In vivo CRISPR/Cas9 editing of *KLKB1* in patients with Hereditary Angioedema: A First-in-Human Study

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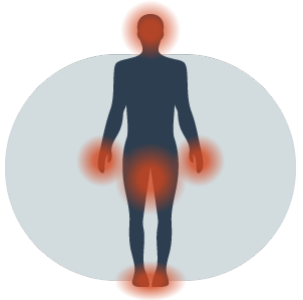
Hereditary Angioedema (HAE) is a genetic disease associated with significant morbidity

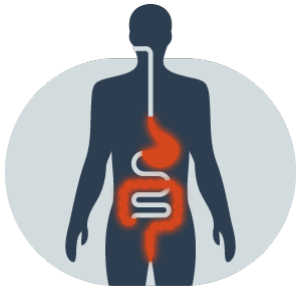
WHAT IS HAE?

- Rare, autosomal dominant genetic disease
- Associated with frequent, severe and unpredictable attacks of painful swelling due to dysregulated bradykinin production

SYMPTOMS OF HAE

- Painful swelling attacks in extremities, face, stomach and GI tract
- Swelling of throat may cause difficulty swallowing or breathing, and in severe cases, can be fatal





~1 in 50,000

HAE patients worldwide[1]

Every 7-14 days

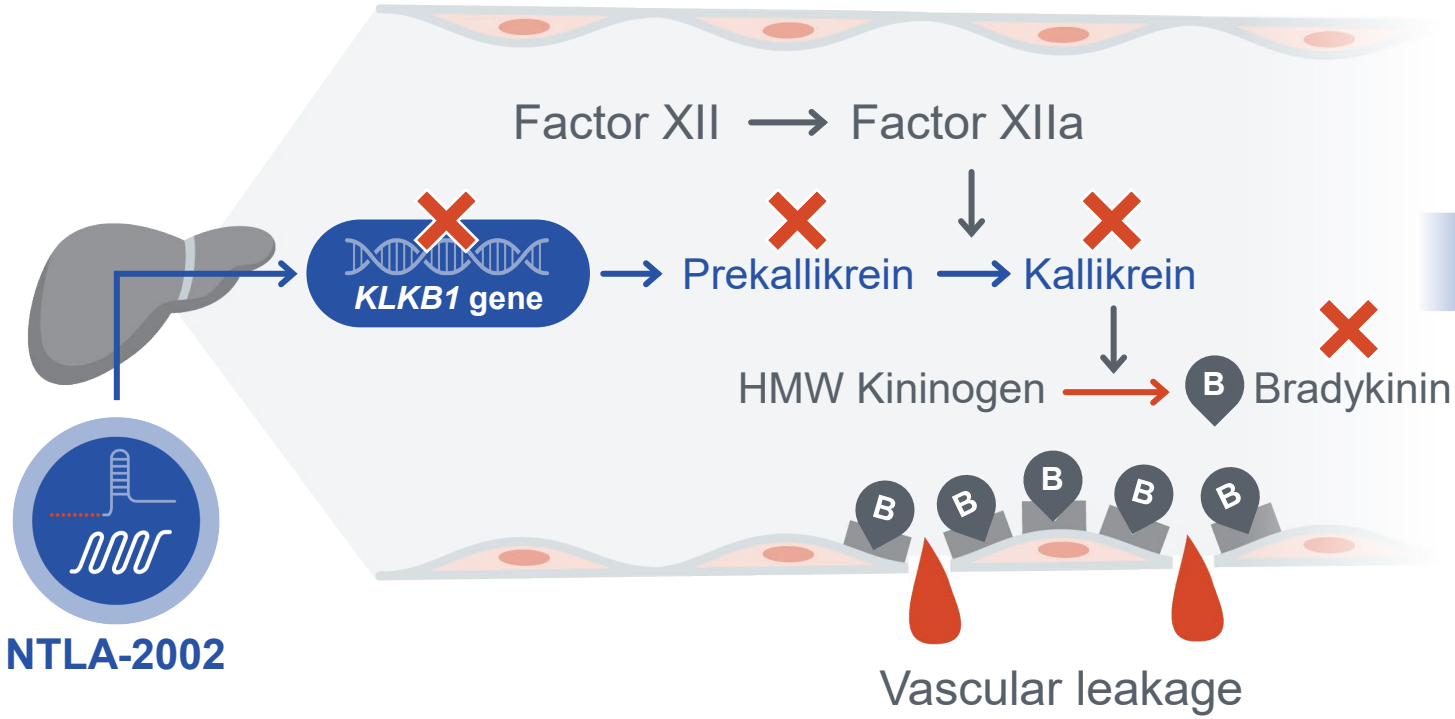
Average frequency of attacks for untreated patients[1]

