2021 PNS ANNUAL MEETING

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12-13 JUNE / 25-27 JUNE 2021

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PERIPHERAL NERVE SOCIETY

In vivo CRISPR/Cas9 Editing of the *TTR* Gene by NTLA-2001 in Patients with Transthyretin Amyloidosis

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Disclosures

- JDG: Expert adviser for Alnylam Pharmaceuticals, Eidos Therapeutics, Ionis Pharmaceuticals Inc., and Intellia Therapeutics Inc.

Potential for gene editing to address unmet need for hATTR/ATTRv amyloidosis

- Therapy in amyloidosis is intended to reduce or stabilize precursor protein, in ATTR amyloidosis = transthyretin (TTR)
  - Gene silencing therapy (patisiran) knocks serum TTR down by ~80% (mean) and benefits neuropathy in ATTRv[1]
  - Patients on standard treatment experience debilitating effects, disease progression and ultimately fatal complications
  - Greater TTR knockdown is expected to achieve better clinical outcomes, and can potentially reverse the disease

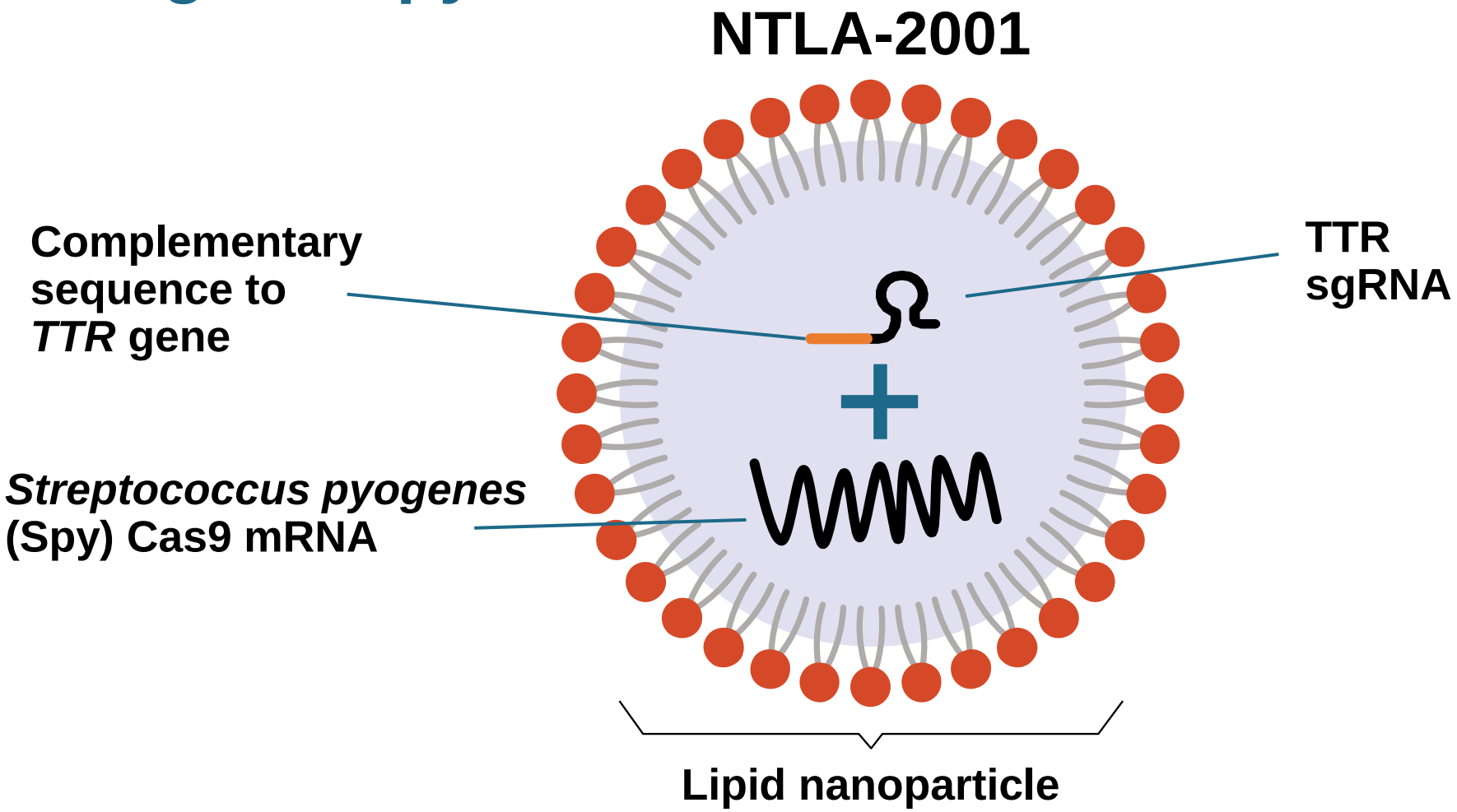
- Editing of the *TTR* gene is an attractive alternative therapeutic strategy

