NTLA-2002 Interim Clinical Data Update from Ongoing First-in-Human Study

June 12, 2023

Shanna
Living with hereditary angioedema

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Agenda

Welcome

Introduction

Dr. John Leonard

Chief Executive Officer, Intellia Therapeutics

Review of NTLA-2002 Interim Clinical Data

Dr. David Lebwohl

Chief Medical Officer, Intellia Therapeutics

Overview of Current HAE Treatment Landscape and Unmet Medical Need

Dr. Timothy J. Craig

Tenured Professor of Medicine, Pediatrics and Biomedical Sciences; Penn State University

Closing Remarks and Q&A Session

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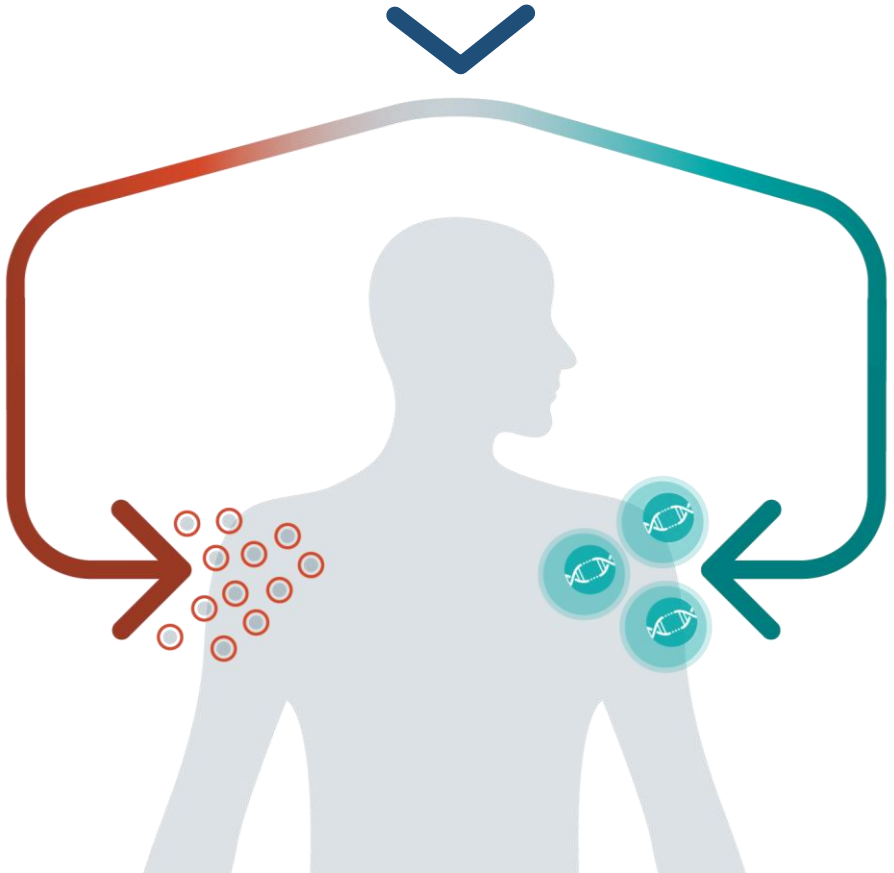
Advancing a full-spectrum genome editing company

CRISPR-based Modular Platform

EMPLOY NOVEL EDITING AND DELIVERY TOOLS



In Vivo

CRISPR *is* the therapy

FIX THE TARGET GENE

Genetic diseases

Ex Vivo

CRISPR *creates* the therapy

REWIRE & REDIRECT CELLS

Immuno-oncology

Autoimmune diseases

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NTLA-2002 for Hereditary Angioedema (HAE)

About HAE

- Genetic disease characterized by recurring, severe and unpredictable swelling in various parts of the body
- Despite availability of existing therapies, significant unmet need persists
- Chronic dosing is required with current treatment options

Our Approach

Knock out *KLKB1* gene with a single dose

- Reduce kallikrein activity to prevent attacks

Key Advantages

Potential to:

- Be a single-dose treatment
- Provide extensive and continuous reduction in kallikrein activity
  - Intended to minimize the risk of breakthrough attacks
- Eliminate significant treatment burden

