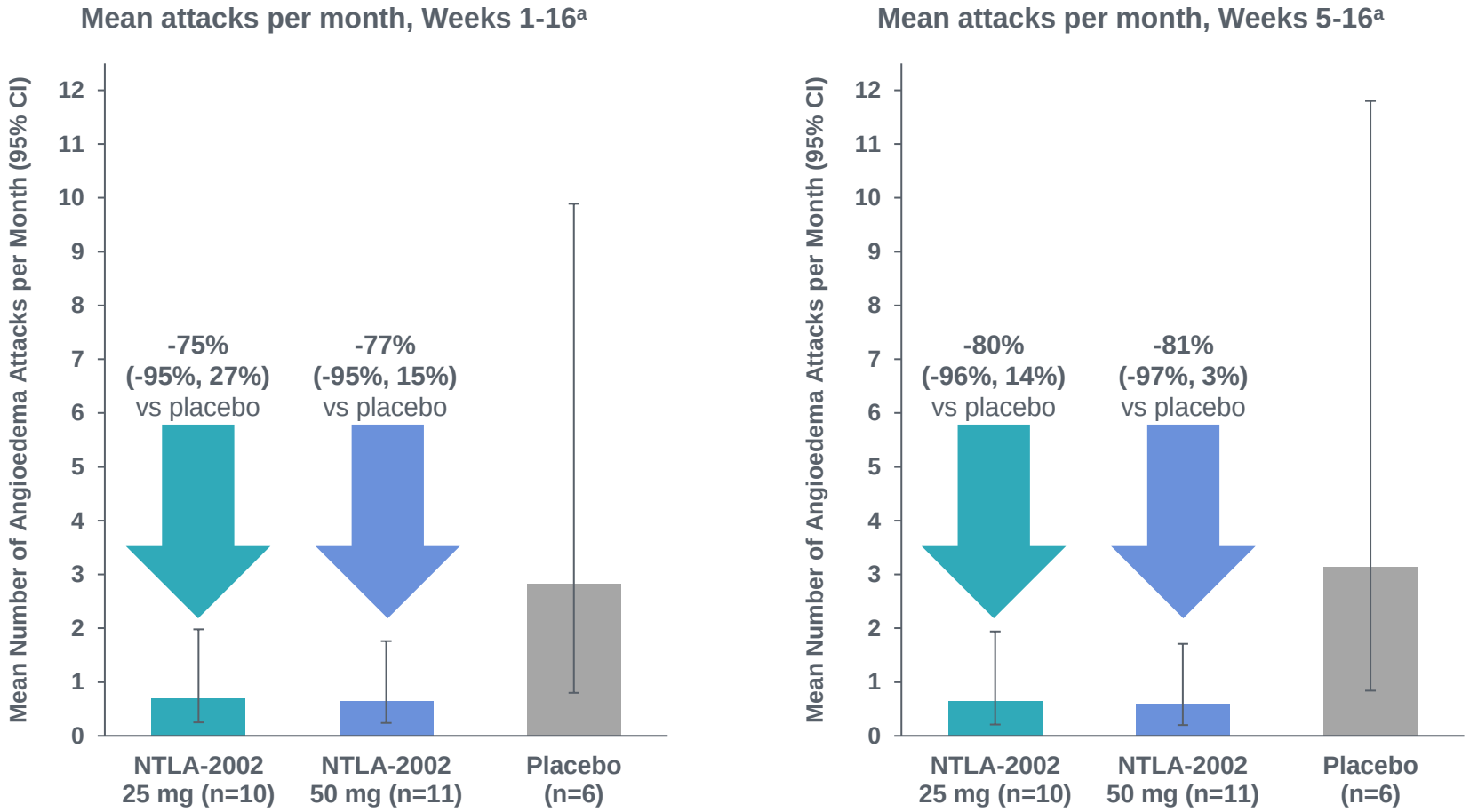
Data cutoff date: 4 Apr 2024

A Single Dose of NTLA-2002 Led to Reductions in Attacks Per Month

Mean Number of Investigator-Confirmed Attacks Per Month



In the NTLA-2002 50-mg group, 10 of 11 were without LTP and 8 of 11 patients were attack-free with no additional treatments after a median of 24.4 weeks (range, 12.6-50.0) follow-up

[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.

LTP, long-term prophylaxis.