Significant treatment burden exists

Chronic dosing is required with current treatments

[1]Zuraw BL. Hereditary angioedema. *N Engl J Med*. 2008;359:1027-1036

Targeting *KLKB1* gene expression for long-term prophylaxis of HAE attacks



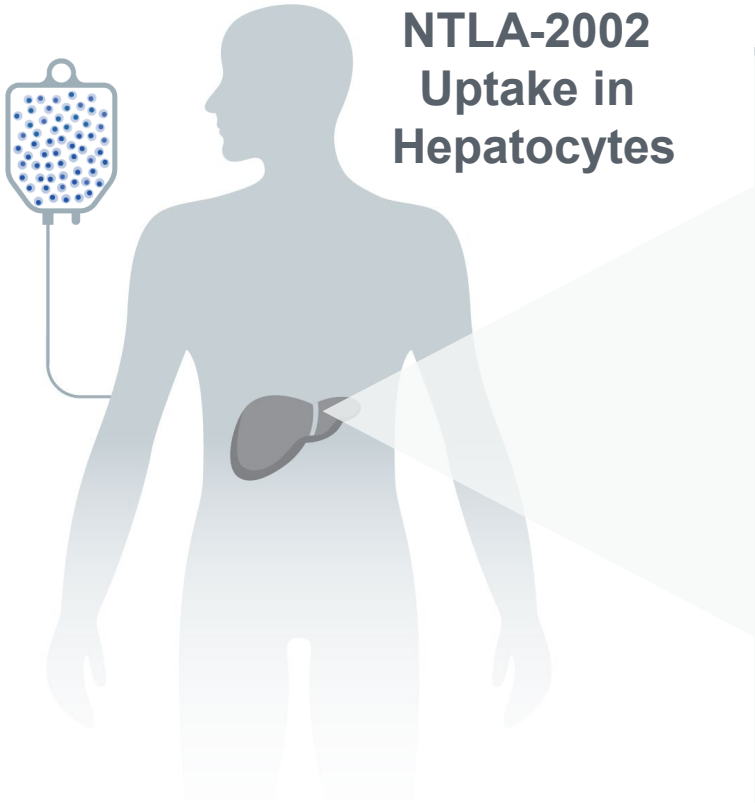
1. Knocking out *KLKB1* gene is intended to prevent production of kallikrein
2. Decreasing kallikrein rebalances the pathway by reducing bradykinin production
3. Reducing bradykinin prevents HAE attacks

Kallikrein is a clinically validated therapeutic target for preventing HAE attacks

