CRISPR-Based Gene Editing of *KLKB1* Resulted in Long-Term Plasma Kallikrein Protein Reduction and Decreased Attack Rate in Patients With Hereditary Angioedema

Updated Results From a Phase 1 Study

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Disclosures

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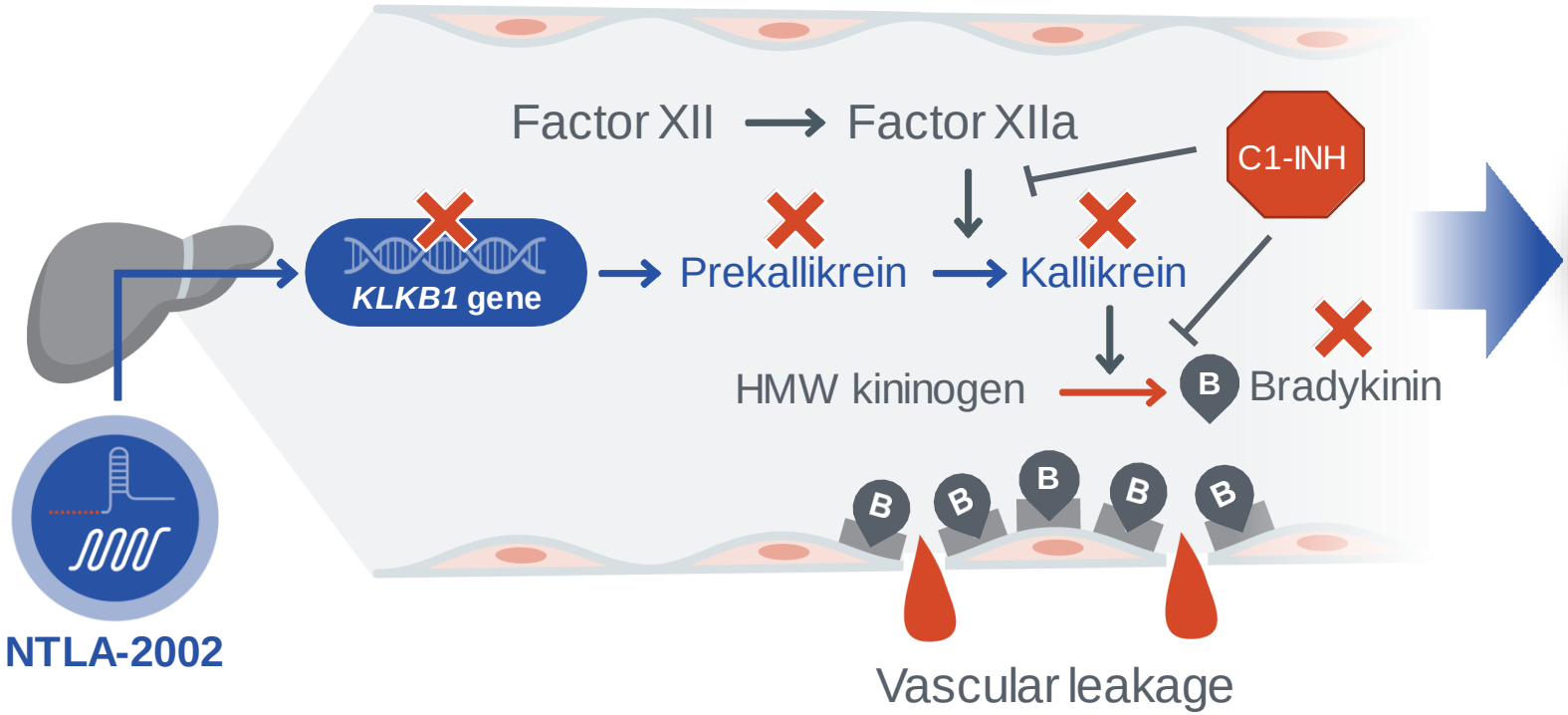
Targeting *KLKB1* Gene Expression for Long-Term Prophylaxis of HAE Attacks



