Transient exposure to NTLA-2002, an investigational CRISPR/Cas9-based gene editing therapy, leads to durable pharmacodynamic responses and attack control in patients with hereditary angioedema

Hilary Longhurst[1], Padmalal Gurugama[2], Carri Boiselle[3], Stacey Shea[3], Christina Picornell[3], Ahmed Abdelhady[3], Adele Golden[3], Mrinal Y. Shah[3], David Maag[3], Danny M. Cohn[4]

[1]Te Whatu Ora | Te Toka Tumai Auckland, New Zealand [2]Cambridge University Hospitals, NHS Foundation Trust, Cambridge, UK [3]Intellia Therapeutics, Cambridge, MA, U.S. [4]Amsterdam University Medical Center, Amsterdam, Netherlands

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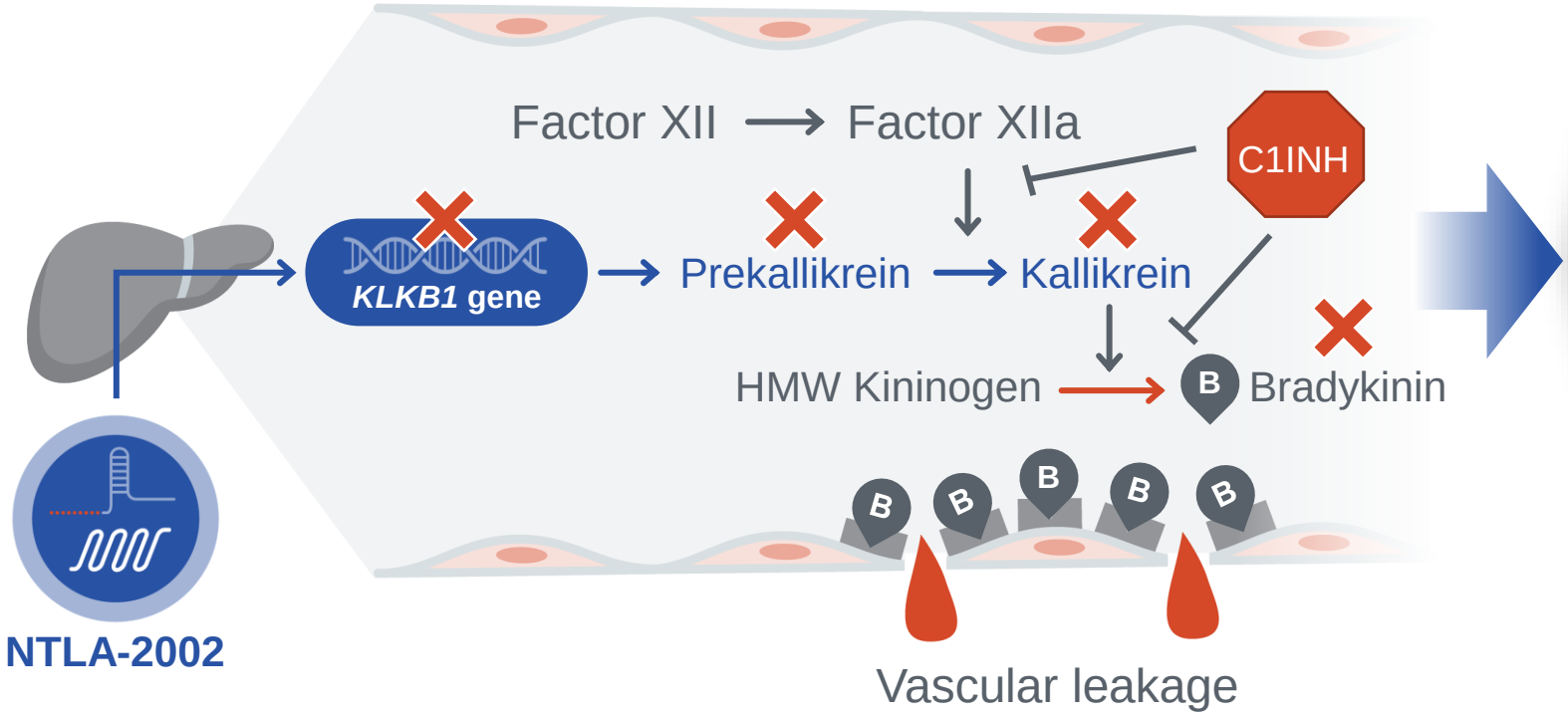
Targeting *KLKB1* gene expression for long-term prophylaxis of HAE attacks