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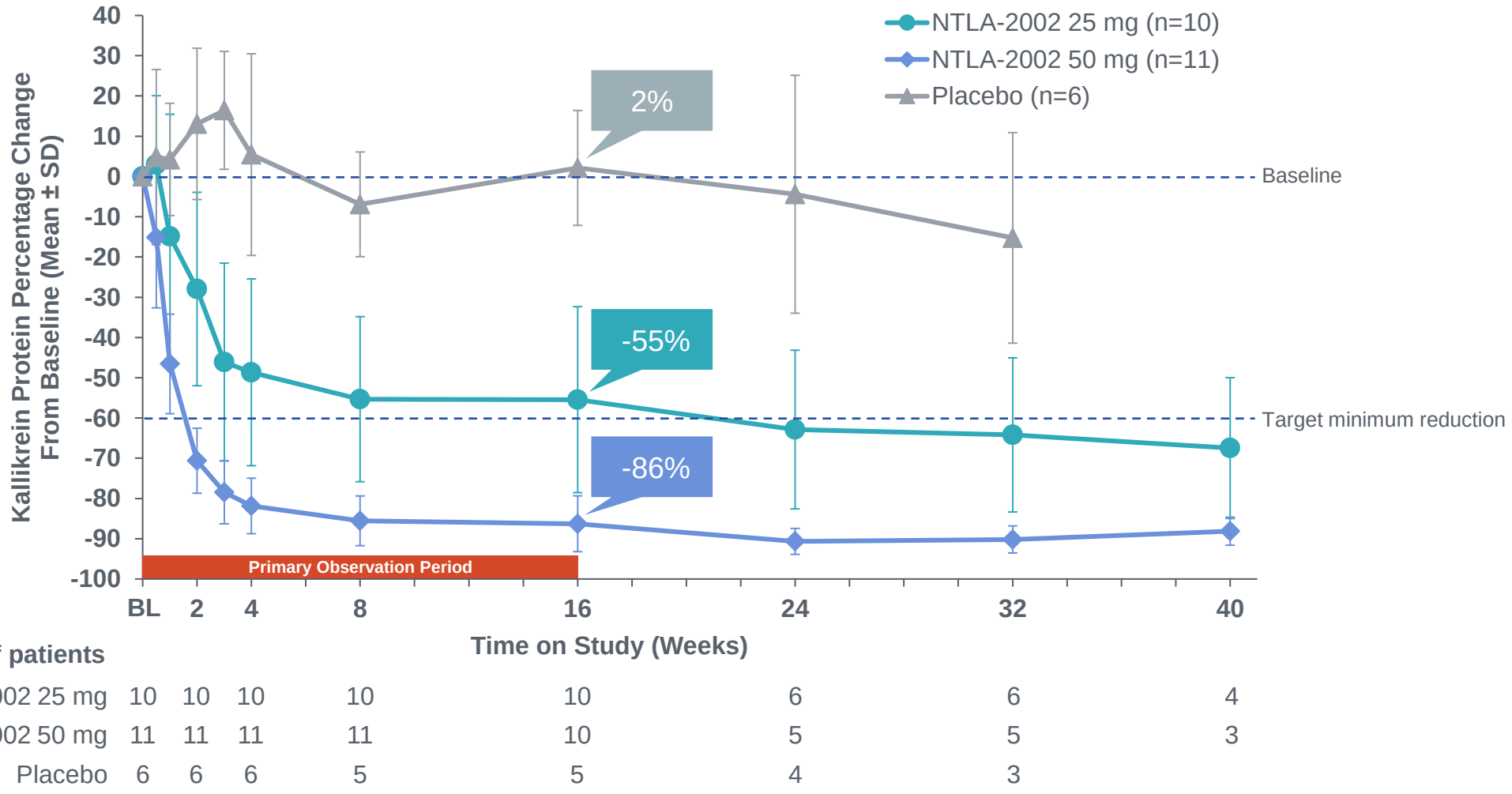
A Single Dose of NTLA-2002 Continues to Show Dose-Dependent and Durable Reductions in Plasma Kallikrein Protein Over Time



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.
Cohn DM, et al. *N Engl J Med.* 2025;392:458-467.

