NTLA-2002 Long-Term Phase 1 Data Update from the Ongoing Phase 1/2 Study

June 3, 2024

SHANNA
Living with hereditary angioedema type 1

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Intellia THERAPEUTICS

Agenda

Welcome

Introduction
Dr. John Leonard *Chief Executive Officer*, Intellia Therapeutics

Review of NTLA-2002 Long-Term Phase 1 Data
Dr. Hilary Longhurst *Senior Medical Officer*, Auckland District Health Board, *Honorary Associate Professor*; University of Auckland, New Zealand, trial's principal investigator in New Zealand

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Advancing a Full-Spectrum Genome Editing Company

CRISPR-Based Modular Platform

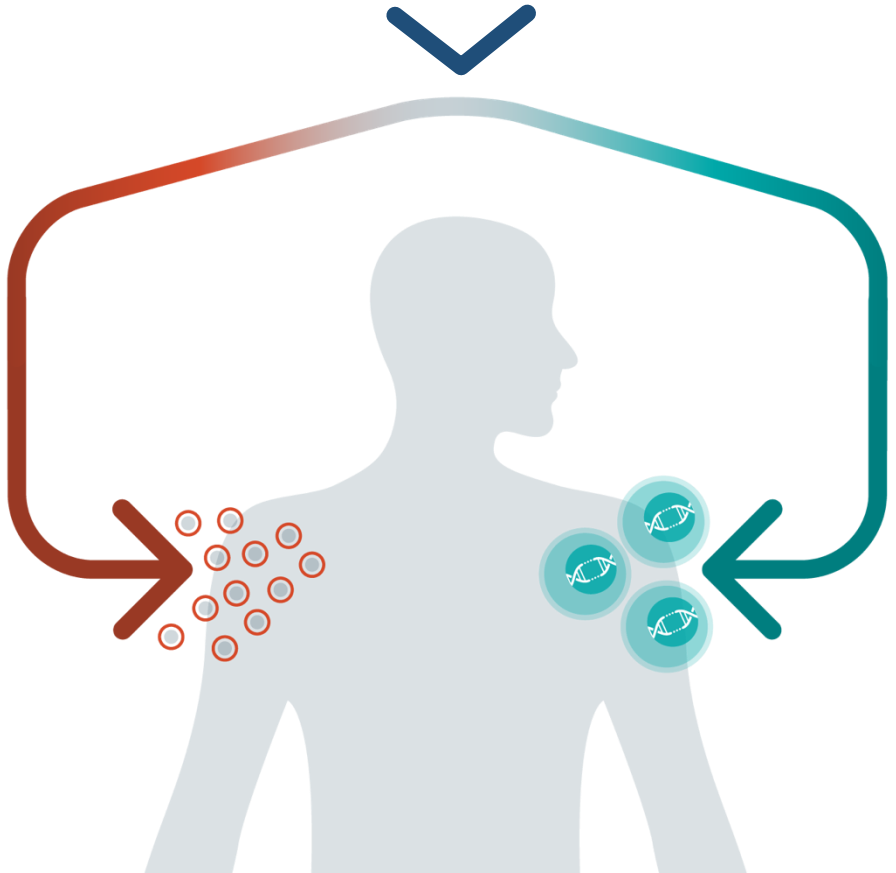
EMPLOY NOVEL EDITING AND DELIVERY TOOLS

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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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

Hilary Longhurst,[1*] Padmalal Gurugama,[2] Karen Lindsay,[1] Remy S. Petersen,[3] Lauré M. Fijen,[3] Carri Boiselle,[4] Yuanxin Xu,[4] Adele Golden,[4] James Butler,[4] Mrinal Y. Shah,[4] David Maag,[4] Danny M. Cohn[2]

[1]Te Whatu Ora/Te Toka Tumai, Auckland, New Zealand and Department of Medicine, University of Auckland, New Zealand;
[2]Cambridge University Hospitals, NHS Foundation Trust, Cambridge, UK;
[3]Amsterdam University Medical Center, Amsterdam, The Netherlands; [4]Intellia Therapeutics, Cambridge, MA, USA

