

# ***In vivo* CRISPR/Cas9 editing of KLKB1 in patients with HAE**

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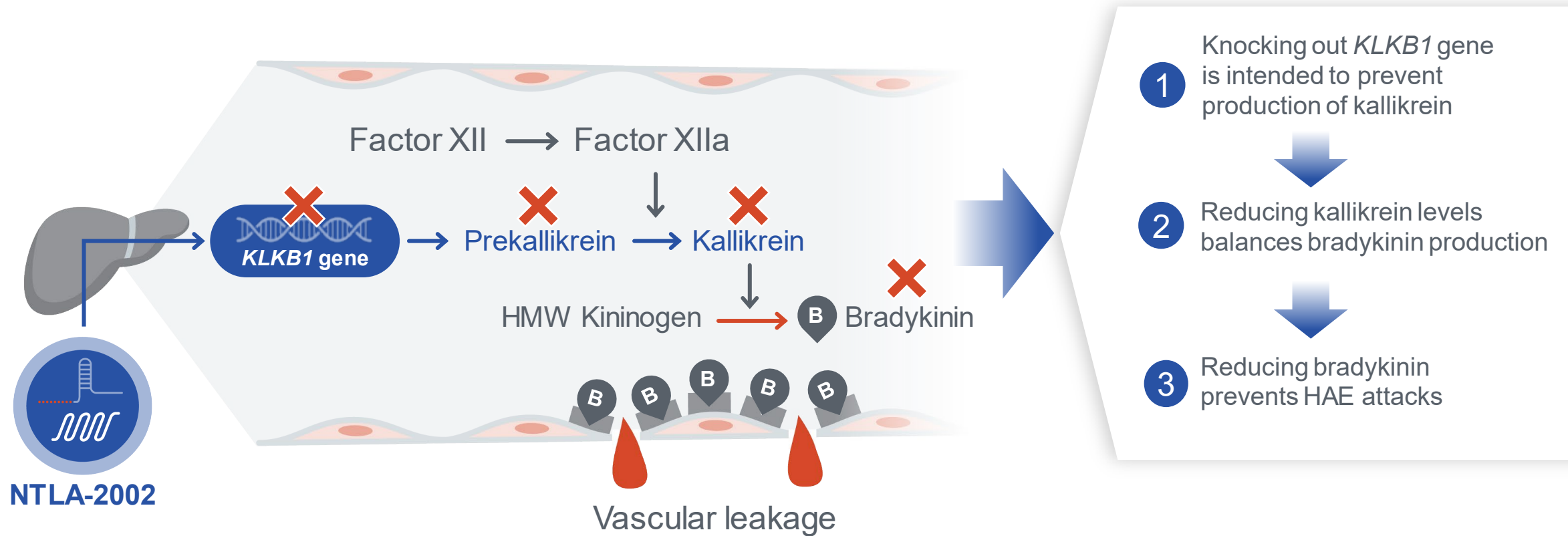