➢ **Potentially providing permanent, profound TTR knockdown, without the need for chronic therapy**

TTR, transthyretin

1. Adams D, et al. N Engl J Med 2018;379:11–21.

NTLA-2001 is a novel CRISPR/Cas9-based *in vivo* gene editing therapy



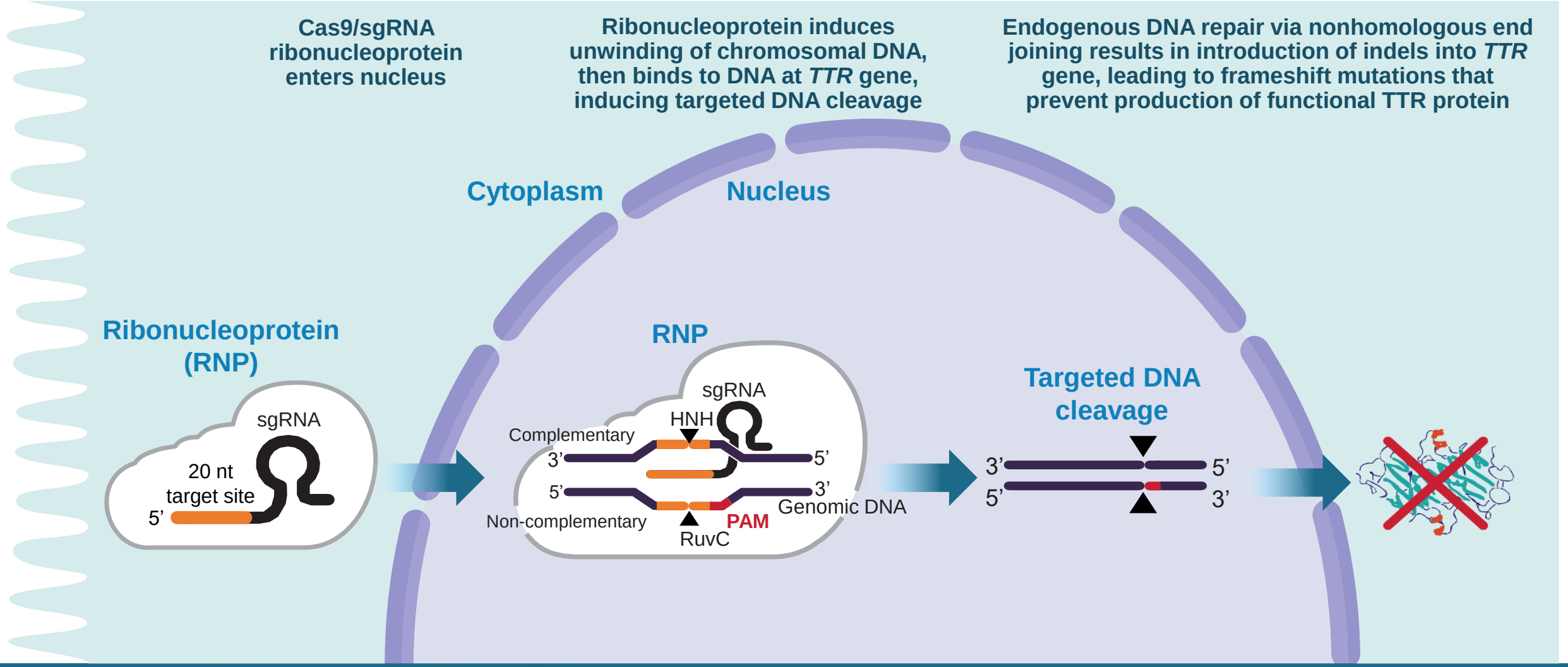
sgRNA; single guide RNA; TTR, transthyretin

NTLA-2001 delivers sgRNA and Cas9 into the nucleus, which precisely edit and inactivate the *TTR* gene