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

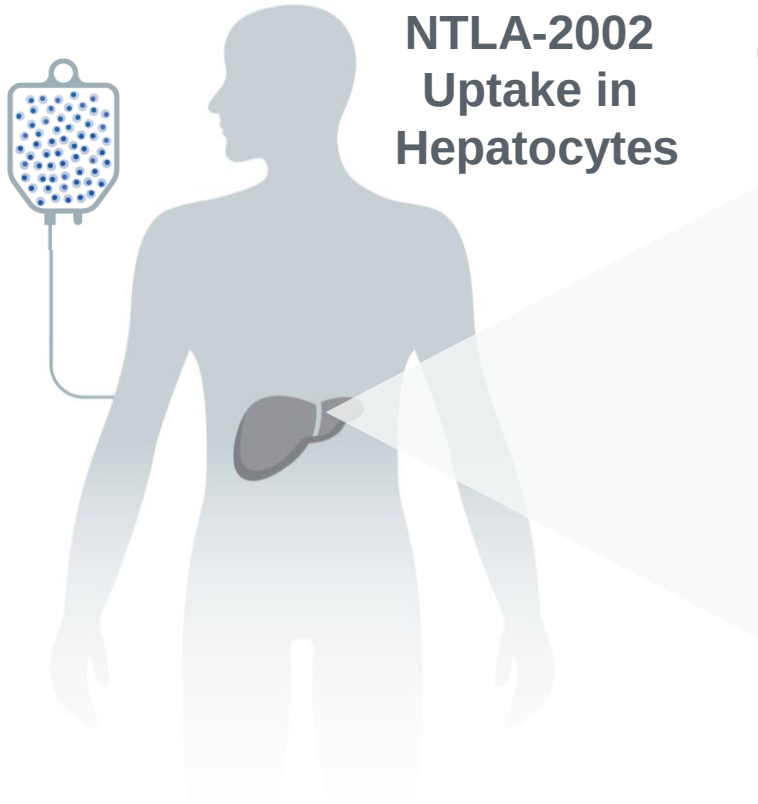
Kallikrein is a clinically validated therapeutic target for preventing HAE attacks