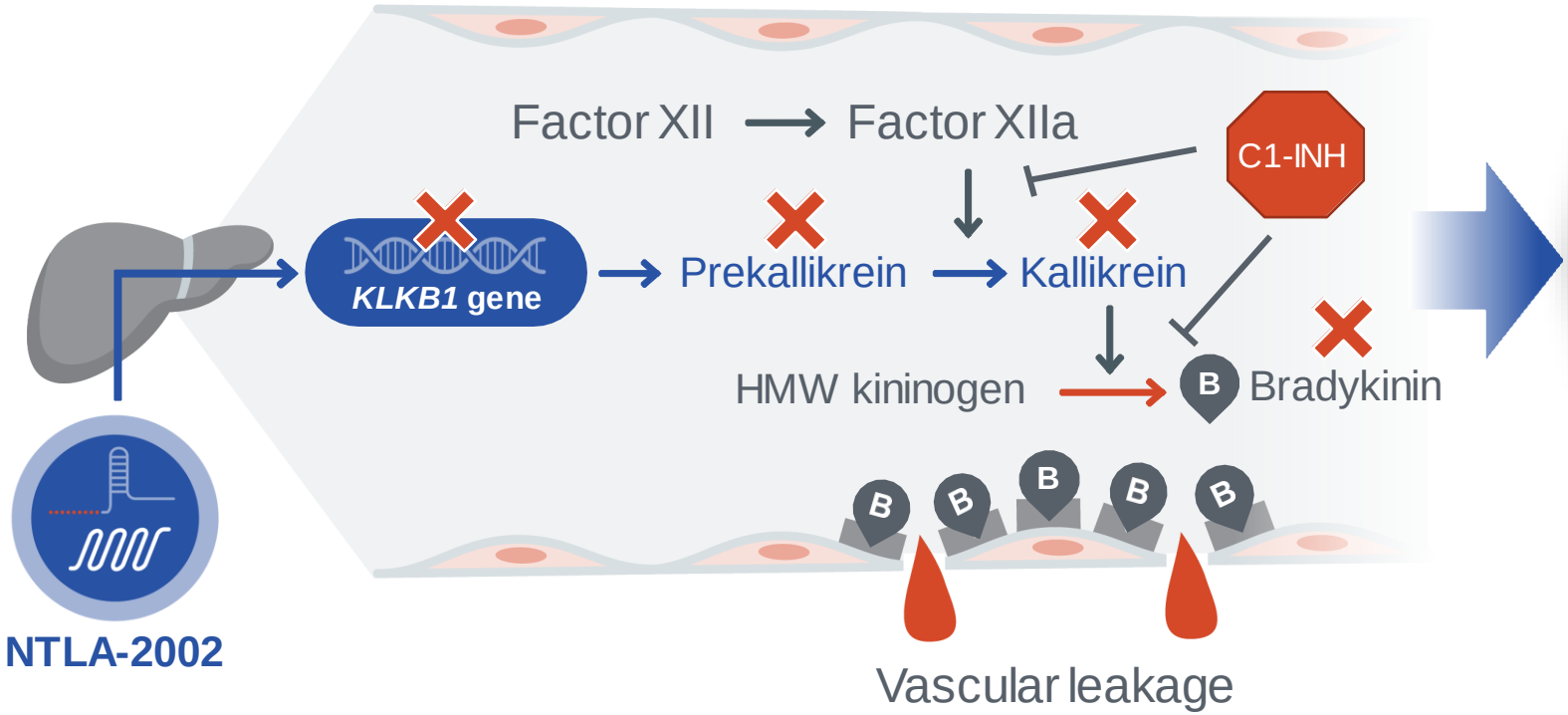
**Presenting author*

Presented at the EAACI Congress 2024, May 31-June 3, 2024, Valencia, Spain

Disclosures

Dr. Longhurst has acted as a consultant or speaker, received educational sponsorship or participated in research with BioCryst Pharmaceuticals, CSL Bering, Intellia Therapeutics, KalVista Pharmaceuticals, Pharming, and Takeda.