Cas9/sgRNA ribonucleoprotein enters nucleus

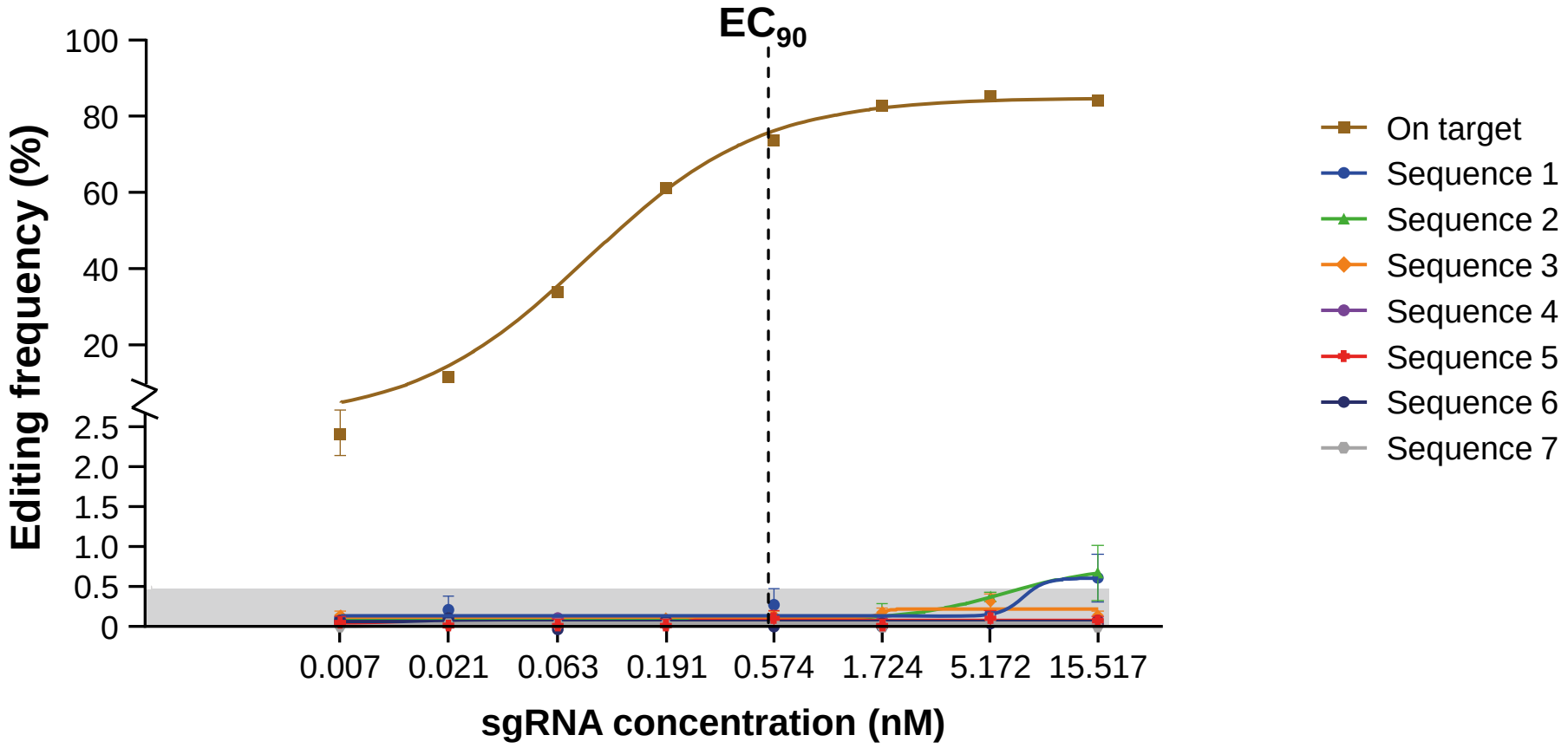
Ribonucleoprotein induces unwinding of chromosomal DNA, then binds to DNA at *TTR* gene, inducing targeted DNA cleavage

Endogenous DNA repair via nonhomologous end joining results in introduction of indels into *TTR* gene, leading to frameshift mutations that prevent production of functional TTR protein