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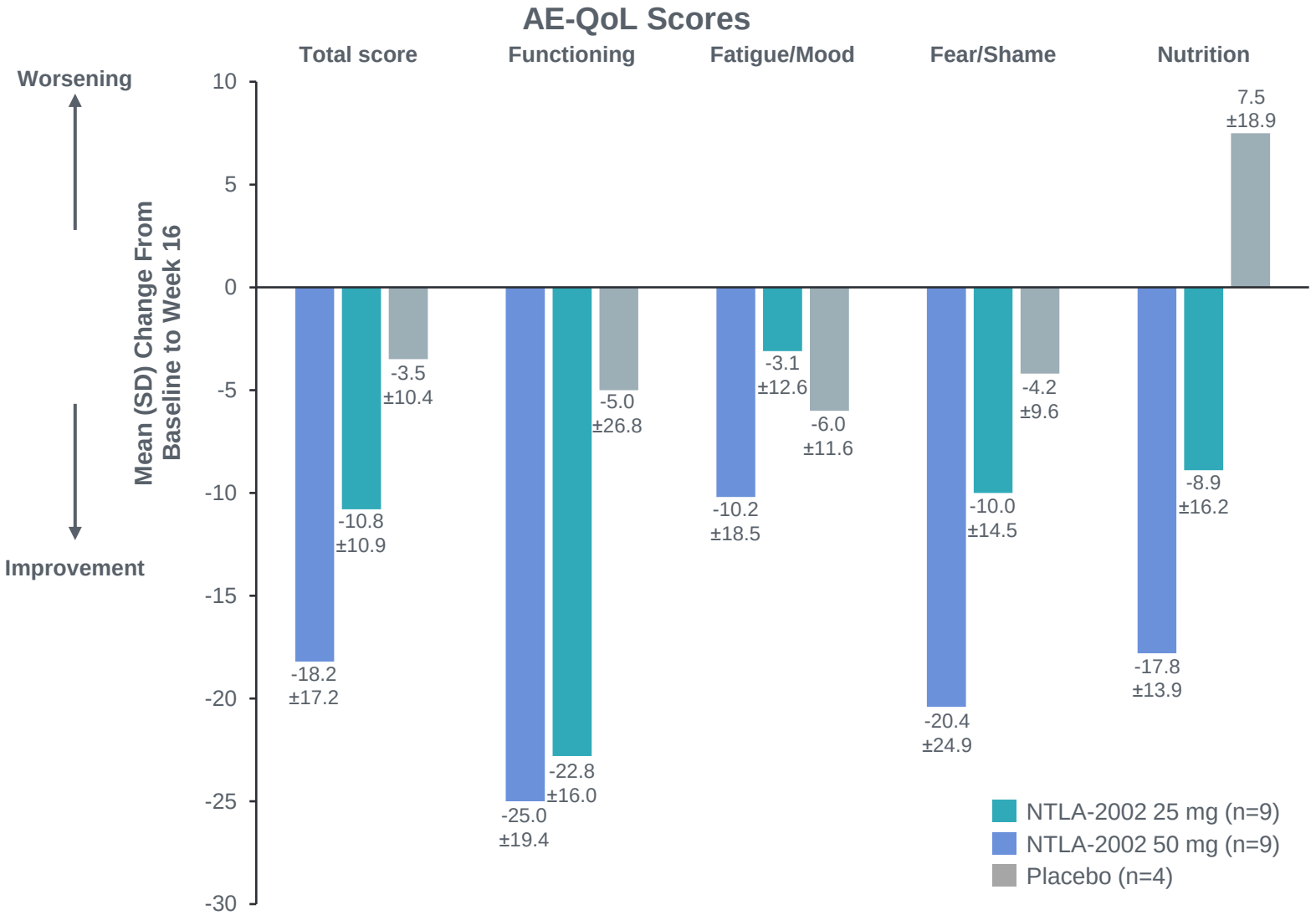
A Single Dose of NTLA-2002 50 mg Demonstrated Notable Improvement in Mean AE-QoL Across All Domains



- A single dose of NTLA-2002 showed dose-dependent improvements in mean AE-QoL scores
- Greatest improvements were seen in functioning and fear/shame domains after a single administration of NTLA-2002 50 mg

Only patients with both baseline and Week 16 AE-QoL assessments were included in the analysis.
AE-QoL, angioedema quality of life questionnaire; SD, standard deviation.
Cohn DM, et al. *N Engl J Med.* 2025;392:458-467.

