Activity of Follow-On Dosing for an Investigational *In Vivo* CRISPR-Based Lipid Nanoparticle Therapy in Transthyretin Amyloidosis

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Disclosures

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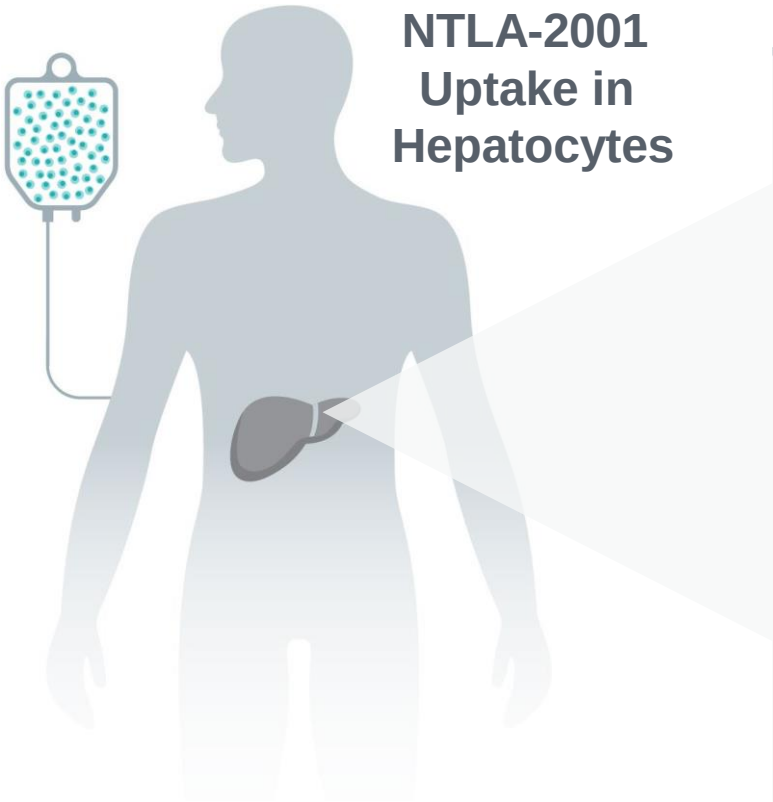
Gene Editing Has the Potential to Address the Unmet Need in ATTR Amyloidosis