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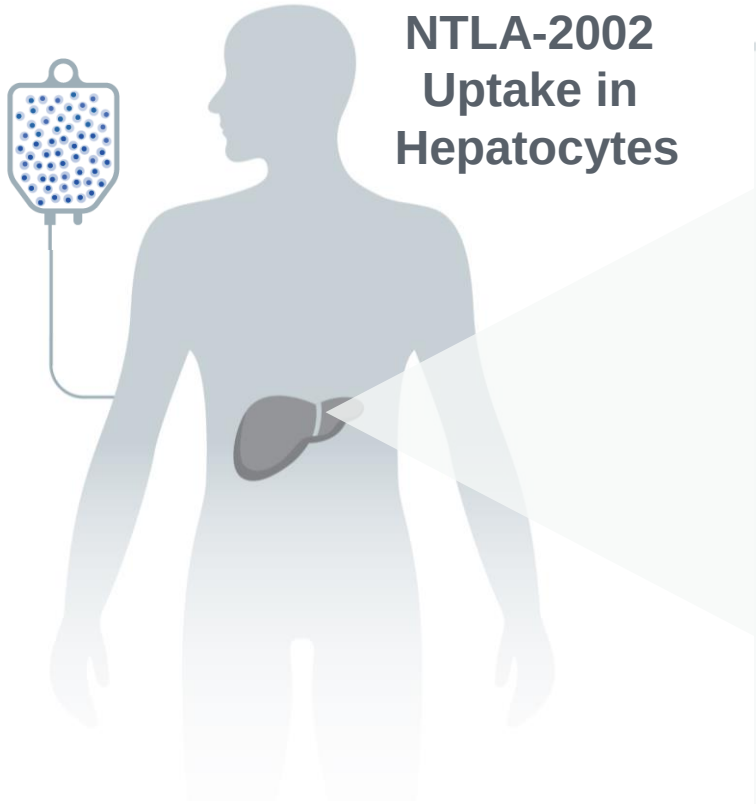
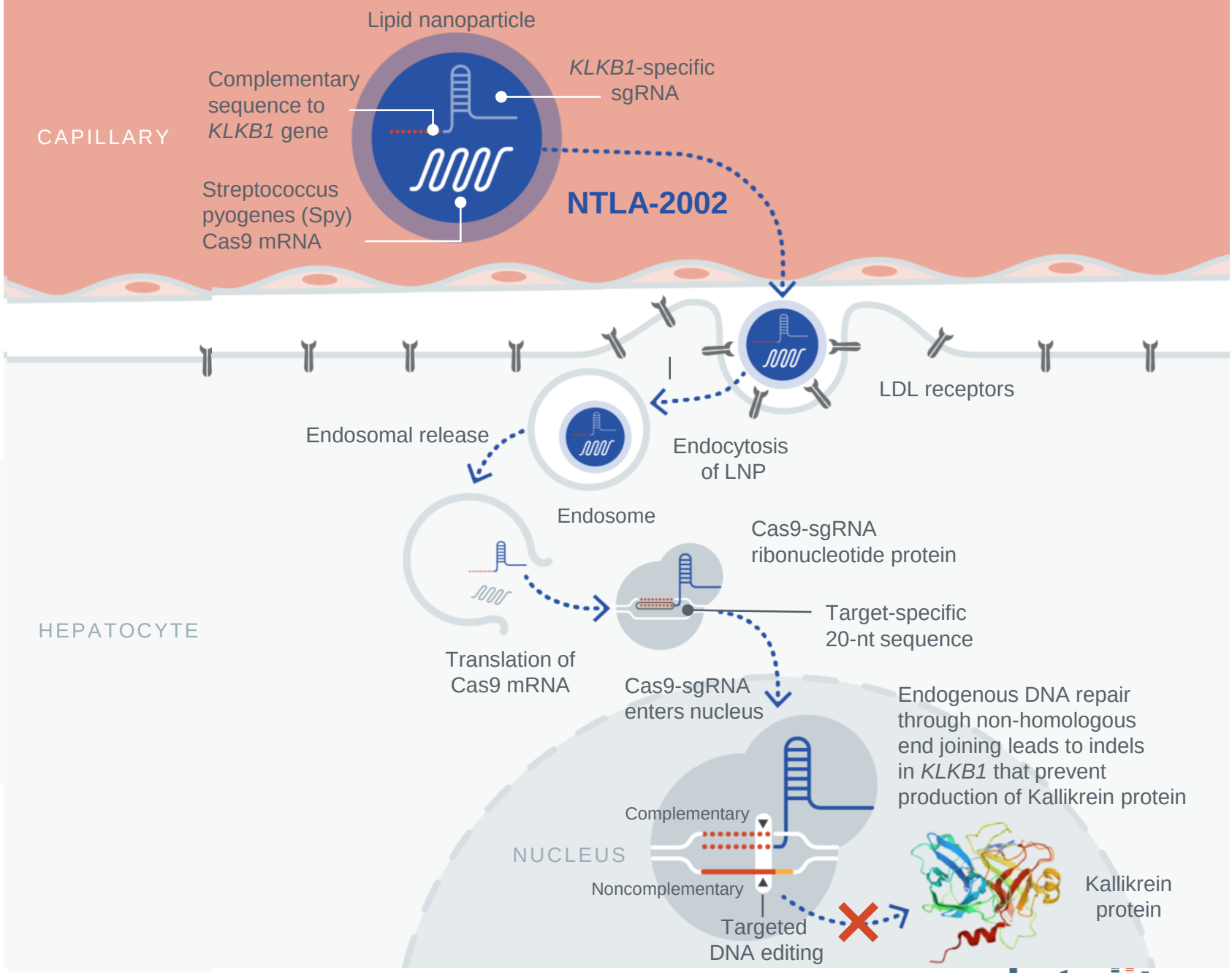
NTLA-2002 is a novel, investigational CRISPR/Cas9-based *in vivo* gene editing therapy