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

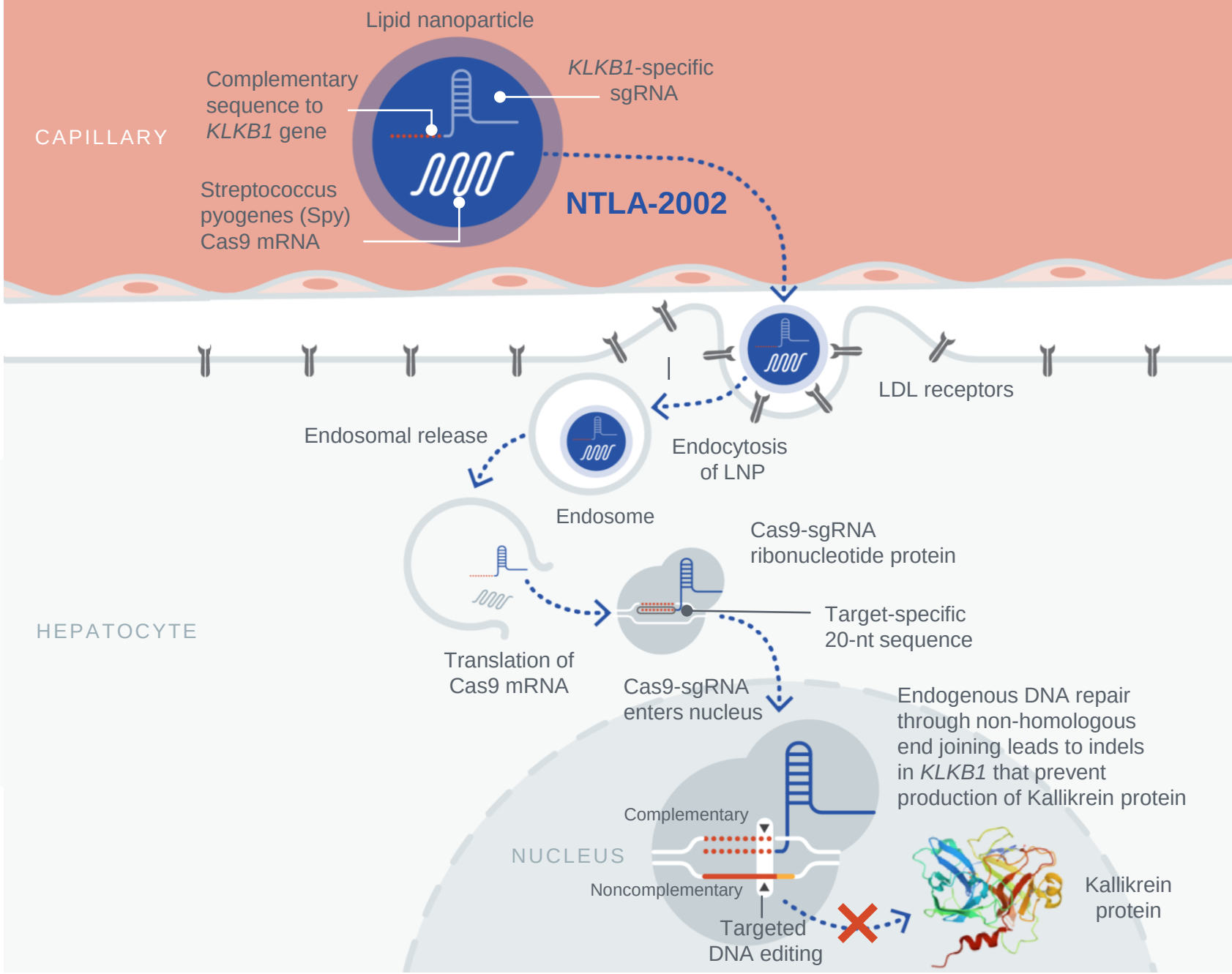
HAE, Hereditary Angioedema; **HMW**, High-molecular weight

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 Phase 1/2 study design: Two-part, multicenter study in adults with HAE Types I and II

Total Enrollment:

Up to 55 patients, age 18 and older

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

- 50 mg (n=10)
- 25 mg (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

C1-INH, C1 esterase inhibitor; **H1**, Histamine receptor 1; **H2**, Histamine receptor 2; **PD**, pharmacodynamics; **PK**, pharmacokinetics; **QoL**, quality of life.

Patient demographics & 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 Female	 3 (100%) –	 1 (25%) 3 (75%)	 2 (67%) 1 (33%)	 6 (60%) 4 (40%)
Weight, kg Median (range)	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%)

*Per communication with investigator, genotyping supports Type I diagnosis.

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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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SD, Standard Deviation

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

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	–

Across all dose levels, the most frequent AEs were infusion-related reactions and fatigue