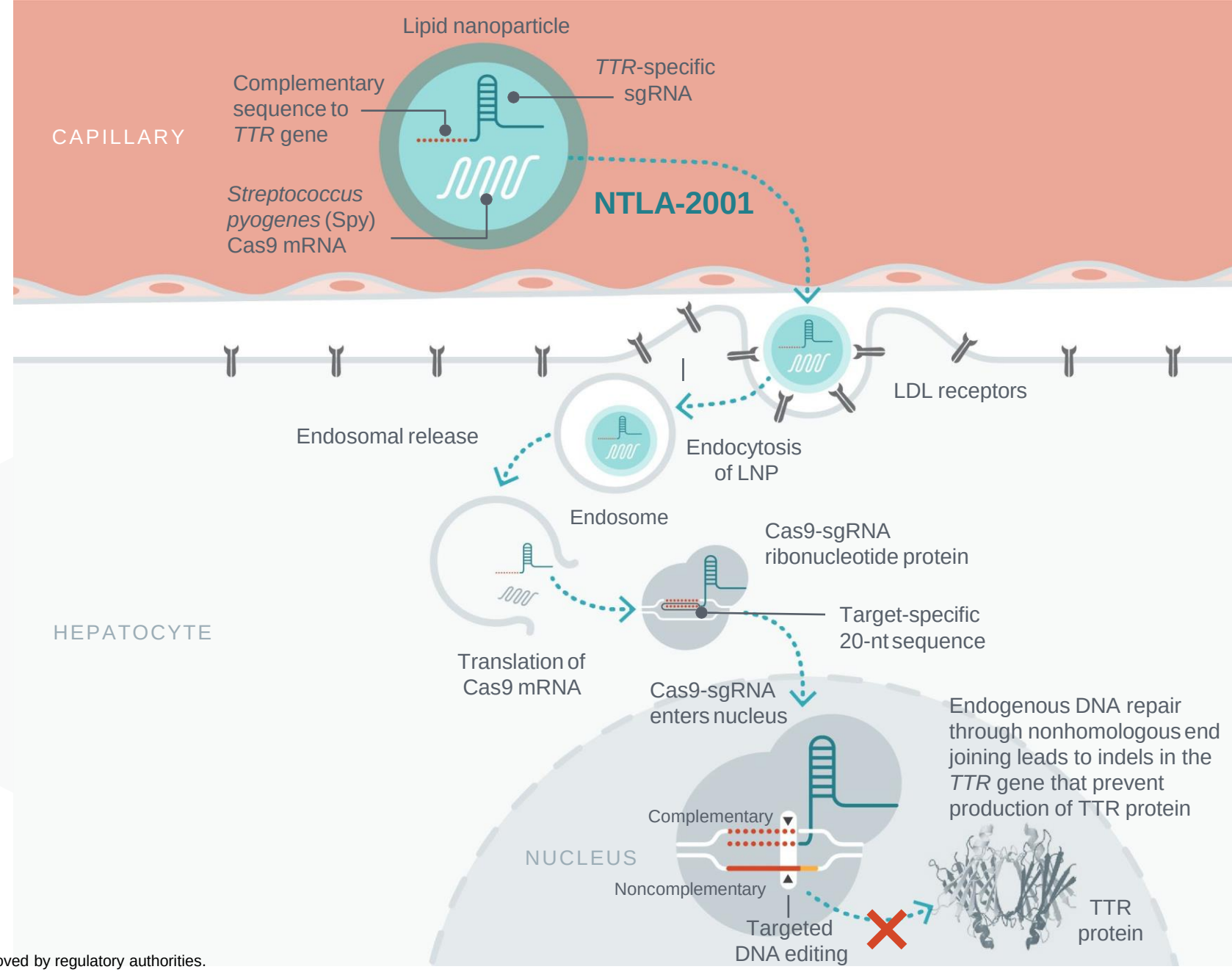
- Current therapies are intended to reduce or stabilize the precursor protein, transthyretin (TTR)
- Patients may continue to progress despite treatment with TTR stabilizers or TTR silencers leading to debilitating effects, disease progression, and ultimately, fatal complications
- Many patients do not achieve sufficiently low serum [TTR] necessary to change the equilibrium state from amyloid fibril formation and deposition to amyloid fibril degradation
- NTLA-2001, an investigational, *in vivo,* CRISPR-based, one-time therapy for the treatment of ATTR amyloidosis, may consistently lower serum [TTR] in patients to achieve better clinical outcomes and potentially reverse the disease

Editing the *TTR* gene offers potential to provide permanently low serum [TTR] without the need for chronic therapy

NTLA-2001 Is an Investigational, *In Vivo*, One-Time CRISPR-Based Gene Editing Therapy