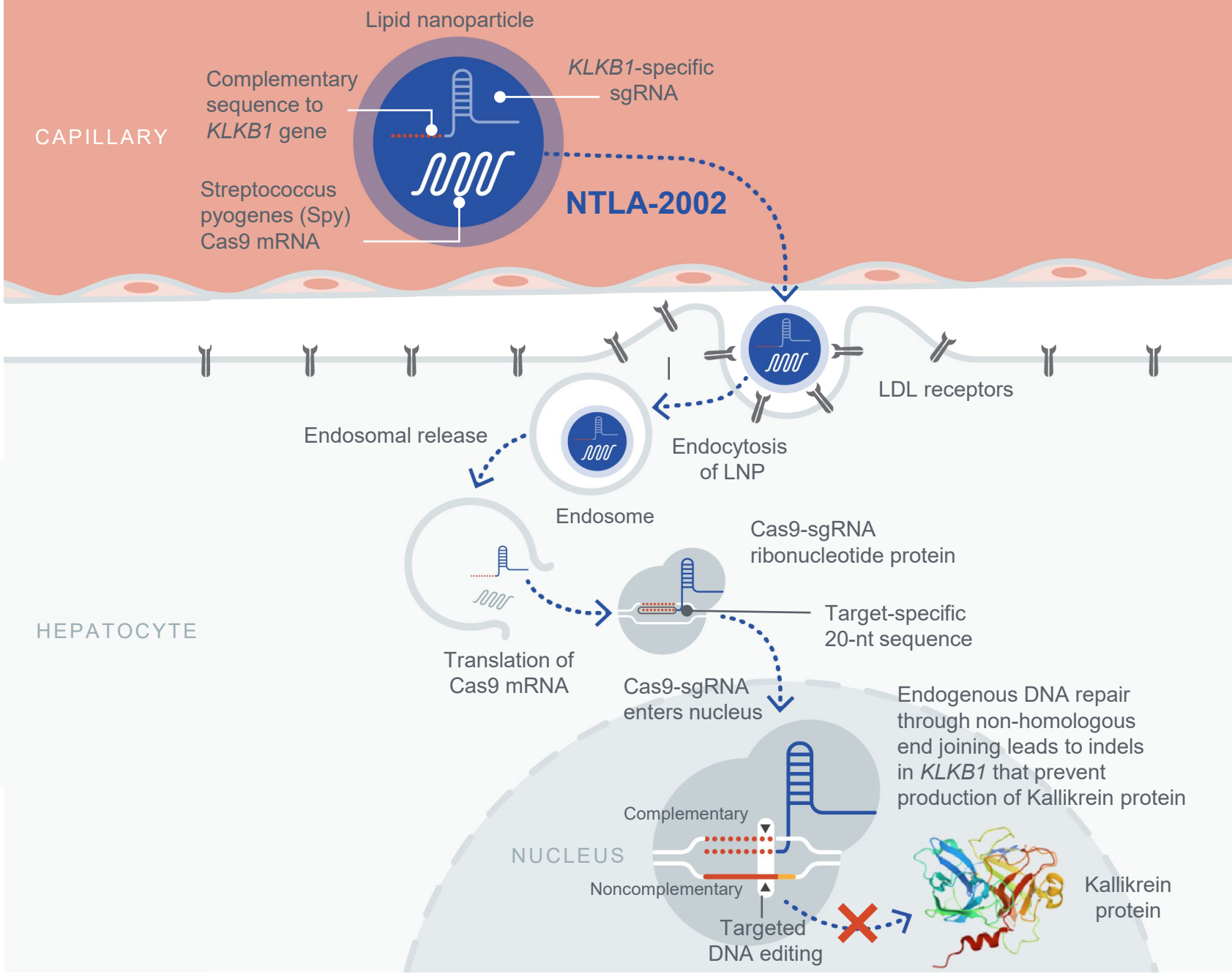
3 This presentation includes data for an investigational product not yet approved by regulatory authorities.

HAE, Hereditary Angioedema; **HMW**, High-molecular weight
Adapted from Zuraw BL. Hereditary angioedema. *N Engl J Med*. 2008;359:1027-1036

NTLA-2002 is a novel, investigational CRISPR/Cas9-based *in vivo* gene editing therapy



NTLA-2002 Uptake in Hepatocytes



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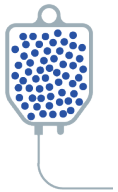
LNP, Lipid Nanoparticle; **sgRNA**, Single Guide RNA

NTLA-2002 global Phase 1/2 study design: Two-part, multi-center study of NTLA-2002 in adults with HAE Types I and II

Today's interim data cover the Phase 1 part of the study
(Data cut-off: 28 September 2022)

Intervention:
Single dose administered via an intravenous (IV) infusion



PHASE 1
Open-label, single-ascending dose

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

PHASE 2
Expansion study to confirm recommended dose

Randomized

- Dose 1 (n=10)
- Dose 2 (n=10)
- Placebo Arm (n=5)

PRE-TREATMENT 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 & tolerability

OTHER OBJECTIVES

PK, PD, clinical efficacy (attacks)

PRIMARY OBJECTIVES

Clinical efficacy (attacks through week 16)

OTHER OBJECTIVES

PD, safety & tolerability, PK, QoL

50 mg cohort allowed up to 6 patients per protocol

C1-INH, C1 Esterase Inhibitor; **H1,** Histamine Receptor 1; **H2,** Histamine Receptor 2
PD, Pharmacodynamics; **PK,** Pharmacokinetics; **QoL**, Quality of Life

Key eligibility criteria (Phase 1)