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

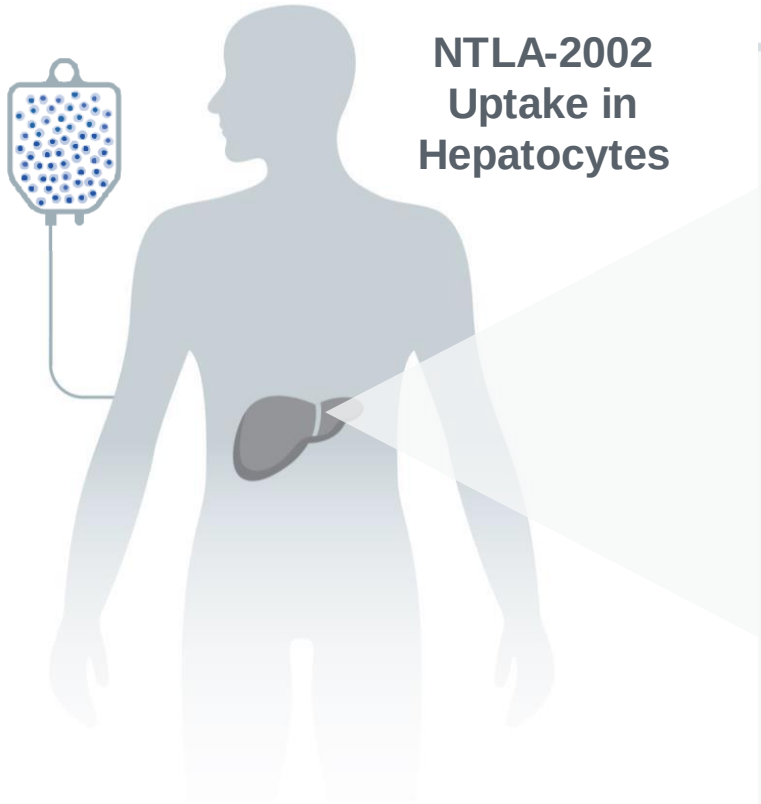


1. Knocking out *KLKB1* gene is intended to prevent production of kallikrein
2. Decreasing kallikrein rebalances pathway by reducing bradykinin production
3. Reducing bradykinin is intended to prevent HAE attacks