NTLA-2001 Uptake in Hepatocytes

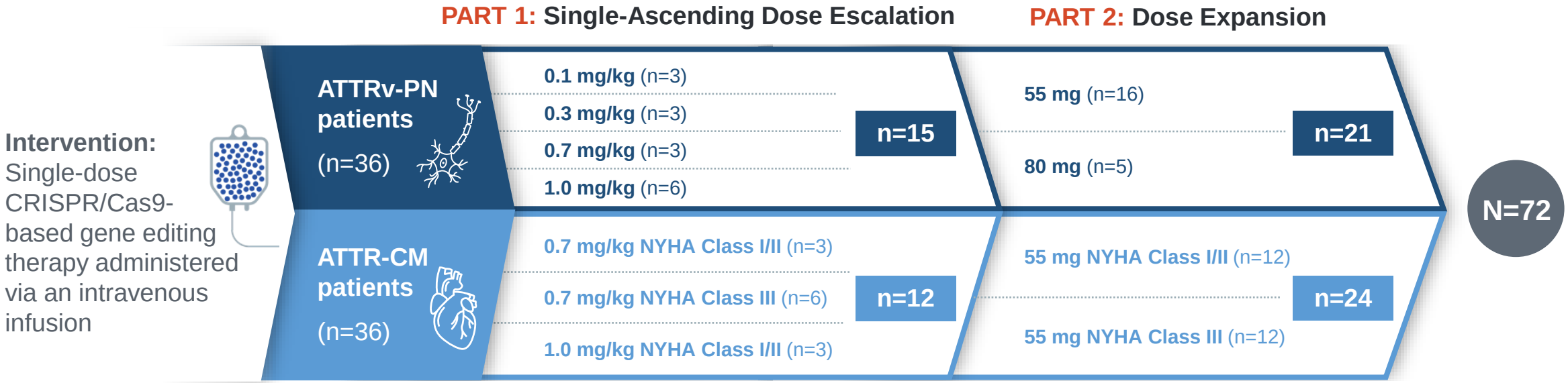


This presentation includes data for an investigational product not yet approved by regulatory authorities.

Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; indel, insertion-deletion; LDL, low-density lipoprotein; LNP, lipid nanoparticle; mRNA, messenger RNA; nt, nucleotide; sgRNA, single-guide RNA; TTR, transthyretin.

Gillmore JD et al. *N Engl J Med.* 2021;385(6):493-502.

Two-Part, Open-Label, Multicenter Study in Adults With Hereditary ATTR Amyloidosis With Polyneuropathy (ATTRv-PN) or ATTR Amyloidosis With Cardiomyopathy (ATTR-CM)



PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK, and PD

- *Measure serum [TTR] levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of:

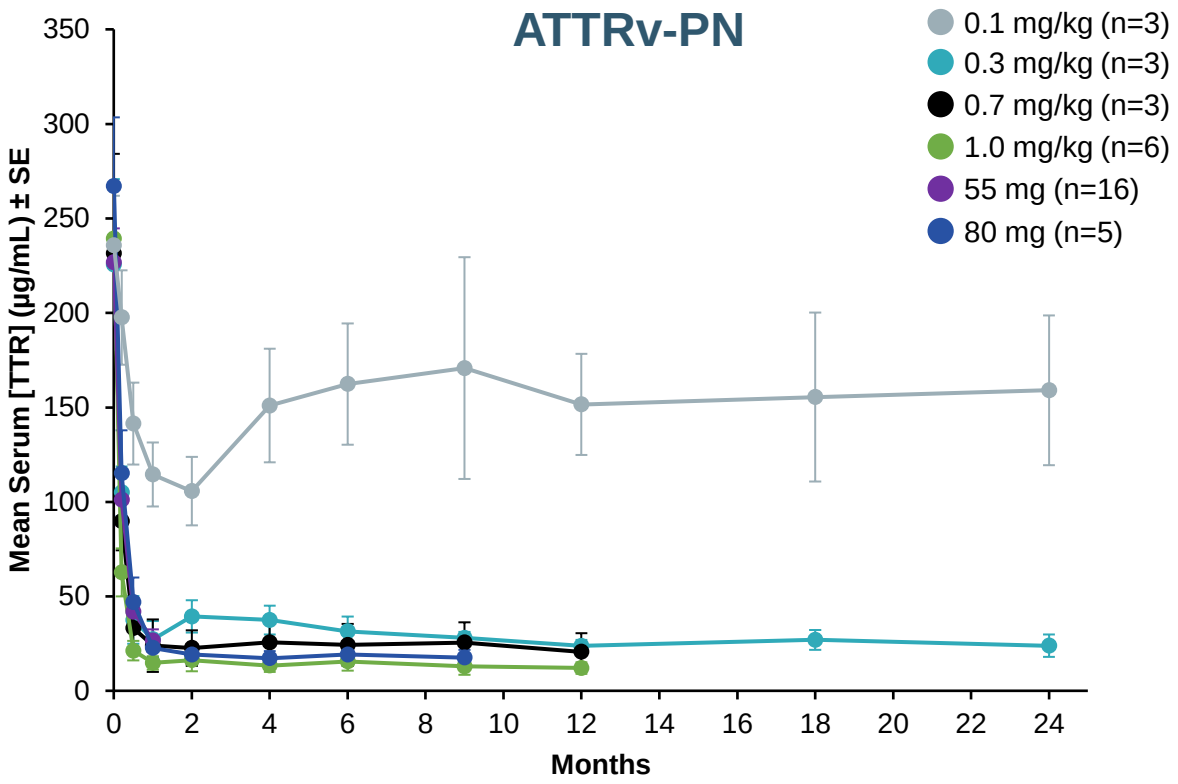
- *Neurologic function in patients with ATTRv-PN*
- *Cardiac disease in patients with ATTR-CM*