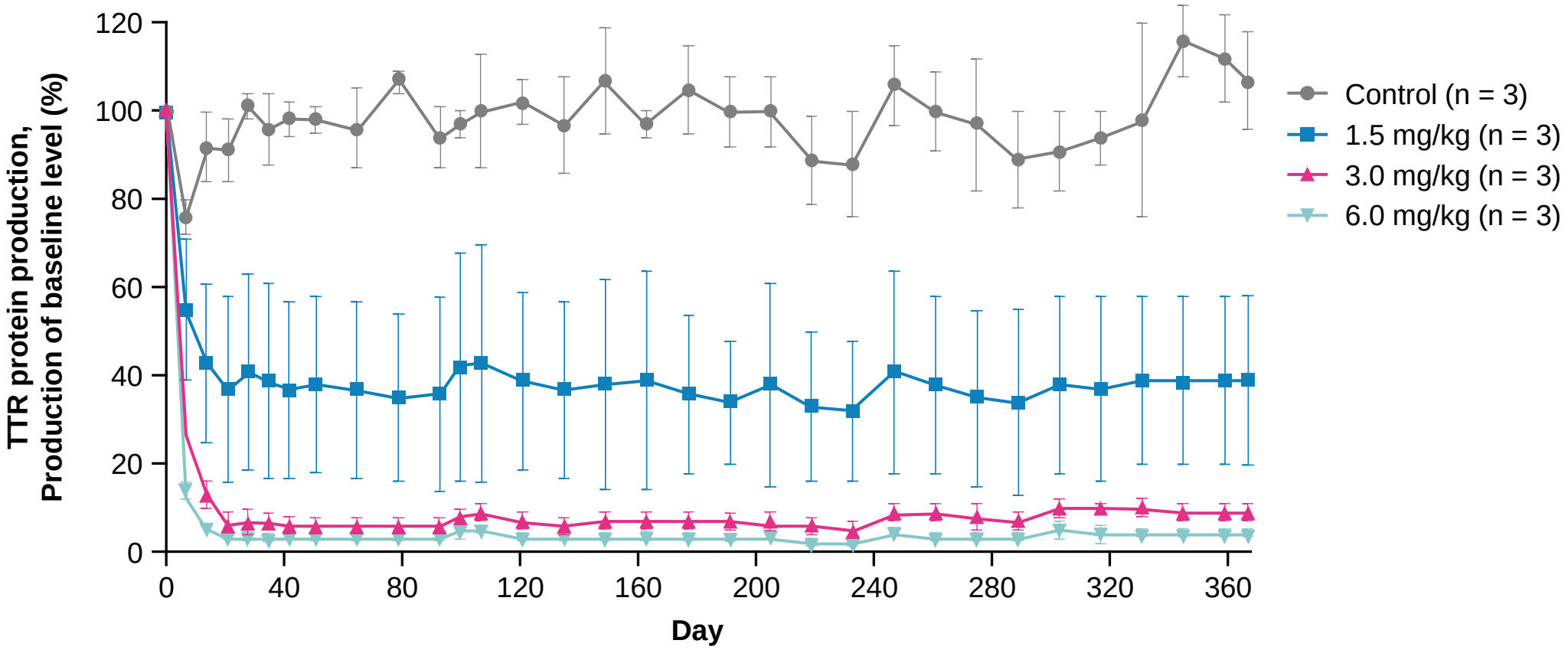
HNH, an endonuclease domain named for characteristic histidine and asparagine residues; nt, nucleotide; RNP, ribonucleoprotein; RuvC, an endonuclease domain; sgRNA, single guide RNA; TTR, transthyretin

In vitro: No detectable off-target editing with pharmacologic concentration of sgRNA



EC_{90}, concentration inducing 90% of maximal effect; sgRNA, single guide RNA

NHP: Durable, >95% TTR reduction after a single dose



NHP; non-human primate, TTR, transthyretin

First-in-human: Two-part phase 1 study of NTLA-2001

Population: Adults with ATTRv with polyneuropathy

Intervention:
Single dose administered via an intravenous infusion

Part I
Single-ascending dose

Up to 4 doses

Part II
Single-dose expansion cohort

Administer recommended dose selected from Part I

Today's interim data cover the first six patients dosed across two cohorts through Day 28

Primary objectives

- Evaluate safety, tolerability, PK and PD
- Measure TTR levels

PD, pharmacodynamics; PK, pharmacokinetics; TTR, transthyretin.
ClinicalTrials.gov identifier: NCT04601051

NTLA-2001 first-in-human study: Demographics

Parameter	0.1 mg/kg dose (n = 3)	0.3 mg/kg dose (n = 3)
Age, years		
Median (min, max)	54 (50, 63)	53 (46, 64)
Sex, n		
Male	1	3
Female	2	0
Weight, kg		
Median (min, max)	82 (70, 89)	84 (82, 90)
Mutation status, n		
p.H110D	0	1
p.S97Y	1	1
p.T80A	2	1
Prior therapy, n		
None	1	2
Diflunisal	2	1

Parameter	0.1 mg/kg dose (n = 3)	0.3 mg/kg dose (n = 3)
Clinical scores, n		
Polyneuropathy disability score 1	3	3
NYHA Functional Classification I	3	3
NT-proBNP (ng/L), median (min, max)	127 (89, 596)	119 (50, 359)
Years since diagnosis (min, max)	2 (2, 9)	3 (1, 11)

NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association

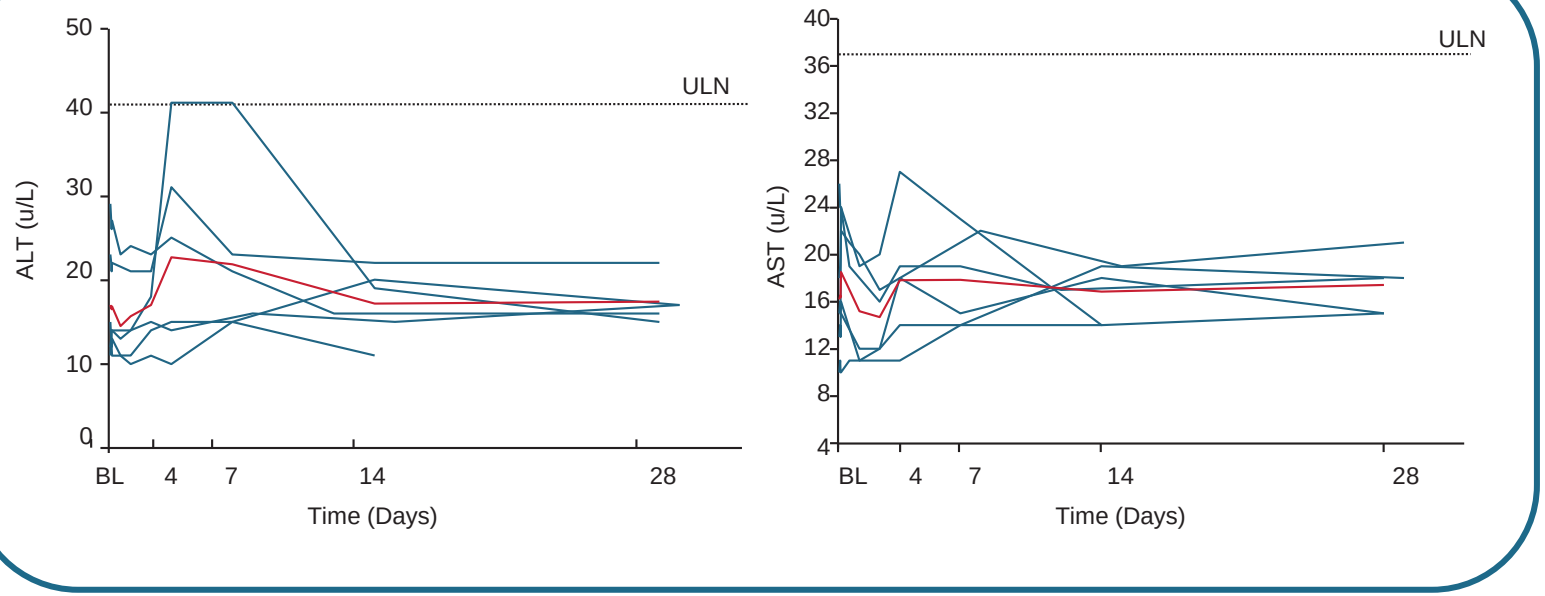
NTLA-2001 generally well tolerated in acute phase (N=6): all AEs Grade 1 with no serious AEs

Preferred Term	0.1 mg/kg (n = 3)	0.3 mg/kg (n = 3)
Subjects with at least one TEAE	**2**	**1**
Headache	2	
Diarrhea	1	
Nausea	1	
Infusion-related reaction	1	
Skin abrasion		1
Vertigo positional	1	
Foreign body sensation in eyes	1	
Catheter site swelling	1	
Acute sinusitis	1	
Thyroxine decreased	1	
Rhinorrhea	1	
Pruritis	1	
Rash	1	

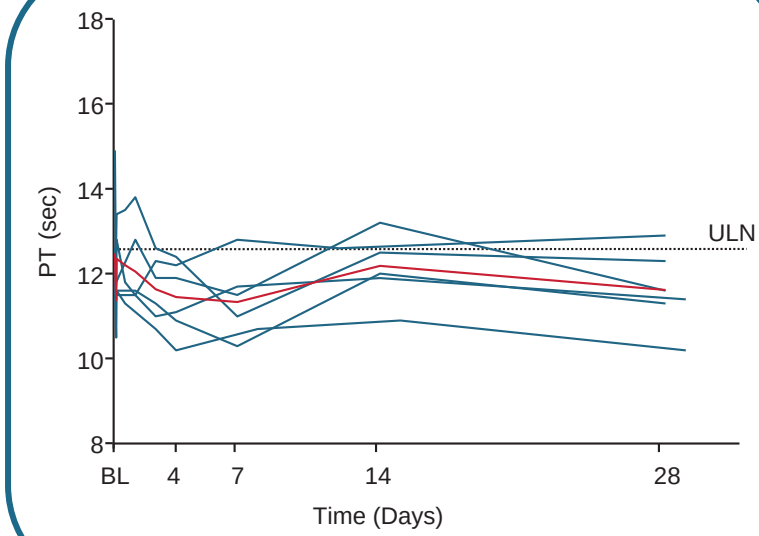
AE, adverse event; TEAE, treatment-emergent adverse event

