NTLA-2001 and NTLA-2002 Interim Clinical Data Update

Bill, living with transthyretin amyloidosis, and his wife, Maura

Intellia THERAPEUTICS

September 16, 2022

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Introduction

John Leonard, M.D.
Chief Executive Officer, Intellia Therapeutics

Review of NTLA-2001 Interim Clinical Data

Julian Gillmore, M.D., Ph.D., FRCP, FRCPath
Professor of Medicine, National Amyloidosis Centre, UCL Division of Medicine, Royal Free Hospital, U.K.; National Coordinator for Intellia's Phase 1 Study of NTLA-2001 in the U.K.

Next Steps for NTLA-2001 and NTLA-2002 Interim Clinical Data

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Closing Remarks and Q&A Session

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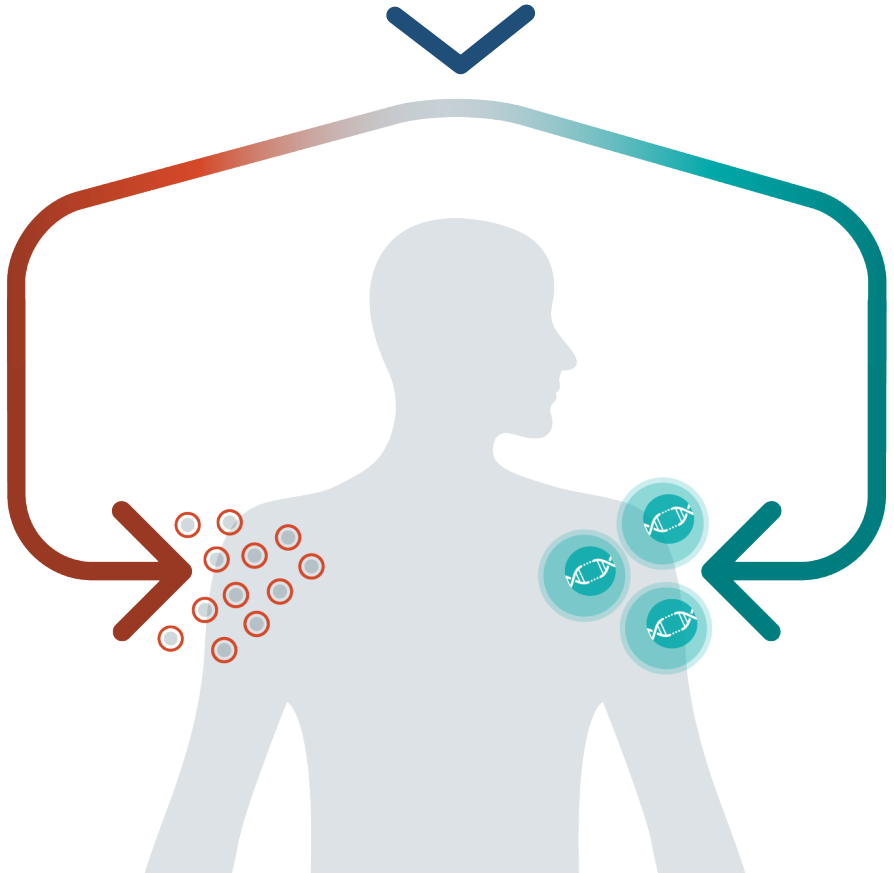
Intellia THERAPEUTICS

Building 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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Transthyretin (ATTR) amyloidosis is a progressive and fatal disease

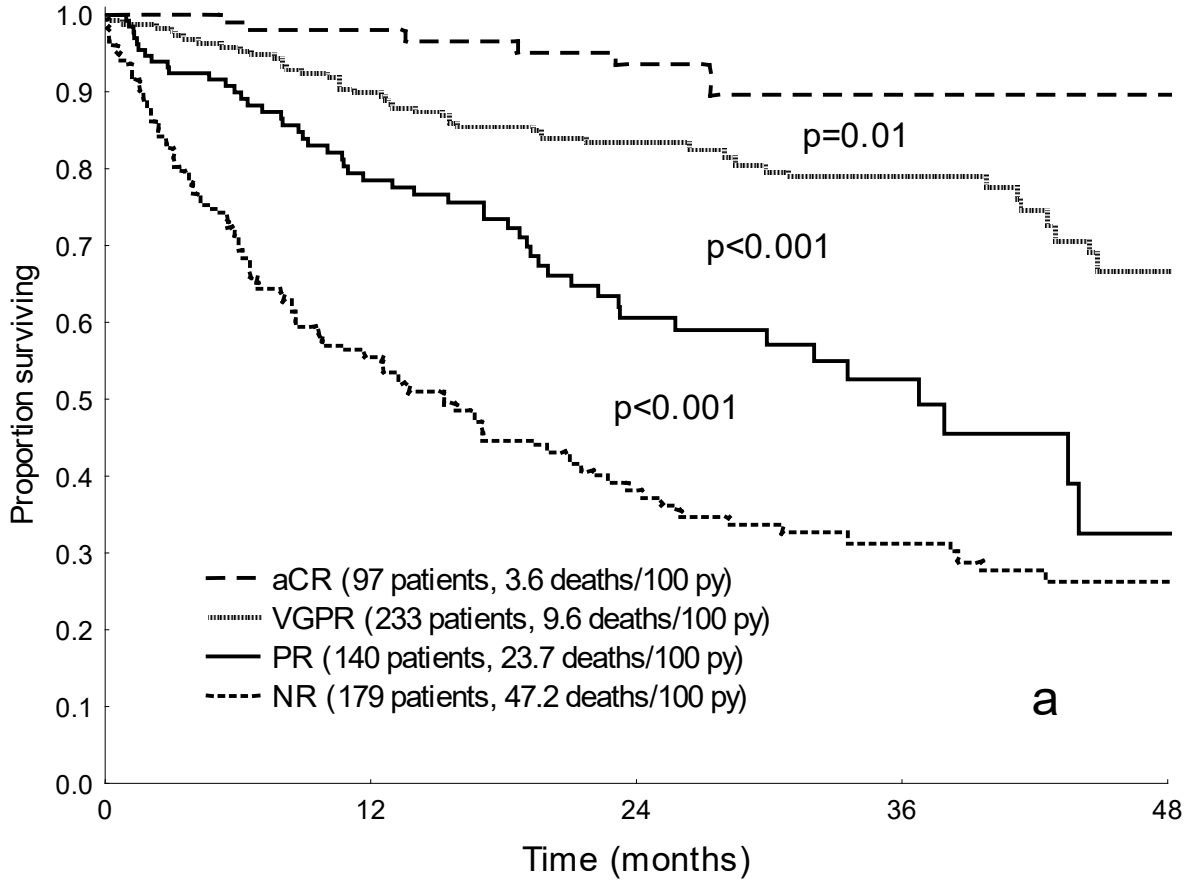
- **Accumulation of amyloid deposits composed of misfolded transthyretin (*TTR*) protein**
  - ~50,000 hereditary ATTR amyloidosis (ATTRv) patients worldwide
  - ~200,000 – 500,000 wild-type ATTR amyloidosis (ATTRwt) patients worldwide
- **Cardiac phenotype (ATTR-CM)**
  - Amyloid deposits cause heart failure, myopathy, impaired diastolic/systolic function and conduction disorders
  - Fatal within 3 to 10 years without treatment
  - Low rates of diagnosis
- **Unmet medical need in ATTR-CM**
  - Progressive heart damage leads to impaired QoL and high mortality and morbidity
  - Current treatment only slows disease progression and requires lifelong administration
  - Limited regional access to approved therapies

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

QoL, Quality of life;

Donnelly JP, Hanna M. Cleve Clin J Med 2017; 84:12–26
Lane T *et al*. Circulation 2019; 140:16–26
Pinney JH *et al*. J Am Heart Assoc 2013; 2:e000098
Rowczenio D *et al*. Orphanet J Rare Dis 2017; 12(Suppl 1):165; Abstract P1