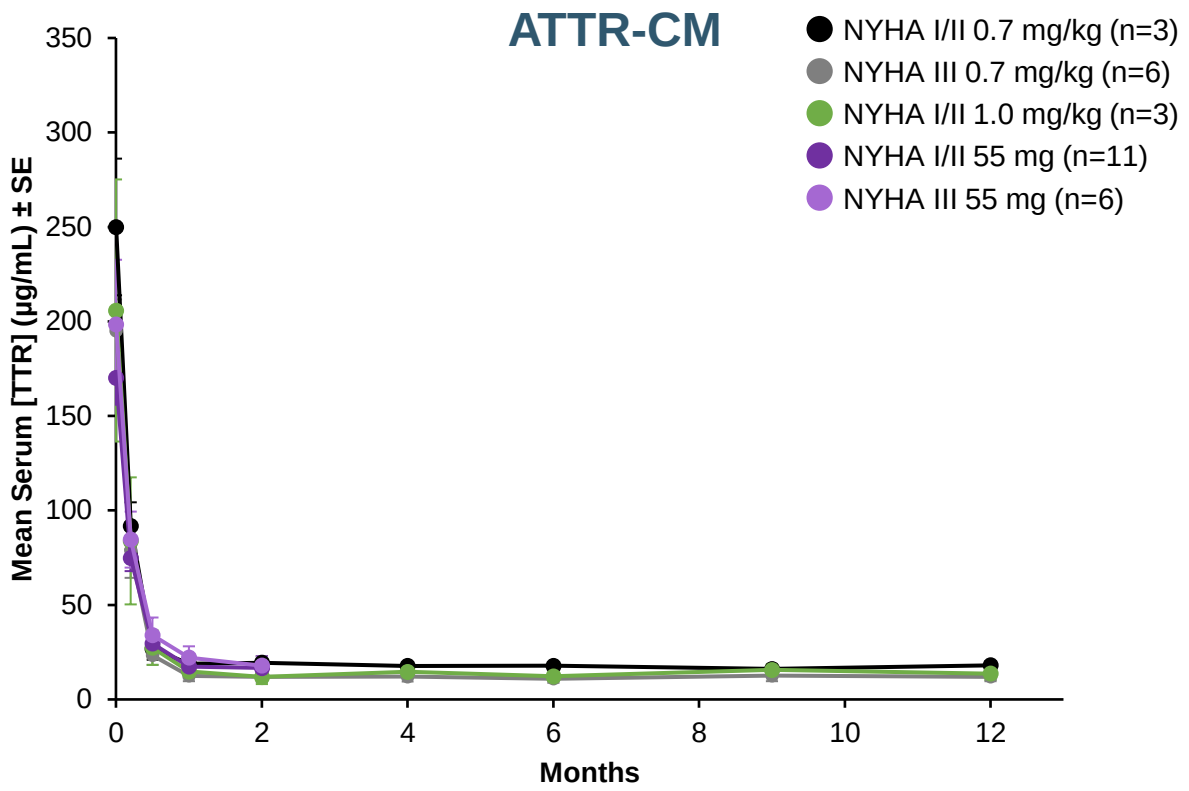
Clinicaltrials.gov ID: NCT04601051.

After completing the protocol-specified 2-year observation period, patients who received the lowest dose (0.1 mg/kg) were offered a follow-on dose (55 mg) to achieve target PD effect

Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; NYHA, New York Heart Association; PD, pharmacodynamics; PK, pharmacokinetics.