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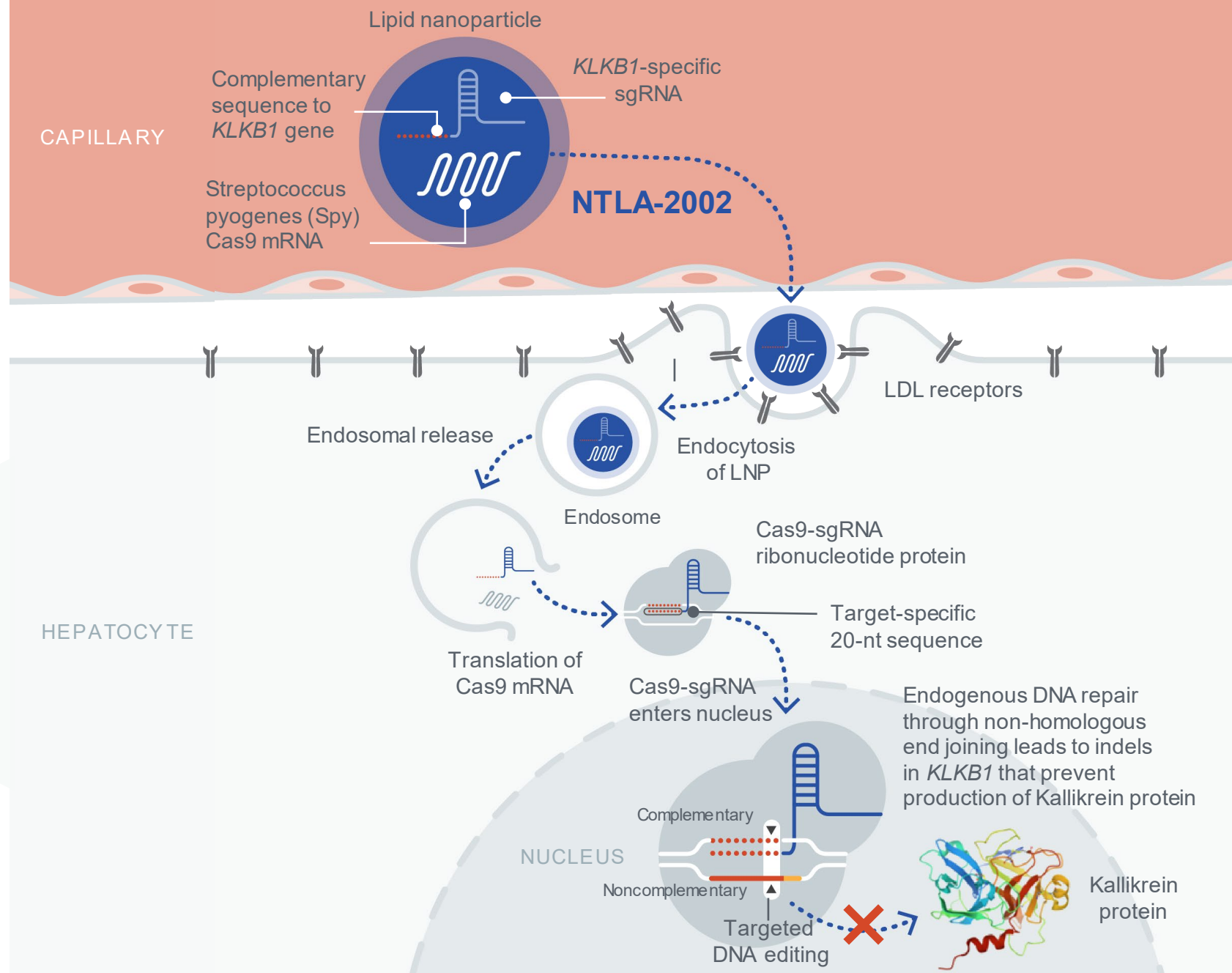
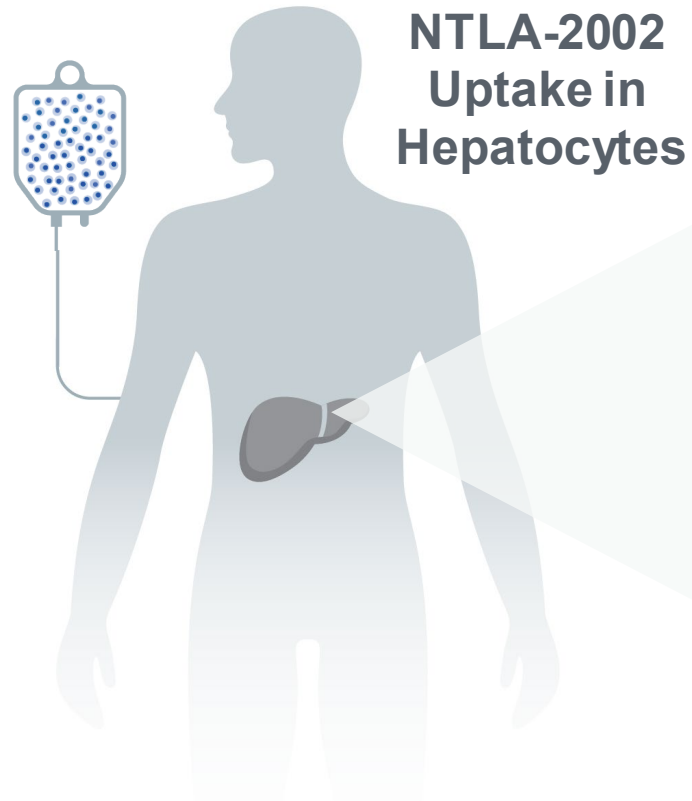
# Targeting *KLKB1* gene expression for long-term prophylaxis of HAE attacks