INCLUSION

- ✓ 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

EXCLUSION

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

Patient demographics & characteristics

Parameter	25 mg n = 3	50 mg n = 4	75 mg n = 3	All patients N = 10
Median Age, years (Min, Max)	30 (26, 52)	65 (52, 73)	45 (27, 49)	51 (26, 73)
Sex, n (%) Male Female	 3 (100%) –	 1 (25%) 3 (75%)	 2 (67%) 1 (33%)	 6 (60%) 4 (40%)
Median Weight, kg (Min, Max)	83 (78, 135)	86 (74, 107)	72 (64, 84)	83 (64, 135)
HAE Type, n (%) Type I Type II Unknown*	 2 (67%) 1 (33%) –	 1 (25%) 2 (50%) 1 (25%)	 2 (67%) 1 (33%) –	 5 (50%) 4 (40%) 1 (10%)

*Patient diagnosed based on C1-INH functional assay alone

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Data Cut Off: 28 September 2022
HAE, Hereditary Angioedema

Patient reported HAE attack history

Parameter	25 mg n = 3	50 mg n = 4	75 mg n = 3	All patients N = 10
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 (%)				
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%)

*Ongoing at time of study drug infusion

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Data Cut Off: 28 September 2022

SD, Standard Deviation

NTLA-2002 was generally well-tolerated across all dose levels evaluated

- **Across all dose levels, the most frequent AEs were infusion-related reactions and fatigue**
  - All TEAEs were mild or moderate in severity (Grade 1 or 2 only)
  - All infusion-related reactions were considered mild (n = 5) or moderate (n = 2), resolving without clinical sequelae
  - All patients received a full dose of NTLA-2002

- **No clinically significant laboratory findings observed**
  - No increases in activated partial thromboplastin time

- **No treatment emergent SAEs or ≥ Grade 3 TEAEs were observed**

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Data Cut Off: 28 September 2022
AE, adverse events; **SAE**, serious adverse event
TEAE, treatment-emergent adverse event

Majority of adverse events were mild in severity

Adverse events occurring in ≥ 2 patients	25 mg n = 3		50 mg n = 4		75 mg n = 3		All patients N = 10	
	Gr. 1	Gr. 2	Gr. 1	Gr. 2	Gr. 1	Gr. 2	Gr. 1	Gr. 2
Any TEAE (max grade)	2	1	2	1	1	2	5	4
Infusion-related reaction	2	–	1	1	2	1	5	2
Fatigue	1	–	2	1	2	–	5	1
COVID-19	2	–	1	–	1	–	4	–
Oropharyngeal pain	2	–	–	–	1	–	3	–
Headache	–	–	–	–	2	–	2	–
Upper respiratory tract infection	1	–	–	–	1	–	2	–
Viral upper respiratory tract infection	–	–	–	–	2	–	2	–

All other AEs (abdominal discomfort, abdominal pain, abdominal pain upper, arthralgia, asthenia, chest injury, depressed mood, diarrhea, disease prodromal stage, flank pain, insomnia, myalgia, rhinitis, sinusitis, soft tissue injury, somnolence, vomiting) were reported in one patient.

Patients counted once per row with highest grade reported.
Gr., Grade; **TEAE**, treatment-emergent adverse event