No clinically significant laboratory findings observed

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

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

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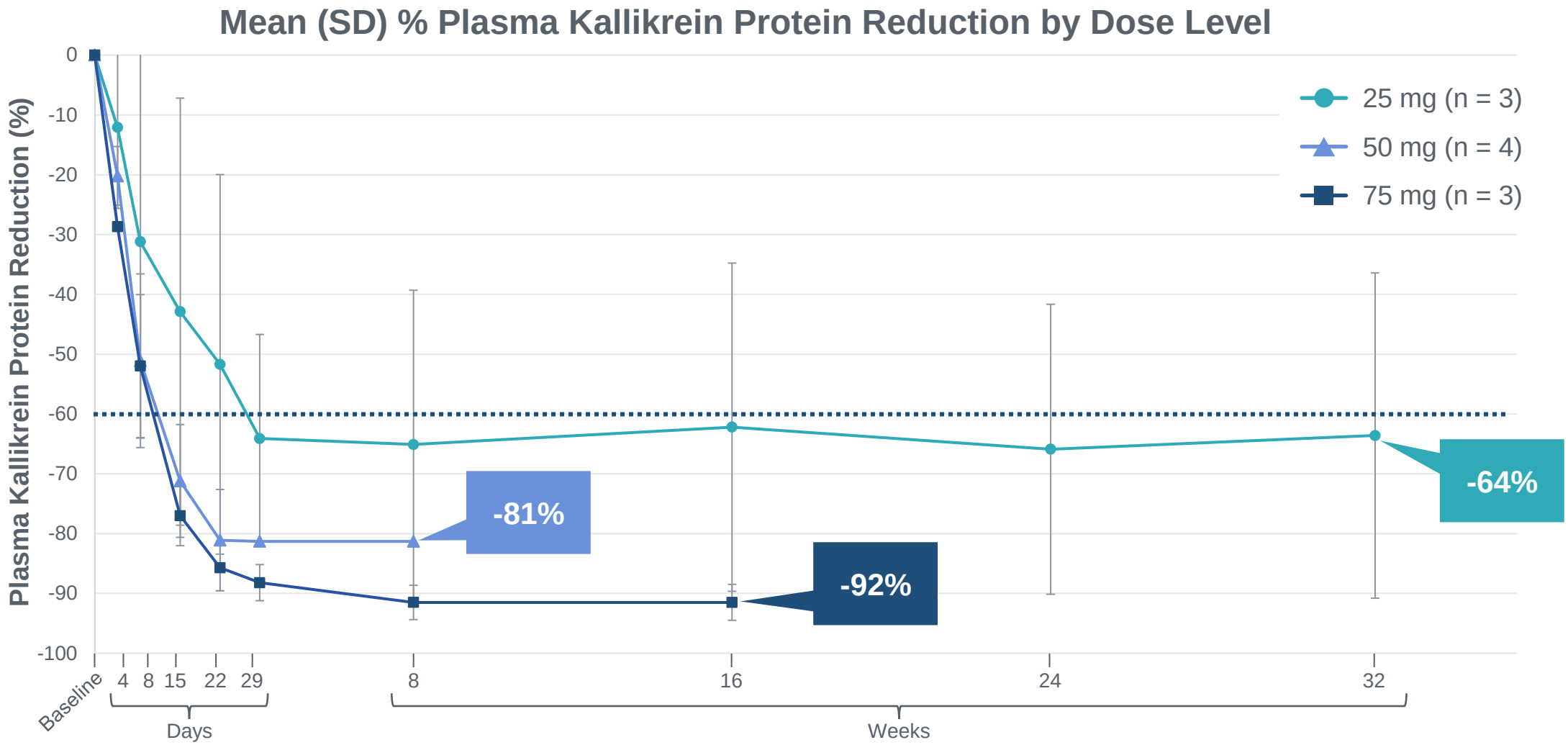
NTLA-2002 resulted in rapid and deep reduction in plasma kallikrein protein at all dose levels