NTLA-2002

**Kallikrein is a clinically validated therapeutic target for preventing HAE attacks**

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

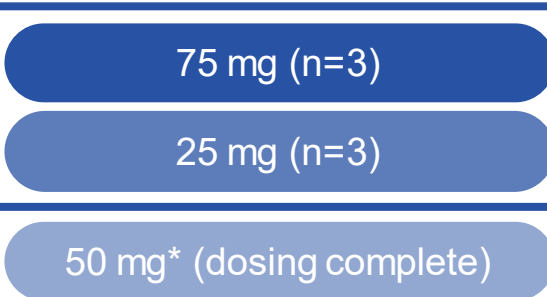
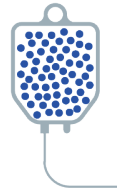


# NTLA-2002 global Phase 1/2 study design: Two-part, multi-center study of NTLA-2002 in adults with HAE Types I and II

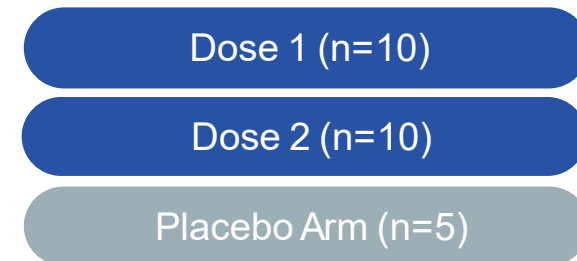
Today's interim data cover  
the first six patients  
(Data cut-off: 27 July 2022)

## PHASE 1 Open-label, single-ascending dose

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



## PHASE 2 Expansion study to confirm recommended dose



### 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)

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Clinical efficacy (attacks through week 16)

### OTHER OBJECTIVES

PD, safety & tolerability, PK, QoL

# 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	75 mg n = 3	All patients N = 6
<b>Median Age, years</b> (Min, Max)	30 (26, 52)	45 (27, 49)	38 (26, 52)
<b>Sex, n (%)</b> Male Female	3 (100%) –	2 (67%) 1 (33%)	5 (83%) 1 (17%)
<b>Median Weight, kg</b> (Min, Max)	83 (78, 135)	72 (64, 84)	81 (64, 135)
<b>HAE Type, n (%)</b> Type I Type II	2 (67%) 1 (33%)	2 (67%) 1 (33%)	4 (67%) 2 (33%)

## Patient reported HAE attack history

Parameter	25 mg n = 3	75 mg n = 3	All patients N = 6
<b>Prior Use of Prophylaxis, n (%)</b>			
Yes	3 (100%)	3 (100%)	6 (100%)
No	–	–	–
<b>Historical Monthly Attack Rate</b>			
Mean (SD)	6.0 (6.9)	7.7 (8.0)	6.8 (6.8)
<b>Typical Attack Severity, n (%)</b>			
Mild	1 (33%)	1 (33%)	2 (33%)
Moderate	1 (33%)	1 (33%)	2 (33%)
Severe	1 (33%)	1 (33%)	2 (33%)

# NTLA-2002 was generally well-tolerated across both dose levels

- **Across both dose levels, the most frequent adverse events were fatigue and infusion-related reactions**
  - Majority of treatment emergent adverse events were mild in severity with 67% (n = 4) and 33% (n = 2) of patients reporting a maximal adverse event severity of Grade 1 or 2, respectively
  - All infusion-related reactions were considered mild (n = 4) or moderate (n = 1), resolving without clinical sequelae
  - All patients received a complete study dose of NTLA-2002
- **No clinically significant laboratory findings observed**
  - Transient Grade 1 elevations in AST (n = 3) and ALT (n = 2) were observed
  - No increases in activated partial thromboplastin time
- **No treatment emergent SAEs or  $\geq$  Grade 3 AEs were observed**