No liver findings or coagulopathy based on laboratory testing

Liver function



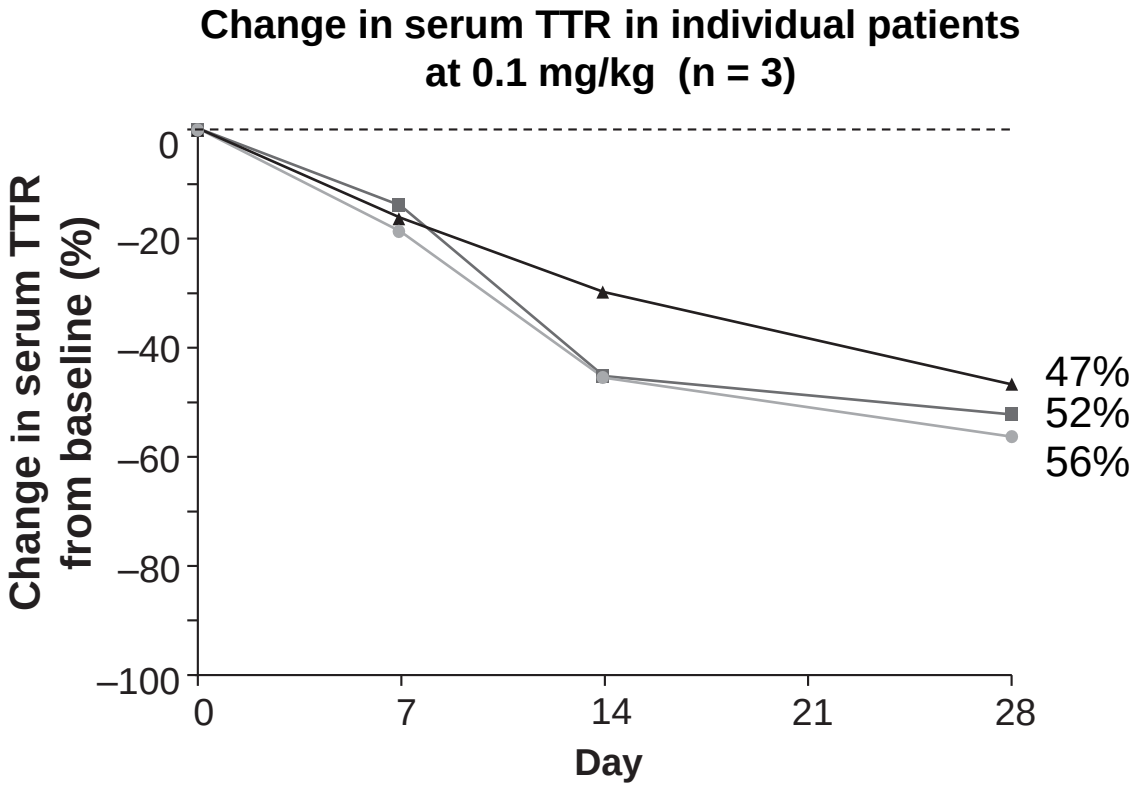
Coagulation



Individual patients — Mean ---- Reference value

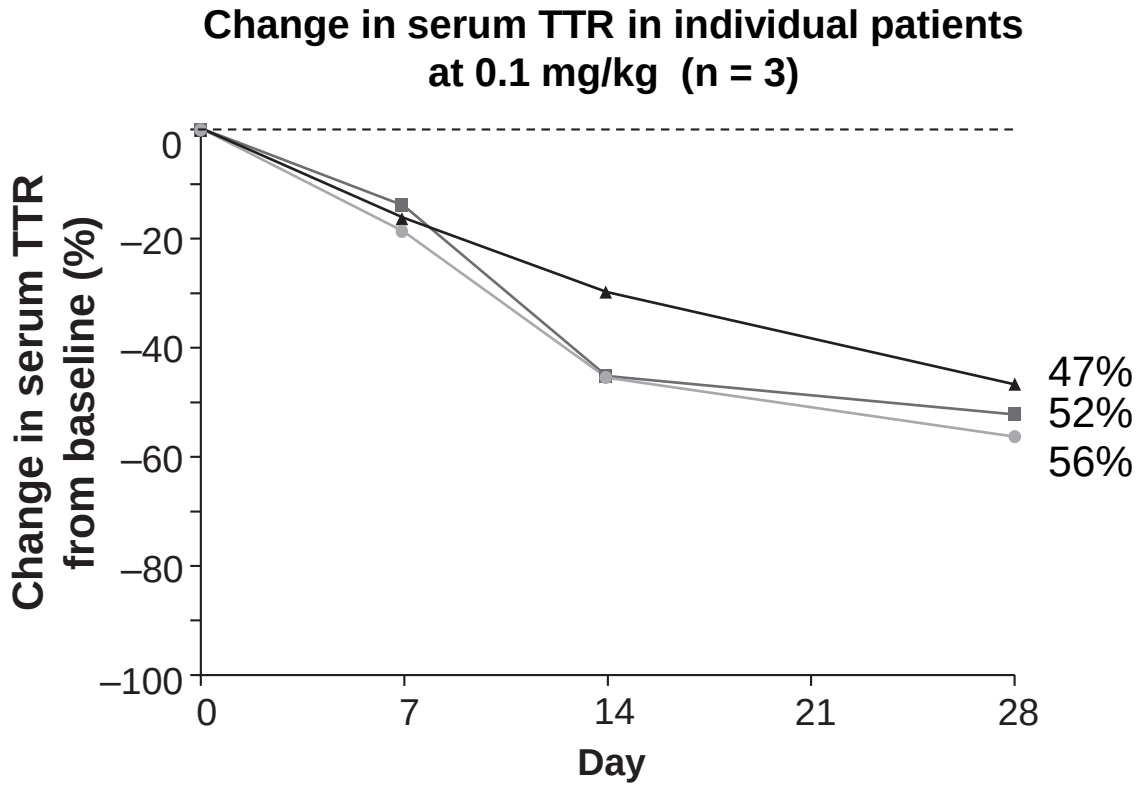
ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, prothrombin, ULN, upper limit of normal.

