Results from Phase 2 Study of NTLA-2002 for Hereditary Angioedema

October 24, 2024

Intellia THERAPEUTICS

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Agenda

Welcome

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

Review of NTLA-2002 Phase 2 Data
Dr. Danny Cohn *Internist, Department of Vascular Medicine,* Amsterdam University Medical Center

NTLA-2002 Clinical Development Update
Dr. David Lebwohl *Chief Medical Officer*, Intellia Therapeutics

Q&A

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NTLA-2002 Has the Potential to Transform the Hereditary Angioedema Treatment Paradigm

Goal with NTLA-2002 = **Functional Cure**

1x

One-time treatment of NTLA-2002

=

Freedom from attacks

+

Freedom from chronic prophylaxis treatment

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Key Learnings from the NTLA-2002 Phase 2 Study

- Deep reductions in hereditary angioedema (HAE) attacks at both dose levels tested
- Safety profile continued to be highly encouraging
- Single 50 mg dose led to majority of patients (8/11) achieving complete elimination of attacks
- 50 mg dose led to greater kallikrein and attack rate reduction vs. 25 mg dose

50 mg dose selected for Phase 3 study

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Results From a Phase 2, Randomized, Placebo-Controlled Trial of CRISPR-Based Therapy NTLA-2002 for Hereditary Angioedema

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*Presenting author

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Disclosures

- Dr. Cohn has acted as a consultant or speaker for or participated in research with Astria, BioCryst, CSL Behring, Intellia Therapeutics, Ionis Pharmaceuticals, KalVista, Pharming, Pharvaris, and Takeda

NTLA-2002 Phase 1/2 Trial Design

International, multicenter study to assess safety, tolerability, PK, PD and effect of NTLA-2002 on attacks in adults with Type I or Type II HAE

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 2:2:1

- 50 mg (n=11)
- 25 mg (n=10)
- Placebo arm (n=6)

PHASE 2 ENDPOINTS

PRIMARY ENDPOINT

- Number of angioedema attacks per month during primary observation period (weeks 1-16)
  - Primary analysis occurred when the 25th patient reached week 16

KEY SECONDARY ENDPOINTS

- Safety
- Number of angioedema attacks per month (weeks 5-16)
- Change from baseline in total plasma kallikrein level

Clinicaltrials.gov ID: NCT05120830

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Clinical Development Supporting Phase 3 Study Initiation

	PHASE 1	PHASE 2
Trial Dynamics		
	• N = 10 patients	• N = 27 patients
	• Open-label study, no placebo-control	• Double-blind study, randomized, **placebo-control**
	• No washout of chronic prophylaxis therapy	• **Required washout of chronic prophylaxis therapy**
	• 16-week primary observation period *Median of 20 months of follow-up previously presented*	• 16-week primary observation period *Median of 8 months of follow-up*
Attack Rate Calculation		
	• Change in attack rate relative to patient's baseline	• **Difference in attack rate relative to placebo**
GOAL		
	• **Evaluate safety, dose range and initial efficacy**	• **Evaluate efficacy and safety findings in a larger number of patients to support Phase 3 dose selection**

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Patient Demographics and Characteristics

Characteristic		NTLA-2002 25 mg (n=10)	NTLA-2002 50 mg (n=11)	Placebo (n=6)
Median age (range), years		48.5 (34-62)	44.0 (18-61)	47.0 (31-76)
Sex, n (%)	Male	7 (70.0)	5 (45.5)	2 (33.3)
Median weight (range), kg		89 (58-133)	78 (56-107)	79 (50-92)
HAE type, n (%)	HAE-C1INH-Type1 HAE-C1INH-Type2	8 (80.0) 2 (20.0)	10 (90.9) 1 (9.1)	5 (83.3) 1 (16.7)
Prior use of long-term prophylaxis, n (%)		6 (60.0)	6 (54.5)	5 (83.3)
Long-term prophylaxis prior to study entry, n (%)	Lanadelumab Attenuated androgens Berotralstat C1INH Tranexamic acid	2 (20.0) 2 (20.0) 1 (10.0) 1 (10.0) 0	2 (18.2) 1 (9.1) 2 (18.2) 0 1 (9.1)	1 (16.7) 2 (33.3) 1 (16.7) 1 (16.7) 0
Median no. of angioedema attacks during the historical attack period (range)[a]		6.5 (3-24)	4.0 (3-11)	5.5 (3-9)
Typical attack severity, n (%)	Mild Moderate Severe	1 (10.0) 6 (60.0) 3 (30.0)	0 9 (81.8) 2 (18.2)	1 (16.7) 4 (66.7) 1 (16.7)
Mean baseline monthly attack rate, n		3.6	3.6	3.7

[a]The historical attack period is defined as the 90 days before the screening period, which coincided with washout of any long-term prophylaxis by a patient prior to study entry.
C1INH, C1 inhibitor; HAE, hereditary angioedema.

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Data cutoff date: 04Apr2024.