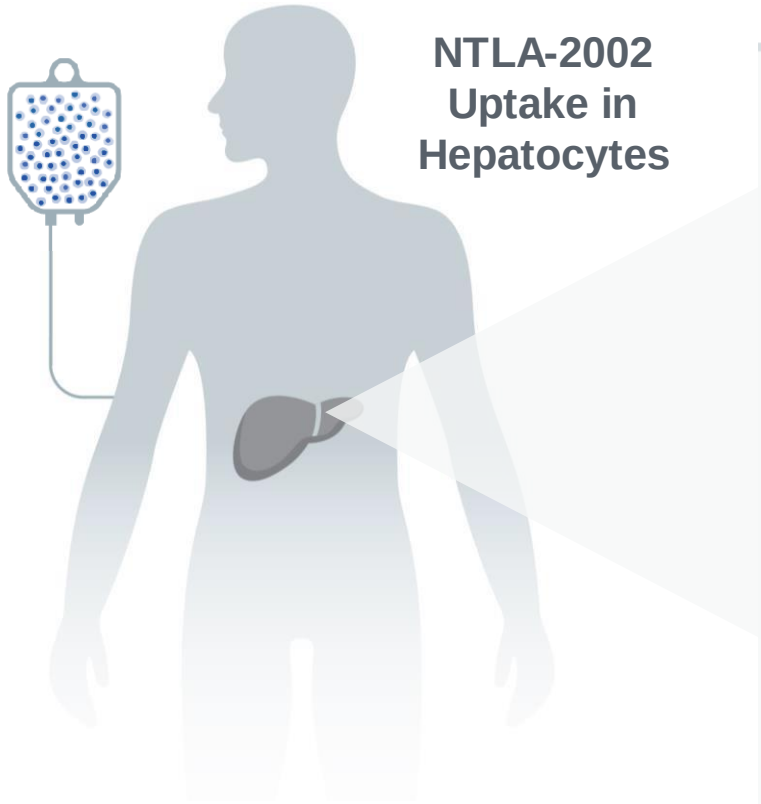
1. Knocking out *KLKB1* gene is intended to prevent production of kallikrein
2. Decreasing kallikrein rebalances pathway by reducing bradykinin production
3. Reducing bradykinin is intended to prevent HAE attacks

Kallikrein is a clinically validated therapeutic target for preventing HAE attacks

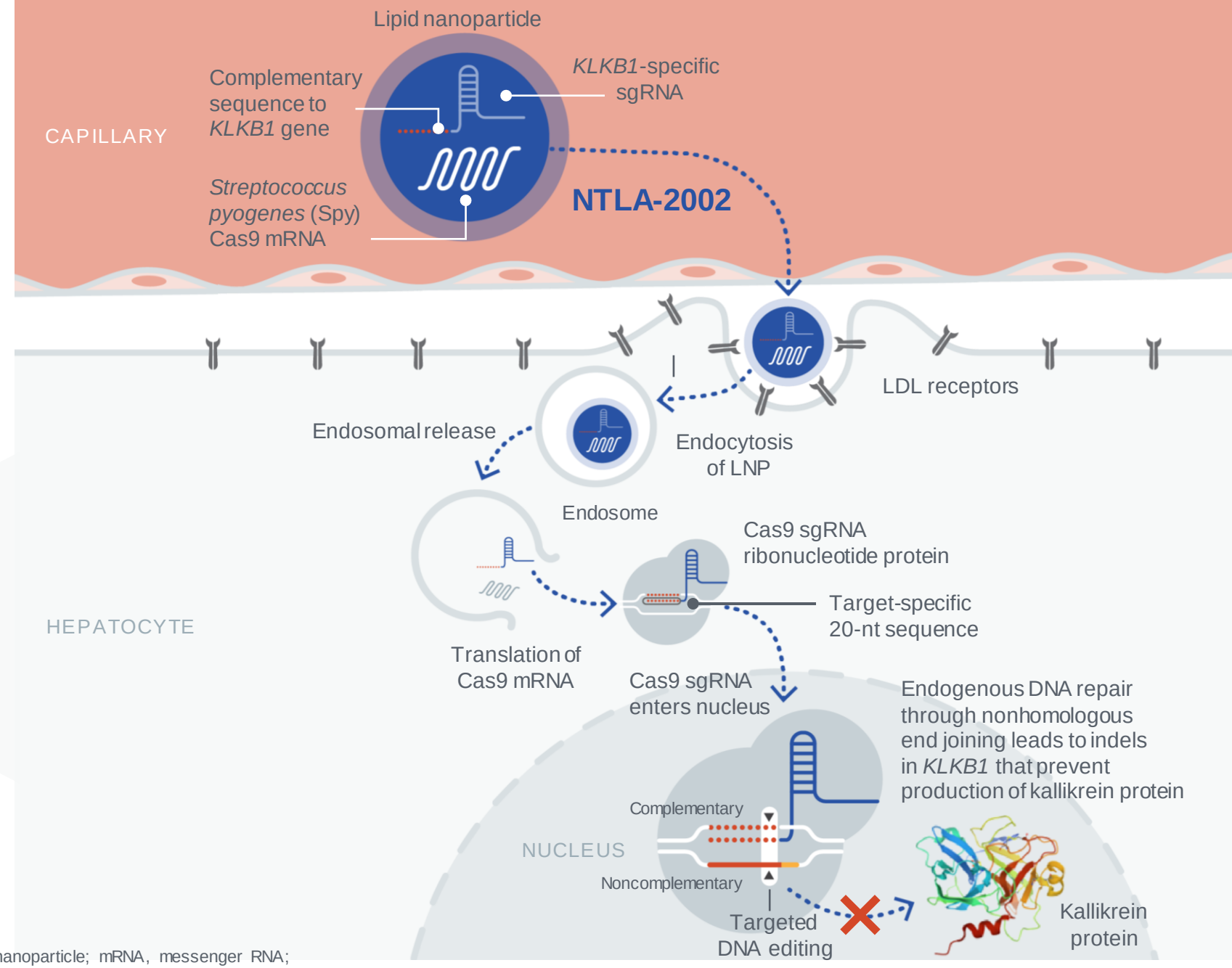
C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; HMW, high-molecular weight.
Adapted from Zuraw BL. *N Engl J Med*. 2008;359(10):1027-1036.