Dashed line represents targeted minimum reduction

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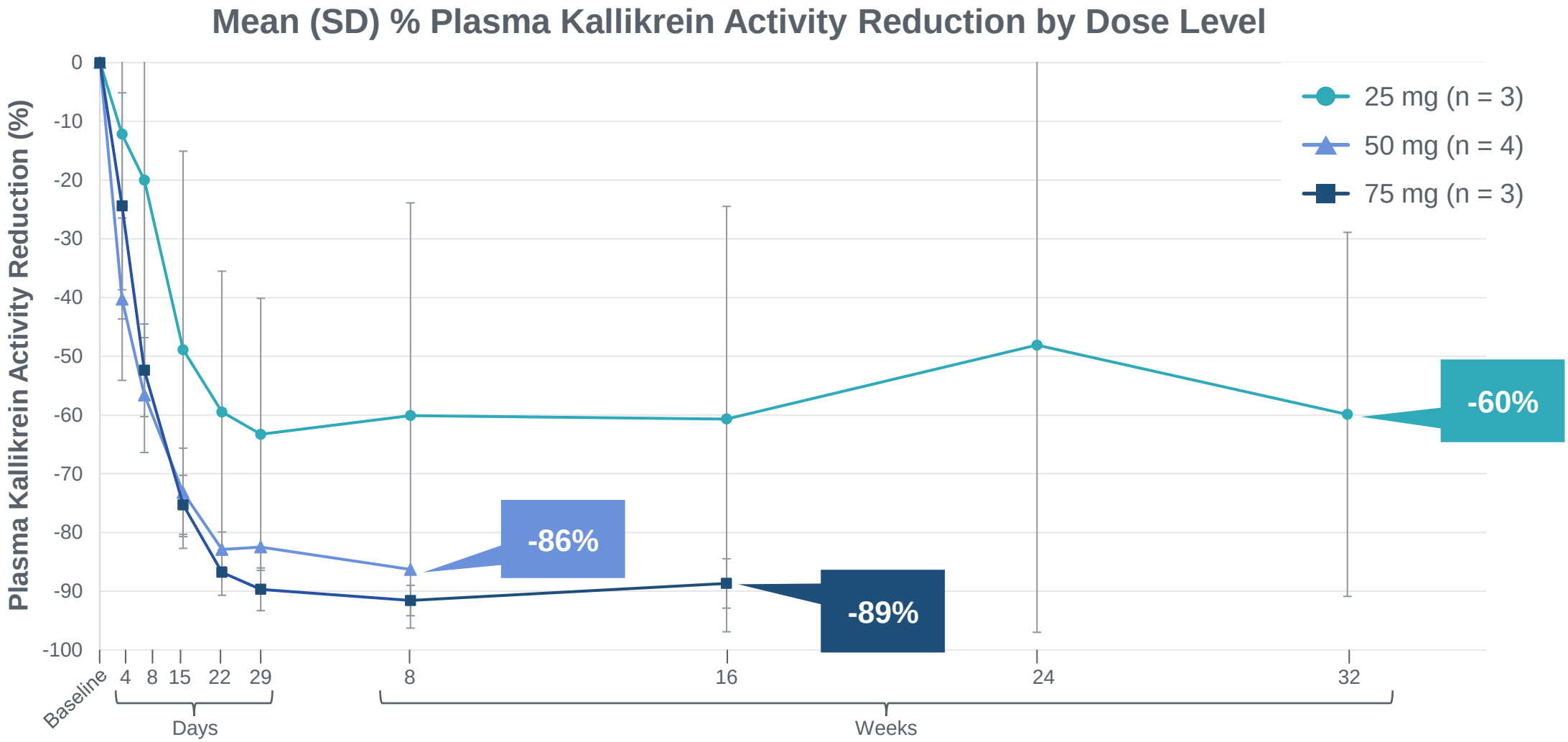
NTLA-2002 elicited a similar trend in plasma kallikrein activity reduction across all dose levels