NTLA-2002 Continues to Be Well Tolerated Across All Dose Levels

TEAEs in ≥2 Patients After NTLA-2002 Administration (pooled), n (%)	NTLA-2002 25 mg (n=10)	NTLA-2002 50 mg (n=11)	Placebo (n=6)
Any TEAE	10 (100)	11 (100)	6 (100)
Headache	4 (40)	4 (36)	1 (17)
Fatigue	3 (30)	3 (27)	2 (33)
Nasopharyngitis	3 (30)	3 (27)	2 (33)
Back pain	3 (30)	2 (18)	0
Upper respiratory tract infection	3 (30)	2 (18)	1 (17)
Cough	3 (30)	1 (9)	0
Infusion-related reaction	1 (10)	3 (27)	1 (17)
COVID-19	2 (20)	1 (9)	1 (17)
Ear infection	2 (20)	0 (0.0)	0
Epistaxis	0	2 (18)	1 (17)
Influenza-like illness	1 (10)	1 (9)	0
Oropharyngeal pain	1 (10)	1 (9)	1 (17)
Pyrexia	0	2 (18.2)	0
Sinusitis	1 (10)	1 (9)	0

- All TEAEs were Grade 1 or 2*
- No SAEs in patients treated with NTLA-2002
- 4 IRRs with NTLA-2002; 2 led to temporary interruption of study drug
  - Each instance resolved without sequelae and both patients received the full dose
- No clinically significant laboratory abnormalities
  - 1 patient had transient Grade 2 increase in ALT on Day 22

ALT, alanine aminotransferase; IRR, infusion-related reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
*Common Terminology Criteria for Adverse Events (CTCAE) Grading

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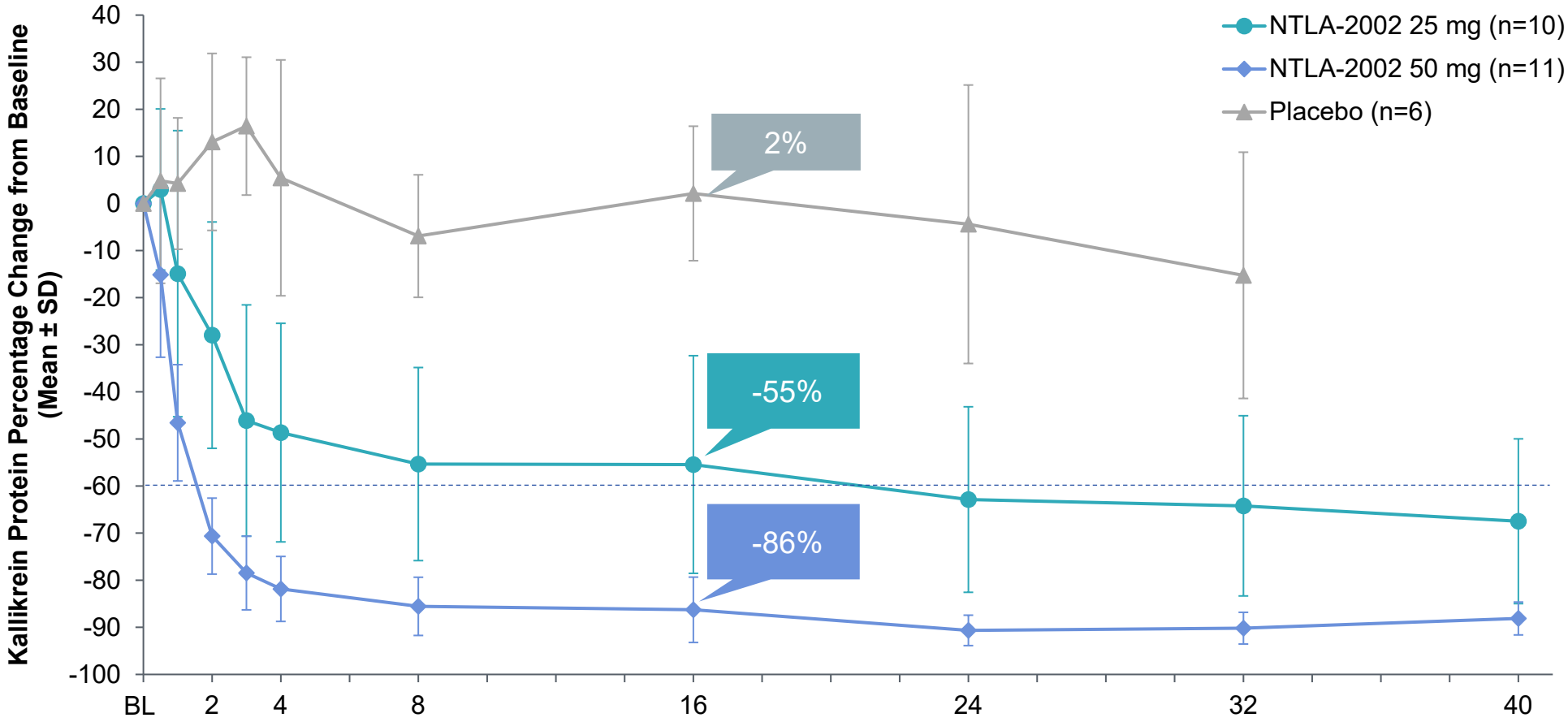
A Single Dose of NTLA-2002 Showed Dose-Dependent and Durable Reductions in Plasma Kallikrein Protein Over Time