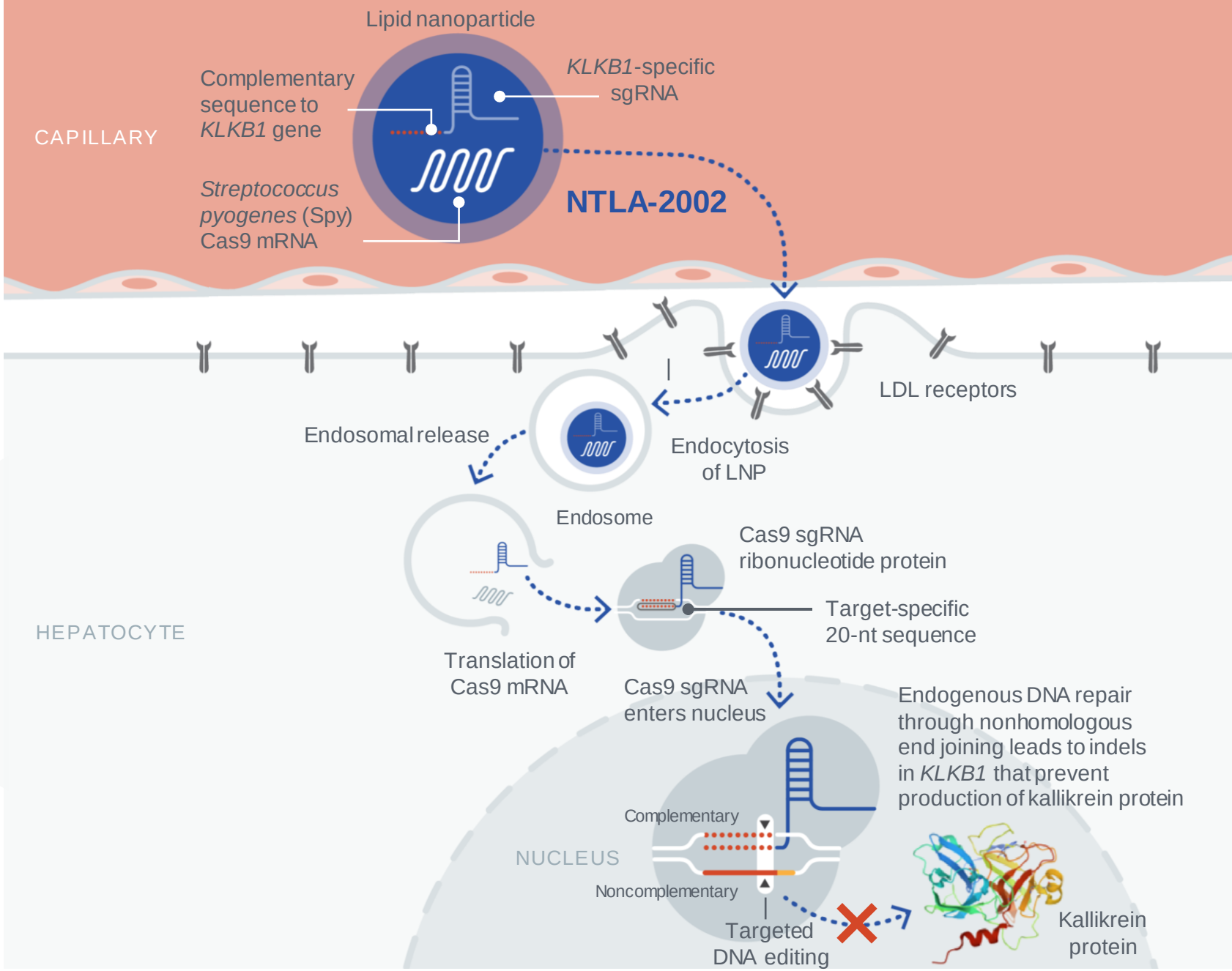
Kallikrein is a clinically validated therapeutic target for preventing HAE attacks

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.

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

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

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.
Longhurst HJ, et al. *N Engl J Med*. 2024;390:432-441.
This presentation includes data for an investigational product not yet approved by regulatory authorities.