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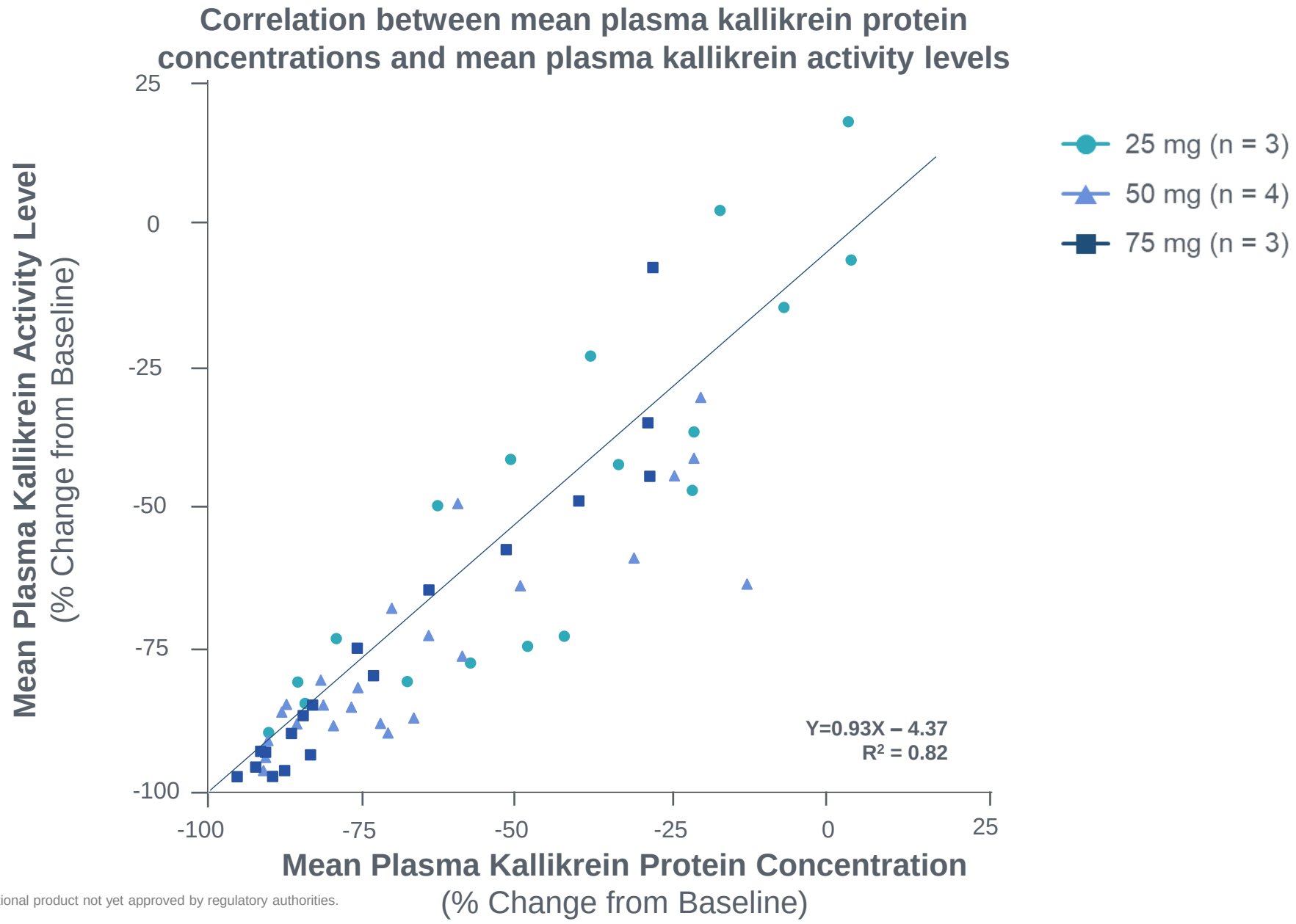
Plasma kallikrein protein concentration and activity levels demonstrate strong correlation