NTLA-2002 Uptake in Hepatocytes



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

This presentation includes information on an investigational product not yet approved by regulatory authorities.

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NTLA-2002 global Phase 1/2 study design:
Two-part, multi-center study of NTLA-2002 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)

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.

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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

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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	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 (%)				
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 administration.
SD, standard deviation.

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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	3	–	1	–	1	–	5	–
Upper respiratory tract infection	1	–	1	–	2	–	4	–
Oropharyngeal pain	2	–	–	–	1	–	3	–
Abdominal pain	1	–	–	–	1	–	2	–
Headache	–	–	–	–	2	–	2	–
Viral upper respiratory tract infection	–	–	–	–	2	–	2	–

No clinically significant laboratory findings observed

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

Median duration of follow-up for all patients was 9.0 months (range, 5.6-14.1 months)

Patients counted once per row with highest grade reported.
Gr., Grade (NCI-CTCAE version 5.0); **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event

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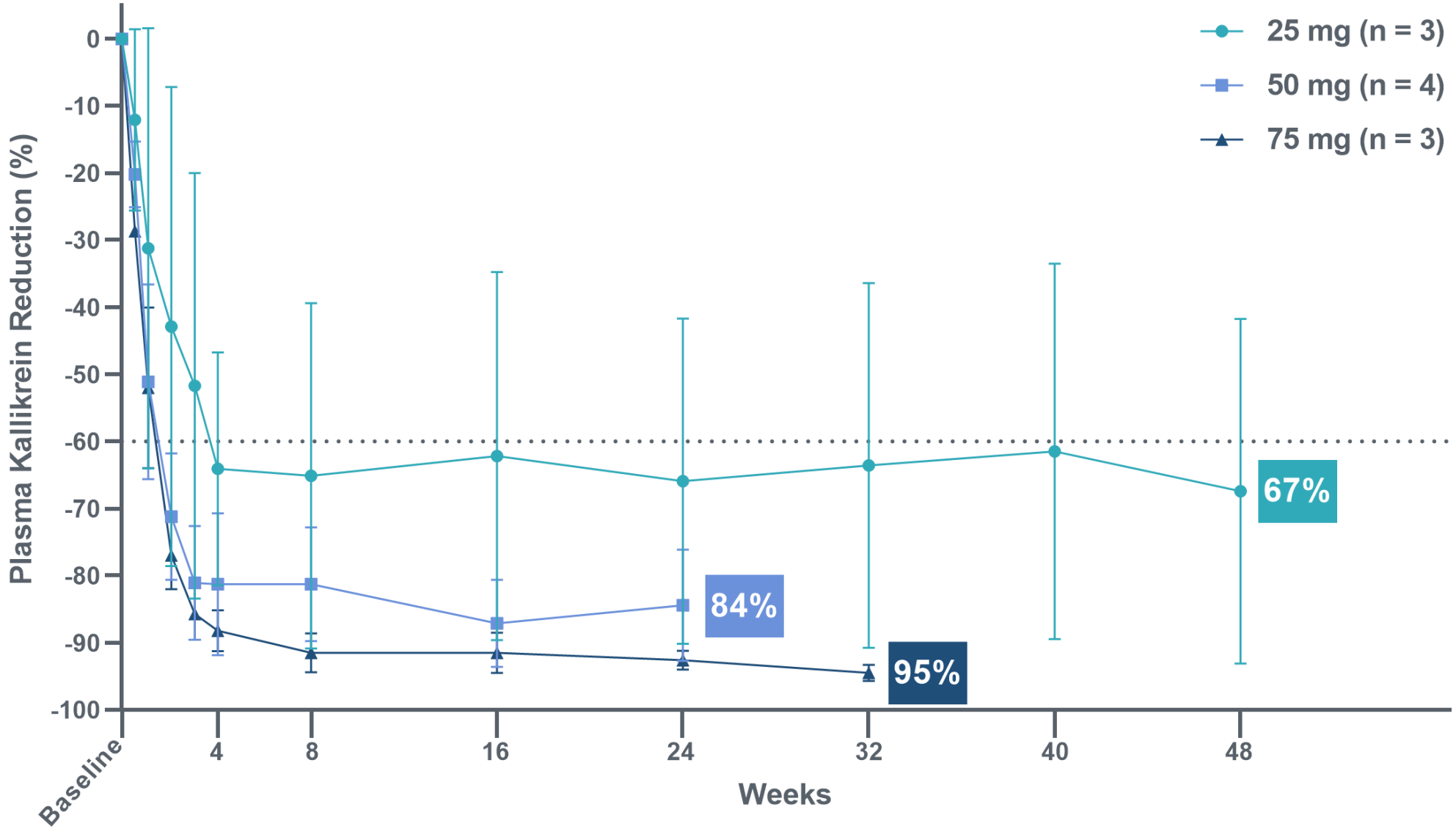
NTLA-2002 resulted in dose-dependent and durable reductions in plasma kallikrein protein