Number of patients	BL	2	4	8	16	24	32	40
NTLA-2002 25 mg	10	10	10	10	10	6	6	4
NTLA-2002 50 mg	11	11	11	11	10	5	5	3
Placebo	6	6	6	5	5	4	3	

For post-baseline assessments, only scheduled visits completed by at least 3 patients in each arm are presented. Dashed line represents targeted minimum reduction.
BL, baseline; SD, standard deviation.
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Data cutoff date: 04Apr2024.

A Single Dose of NTLA-2002 Led to a Reduction in Monthly Angioedema Attack Rate Compared With Placebo

VARIABLE	NTLA-2002 25 mg (n=10)	NTLA-2002 50 mg (n=11)	Placebo (n=6)
Median follow-up (range), month	8.2 (4.4-11.8)	5.6 (2.9-11.5)	6.9 (1.9-12.5)
Weeks 1-16			
Mean no. of angioedema attacks per month (95% CI)[a]	0.7 (0.3, 2.0)	0.7 (0.2, 1.8)	2.8 (0.8, 9.9)
Percentage difference vs. placebo (95% CI)	**−75%** (-95%, 27%)	**−77%** (-95%, 15%)	
Weeks 5-16			
Mean no. of angioedema attacks per month (95% CI)[a]	0.6 (0.2, 1.9)	0.6 (0.2, 1.7)	3.1 (0.8, 11.8)
Percentage difference vs. placebo (95% CI)	**-80%** (-96%, 14%)	**-81%** (-97%, 3%)	

[a]The mean number of angioedema attacks per month was estimated using a negative binomial model with treatment arm and baseline attack rate as independent variables. Baseline is defined as the time from date of informed consent to randomization. A month is defined as 28 days.

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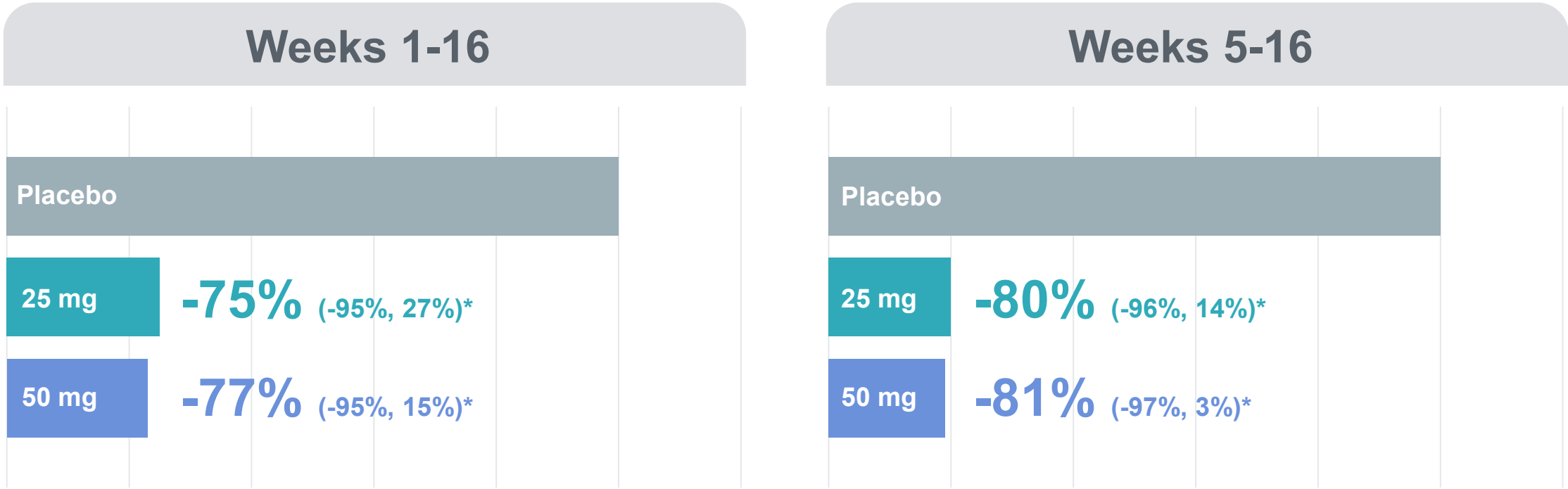
Deep Reductions in Monthly HAE Attack Rate Compared to Placebo at Both Dose Levels