NTLA-2001 Led to Consistently Low and Sustained Absolute Serum [TTR]





Cohort	Serum [TTR] at Day 28	Median (IQR)
0.1 mg/kg (n=3)	Residual absolute TTR concentration	130 µg/mL (81 to 133)
	% Change from baseline in serum [TTR]	-52% (-47 to -57)
All other doses (n=62)	Residual absolute TTR concentration	17 µg/mL (11 to 24)
	% Change from baseline in serum [TTR]	-91% (-88 to -94)

Data cutoff May 11, 2023.

Figure notes: Results in each figure are shown out to the last time point with complete follow-up for the cohort. The 55-mg and 80-mg doses are the fixed doses corresponding to 0.7 mg/kg and 1.0 mg/kg, respectively.

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; IQR, interquartile range; NYHA, New York Heart Association; SE, standard error; TTR, transthyretin.

Demographics

Characteristic		PN Patients 0.1 mg/kg (n=3)	PN Patients (n=36)	CM Patients (n=29)	All Patients (N=65)
Age, years	Median (min, max)	54 (50, 63)	61 (19, 75)	78 (46, 86)	68 (19, 86)
Sex, n (%)	Male	1 (33)	26 (72)	28 (97)	54 (83)
Weight, kg	Median (min, max)	82 (70, 89)	77 (55, 117)	82 (63, 115)	81 (55, 117)
TTR genotype, n (%)	p.V50M	0	11 (31)	0	11 (17)
	p.V142I	0	1 (3)	6 (21)	7 (11)
	p.T80A	2 (67)	7 (19)	1 (3)	8 (12)
	p.S97Y	1 (33)	7 (19)	0	7 (11)
	p.E62D	0	4 (11)	0	4 (6)
	Other	0	6 (17)	2 (7)	8 (12)
	WT	0	0	20 (69)	20 (31)
NYHA Class, n (%)	No diagnosis of heart failure	0	12 (33)	0	12 (18)
	I	3 (100)	19 (53)	3 (10)	22 (34)
	II	0	5 (14)	14 (48)	19 (29)
	III	0	0	12 (41)	12 (18)
NT-proBNP, ng/L	Median (min, max)	127 (89, 596)	127 (<50, 1878)	1845 (851, 19,624)	757 (<50, 19,624)

Data cutoff May 11, 2023.
Interim data presented are for the first 65 (dosed and reached at least 28 days post-infusion by the data cutoff) of 72 patients dosed. Results from the final 7 patients will be reported at a future date.
CM, cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PN, polyneuropathy; TTR, transthyretin; WT, wild type.

Follow-On Dosing Was Well Tolerated and Did Not Lead to Any Safety Findings

TEAEs by Maximum Toxicity Grade and Preferred Term Reported in Patients After Receipt of a Follow-On Dose (n=3)

Preferred Term,[a] n (%)	0.1 mg/kg + 55 mg (n=3)	Maximum CTCAE Toxicity Grade
Any TEAE	2 (67%)	
COVID-19	1 (33%)	1
Fatigue	1 (33%)	1
Hand fracture	1 (33%)	1
Headache	1 (33%)	1
Infusion-related reaction	1 (33%)	1
Nausea	1 (33%)	1
Vulvovaginal candidiasis	1 (33%)	2

- No clinically significant changes in liver enzymes, platelets, or coagulation parameters

8-12 months of follow-up for patients who received a follow-on dose

Data cutoff April 12, 2024. Note: For each preferred term, patient reporting more than one adverse event are counted only once. A Grade 1 AE of “Hereditary neuropathic amyloidosis” was reported for one patient at the time of the data cutoff and confirmed to be entered in error.