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; nt, nucleotide; sgRNA, single-guide 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 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
- × 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.

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Patient Demographics and Characteristics

Parameter	25 mg (n=3)	50 mg (n=4)	75 mg (n=3)	All Patients (N=10)
Age, years				
Median (range)	30 (26-52)	65 (52-73)	45 (27-49)	51 (26-73)
Sex, n (%)				
Male	3 (100)	1 (25)	2 (67)	6 (60)
Female	–	3 (75)	1 (33)	4 (40)
Weight, kg				
Median (range)	83 (78-135)	86 (74-107)	72 (64-84)	83 (64-135)
HAE type, n (%)				
Type I	2 (67)	2 (50)	2 (67)	6 (60)
Type II	1 (33)	2 (50)	1 (33)	4 (40)
Prior use of long-term prophylaxis, n (%)				
Yes	2 (67)	4 (100)	3 (100)	9 (90)
No	1 (33)	–	–	1 (10)
Concomitant long-term prophylaxis, n (%)[a]				
Yes	2 (67)	3 (75)	1 (33)	6 (60)
No	1 (33)	1 (25)	2 (67)	4 (40)
Historical monthly attack rate, mean (SD)	6.0 (6.92)	1.2 (0.47)	7.7 (8.00)	4.6 (5.83)
Typical attack severity, n (%)				
Mild	1 (33)	2 (50)	1 (33)	4 (40)
Moderate	1 (33)	2 (50)	1 (33)	4 (40)
Severe	1 (33)	0	1 (33)	2 (20)

[a]Ongoing at time of study drug administration. HAE, hereditary angioedema; SD, standard deviation.

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Data cutoff date: 12Feb2024.

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

TEAEs Occurring in ≥2 Patients	25 mg (n=3)	50 mg (n=4)	75 mg (n=3)	All Patients (N=10)
Any TEAE	**3**	**4**	**3**	**10**
Infusion-related reaction	2	2	3	7
COVID-19	3	1	2	6
Fatigue	1	3	2	6
Upper respiratory tract infection	1	1	3	5
Myalgia	0	0	3	3
Oropharyngeal pain	2	0	1	3
Abdominal discomfort	0	2	0	2
Headache	0	0	2	2
Viral upper respiratory tract infection	0	0	2	2

With a median follow-up time of 20.1 months:

- No treatment-emergent AEs ≥ Grade 3
- No treatment-emergent SAEs
- No AESIs other than IRRs
- No liver enzyme elevations or platelet count decreases > Grade 1
- No clinically significant shifts in coagulation parameters