AL amyloidosis: Magnitude of precursor protein knockdown is associated with survival



Incremental improvements in precursor protein reduction led to improved clinical outcomes

AL, amyloid light chain; **aCR**, amyloid complete response; **VGPR**, very good partial response; **PR**, partial response; **NR**, no response

Palladini G *et al*, JCO 2012;30:4541-4549

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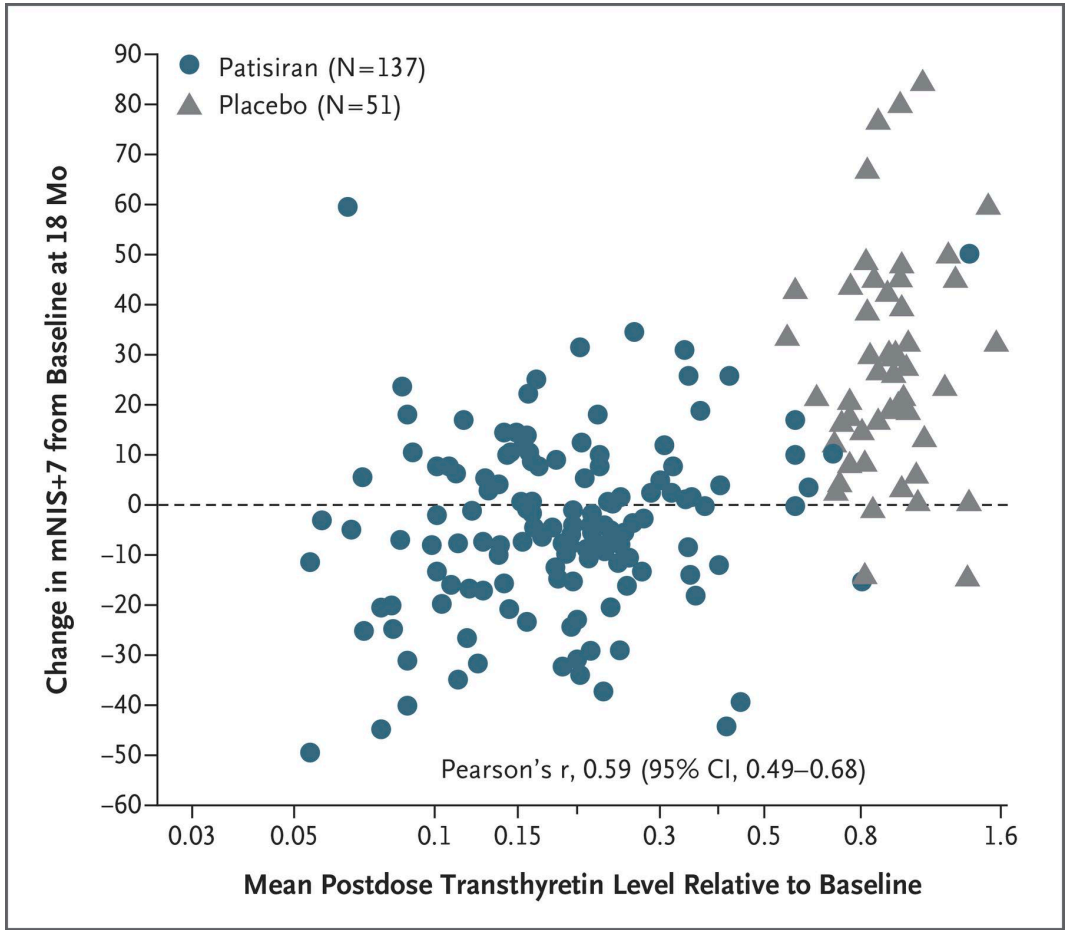
ATTR amyloidosis: Greater TTR knockdown improves patient outcomes



- Greater TTR knockdown is associated with improved neuropathy scores for ATTRv-PN
- Emerging evidence indicates that deep TTR reductions are clinically beneficial for patients with ATTR-CM

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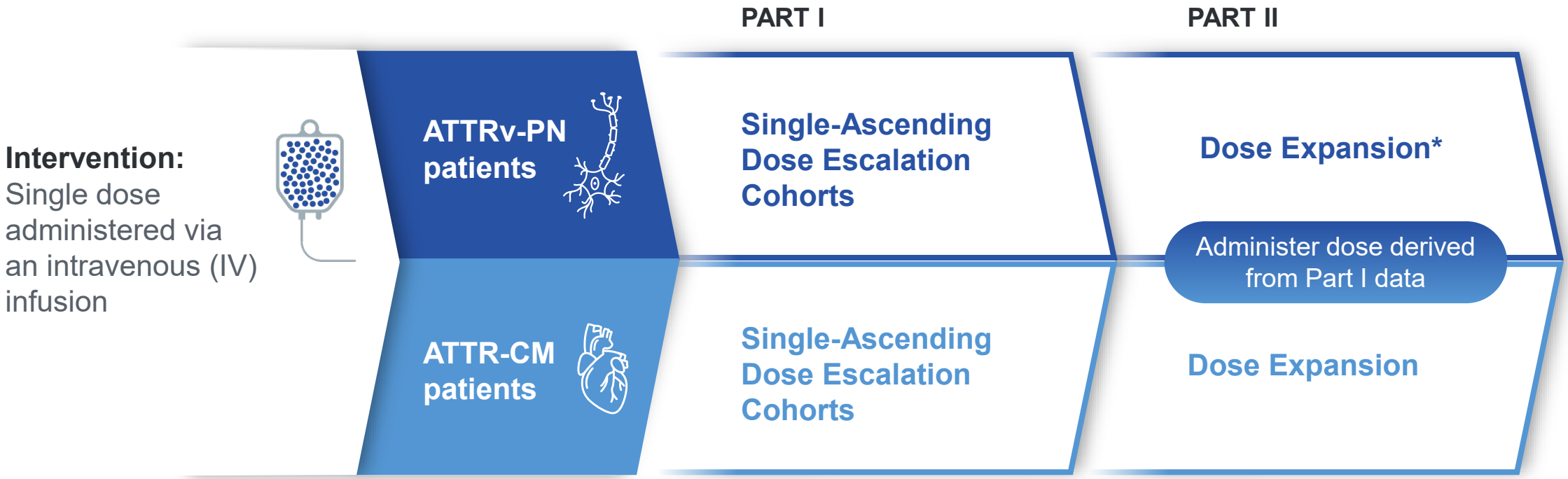
Adams D *et al*, NEJM 2018;379:11–21

NTLA-2001 expanded Phase 1 study

Two-part, open-label, multi-center study in adults with hereditary ATTR with polyneuropathy (ATTRv-PN) or ATTR amyloidosis with cardiomyopathy (ATTR-CM)



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

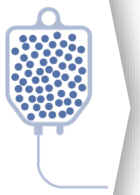
Clinicaltrials.gov ID: NCT0460105

* Plan to add a second dose expansion cohort, subject to regulatory feedback; Announced August 4, 2022

NTLA-2001 Phase 1 study: Cardiomyopathy arm

Hereditary transthyretin amyloidosis with cardiomyopathy (ATTRv-CM) or wild-type cardiomyopathy (ATTRwt-CM), NYHA Class I - III

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



PART I – DOSING COMPLETE
Single-Ascending Dose

- 1.0 mg/kg NYHA Class I/II (n=3†)
- 0.7 mg/kg NYHA Class III (n=6*)
- 0.7 mg/kg NYHA Class I/II (n=3)

PART II
Dose Expansion

Administer dose derived from Phase I data

PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK and PD

- *Measure serum TTR levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of cardiac disease