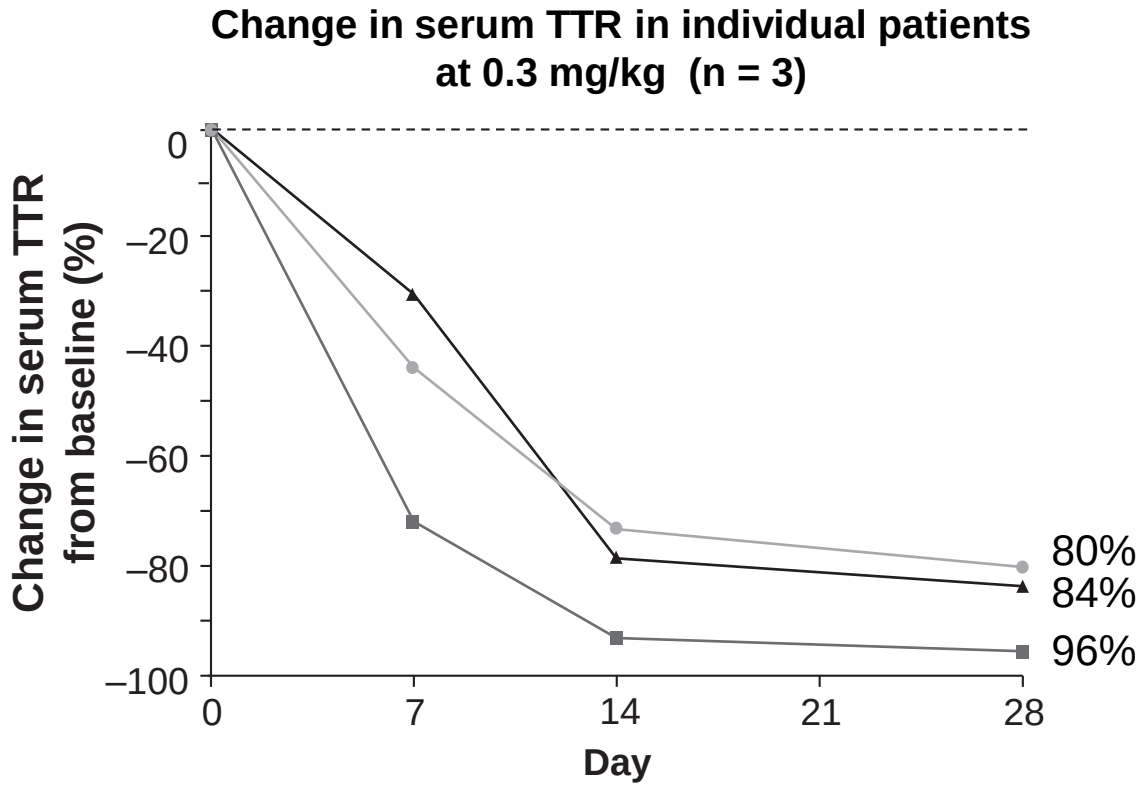
Dose-dependent serum TTR reduction after NTLA-2001