*95% CI of the mean attack rate percentage difference relative to placebo.
Following the 16-week primary observation period, patients were allowed to go back to their previous chronic prophylaxis therapy so no placebo comparisons can be made beyond week 16.
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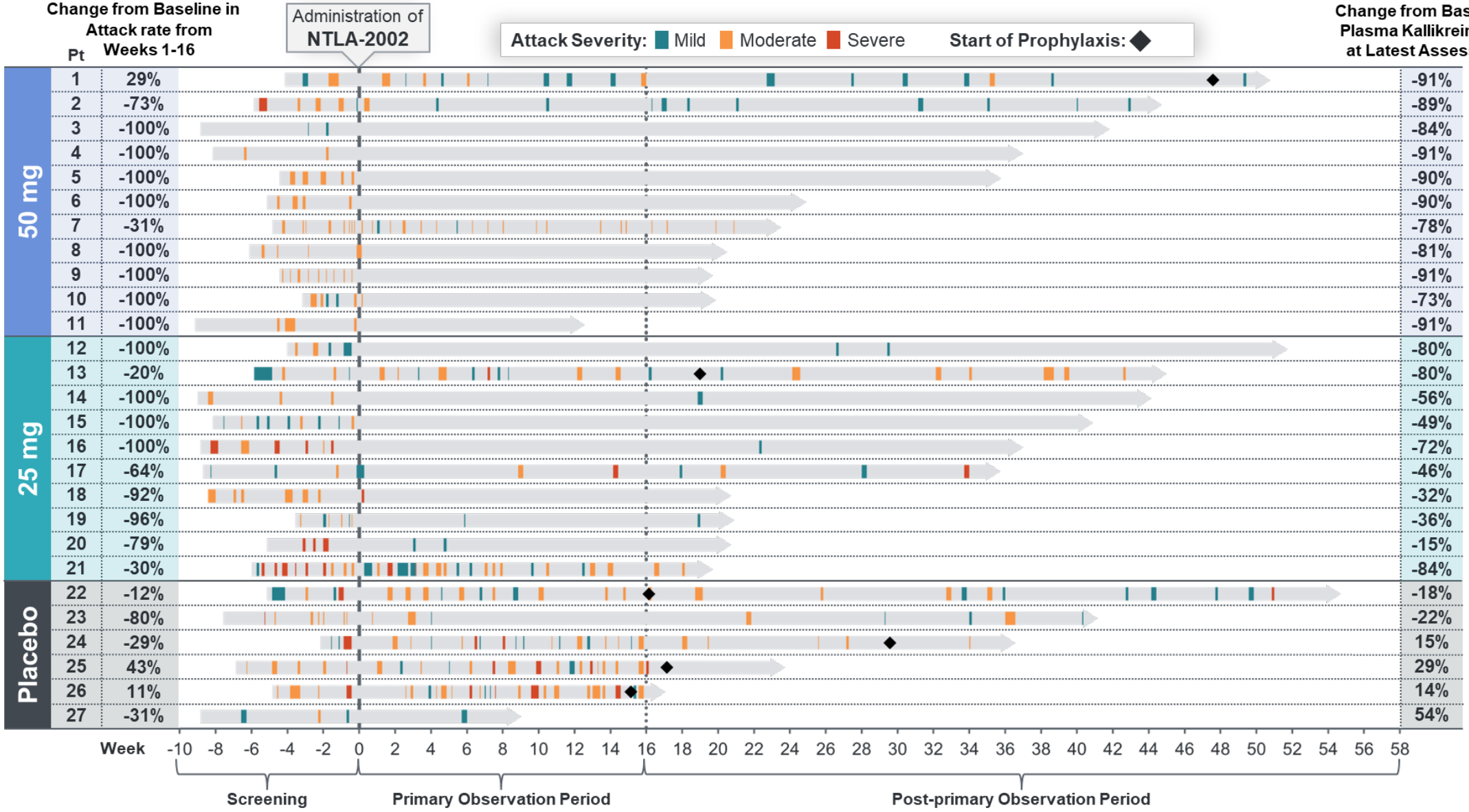
Data cutoff date: 04Apr2024.