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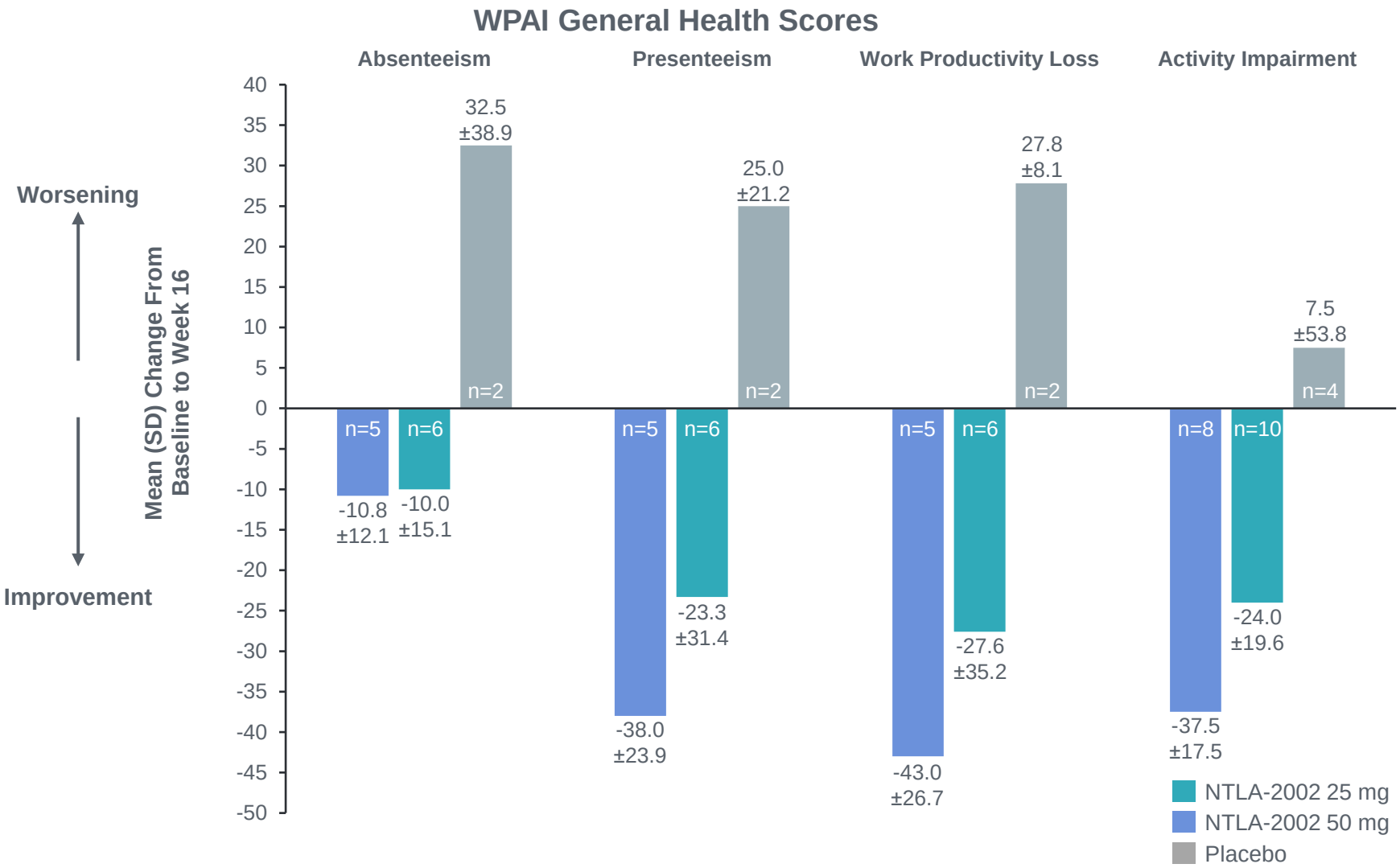
Dose-Dependent Improvements Were Observed Across all WPAI Domains After a Single Dose of NTLA-2002



- Patients who received NTLA-2002 50 mg experienced substantial improvements in all WPAI domains, especially in presenteeism and overall activity impairment

Absenteeism: percent of work time missed. Presenteeism: percent of work time spent with impairment. Work productivity loss: percent of total impairment calculated as addition of absenteeism and presenteeism.
Activity impairment: percent of impairment in activities other than work.
SD, standard deviation; WPAI, work productivity and activity impairment.

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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
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.
ALT, alanine aminotransferase; IRR, infusion-related reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
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Phase 2 Data Reinforce the Potential of NTLA-2002 to Be a Functional Cure With Favorable Impact on Quality of Life in Patients With HAE

- NTLA-2002 is the first CRISPR-based treatment to demonstrate robust and durable attack rate reductions compared with placebo, with notable improvements in health-related QOL in patients with HAE
- Greater improvement in specific domains of AE-QoL and WPAI assessments suggests patients may be able to achieve normalization of their lives, with a majority of patients treated with NTLA-2002 50 mg remaining without LTP through the follow-up period
- NTLA-2002 resulted in deep, dose-dependent, and durable reductions in plasma kallikrein protein, which have remained stable for the duration of follow-up
- NTLA-2002 continues to be well tolerated with an acceptable safety profile
- Based on these results, efficacy, safety, and QOL of patients treated with NTLA-2002 50 mg are currently being assessed in the randomized, double-blind, placebo-controlled Phase 3 HAELO trial (NCT06634420)

AE-QoL, angioedema quality of life questionnaire; CRISPR, clustered regularly interspaced short palindromic repeats; HAE, hereditary angioedema; LTP, long-term prophylaxis; QOL, quality of life; WPAI, work productivity and activity impairment.

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