TTR, transthyretin

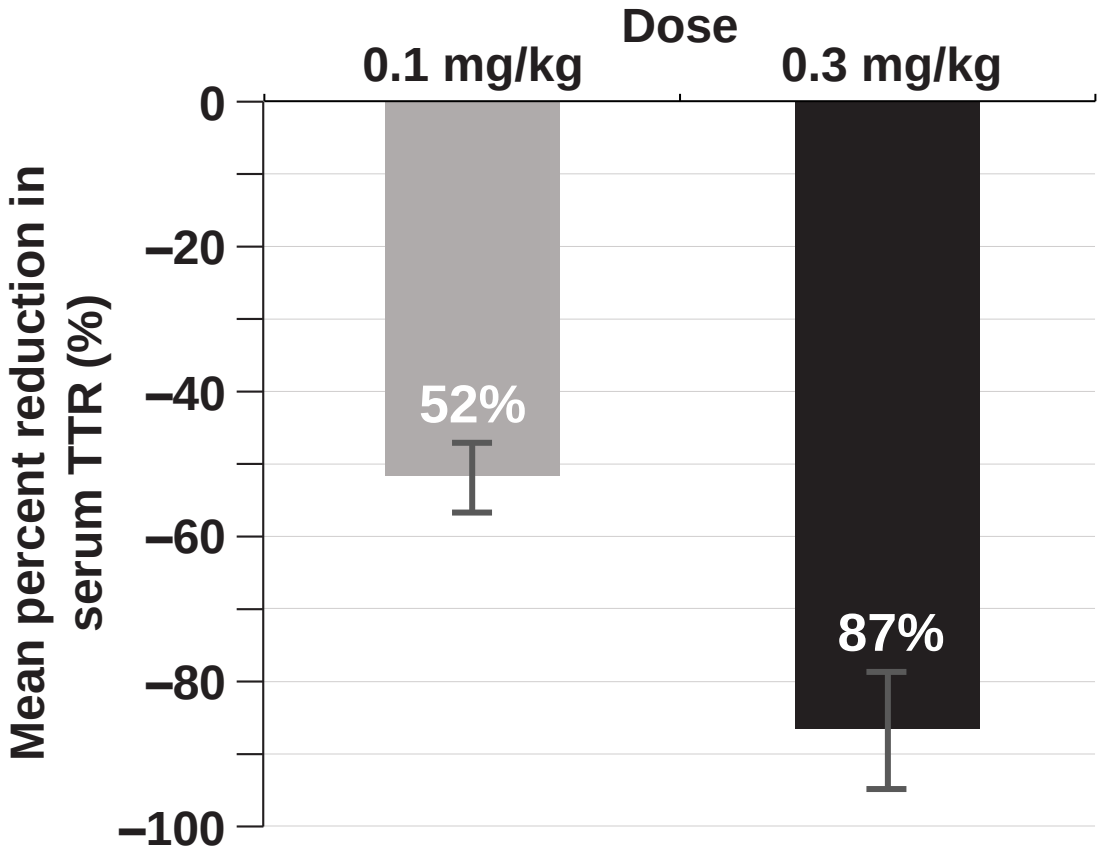
Dose-dependent serum TTR reduction after NTLA-2001





TTR, transthyretin

Average TTR reduction of 87% for 0.3 mg/kg: Predicted to result in clinical benefit for patients



Bars represent standard deviation.
TTR, transthyretin

Conclusions:
In vivo CRISPR/Cas9 editing of the *TTR* gene by NTLA-2001

- A single systemic administration of NTLA-2001 in patients with ATTRv amyloidosis-PN caused a profound reduction in serum TTR protein concentrations
  - Effect of NTLA-2001 was dose-dependent
  - 0.1 mg/kg: 52% mean reduction in TTR (56% maximum)
  - 0.3 mg/kg: 87% mean reduction in TTR (96% maximum)
- NTLA-2001 treatment was generally well tolerated: all acute AEs were of mild severity
- Further dose escalation is ongoing in this First-In-Human study
  - Greater reduction in TTR than provided by currently available agents may be achieved
  - Those greater reductions in TTR are expected to result in improved clinical benefit

- This is the first demonstration of CRISPR-based *in vivo* gene editing in humans
  - ➢ Provides proof-of-concept for a promising new therapeutic strategy

AE, adverse event; ATTRv, hereditary transthyretin amyloidosis; PN, polyneuropathy; TTR, transthyretin

Acknowledgements

- We thank the patients who participated in this trial, and their families
- We thank New Zealand Clinical Research and Richmond Pharmacology for contract research assistance, and Charles River Laboratory, Altasciences, Precision for Medicine, PPD, and QPS for serum TTR ELISA measurements and PK and biomarker tests
- We acknowledge valuable input in the development of NTLA-2001 from:
  - Intellia Therapeutics: Carri Boiselle, James Butler, David Cooke, Tracy DiMezzo, Richard Duncan, Eva Essig, Noah Gardner, Bo Han, Denise Hernandez, Kellie Kolb, John Leonard, Rebecca Lescarbeau, Reynald Lescarbeau, Mark McKee, Nishit Patel, Austin Ricker, Joseph Rissman, Matthew Roy, Andrew Schiermeier, Philipp Schneggenburger, Palak Sharma, Samantha Soukamneuth, and Kathryn Walsh
  - Regeneron Pharmaceuticals: Olivier Harari, Christos Kyratsous, Andrew Murphy, Randy Soltys, and Brian Zambrowicz
- Medical writing support was provided by Ben Caldwell, BSc, ISMPP CMPP™ of Arc, a division of Spirit Medical Communications Group Limited, and funded by Intellia Therapeutics and Regeneron Pharmaceuticals, in accordance with Good Publication Practice 3 (GPP3) guidelines (www.ismpp.org/gpp3)