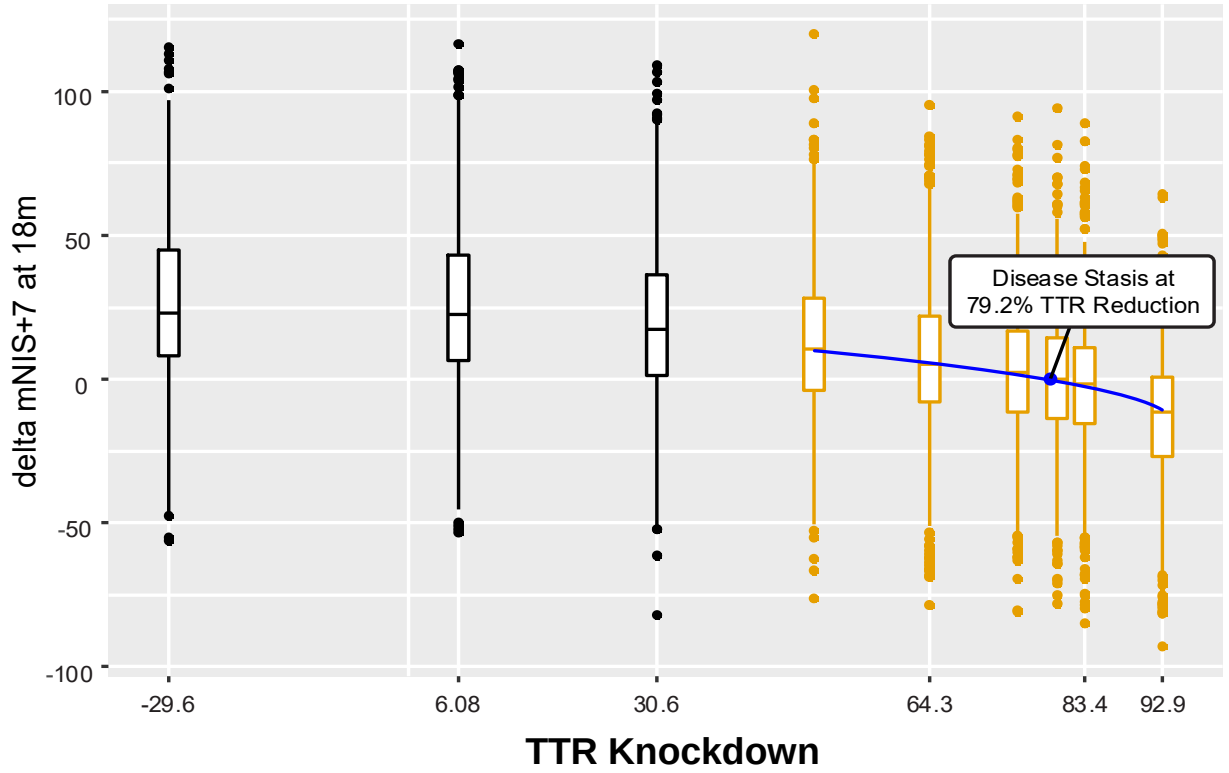
[a]Adverse events are coded to preferred term using MedDRA, version 26.0.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Percent Reduction in Serum [TTR] Is Associated With Clinical Benefit in ATTR Amyloidosis, but Residual Absolute Serum [TTR] Could Be More Informative