Eight of 11 Patients Were Completely Attack Free Following a Single 50 mg Dose



The length of the gray bars indicates the interval from the start of the screening period to the last assessment as of the data cutoff date. Arrows indicate the patient is still on study.
The width of the colored bars indicates the duration of the attack. Black diamonds indicate when a patient resumed long-term prophylaxis, which was permitted after Week 16. Pt, patient.
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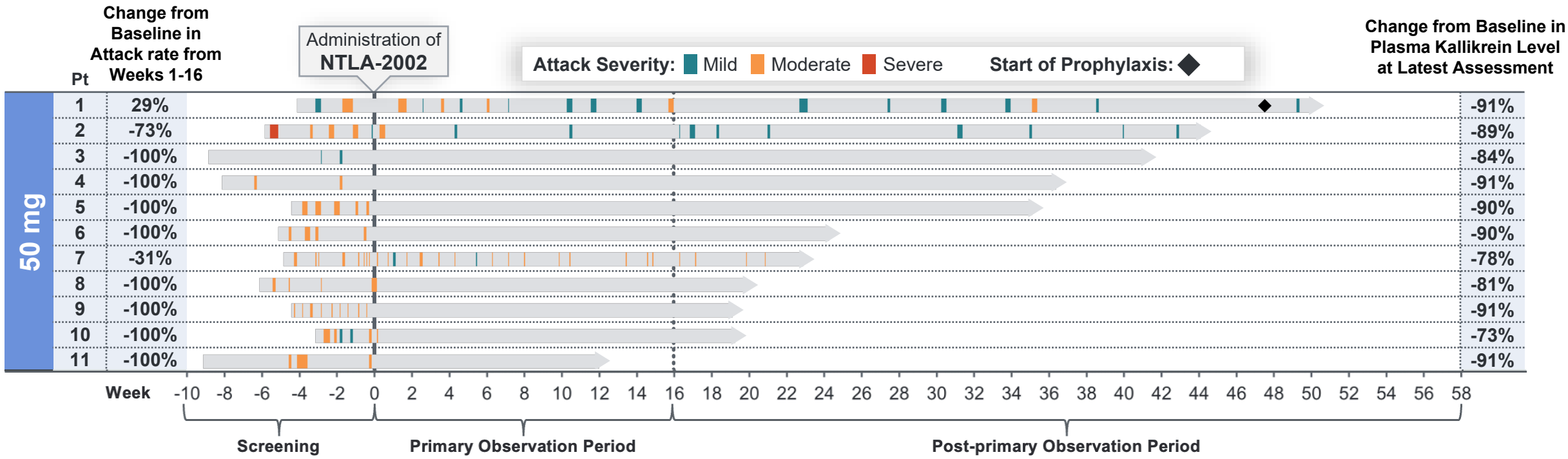
Eight of 11 Patients Were Completely Attack Free Following a Single 50 mg Dose



During Primary Observation Period

- Eight of 11 patients were completely attack free
- 10 of 11 patients with a clinically meaningful reduction in attacks

Post-Primary Observation Period*

- Eight of 11 patients remain completely attack free
- All 11 patients experienced clinically meaningful attack rate reduction with extended follow-up

*No placebo comparisons can be made beyond week 16, which is when patients were permitted to resume long-term prophylaxis.
The length of the gray bars indicates the interval from the start of the screening period to the last assessment as of the data cutoff date. Arrows indicate the patient is still on study.
The width of the colored bars indicates the duration of the attack. Black triangles indicate when a patient resumed long-term prophylaxis, which was permitted after week 16.
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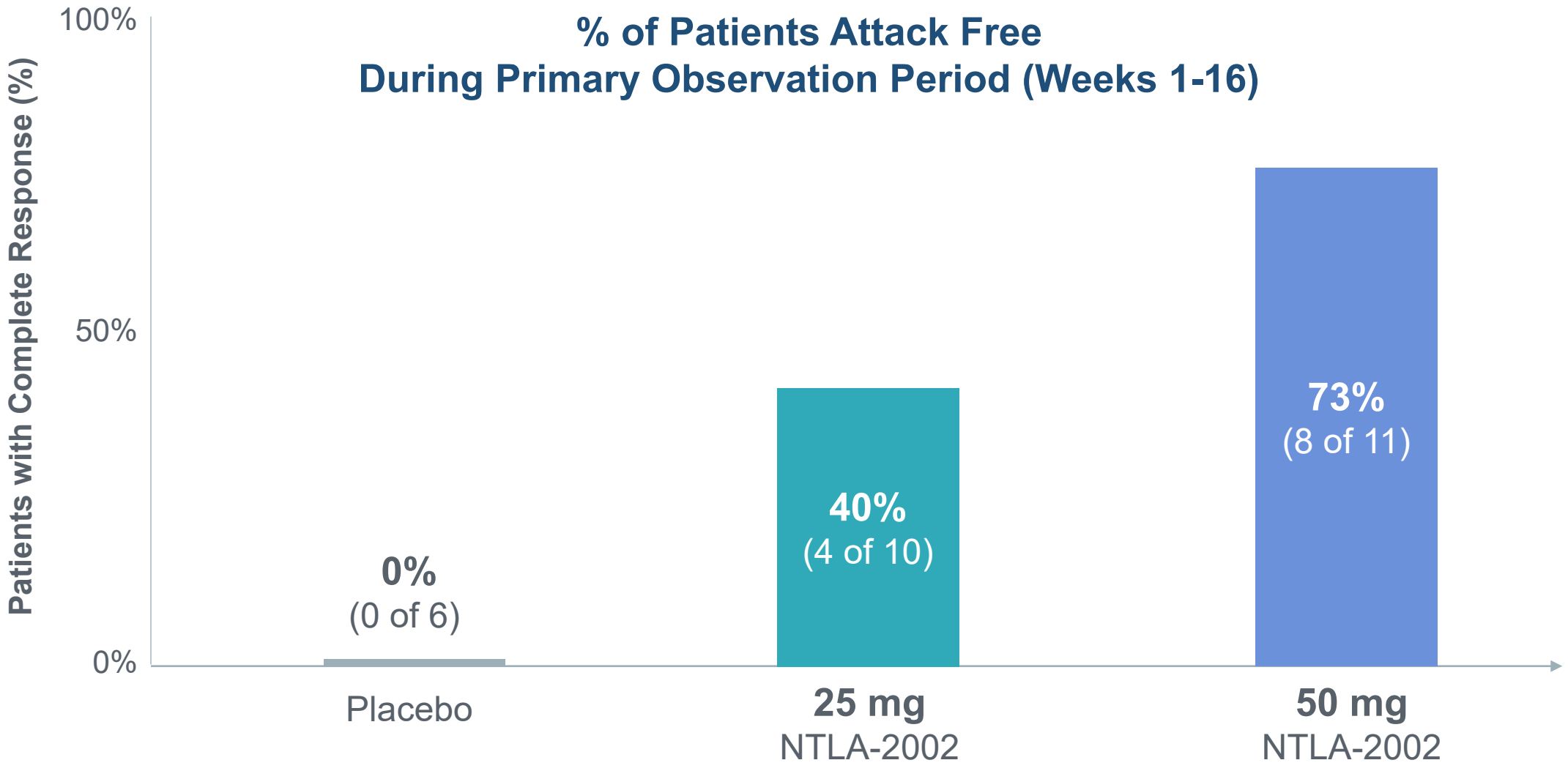
Eight of 11 Patients Receiving a Single 50 mg Dose Experienced a Complete Response – Attack-Free and No Subsequent Treatment Required