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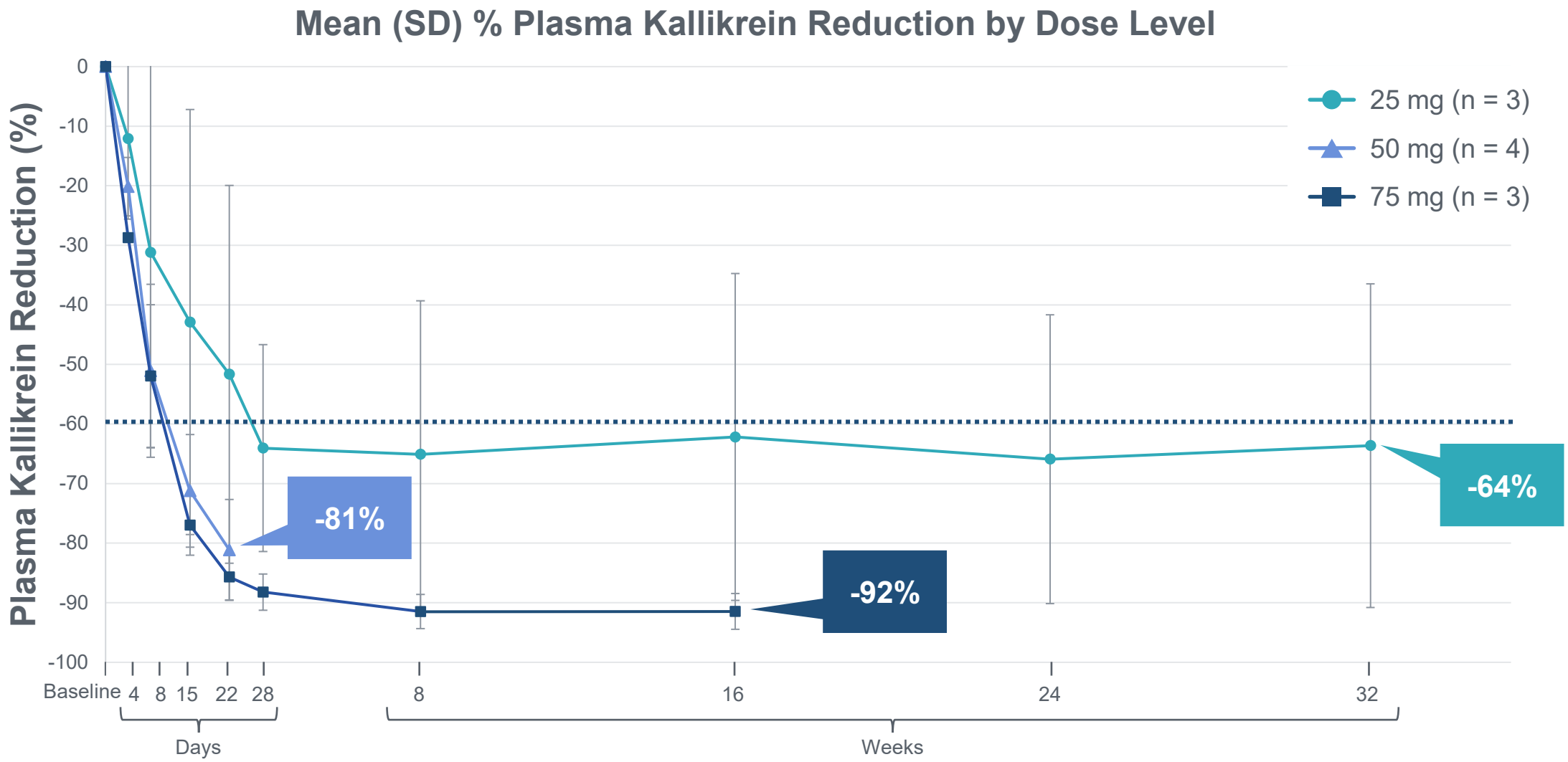
NTLA-2002 resulted in rapid and deep plasma kallikrein reduction at all dose levels



Dashed line represents targeted minimum reduction

SD, Standard Deviation

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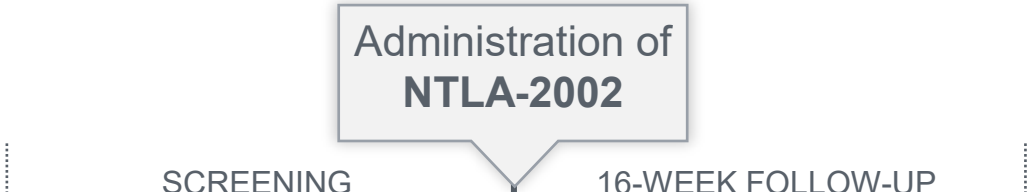
Clinically meaningful reductions in investigator-confirmed monthly attack rate observed through pre-specified 16-week follow-up period



		Attacks in Screening Period	Attacks in 16-Week Primary Observation Period	Mean (SD) % Change from Baseline Weeks 1-16	Mean (SD) % Change from Baseline Weeks 5-16
25 mg n = 3	Patient 1	1.1 / month	0.0 / month	**-91% (16%)**	**-89% (19%)**
	Patient 2	7.2 / month	2.0 / month		
	Patient 3	2.9 / month	0.0 / month		
75 mg n = 3	Patient 1	5.9 / month	3.5 / month	**-78% (32%)**	**-89% (19%)**
	Patient 2	4.0 / month	0.0 / month		
	Patient 3	4.3 / month	0.3 / month		

Analysis including 90-Day patient reported historical and screening period resulted in mean (SD) percent change of -94% (10%) and 90% (13%) in monthly attack rate for Week 1 to 16 in the 25 mg and 75 mg cohorts, respectively