% serum [TTR] reduction vs ΔmNIS+7 by nonile in APOLLO

At the population level, >80% TTR reduction is associated with improved score



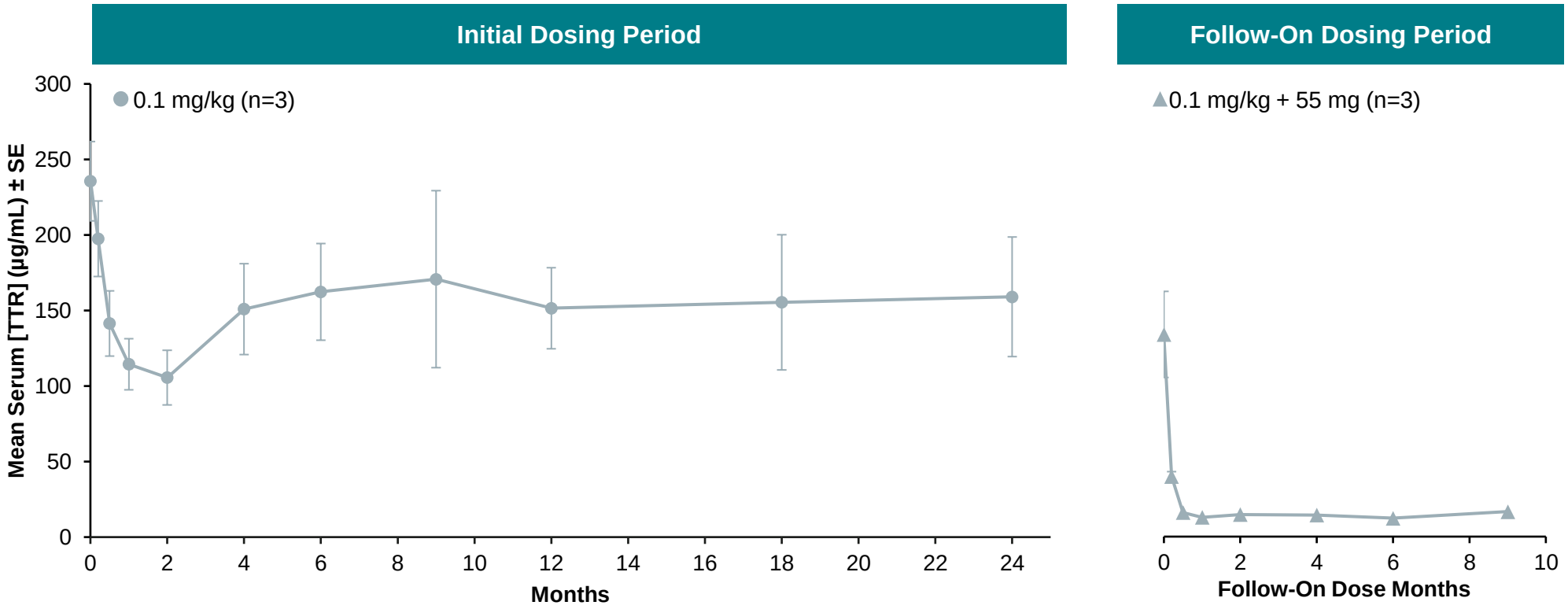
The same % serum [TTR] reduction can mean different risk for ongoing fibril formation

	80% Knockdown	
	Patient 1	Patient 2
Predose [TTR] (µg/mL)	350	150
Postdose [TTR] (µg/mL)	70	30

In both patients, there is 80% knockdown, but **patient 1 has > 2× available substrate** for ongoing amyloid formation post treatment

ΔmNIS+7, change in modified neuropathy impairment score +7; TTR, transthyretin.
Polydefkis M et al. Presented at ISA; Mar 26-29, 2018; Kumamoto, Japan. Graph used with permissions from first author.

Serum [TTR] Reduction in Patients Who Received Follow-On Dosing Were Consistent With Those Treated With a Single 55-mg Dose



	Serum [TTR] at Day 28	
	Median (IQR) Serum [TTR]	**Median (IQR) % Change in Serum [TTR]**
0.1 mg/kg (n=3)	130 µg/mL (81 to 133)	-52% (-47 to -57)
0.1 mg/kg + 55 mg (n=3)	13 µg/mL (9 to 14)	-90% (-82 to -95)*

Data cutoff April 12, 2024.
*Corresponding reduction from original baseline levels is a 95% median reduction in serum [TTR].
IQR, interquartile range; SE, standard error; TTR, transthyretin; 55 mg is the fixed dose equivalent to the 0.7 mg/kg dose.