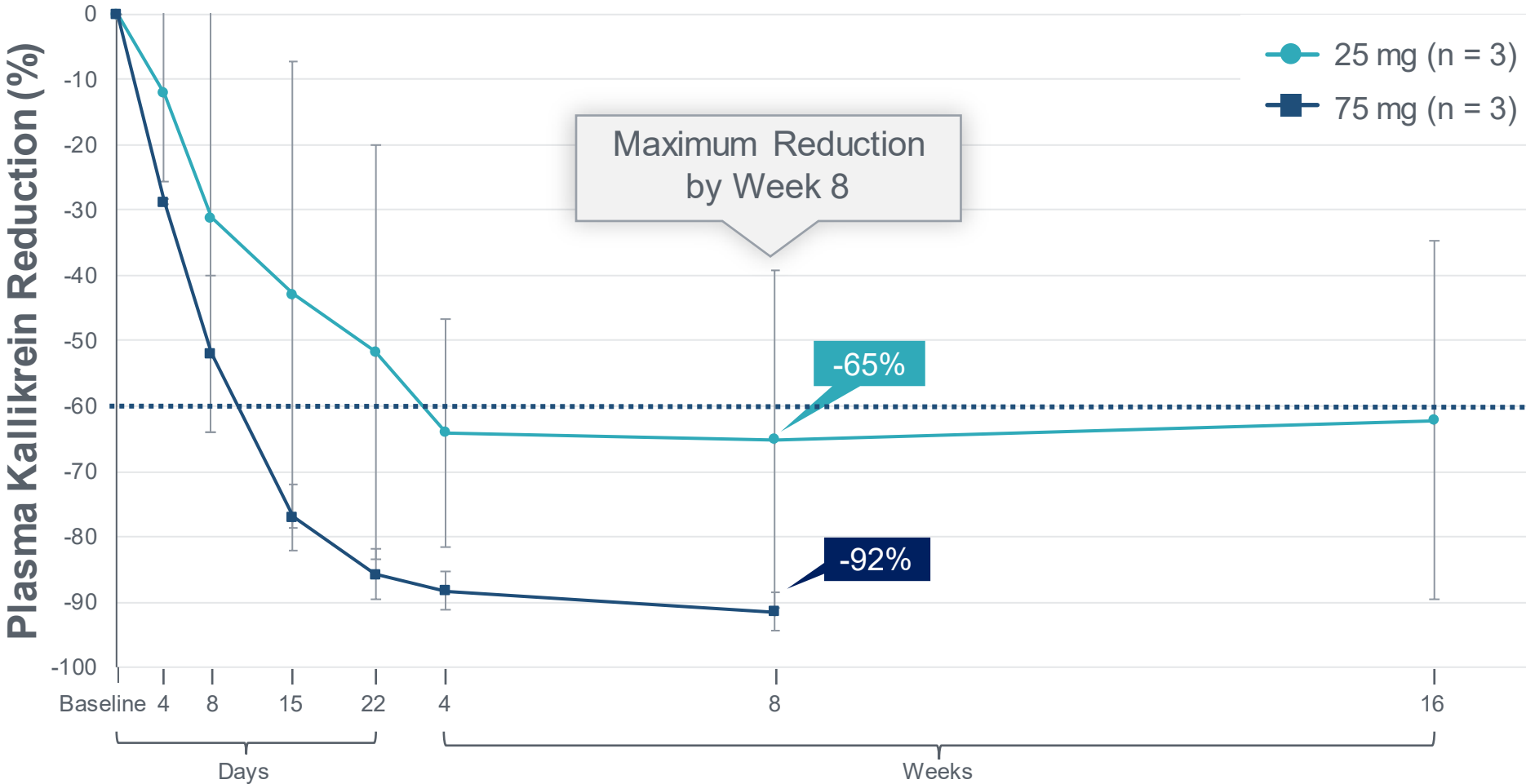
## Majority of adverse events were mild in severity