SD, Standard Deviation

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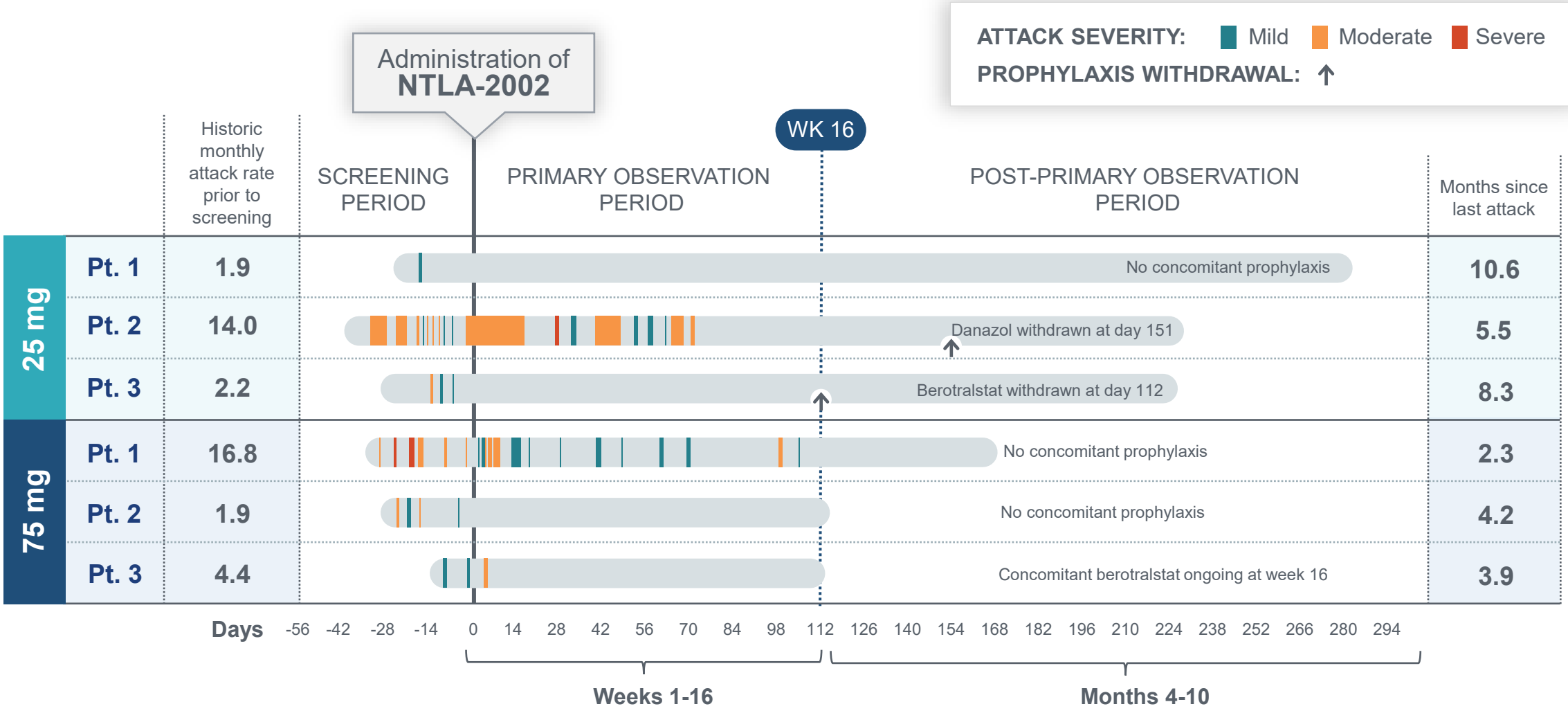
All patients have an ongoing attack-free interval with range of 2.3 to 10.6 months



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A single dose of NTLA-2002 led to robust, dose-dependent and durable reductions in total plasma kallikrein levels

- Mean plasma kallikrein reductions between 65% and 92% were observed at nadir, with responses persisting for the duration of follow-up
- All patients in 25 mg and 75 mg cohorts have an ongoing attack-free interval of 2.3 to 10.6 months
  - First three patients treated have now been attack-free for 5.5 – 10.6 months
- Mean reductions in attacks from baseline of 89% at both 25 mg and 75 mg dose level (weeks 5-16)
- Patients who discontinued prophylactic therapy after NTLA-2002 infusion remained attack-free
- NTLA-2002 was generally well-tolerated; all AEs were of mild or moderate severity
- No further dose escalation is planned, Phase 2 expected to commence in first half of 2023

These data support the promise of CRISPR-based *in vivo* genome editing in humans

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