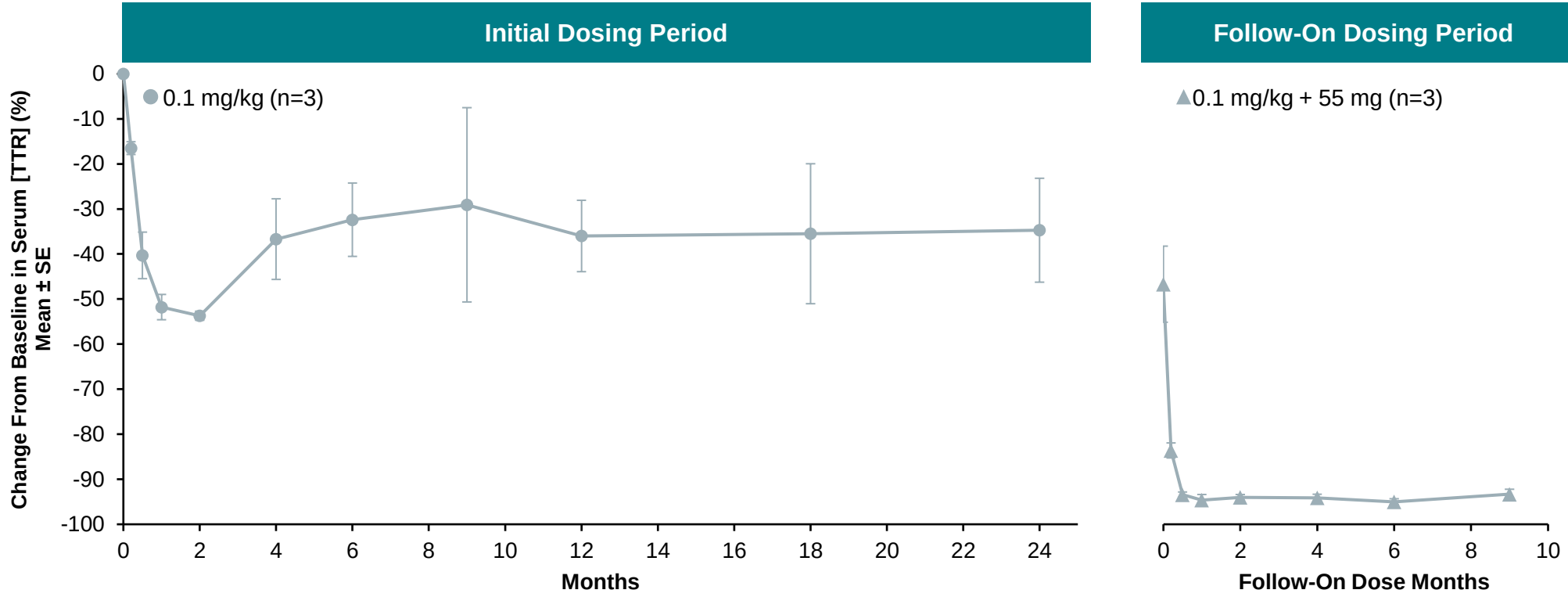
Conclusions

- At doses ≥0.3 mg/kg, deep, durable reductions in serum [TTR] were achieved in all patients with ATTR amyloidosis following a single dose of NTLA-2001
- Preclinical studies supported a follow-on dose to achieve a therapeutic effect for patients who received NTLA-2001 at 0.1 mg/kg
- For patients who received the follow-on dose, serum [TTR] was similar to patients who received a single 55-mg dose
- Follow-on dose was well tolerated with no safety findings
- While NTLA-2001 is intended to be a single-dose treatment, these initial findings suggest that Intellia's *in vivo* CRISPR/Cas9 LNP–based delivery platform has flexibility in redosing to achieve additive pharmacodynamic effect

ATTR, transthyretin amyloidosis; Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; LNP, lipid nanoparticle; TTR, transthyretin.

Appendix

Percent Change in Serum [TTR] in Patients Who Received Follow-On Dosing Were Consistent With Those Treated With a Single 55-mg Dose



	Serum [TTR] at Day 28	
	Median (IQR) Serum [TTR]	Median (IQR) % Change in Serum [TTR]
0.1 mg/kg (n=3)	130 µg/mL (81 to 133)	-52% (-47 to -57)
0.1 mg/kg + 55 mg (n=3)	13 µg/mL (9 to 14)	-95% (-92 to -96)*

Data cutoff April 12, 2024.
The figure and table display the percent reduction from the original baseline level.
*The corresponding reduction relative to the serum [TTR] level prior to the follow-on dose is a 90% median reduction.
IQR, interquartile range; SE, standard error; TTR, transthyretin; 55 mg is the fixed dose equivalent to the 0.7 mg/kg dose.