AE, adverse event; AESI, adverse event of special interest; IRR, infusion-related reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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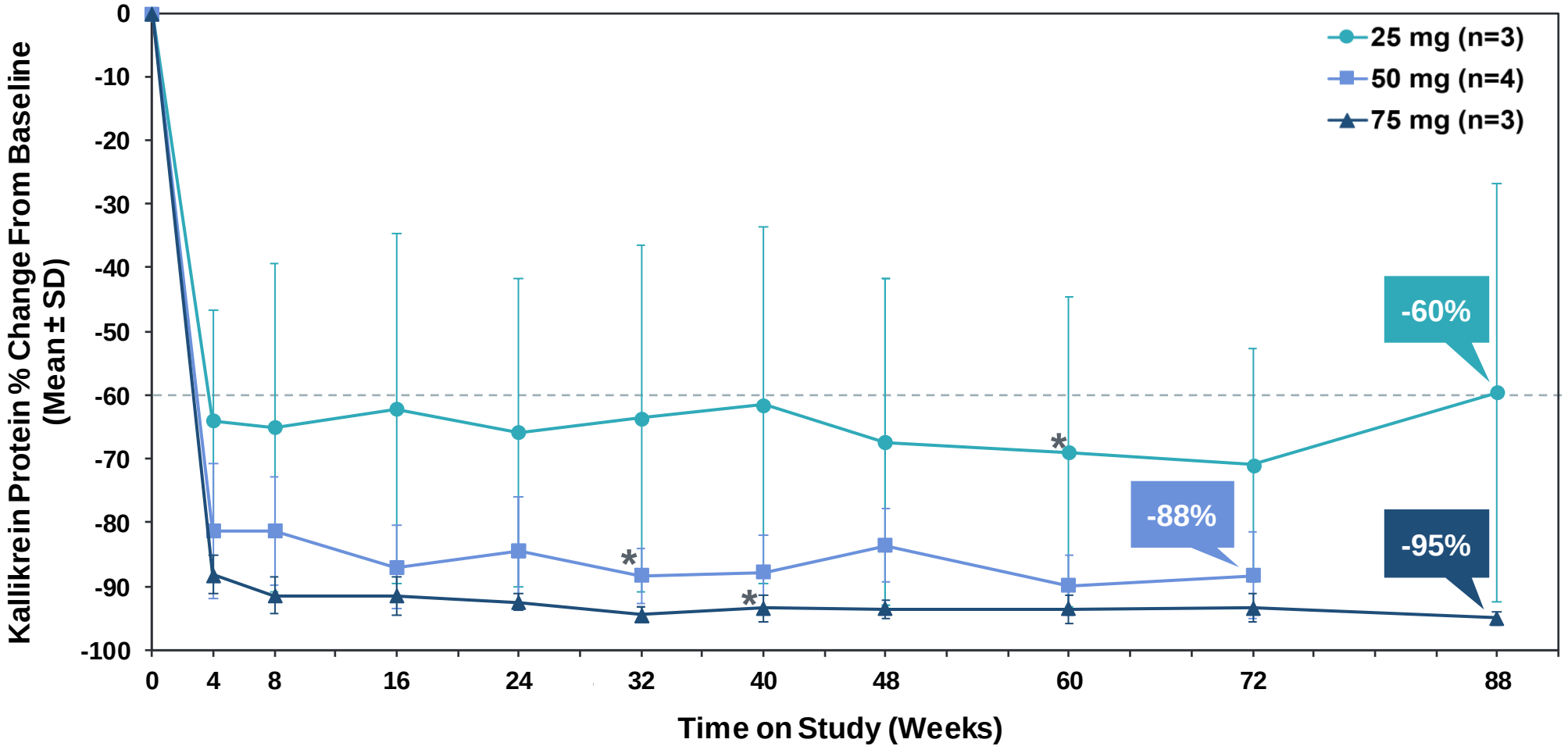
A Single Dose of NTLA-2002 Continues to Show Dose-Dependent and Durable Reductions in Plasma Kallikrein Protein Over Time



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.
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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.