Data are mean values with standard deviation.
Dashed line represents targeted minimum reduction.
Mean percentage reduction callout on graph refers to last measurement as of the data cutoff date.

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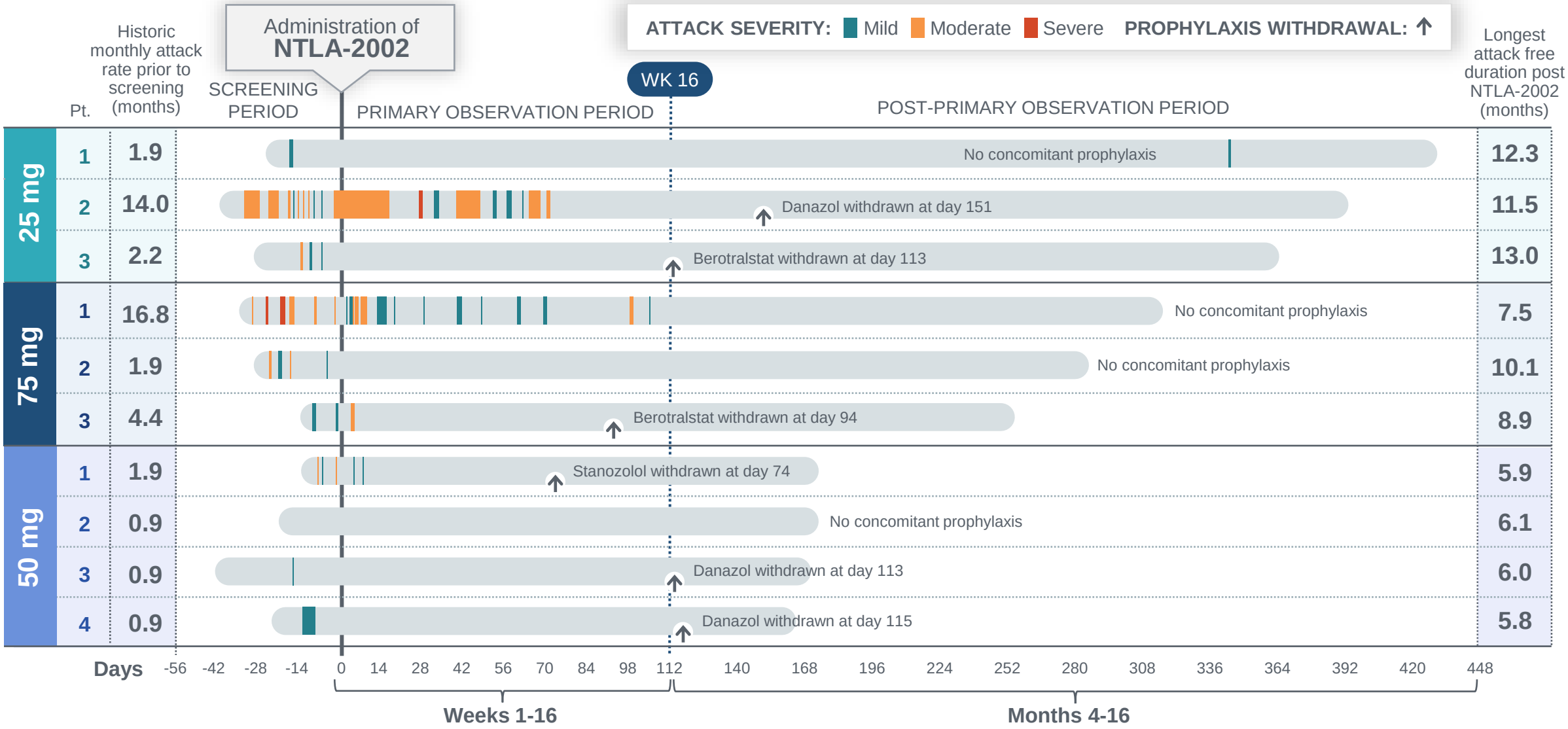
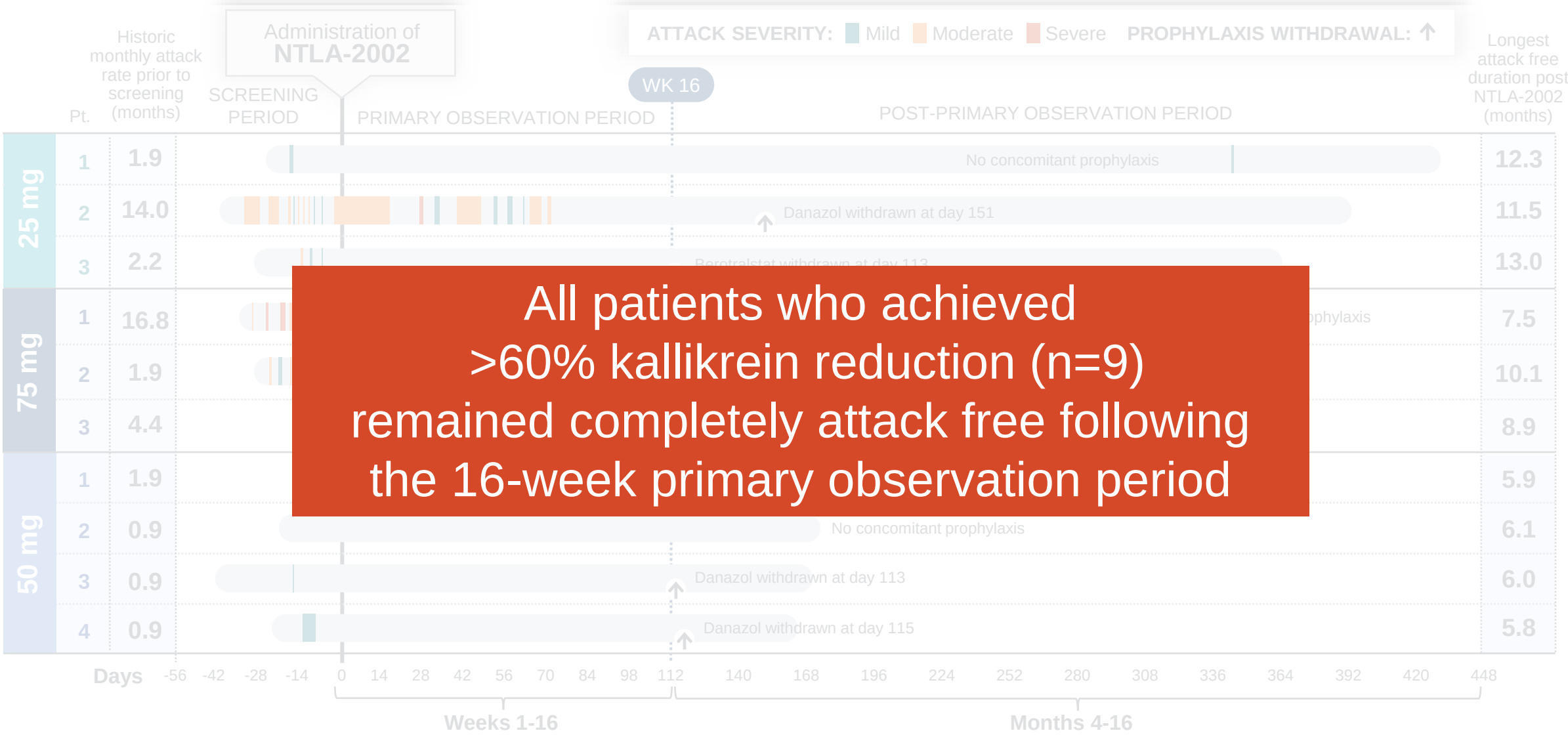
Robust and durable HAE attack reductions observed in all patients after a single dose of NTLA-2002



Robust and durable HAE attack reductions observed in all patients after a single dose of NTLA-2002



All patients who achieved >60% kallikrein reduction (n=9) remained completely attack free following the 16-week primary observation period