- *Cardiac imaging, biomarkers, cardiopulmonary exercise test, 6MWT*

Clinicaltrials.gov ID: NCT04601051;
† Based on safety and PD profile at 0.7 mg/kg, further dose escalation to 1.0 mg/kg in NYHA Class III was not undertaken;
*Cohort expanded to 6 patients to further assess safety and PD
NYHA, New York Heart Association; **PK,** Pharmacokinetics; **PD,** Pharmacodynamics; **6MWT**, 6 Minute Walk Test

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

Patient demographics & characteristics

Parameter	NYHA Class I/II 0.7 mg/kg n = 3	NYHA Class III 0.7 mg/kg n = 6	NYHA Class I/II 1.0 mg/kg n = 3	All patients N = 12
Median age, years (min, max)	74 (71, 75)	78 (75, 86)	71 (68, 72)	75 (68, 86)
Sex, n (%)				
Male	3 (100%)	6 (100%)	3 (100%)	12 (100%)
Median weight, kg (min, max)	85 (63, 88)	86 (71, 106)	85 (75, 88)	85 (63, 106)
***TTR* genotype, n (%)**				
p.V142I	–	–	1 (33%)	1 (8%)
p.T80A	–	1 (17%)	–	1 (8%)
WT	3 (100%)	5 (83%)	2 (67%)	10 (83%)
NYHA classification, n (%)				
I	1 (33%)	–	–	1 (8%)
II	2 (67%)	–	3 (100%)	5 (42%)
III	–	6 (100%)	–	6 (50%)
Median NT-proBNP, ng/L (min, max)	2480 (2103, 3637)	2463 (2112, 16690)	2408 (1607, 3474)	2461 (1607, 16690)

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

Data Cut Off : July 1, 2022

NYHA, New York Heart Association; **TTR**, Transthyretin; **NT-proBNP**, N-terminal prohormone of brain natriuretic peptide

NTLA-2001 was generally well-tolerated across all cohorts through the follow-up period

- **Across all cohorts, majority of adverse events were mild in severity**
  - Infusion-related reactions were reported in 2 patients
  - 25% (n=3) of patients reported no AEs and 58% (n=7) reported mild AEs as their highest grade
  - All patients received a complete study dose of NTLA-2001

- **A single Grade 3 infusion-related reaction was reported at the 0.7 mg/kg dose in a NYHA Class III patient and resolved without any clinical sequelae**
  - NYHA Class III 0.7 mg/kg dose level cohort expanded per protocol to 6 patients to further characterize safety and PD
  - No additional patients in this cohort reported a treatment-related AE higher than Grade 1

- **No clinically significant laboratory findings**
  - Transient Grade 1 liver enzyme elevations observed

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Data Cut Off: July 1, 2022
Median follow-up for all subjects is 3.7 months
PD, pharmacodynamics; **AE**, adverse event

Majority of adverse events were mild in severity

Parameter	NYHA Class I/II 0.7 mg/kg n=3			NYHA Class III 0.7 mg/kg n=6			NYHA Class I/II 1.0 mg/kg n=3			All Patients N=12		
	Gr. 1	Gr. 2	Gr. 3	Gr. 1	Gr. 2	Gr. 3	Gr. 1	Gr. 2	Gr. 3	Gr. 1	Gr. 2	Gr. 3
Patients with at least one TEAE	2	–	–	3	1*	1	2	–	–	7	1	1
Infusion-related reaction	–	–	–	–	–	1	1	–	–	1	–	1
Inguinal hernia	1	–	–	–	–	–	1	–	–	2	–	–
COVID-19	–	–	–	1	–	–	1	–	–	2	–	–

Data Cut Off: July 1, 2022
TEAEs Occurring in ≥ 2 Patients; *Gr.2 urinary retention in 1 patient;
TEAE, treatment emergent adverse event; **Gr.**, Grade

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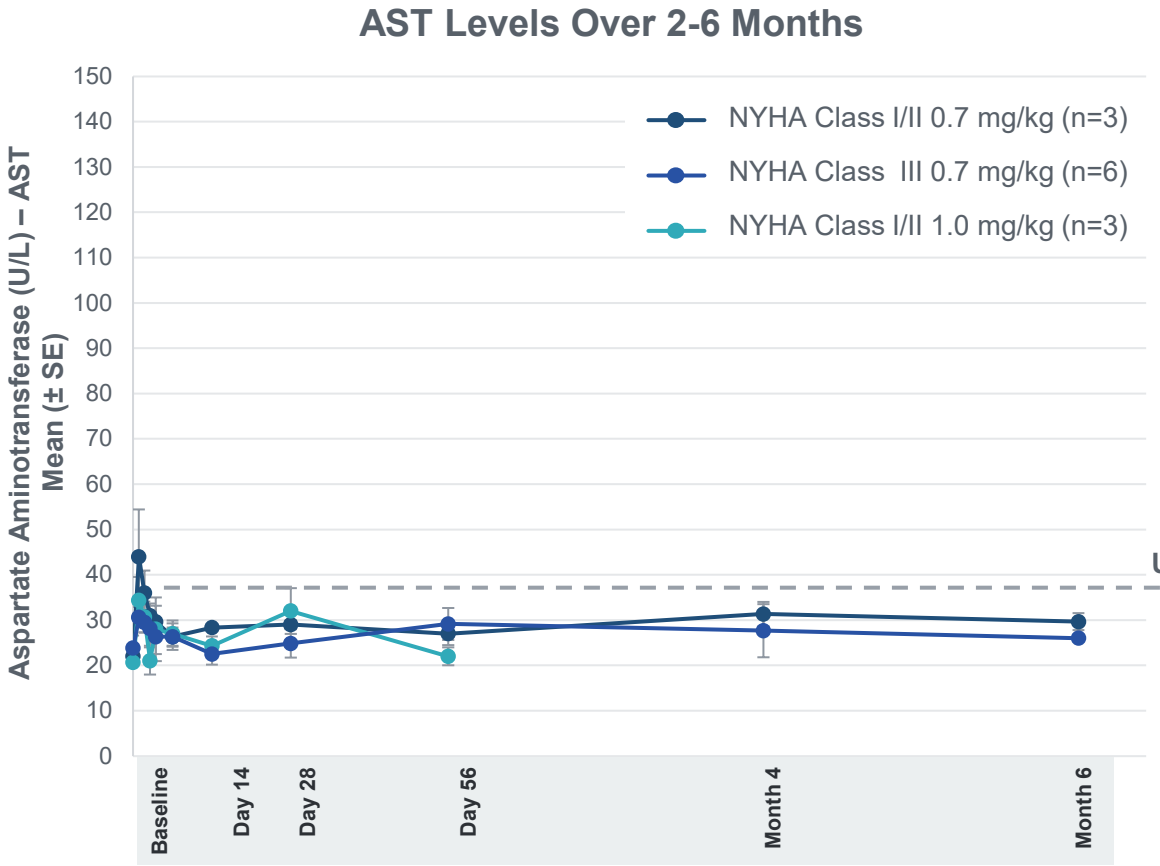
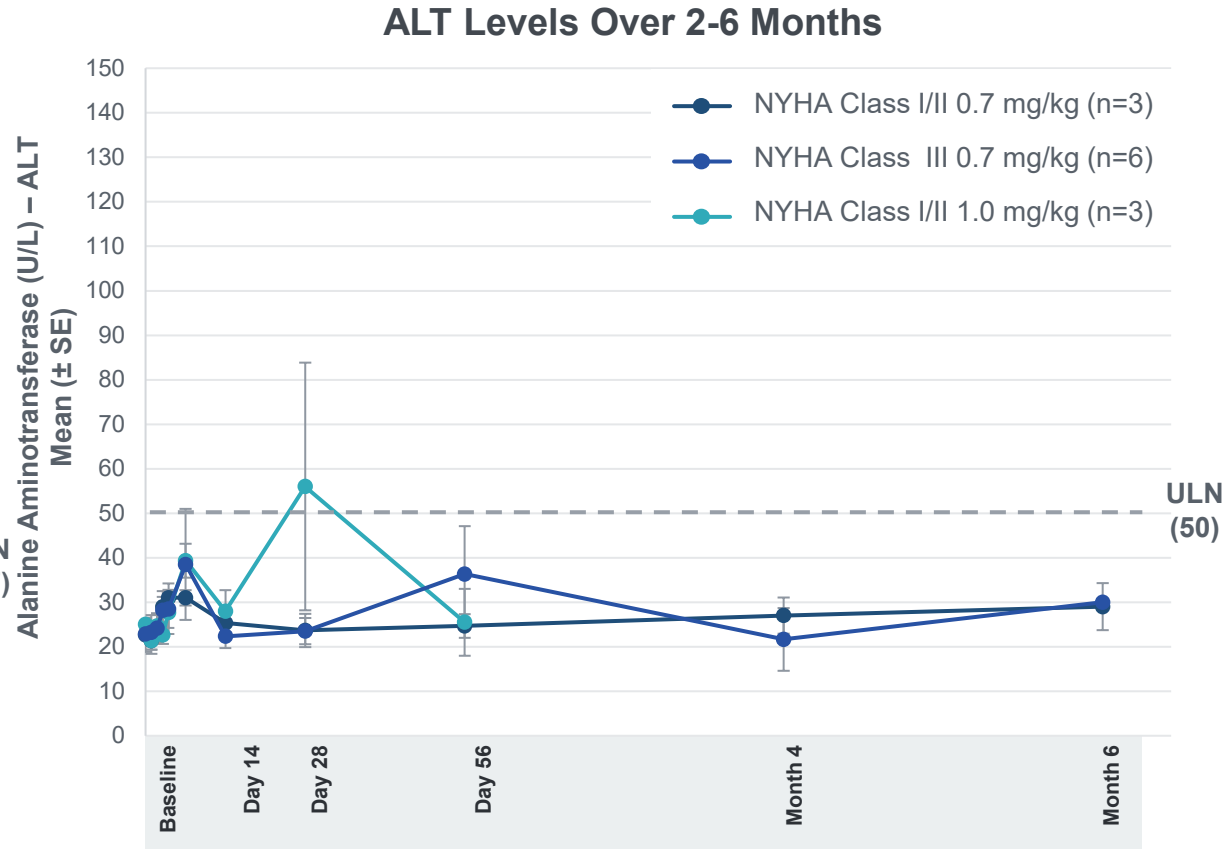
Minor, transient changes in AST and ALT levels observed post NTLA-2001 infusion