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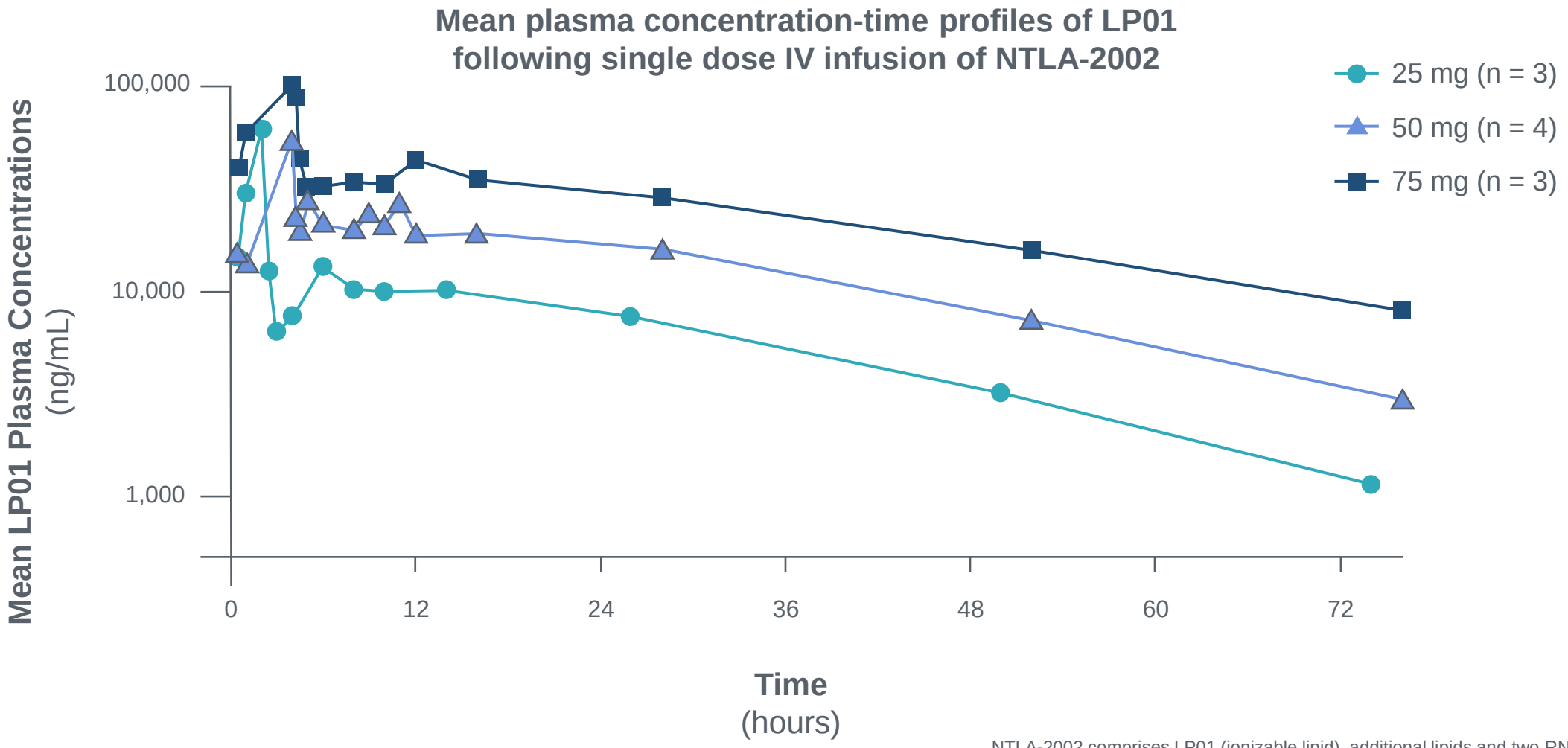
The concentration-time profile of LP01, a representative component of NTLA-2002, demonstrates dose-dependent exposure and rapid clearance



NTLA-2002 comprises LP01 (ionizable lipid), additional lipids and two RNA drug substances.
Estimated mean $t_{1/2}$ range, 16.8 – 21.3 h.
Lower limit of quantitation is 10 ng/mL.