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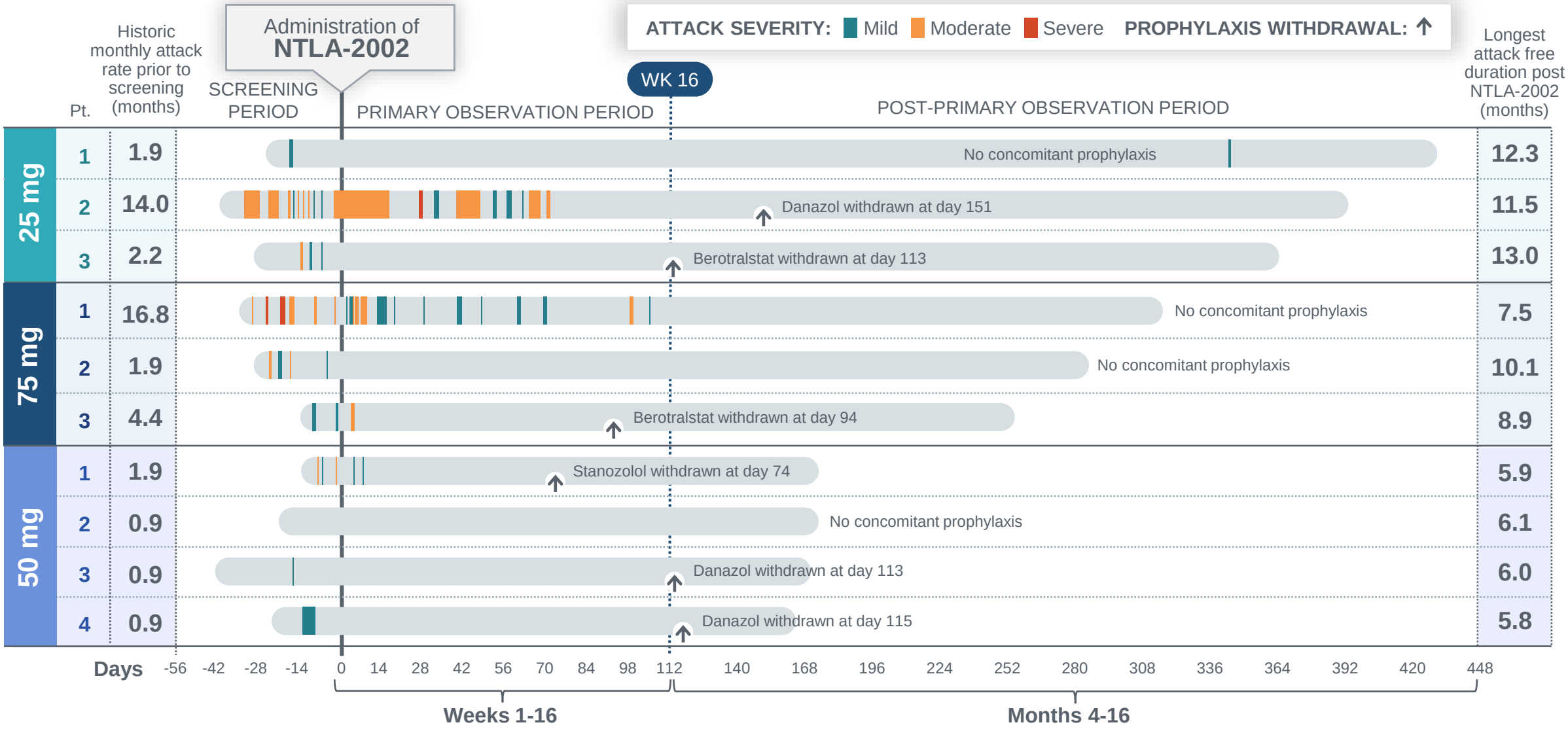
Robust and durable HAE attack reductions observed in all patients after a single dose of NTLA-2002



Across all patients, a single dose of NTLA-2002 led to a 95% mean reduction in monthly HAE attack rate through the latest follow-up

	25 mg n = 3	50 mg n = 4	75 mg n = 3	All patients N = 10
Week 1-16	-91% (16%)	-97 (5%)	-80% (30%)	-89 (19%)
Week 5-16	-89% (19%)	-100% (0%)	-87% (23%)	-92% (16%)
Week 1-24	-94% (11%)	-98% (3%)	-86% (20%)	-93% (13%)
On-study period	-95% (4%)	-98% (3%)	-93% (11%)	**-95% (6%)**

Data are mean % change from baseline (standard deviation).
Baseline is defined as up to 42 days screening period prior to the administration of NTLA-2002.
On-study period is defined as the time from the dosing of NTLA-2002 through the last HAE attack assessment as of the data cutoff date.
For the 50 mg cohort, one of four patients was not evaluable as they reported zero attacks during the screening period.