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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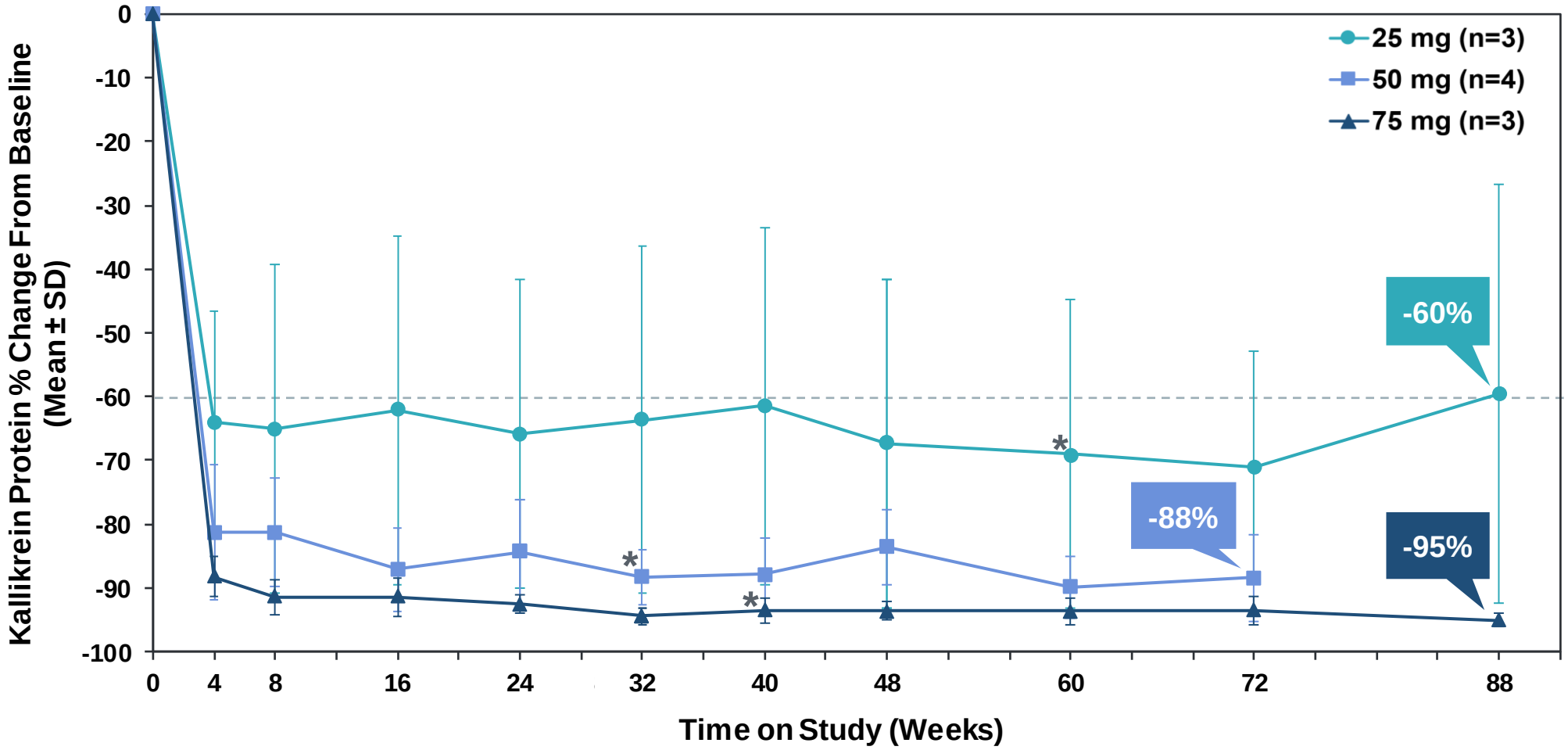
Data cutoff date: 12Feb2024.

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

Data cutoff date: 12Feb2024.

A Single Dose of NTLA-2002 Led to a 98% Mean Reduction in Monthly HAE Attack Rate Through the Latest Follow-up