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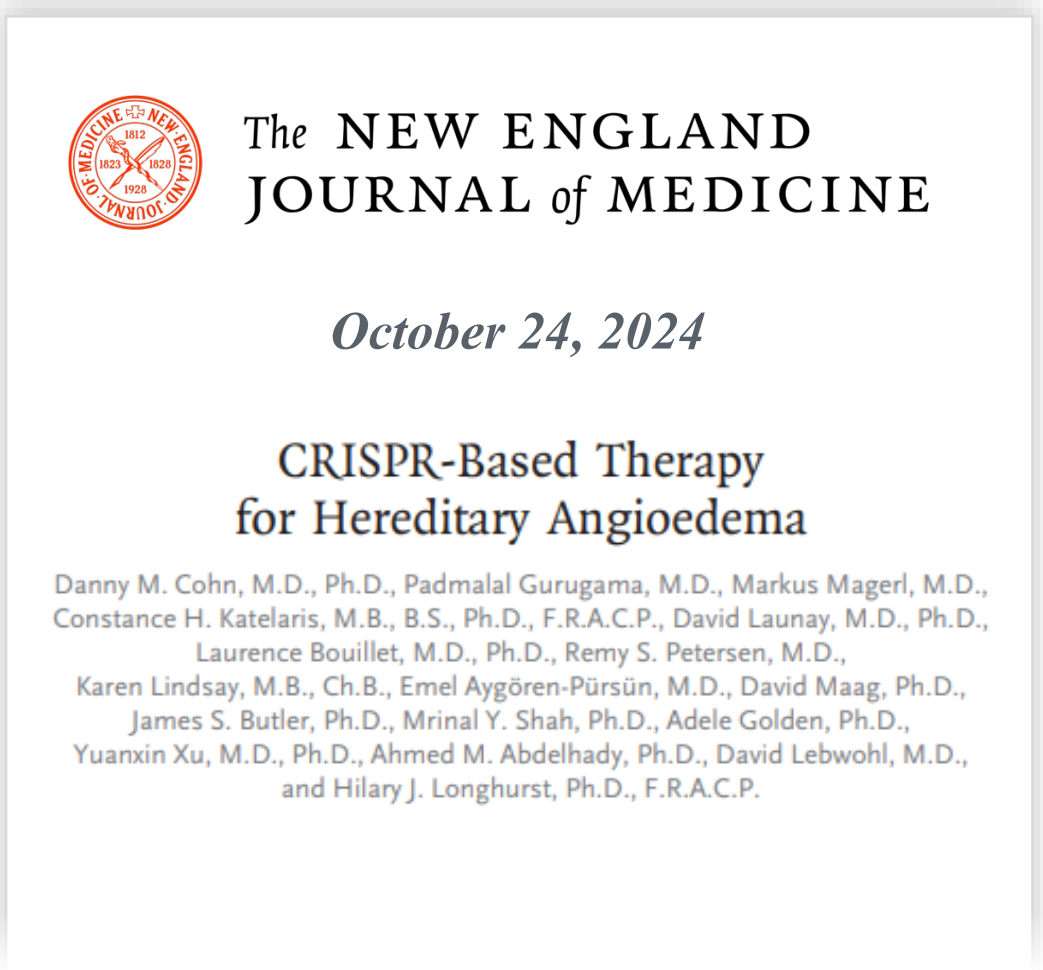
NTLA-2002 Phase 2 Clinical Data Results Published in NEJM