	Baseline	Day 14	Day 28	Day 56	Month 4	Month 6
NYHA Class I/II 0.7 mg/kg (n):	3	3	3	3	3	3
NYHA Class III 0.7 mg/kg (n):	6	6	6	6	3	1
NYHA Class I/II 1.0 mg/kg (n):	3	3	3	2	–	–



	Baseline	Day 14	Day 28	Day 56	Month 4	Month 6
NYHA Class I/II 0.7 mg/kg (n):	3	3	3	3	3	3
NYHA Class III 0.7 mg/kg (n):	6	6	6	6	3	1
NYHA Class I/II 1.0 mg/kg (n):	3	3	3	2	–	–

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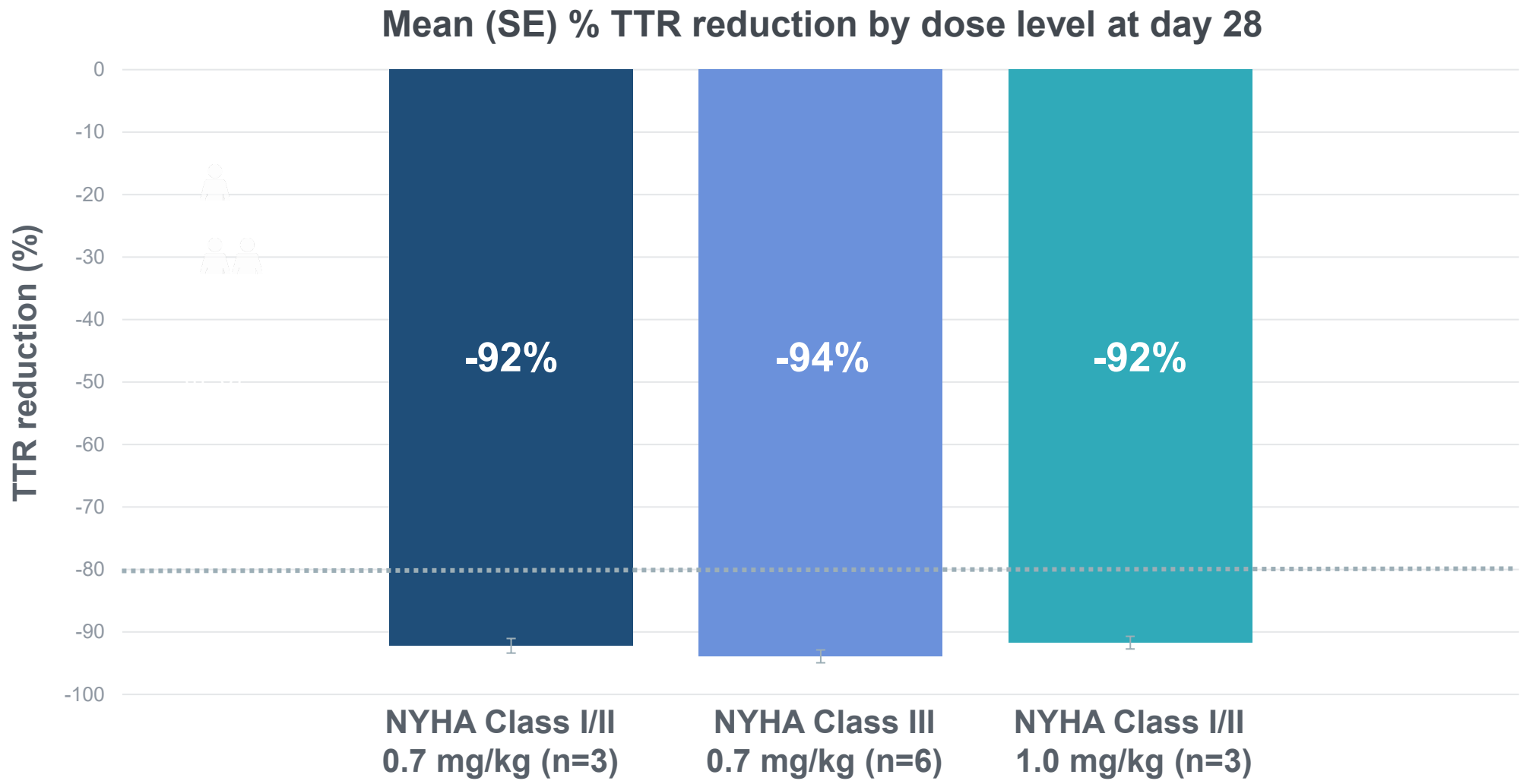
Data Cut Off: July 1, 2022

ALT, Alanine Aminotransferase; **AST**, Aspartate Aminotransferase; **ULN**, Upper Limit Normal

Mean reductions in serum TTR > 90% observed across cohorts at day 28



Data Cut Off: July 1, 2022
Dashed line represents the targeted minimum reduction
SE, standard error; **TTR**, transthyretin