Adverse events occurring in ≥ 2 patients	Cohort 1 (25 mg) n=3		Cohort 2 (75 mg) n=3		All Patients N=6	
	Gr. 1	Gr. 2	Gr. 1	Gr. 2	Gr. 1	Gr. 2
Infusion-related reaction	2	–	2	1	4	1
Fatigue	1	–	2	–	3	–
Headache	–	–	2	–	2	–
COVID-19	2	–	–	–	2	–
Upper respiratory tract infection	1	–	1	–	2	–

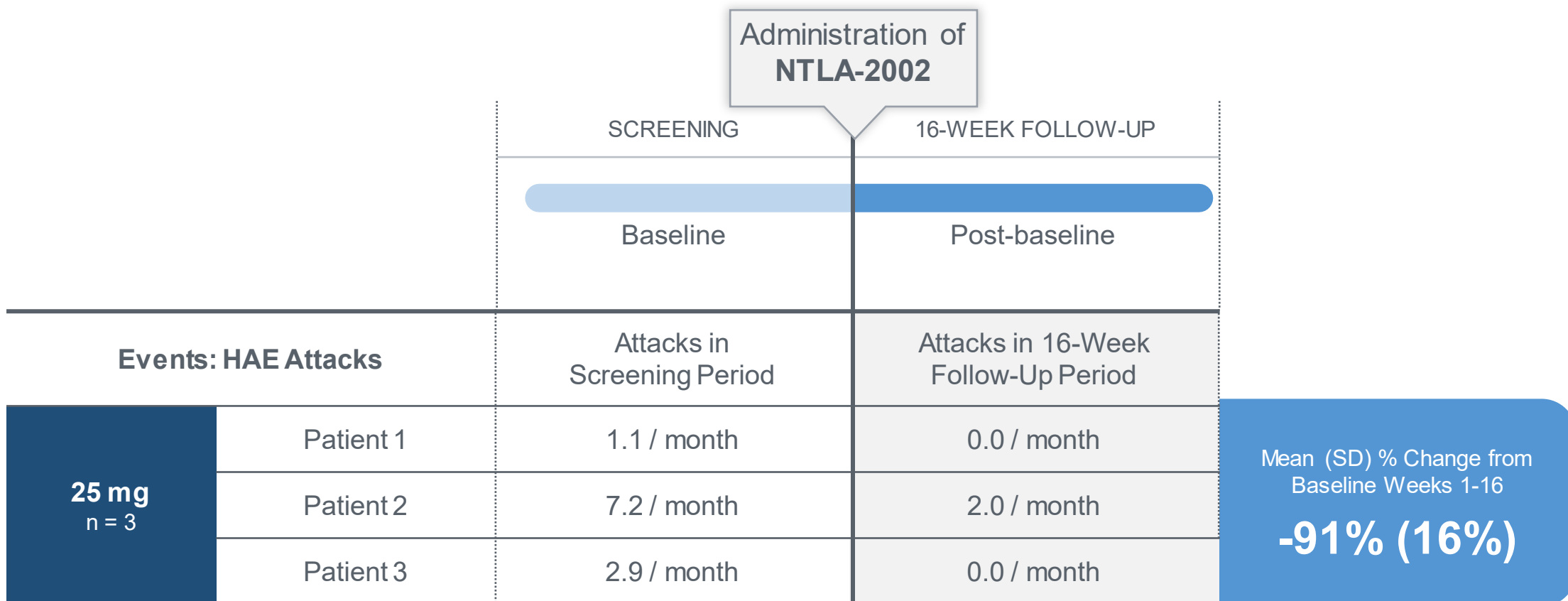
All other AEs (abdominal pain, chest injury, soft tissue injury, disease prodromal stage, rhinitis, diarrhea, vomiting, somnolence, myalgia, insomnia, oropharyngeal pain, viral upper respiratory tract infection) were reported in one patient.