The NEW ENGLAND JOURNAL of MEDICINE

October 24, 2024

CRISPR-Based Therapy for Hereditary Angioedema

Danny M. Cohn, M.D., Ph.D., Padmalal Gurugama, M.D., Markus Magerl, M.D., Constance H. Katelaris, M.B., B.S., Ph.D., F.R.A.C.P., David Launay, M.D., Ph.D., Laurence Bouillet, M.D., Ph.D., Remy S. Petersen, M.D., Karen Lindsay, M.B., Ch.B., Emel Aygören-Pürsün, M.D., David Maag, Ph.D., James S. Butler, Ph.D., Mrinal Y. Shah, Ph.D., Adele Golden, Ph.D., Yuanxin Xu, M.D., Ph.D., Ahmed M. Abdelhady, Ph.D., David Lebwohl, M.D., and Hilary J. Longhurst, Ph.D., F.R.A.C.P.

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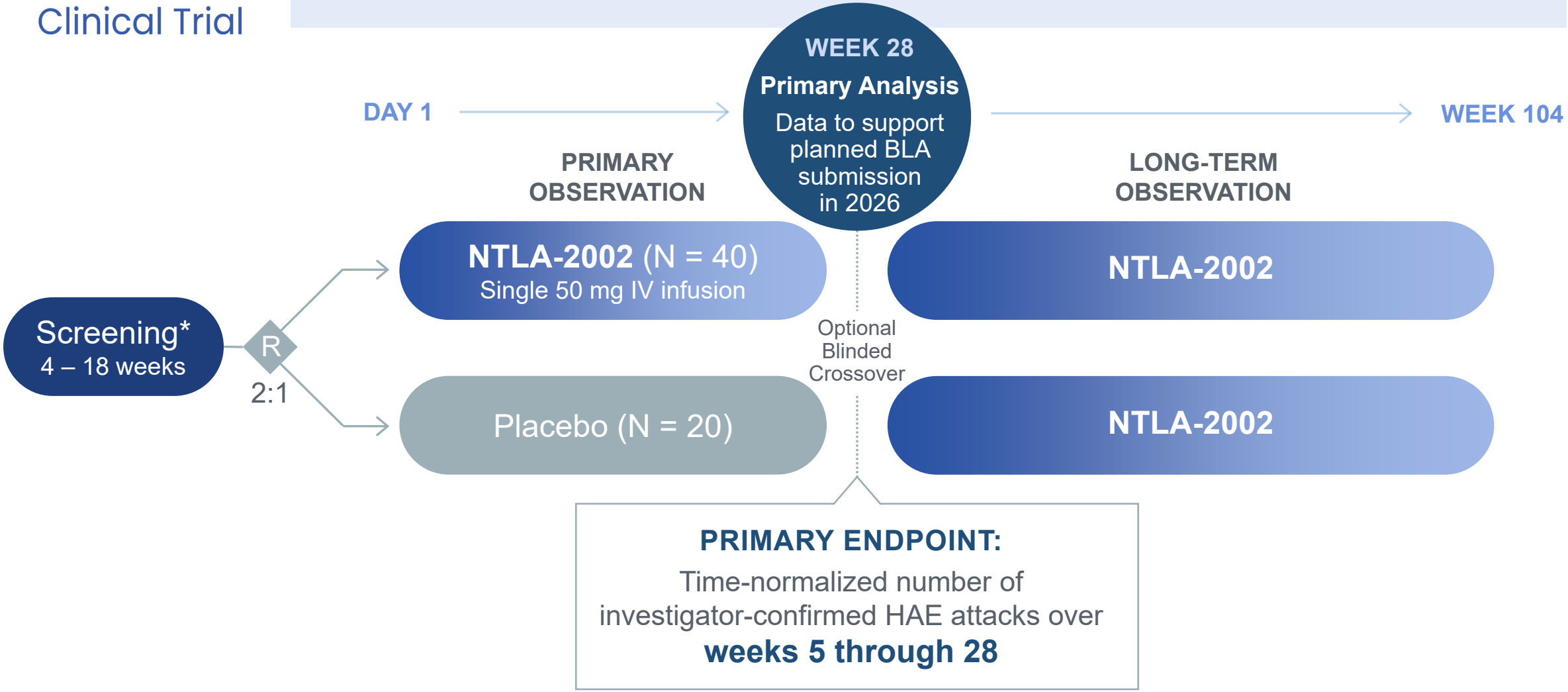
HAELO Clinical Trial

A Phase 3, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of NTLA-2002 in Patients with Hereditary Angioedema (HAE)



Clinicaltrials.gov ID: NCT06634420

* Patients on long-term prophylaxis are required to wash out of therapy prior to the run-in period of screening.