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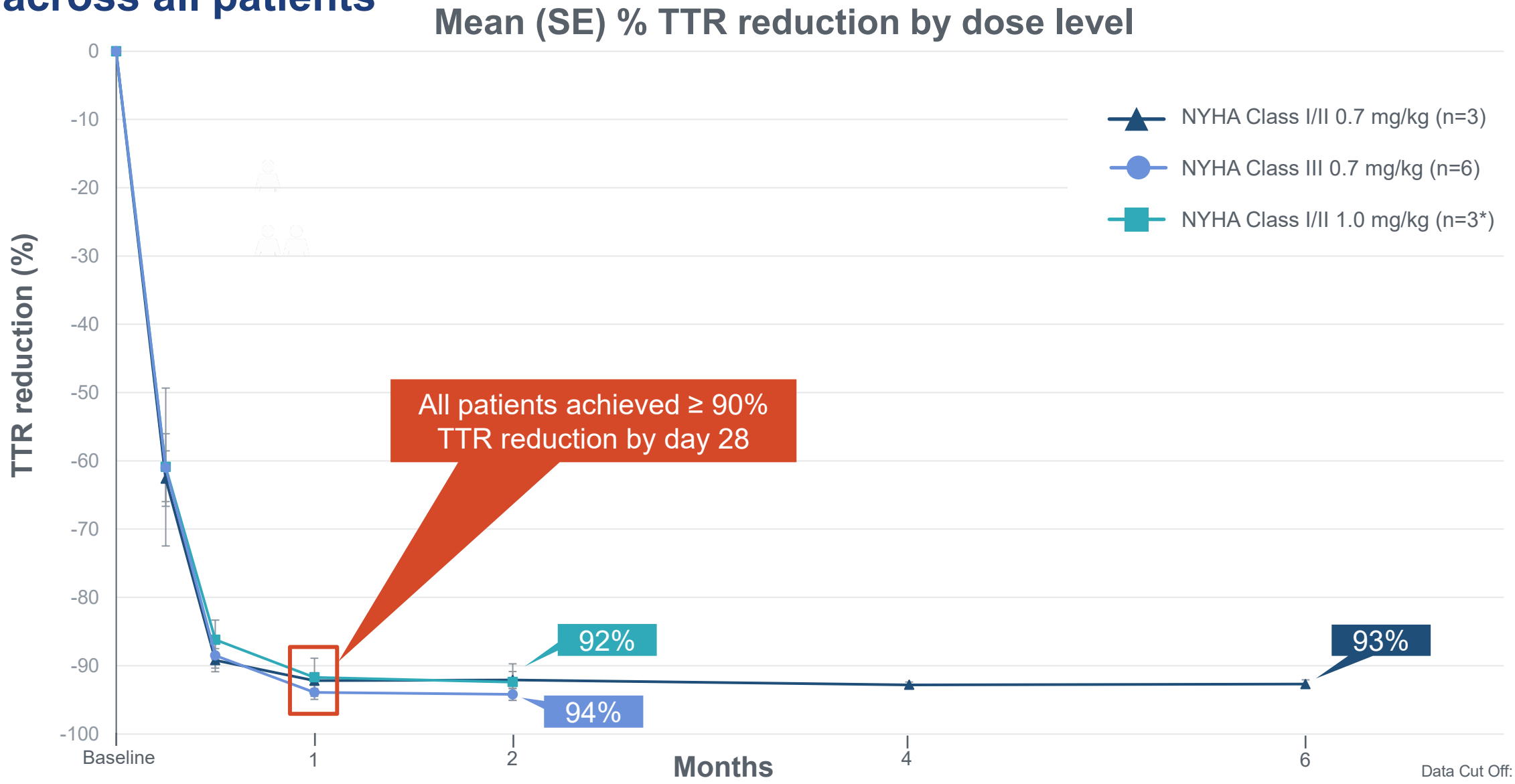
Rapid and deep serum TTR reduction sustained through 2-6 months across all patients



Data Cut Off: July 1, 2022
SE, standard error; **TTR**, transthyretin
*n=2 at Month 2 (missed patient visit)

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Deep, consistent and durable TTR reductions achieved at both 0.7 and 1.0 mg/kg doses

- Mean TTR reduction >90% across both doses by day 28 and sustained 2-6 months (through data cut-off)
- NTLA-2001 was generally well-tolerated; majority of adverse events were mild
  - Similar results across both dose levels
  - Similar results in patients with either NYHA Class I/II or III heart failure
- No clinically significant laboratory findings observed
- Data are consistent with previously reported data from polyneuropathy arm of trial

These data further support and extend early findings from this pioneering trial, demonstrating the promise of CRISPR-based *in vivo* genome editing in humans

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A fixed dose equivalent of 0.7 mg/kg has been selected for CM Part 2

Part 2 dose selection informed by totality of PD and safety data

- **Mean TTR reductions were highly similar at 0.7 and 1.0 mg/kg doses**
  - All patients demonstrated rapid reductions of ≥ 90% by day 28
- **Both doses were generally well-tolerated in NYHA Class I/II and III patients**
  - Transient liver enzyme elevations (all Grade 1) were observed
- **Previously reported transient Grade 4 ALT increase in an asymptomatic patient in the PN arm at 80 mg**
  - No bilirubin increase and resolved to baseline without treatment