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Extended Phase 1 data reinforce the potential of NTLA-2002 to be a functional cure for people living with HAE

- Robust and durable attack reductions observed in all patients after a single dose of NTLA-2002
  - Across all patients, a single dose of NTLA-2002 led to 95% mean reduction in monthly HAE attack rate through the latest follow-up assessment; 89% mean reduction in the 16-week primary observation period
  - Longest attack-free interval is 13.0 months and ongoing through the latest follow-up assessment
  - All patients were well controlled, with 9 out of 10 patients remaining completely attack free, following the 16-week observation period.
- Patients who discontinued concomitant long-term prophylaxis after administration of NTLA-2002 remained well-controlled, with no subsequent HAE attacks
- NTLA-2002 resulted in dose-dependent and durable reductions in plasma kallikrein protein
- NTLA-2002 was generally well-tolerated at all doses; all AEs were either Grade 1 or 2

Phase 2 portion of the study underway with enrollment expected to be completed in the second half of 2023

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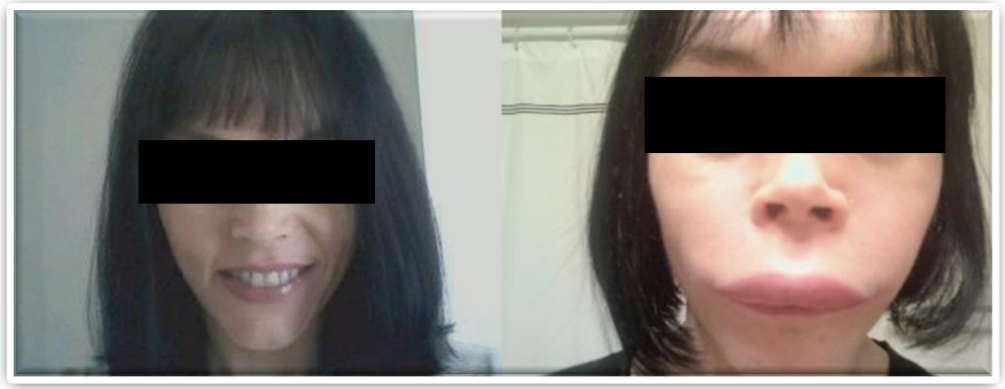
The Future of Hereditary Angioedema

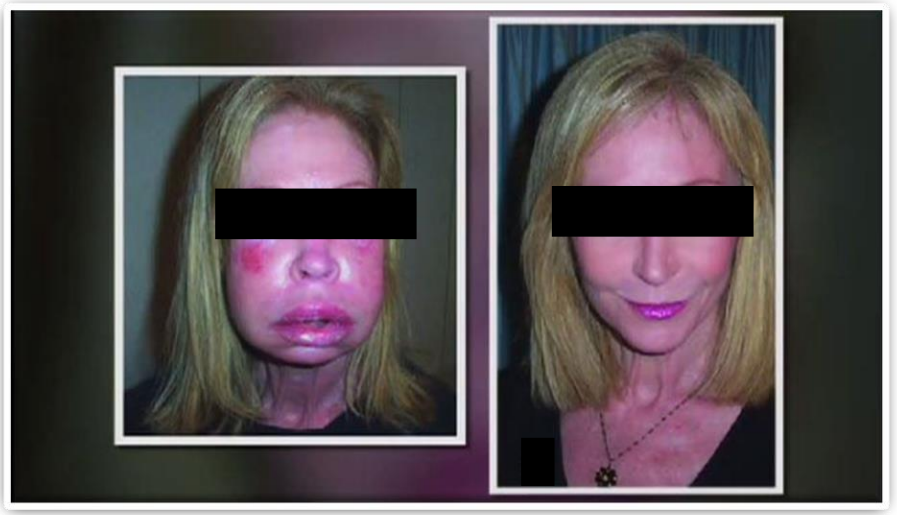
Timothy Craig, FAACAI, FAAAAI, FACP, FACOI
Tenured Professor Medicine, Pediatrics, Biomedical Sciences
Penn State University Distinguished Educator
Director – ACARE Center of Excellence for Angioedema
Director – Alpha-1-Antitrypsin Deficiency Center
Medical Advisory Board for the HAE-A
Director of AI and Respiratory Clinical Research
Senior Advisor, Vinmec Allergy Immunology, Hanoi, VN
Honorary Board of Directors, Lam Dong Medical College

Conflicts of Interest

Company	Research	Consultant	Speaker	Travel
CSL Behring	x	x	x	x
Ionis	x	x		
Takeda	x	x	x	x
Biocryst		x		x
BioMarin	x	x	x	
Kalvista	x	x		
Pharvaris	x			
Intellia	x	x	x	x

Clinical Presentation of HAE





Evolution of HAE Treatment: A Tale of 3 Generations Over 16 Years

- Pre-2008 → Grandmother
  - Rescue: Fresh Frozen Plasma – required ED administration; unreliable results
  - Prophylaxis: Androgens – required yearly assessment for toxicity; ill advised to use in females
- 2008-2018 → Mother
  - Rescue: Self administration – subcutaneous and intravenous
  - Prophylaxis: Intravenous injections twice a week
- 2018-present → Child
  - Rescue: Self administration – subcutaneous and intravenous
  - Prophylaxis: Haegarda: injection twice a week
    Takhzyro: injection twice a month
    Orladeyo: oral, daily