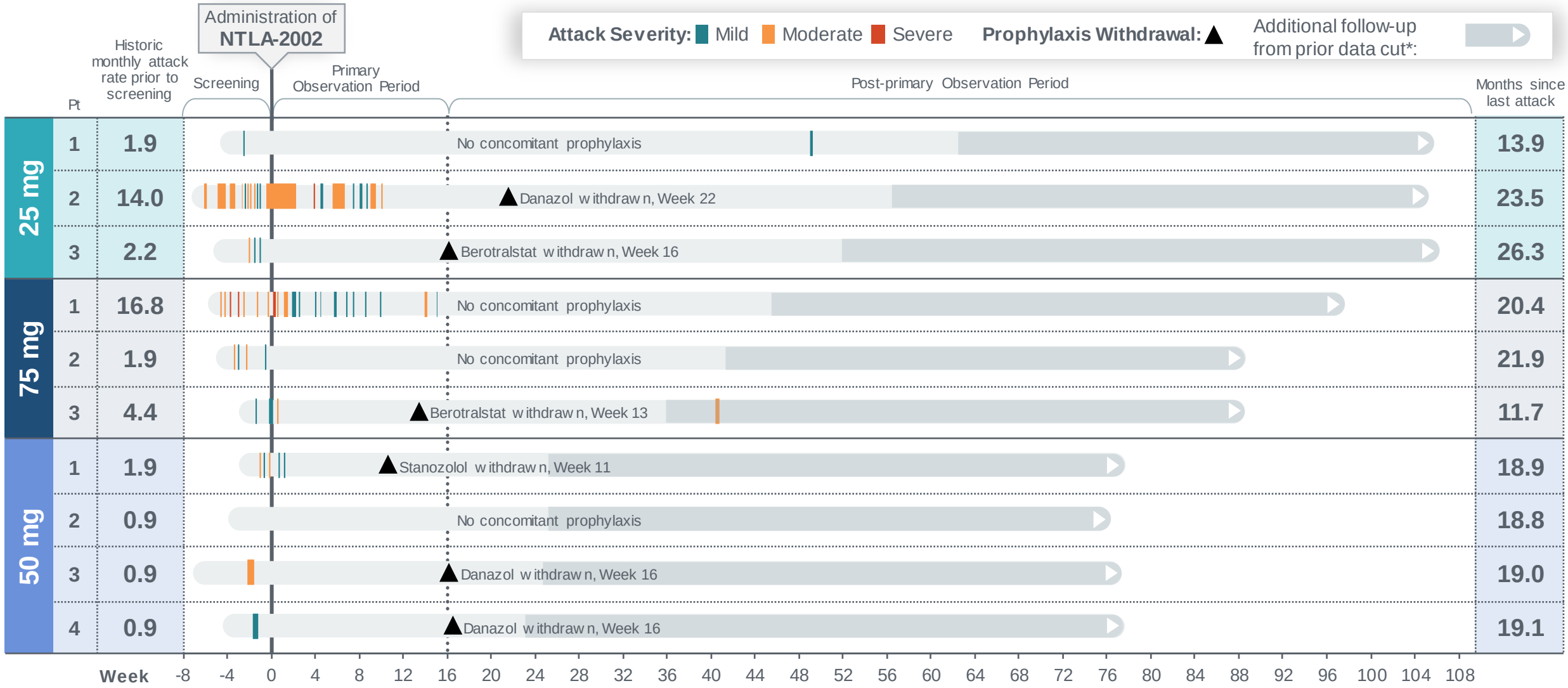
	Percentage Change from Baseline[a] Mean (SD)		
	All Attacks	Attacks Requiring On-Demand Treatment	Moderate-to-Severe Attacks
Weeks 1-16 (Primary observation period)	-90% (17%)	-82% (22%)	-95% (8.2%)
Weeks 5-16	-92% (16%)	-86% (28%)	-96% (7.7%)
Post-primary observation period[b]	-99% (1.4%)	-100% (0.49%)	-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.
This presentation includes data for an investigational product not yet approved by regulatory authorities.

Data cutoff date: 12Feb2024.

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



* Last data cutoff date: 17Feb2023
A month is defined as 28 days.
Pt: patient.
This presentation includes data for an investigational product not yet approved by regulatory authorities.

Data cutoff date: 12Feb2024.

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

Acknowledgements

We wish to extend our gratitude to:

- The patients, their caregivers, and their families
- Study site coordinators and staff
- The staff of Simbec-Orion for assistance with study management and operations support
- Ilia Antonino (employee of Intellia Therapeutics) and Apollo Medical Communications, for editorial support

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NTLA-2002 Clinical Development Plan and Next Steps

PHASE 1

- ✓ **8 of 10 patients have been attack-free** in post-primary observation period
- ✓ **98% attack rate reduction** in patients with HAE
- ✓ **Durable kallikrein reduction**
- ✓ **Favorable safety and tolerability profile observed**


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

CRISPR-Cas9 In Vivo Gene Editing of *KLKB1* for Hereditary Angioedema

January 31, 2024

PHASE 2

- ✓ **Fully enrolled**
- ○ Present topline results mid-year 2024
- ○ Detailed results expected in 2H 2024