REGENERON Intellia THERAPEUTICS

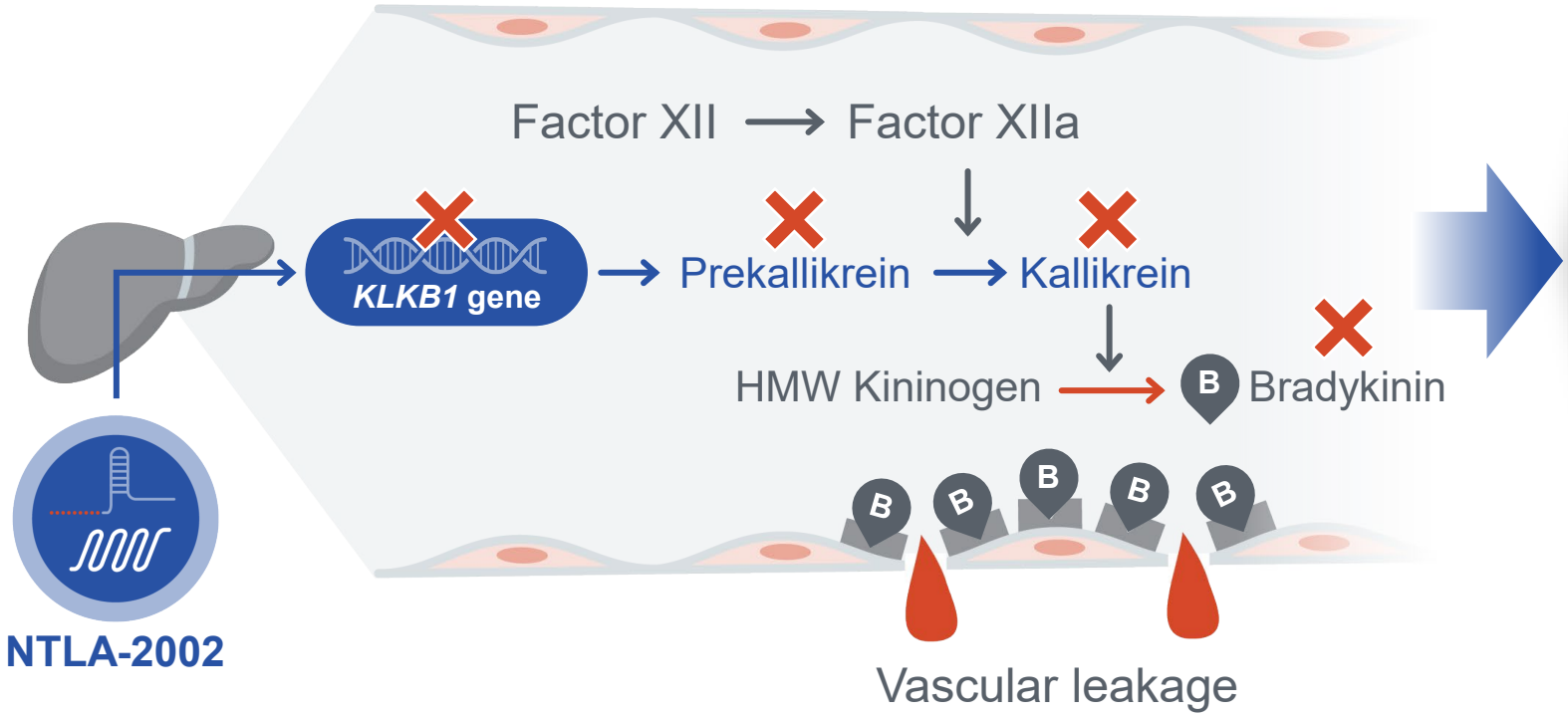
A look ahead

- Recently submitted protocol amendment to include fixed dose equivalent of 0.7 mg/kg for Part 2 of the study
- Anticipate completing enrollment in both polyneuropathy and cardiomyopathy arms by end of 2022, subject to regulatory feedback
- Evaluating study design options for potential future pivotal trials in ATTR-CM and ATTRv-PN

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

Interim data from ongoing Phase 1/2 study of NTLA-2002

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



1. Knocking out *KLKB1* gene is intended to prevent production of kallikrein
2. Reducing kallikrein levels balances bradykinin production
3. Reducing bradykinin prevents HAE attacks

Kallikrein is a clinically validated therapeutic target for preventing HAE attacks

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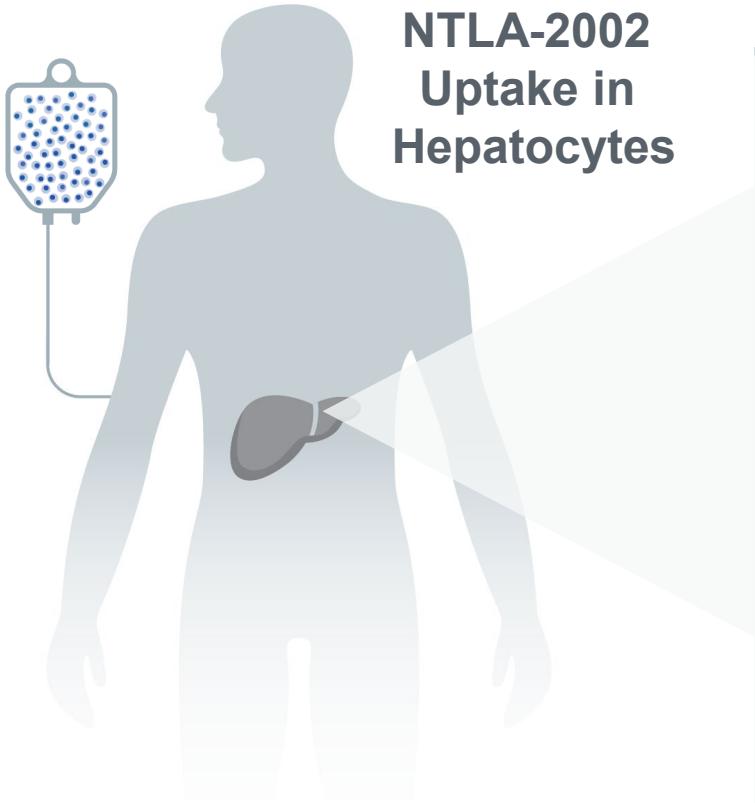
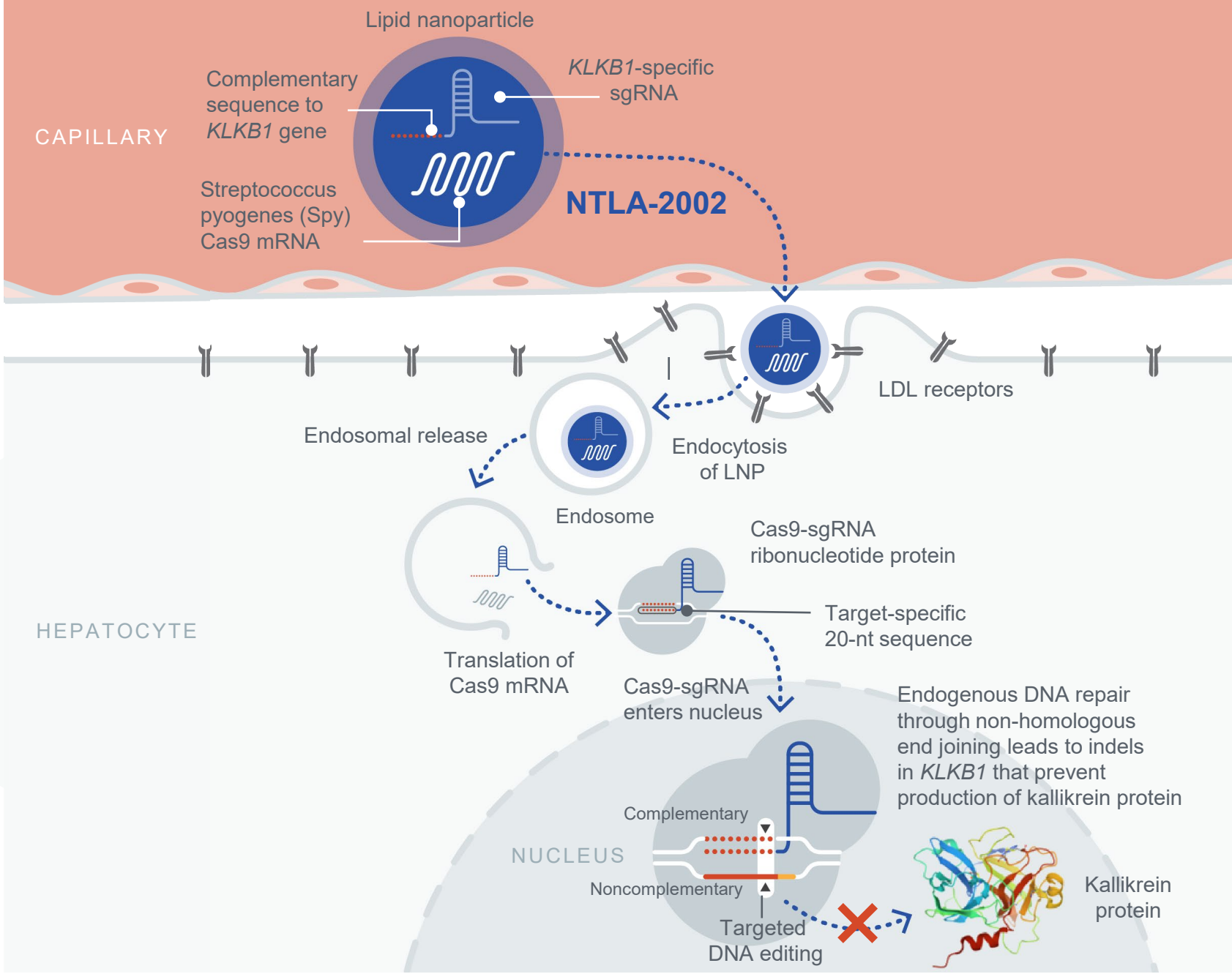
HAE, Hereditary Angioedema

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

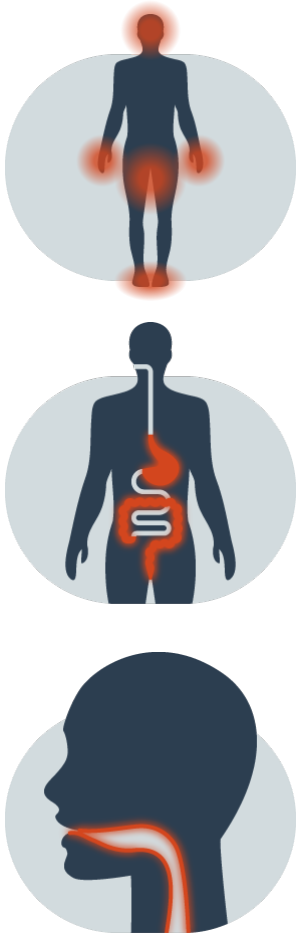
Hereditary Angioedema (HAE)

WHAT IS HAE?