Despite Available Treatments, Patients and Physicians are Highly Receptive to Target Profile of NTLA-2002

75%

of U.S. prescribers surveyed would offer a product with NTLA-2002's target profile to all patients within 3 years of launch

> CRISPR has the potential to be a curative treatment, changing how we manage this disease.
>
> **- HAE Physician**

Patients want better treatment options…

> Treatment has definitely improved but **I am still experiencing a high number of attacks.**
>
> **- HAE Patient on lanadelumab, 24 attacks per year**

> **I would love to not have to ever take another injection or another pill.** It would be amazing.
>
> **- HAE Patient on lanadelumab, 8 attacks per year**

> I am hesitant to switch jobs because I know these are expensive treatments and **I may not always have access**.
>
> **- HAE Patient on lanadelumab, well-controlled**

Source: Intellia commissioned HAE patient and caregiver interviews; Physician quantitative survey (n=192)

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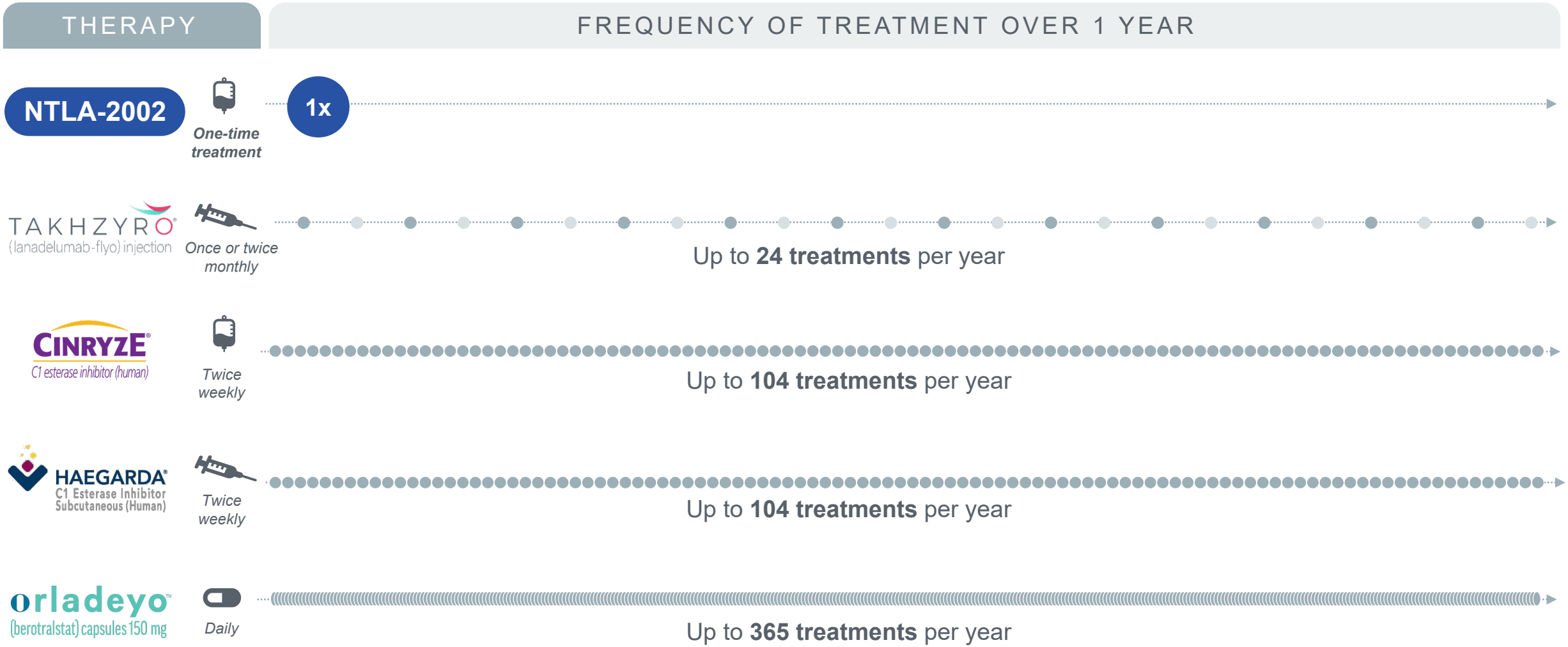
NTLA-2002 is a Potential Paradigm-Shift in Treating HAE Compared to Chronic, Long-Term Prophylaxis Therapies



For illustrative purposes only
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WHERE WE ARE TODAY….

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

Phase 2 data supports the potential of NTLA-2002 to eliminate attacks after a one-time treatment

Rapidly growing commercial opportunity with positive physician and patient receptivity to a potential one-time treatment

Recently initiated a global pivotal Phase 3 trial evaluating a single 50 mg dose of NTLA-2002 and Intellia is planning for a BLA submission in 2026[1]

WHERE WE THINK WE'RE HEADED…

NTLA-2002 could be a functional cure for people living with HAE

[1] Subject to regulatory feedback.

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NTLA-2002 Phase 2 Clinical Data Update

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