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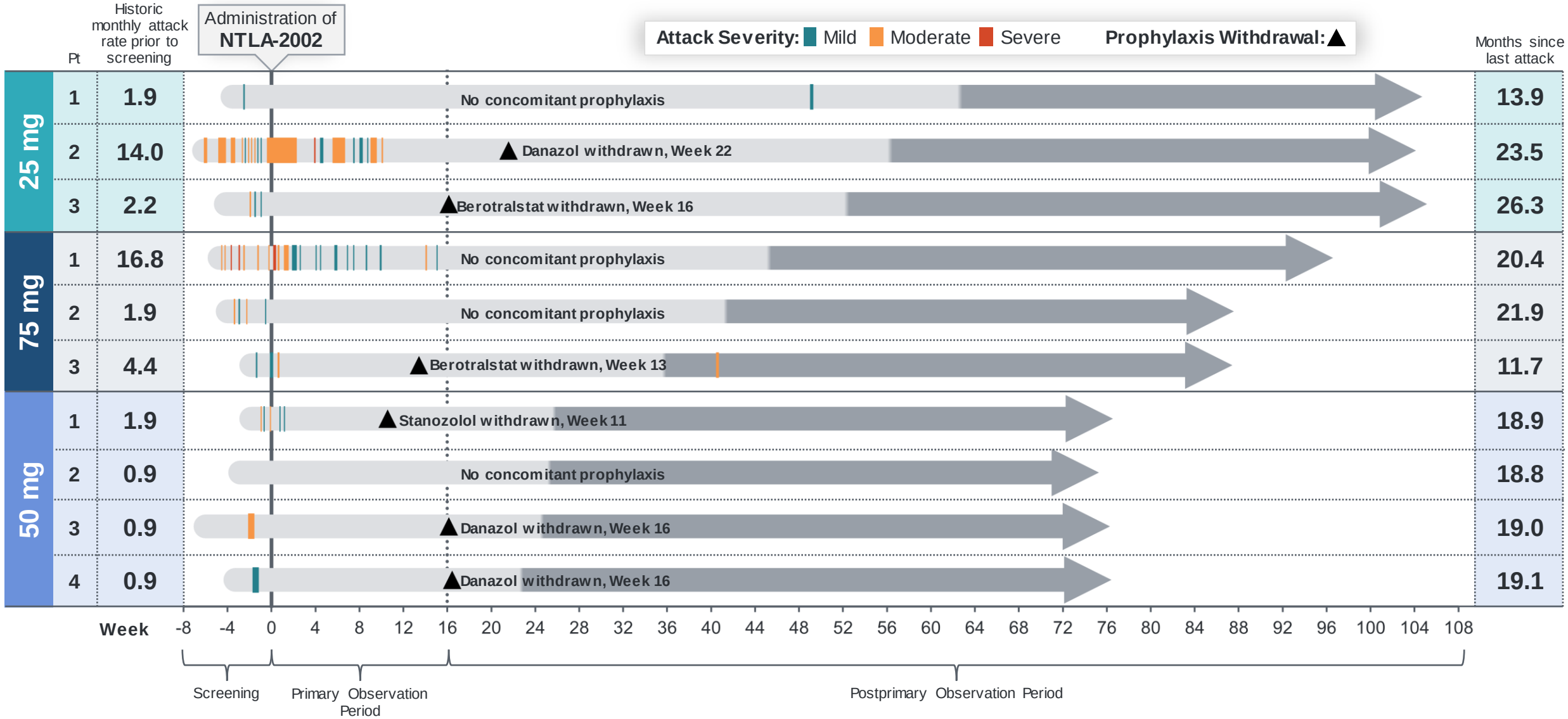
8 of 10 Patients Have Been Attack-Free Since the End of the Primary Observation Period



Pt, patient. A month is defined as 28 days.
Dark gray arrows indicate additional ongoing follow-up since the previous data cut of 17Feb2023.
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Latest Data Continue to Reinforce the Potential of a Single Dose of NTLA-2002 to Be a Functional Cure for Patients With HAE

- NTLA-2002 continues to be well-tolerated at all doses; all AEs were transient and either Grade 1 or 2
- NTLA-2002 resulted in dose-dependent and durable reductions in plasma kallikrein protein, which have remained stable for the duration of follow-up
- Robust and durable attack reductions continue to be observed in all patients following NTLA-2002
  - Across all patients, a 98% mean reduction in monthly HAE attack rate was observed through the latest assessment, with a median follow-up of 20.1 months
  - 8 of 10 patients remain attack-free since the end of the primary observation period
  - Longest attack-free interval was 26 months through the latest assessment
  - No patients have resumed other long-term prophylaxis
- Phase 2 portion of this study is fully enrolled, with results expected in 2024

AE, adverse event; HAE, hereditary angioedema.

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Acknowledgements

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