- Rare, autosomal dominant genetic disease
- Associated with frequent, severe and unpredictable attacks of painful swelling

SYMPTOMS OF HAE

- Painful swelling attacks in extremities, face, stomach and GI tract
- Swelling of throat may cause difficulty swallowing or breathing, and in severe cases, can be fatal



~1 in 50,000

HAE patients worldwide[1]

Every 7-14 days

Average frequency of attacks for untreated patients[1]

Significant treatment burden exists

Chronic dosing is required with current treatments

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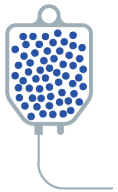
[1]Zuraw BL. Hereditary angioedema. N Engl J Med. 2008;359:1027-1036

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)

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



PHASE 1
Open-label, single-ascending dose

- 75 mg (n=3)
- 25 mg (n=3)
- 50 mg* (dosing complete)

PHASE 2
Expansion study to confirm recommended dose

Randomized

- Dose 1 (n=10)
- Dose 2 (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

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*Minimum of 3 subjects and maximum of 6 patients per cohort
H1, Histamine Receptor 1**; H2,** Histamine Receptor 2**;**
C1-INH, C1 Esterase Inhibitor; **PK,** Pharmacokinetics; **PD**, Pharmacodynamics

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

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Data Cut Off: 27 July 2022
HAE, Hereditary Angioedema

Patient reported HAE attack history

Parameter	25 mg n = 3	75 mg n = 3	All patients N = 6
Prior use of prophylaxis, n (%)			
Yes	3 (100%)	3 (100%)	6 (100%)
No	–	–	–
Historical monthly attack rate			
Mean (SD)	6.0 (6.9)	7.7 (8.0)	6.8 (6.8)
Typical attack severity, n (%)			
Mild	1 (33%)	1 (33%)	2 (33%)
Moderate	1 (33%)	1 (33%)	2 (33%)
Severe	1 (33%)	1 (33%)	2 (33%)

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Data Cut Off: 27 July 2022
SD, Standard Deviation

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

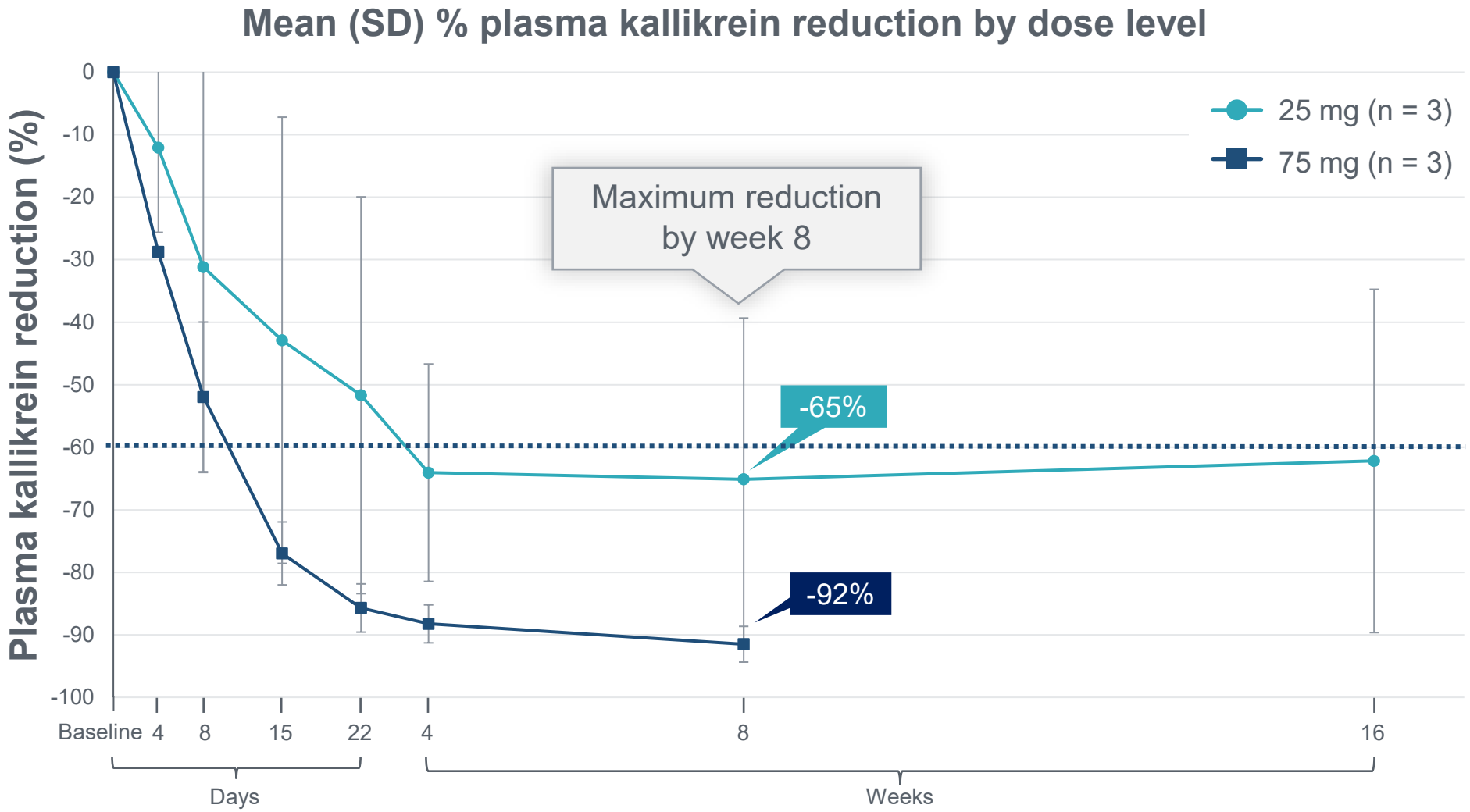
- **Across both dose levels, the most frequent adverse events were fatigue and infusion-related reactions**
  - Majority of treatment emergent adverse events were mild in severity with 67% (n = 4) and 33% (n = 2) of patients reporting a maximal adverse event severity of Grade 1 or 2, respectively
  - 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 ≥ Grade 3 AEs were observed**

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

Data Cut Off: 27 July 2022

AST, Aspartate Aminotransferase; **ALT**, Alanine Aminotransferase; **AE**, Adverse Events; **SAE**, Serious Adverse Event

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



Dashed line represents targeted minimum reduction
SD, Standard Deviation

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Patient backgrounds from the 25 mg cohort prior to administration of NTLA-2002

Patient 1	Patient 2	Patient 3
30-year-old male diagnosed with HAE Type II with a family history of HAE	52-year-old male diagnosed with HAE Type I with a family history of HAE	26-year-old male diagnosed with HAE Type I
Experienced 1.1 attacks* per month	Suffered from 7.2 attacks* per month while on danazol for long-term prophylaxis	Experienced 2.9 attacks* per month despite being on berotralstat, an oral kallikrein inhibitor
Attacks were typically moderate in severity, involving swelling in extremities	Breakthrough attacks were typically severe, involving abdominal swelling, pain and peripheral edema	Breakthrough attacks involved laryngeal swelling, cutaneous swelling in the genitourinary regions and extremities, and abdomen