PHASE 3

- ○ Initiate pivotal study in 2H 2024
- ○ Submit BLA in 2026

Poised to launch first-ever *in vivo* CRISPR gene editing therapy

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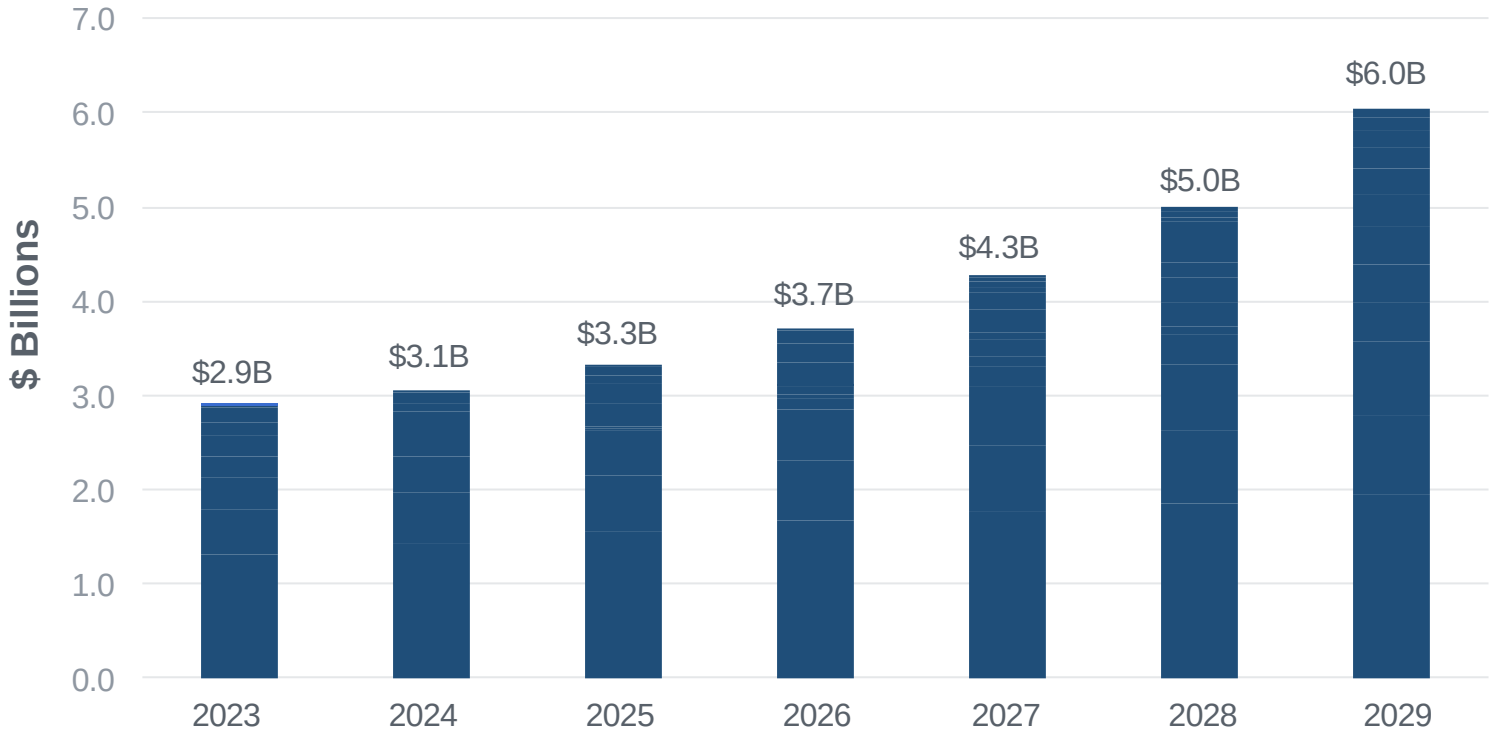
HAE Market is Rapidly Growing and Expected to Reach $6B by 2029