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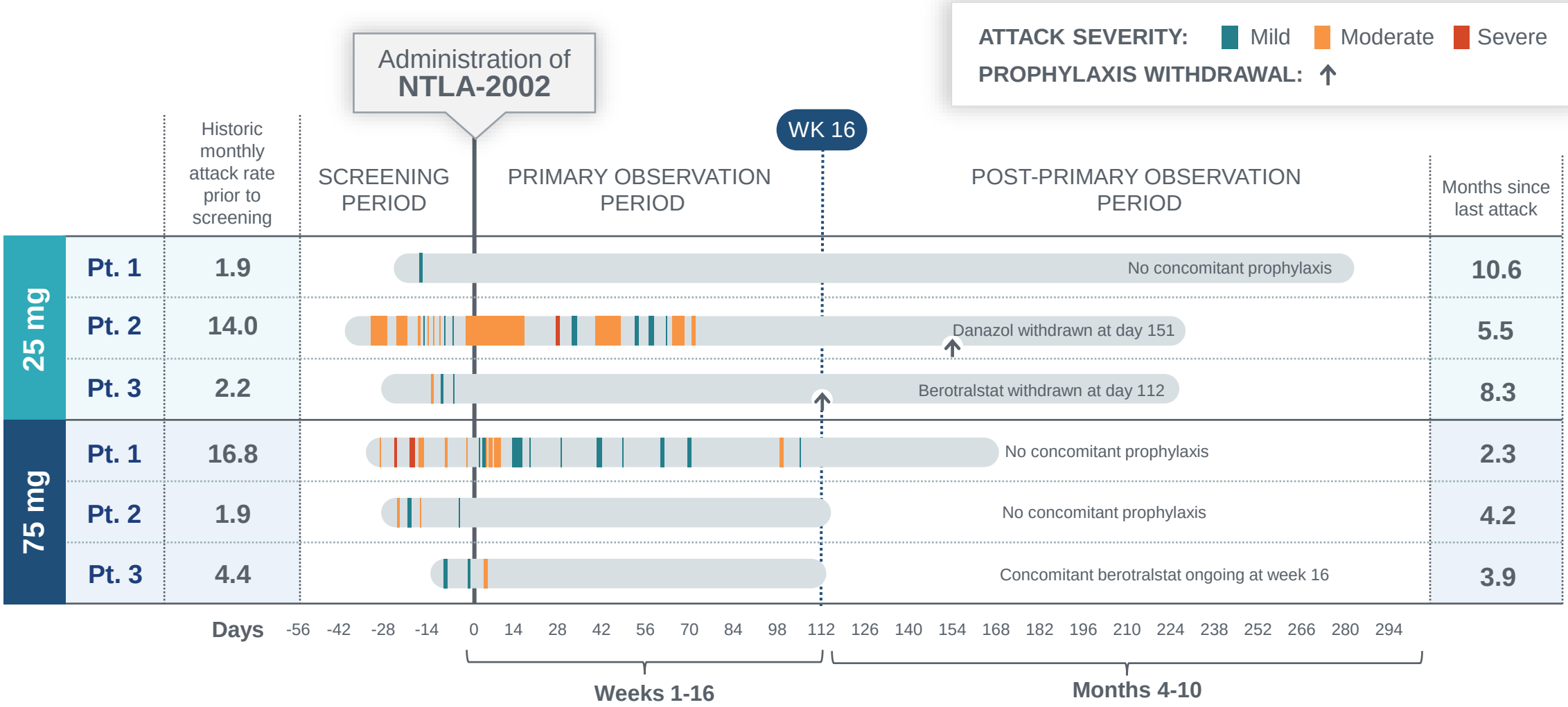
All patients have an ongoing attack-free interval with range of 2.3 to 10.6 months



Clinically meaningful reductions in monthly attack rate were observed across dose levels
Week 1-16: 91% (25 mg) and 78% (75 mg)
Week 5-16: 89% (25 mg) and 89% (75 mg)

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

- NTLA-2002 was generally well tolerated; all AEs were of mild or moderate severity
- Mean plasma kallikrein reductions of 65% (25 mg), 81% (50 mg), and 92% (75 mg) were observed at nadir, with responses persisting for the duration of follow-up
- Strong correlation observed between both reduction in plasma kallikrein concentration and kallikrein activity
- Exposure to NTLA-2002 demonstrated dose dependence and rapid clearance
- All patients in 25 mg and 75 mg cohorts have an ongoing attack-free interval of 2.3 to 10.6 months
- Patients who discontinued prophylactic therapy after NTLA-2002 infusion remained attack-free

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

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