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

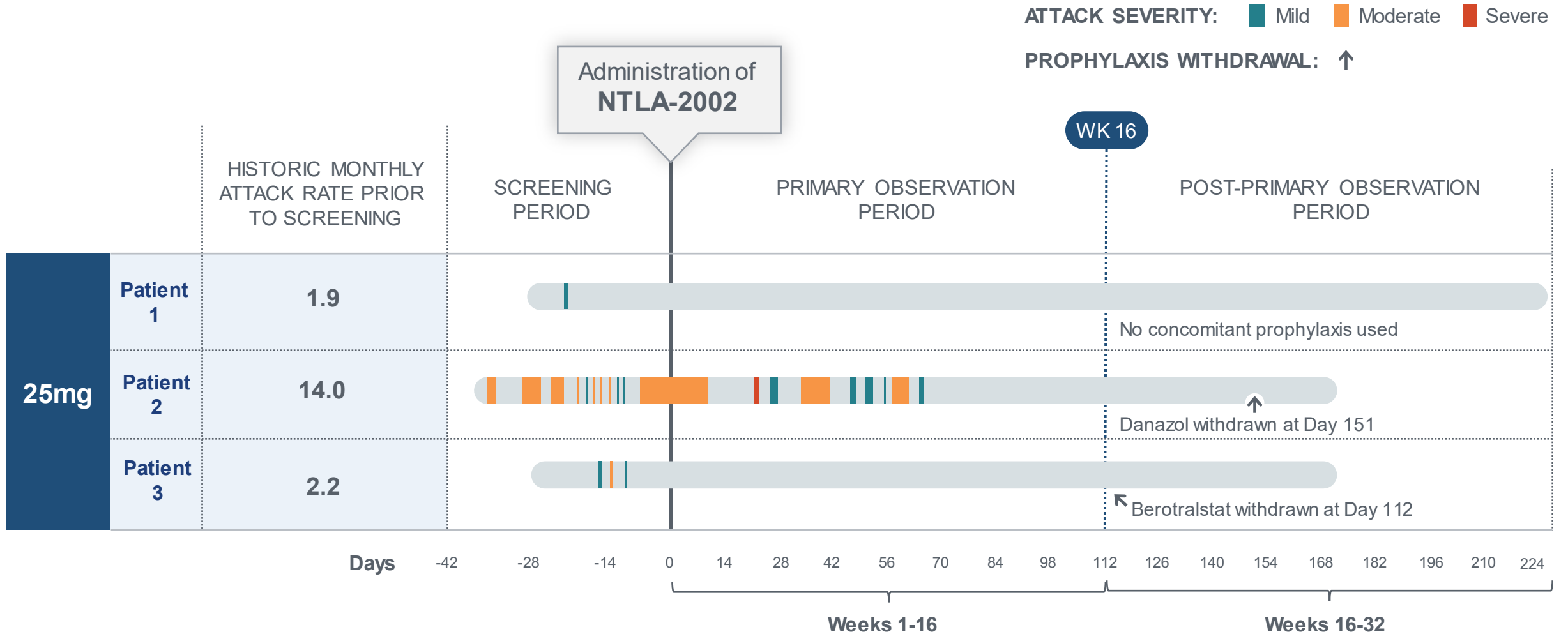
Mean (SD) % Plasma Kallikrein Reduction by Dose Level



# 91% reduction in investigator-confirmed monthly attack rate observed at 25 mg dose through pre-specified 16-week follow-up period



# Two of three patients have remained attack-free since administration with NTLA-2002: All patients have been attack-free since week 10



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

- Mean plasma kallikrein reductions of 65% (25 mg) and 92% (75 mg) achieved at week 8
- Mean >90% reduction in HAE attacks in the 25 mg cohort through week 16
  - All patients in the 25 mg cohort achieved complete attack control
  - Patients on prior prophylactic therapy were able to discontinue and remain attack free
- NTLA-2002 was generally well-tolerated across both dose levels; all AEs were of mild or moderate severity
- Based on these observations of robust pharmacodynamic responses and preliminary evidence of efficacy, no further dose escalation is planned
  - A 50 mg cohort has been enrolled to further inform phase 2 dose selection

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

# Acknowledgements

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