Worldwide Sales For HAE Therapies[1]



Current Leading Branded Prophylaxis Therapies

2023 Sales: Highest → Lowest

Drug	Administration[2]
Takhzyro®	1-2 SQ injections / month
Haegarda®	2 SQ injections / week
Orladeyo®	Oral pill, daily
Cinryze®	2 IV infusions / week

Current approved therapies only achieve an attack free rate of 18-44% in patients treated[3]

[1] Historical and forecasted (2024-2029) sales for prophylaxis and on-demand therapies for HAE from GlobalData 2024.
[2] Based on prescribing information for each referenced drug.
[3] Attack free rate based on pivotal or registrational trial in patients who reported zero attacks during the primary observation period per FDA labels.
IV: intravenous; **SQ**: subcutaneous.

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Significant Enthusiasm for NTLA-2002 Expressed by Physicians and Patients

REDUCED ATTACK FREQUENCY & COMPLETE RESPONSE + **ONE-TIME DOSING** + **SAFETY**

Strong interest in **long-term efficacy and dramatic reduction in attacks** without a waning of effect

Excitement about **one-time dosing** addresses a key unmet need for freedom from treatment burden

Physicians indicated **satisfaction with target safety profile** of only transient Grade 1 or 2 AEs

Patients achieving "attack free" and/or "treatment-free" with NTLA-2002 are considered the key differentiators

Source: Intellia commissioned market research 2023.
AE: adverse event.

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Well-Defined HAE Patient Segments Expected to Drive NTLA-2002 Commercial Uptake

150K+
HAE patients worldwide[1]

~6,000
HAE patients in the U.S.[2]

SIGNIFICANT OPPORTUNITY ACROSS ALL PATIENT SEGMENTS

15-20%
of patients are **inadequately managed on prophylaxis treatments** due to persistent attacks despite treatment or perceived dosing burden

40-55%
of patients on prophylaxis treatments are generally well-managed but show **strong willingness to switch** to more efficacious and/or less burdensome treatment options

25-30%
of patients currently avoid chronic prophylaxis due to burdensome administration but **would consider future treatment options**

Source: Intellia commissioned market research 2023.
[1] Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med. 2008 Sep 4;359(10):1027-36. doi: 10.1056/NEJMcp0803977. PMID: 18768946.
[2] Zilberberg, M. D., Nathanson, B. H., Jacobsen, T., & Tillotson, G. (2011).

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High Lifetime Cost of Branded HAE Prophylaxis Therapies Makes a One-Time Treatment Attractive to Payors

Long-term prophylaxis annual treatment costs

$450K – 650K
annually in the U.S.[1]

~$140K – 450K
annually in key European markets[1]

20 YEARS OLD
average age of diagnosis[2] leads to decades of treatment

Positive initial payor feedback on NTLA-2002 target profile

- Recognize the value of one-time therapy given the high lifetime costs of branded therapies
- Receptive to potential innovative payment models to support a one-time treatment
- Access conditions expected to be similar to other branded prophylactic HAE drugs

Source: Intellia Qualitative Payer Interviews: US, UK, DE, FR, IT, JP.
[1] Based on list prices from publicly available sources.
[2] Farkas et al. Allergy. 2017. 72;300-313.

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WHERE WE ARE TODAY….

HAE patients are seeking improved efficacy and convenience to be free from disease and chronic treatment

Long-term data from 10 patients reinforces the potential of NTLA-2002 to eliminate attacks after a one-time treatment

Rapidly growing commercial market with positive initial payor receptivity to a potential one-time treatment

On track to initiate a global pivotal Phase 3 trial for NTLA-2002 in the second half of 2024 and planned BLA submission in 2026[1]

WHERE WE THINK WE'RE HEADED…

A functional cure for people living with HAE

[1] Subject to regulatory feedback.

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Q&A

NTLA-2002 Phase 1 Clinical Data Update

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