FDA-Approved On-Demand Therapeutic Options

Therapy	Patients	Self Administered	Mechanism	Notable Adverse Events
Ecallantide	≥12 years of age	No (sc)	Inhibits plasma kallikrein	Uncommon antidrug antibodies, risk of anaphylaxis
Icatibant	≥18 years of age*	Yes (sc)	Bradykinin B2 receptor antagonist	Common discomfort at injection site
C1-INH				
Plasma-derived	Children and adults†	Yes (iv)	Inhibits plasma kallikrein, coagulation factors XIIa, XIIf and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Rare anaphylaxis
Recombinant	Adolescents and adults†	Yes (iv)	Inhibits plasma kallikrein, coagulation factors XIIa, XIIf and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin	Uncommon risk of anaphylaxis in rabbit-sensitized persons

* In Europe, approved in ≥2 years of age.
† Also approved in Europe.

C1-INH: C1-esterase inhibitor.
MASP-1, -2, mannose-binding lectin-associated serine proteases 1, 2.

Maurer M, et al. *Allergy.* 2022;Jan 10. Online ahead of print.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.

First-Line Long-Term Prophylactic Therapeutic Options

Therapy	Patients	Approved Recommended Dose	Most Common Adverse Events
C1-INH			
Plasma-derived (iv)	≥6 years of age	Pediatric: 500 U every 3 to 4 days Adolescents/adults: 1000 U every 3 to 4 days (may increase to up to 2500 U)	Headache, nausea, rash, vomiting, and fever
Plasma-derived (sc)	≥6 years of age	60 IU/kg twice weekly	Injection site reactions, hypersensitivity, nasopharyngitis, and dizziness
Lanadelumab (sc) (plasma kallikrein inhibitor monoclonal antibody)	≥2 years of age	300 mg every 2 weeks, reduced dose from 2 to 12 years of age.	Injection site reactions, upper respiratory infections, headache, rash, myalgia, dizziness, and diarrhea
Berotralstat (oral) (plasma kallikrein inhibitor)	≥12 years of age	150 mg qd taken with food	Abdominal pain, vomiting, diarrhea, back pain, and gastroesophageal reflux disease

C1-INH: C1-esterase inhibitor.

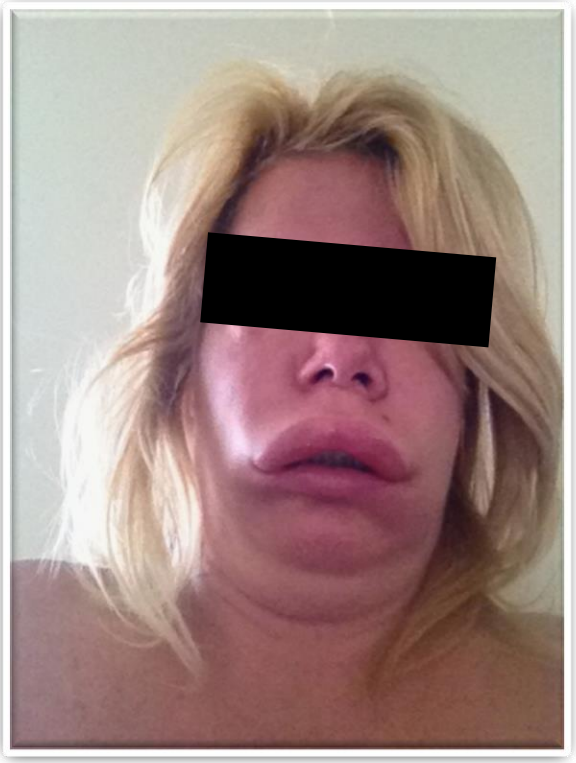
Maurer M, et al. *Allergy.* 2022;Jan 10. Online ahead of print.
Busse PJ, et al. *J Allergy Clin Immunol Pract*. 2021;9:132-150.

Rationale for the Development of New HAE Therapies

- Improve treatment and outcomes for patients with HAE
  - Increased efficacy
  - Improved tolerability
  - Longer lasting prophylactic treatments
- Reduction in treatment burden
  - Improved accessibility
  - Less frequent dosing
  - Improved quality of life

Fijen LM, et al. *Clin Rev Allergy Immunol.* 2021;61:66-76.

Before Control



After Control

Future of HAE Treatment

- In the past, we focused on treating attacks
- Today, we focus on preventing attacks
- Newer medications in development aim to have increased efficacy and less frequent or burdensome dosing and administration
- My hope is that we are approaching a “relative cure” for HAE

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Q&A

NTLA-2002
Interim Clinical Data Update

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