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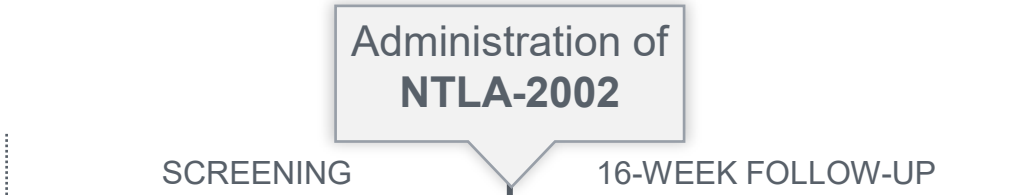
*Monthly attack rate as measured during screening period

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



	Events: HAE attacks	Attacks in screening period	Attacks in 16-week follow-up period
25 mg n = 3	Patient 1	1.1 / month	0.0 / month
	Patient 2	7.2 / month	2.0 / month
	Patient 3	2.9 / month	0.0 / month

Mean (SD) % change from baseline weeks 1-16

-91% (16%)

Analysis including 90-Day patient reported historical and screening period resulted in mean (SD) percent change of -94% (10%) in monthly attack rate
75 mg cohort has not yet completed 16-week primary observation period
SD, Standard Deviation

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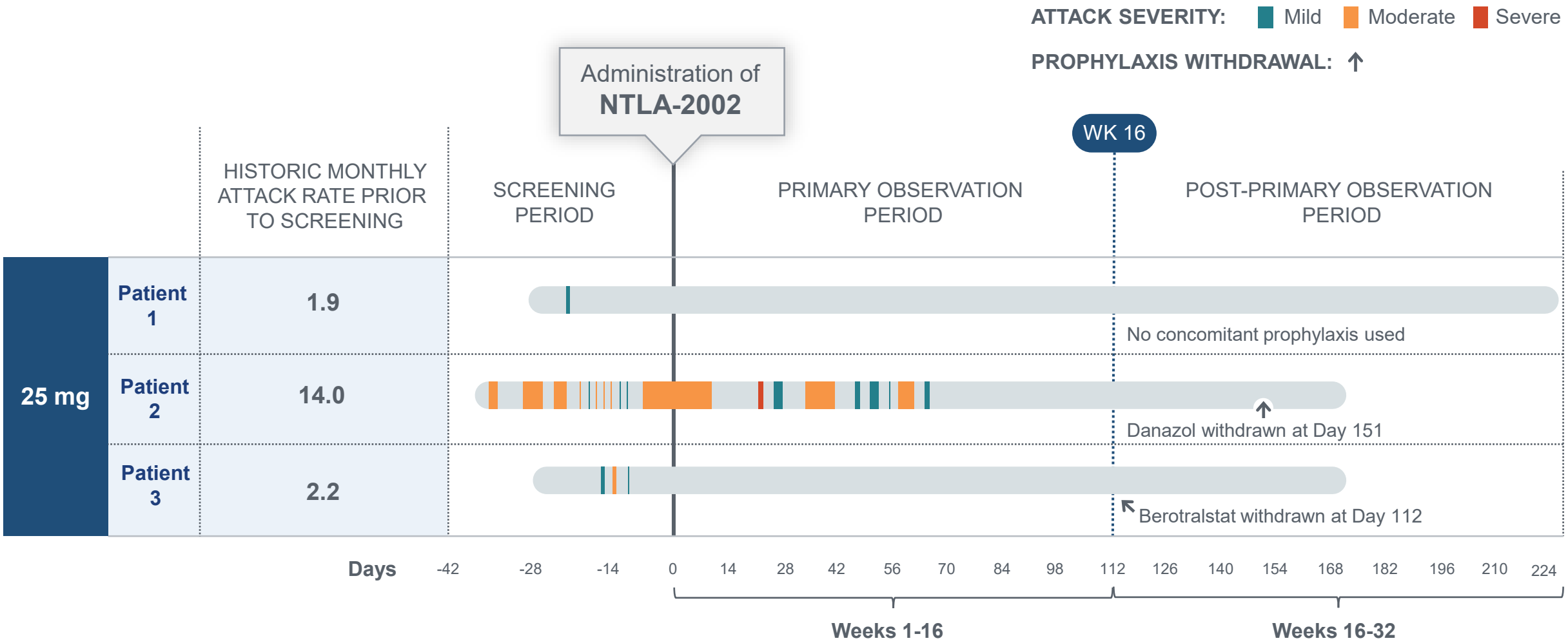
Two of three patients have remained attack free since administration with NTLA-2002: All patients have been attack free since week 10



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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

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Agenda

Welcome

Introduction

John Leonard, M.D.
Chief Executive Officer, Intellia Therapeutics

Review of NTLA-2001 Interim Clinical Data

Julian Gillmore, M.D., Ph.D., FRCP, FRCPath
Professor of Medicine, National Amyloidosis Centre, UCL Division of Medicine, Royal Free Hospital, U.K.; National Coordinator for Intellia's Phase 1 Study of NTLA-2001 in the U.K.

Next Steps for NTLA-2001 and NTLA-2002 Interim Clinical Data

David Lebwohl, M.D.
Chief Medical Officer, Intellia Therapeutics

Closing Remarks and Q&A Session

Intellia THERAPEUTICS

Intellia's strategy for *in vivo* pipeline expansion

Address diseases with genetically defined targets in the liver

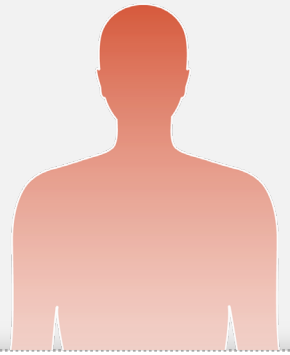
- ☑ Remove a toxic protein via knockout
- ☐ Restore a functional protein via insertion

Enable access to treat diseases across multiple tissue types

Intellia THERAPEUTICS

Platform proof-of-concept enables next wave of clinical programs

ACHIEVED HUMAN PROOF-OF-CONCEPT



NTLA-2001:
ATTR Amyloidosis*

NTLA-2002:
Hereditary Angioedema

NEXT WAVE OF CLINICAL PROGRAMS

NTLA-2003 for AATD	**NTLA-3001** for AATD	Hemophilia A**	Hemophilia B**

Types of edits: knockout or insertion

* In collaboration with Regeneron – Intellia-led
** In collaboration with Regeneron – Regeneron-led

AATD: Alpha-1 Antitrypsin Deficiency

Intellia THERAPEUTICS

Significant opportunities to unlock full potential of *in vivo* platform

CRITERIA USED TO SELECT POTENTIAL FUTURE CANDIDATES:

Unmet need • Population size • Technical feasibility

Potential Liver Development Programs*

Rare Diseases**

- Blood disorders
- Lysosomal storage diseases
- Metabolic diseases

Prevalent Diseases**

- Dyslipidemia
- Hypertension
- NASH
- Viral diseases

Unlocking Full Potential of Genome Editing

Target Tissues


Bone marrow


CNS/PNS


Eye***


Heart


Skeletal muscle

Expansion into tissue-specific diseases

* This is a selection of potential liver targets and does not represent all future opportunities
** Individual targets could be developed by Intellia, Regeneron or through collaborations
*** In collaboration with SparingVision

Intellia THERAPEUTICS

change life stories with genome editing therapies

Vince and David, living with transthyretin amyloidosis

Bill, living with transthyretin amyloidosis

Fiona, living with hereditary angioedema.

Q&A

NTLA-2001 and NTLA-2002
Interim Clinical Data Update

Appendix

Majority of adverse events were mild in severity (NTLA-2002)

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.

Patients counted once per row, per dose level, as highest grade reported.
Gr., Grade; **AE**, adverse events; **TEAE**, treatment-emergent adverse event

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THERAPEUTICS