In vivo CRISPR/Cas9 editing of the *TTR* gene with NTLA-2001 in patients with transthyretin amyloidosis – dose selection considerations

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Transthyretin (ATTR) amyloidosis

Rare, progressive, fatal disease

- Caused by accumulation of amyloid deposits composed of misfolded transthyretin (TTR) protein
- ATTR amyloidosis consists of two forms of the disease: hereditary and wild type
- Rate of new diagnoses is increasing

Hereditary ATTR amyloidosis (ATTRv)

~50,000 patients worldwide

Variable phenotype

- Peripheral and autonomic neuropathy (ATTRv-PN)
- Amyloid cardiomyopathy (ATTRv-CM)
- May occur as mixed phenotype

Wild-type ATTR amyloidosis (ATTRwt)

~200,000 - 500,000 patients worldwide

Cardiomyopathy phenotype

- Increasingly recognized cause of heart failure in patients aged >50 years
- Progressive and fatal within 3 - 10 years
- Majority of cases never diagnosed

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

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

Potential for gene editing to address unmet need for ATTR amyloidosis

- Therapy in ATTR amyloidosis is directed at reducing the circulating amyloid-forming protein
  - Gene silencing therapy knocks serum TTR down by ~80% and benefits neuropathy in ATTRv[1]
- Greater TTR knockdown is expected to achieve better clinical outcomes and can potentially reverse progression of the disease[1]
- Editing of the *TTR* gene is an attractive therapeutic strategy

NTLA-2001 is being studied as a potential one-time treatment to permanently knockout the *TTR* gene

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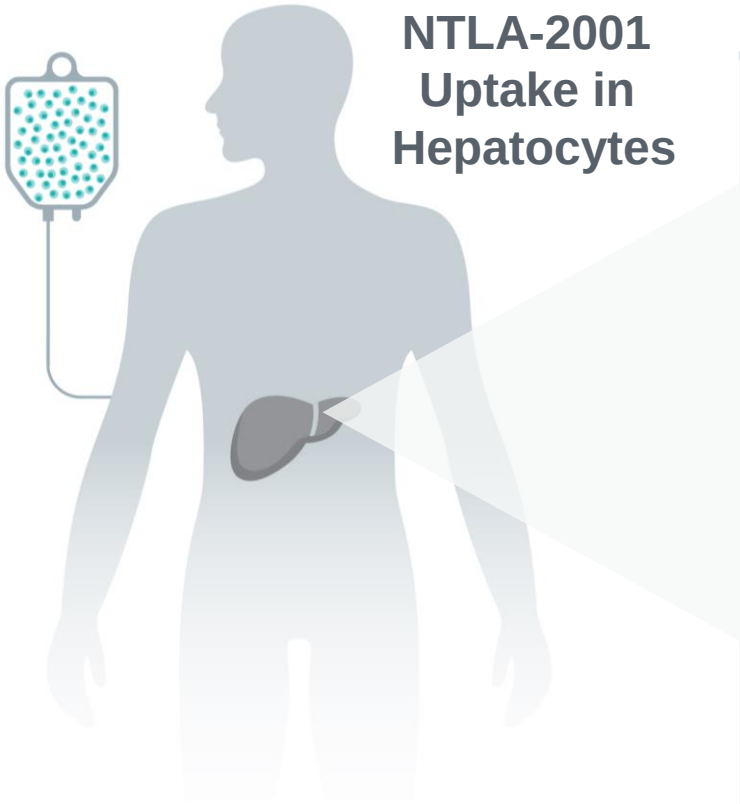
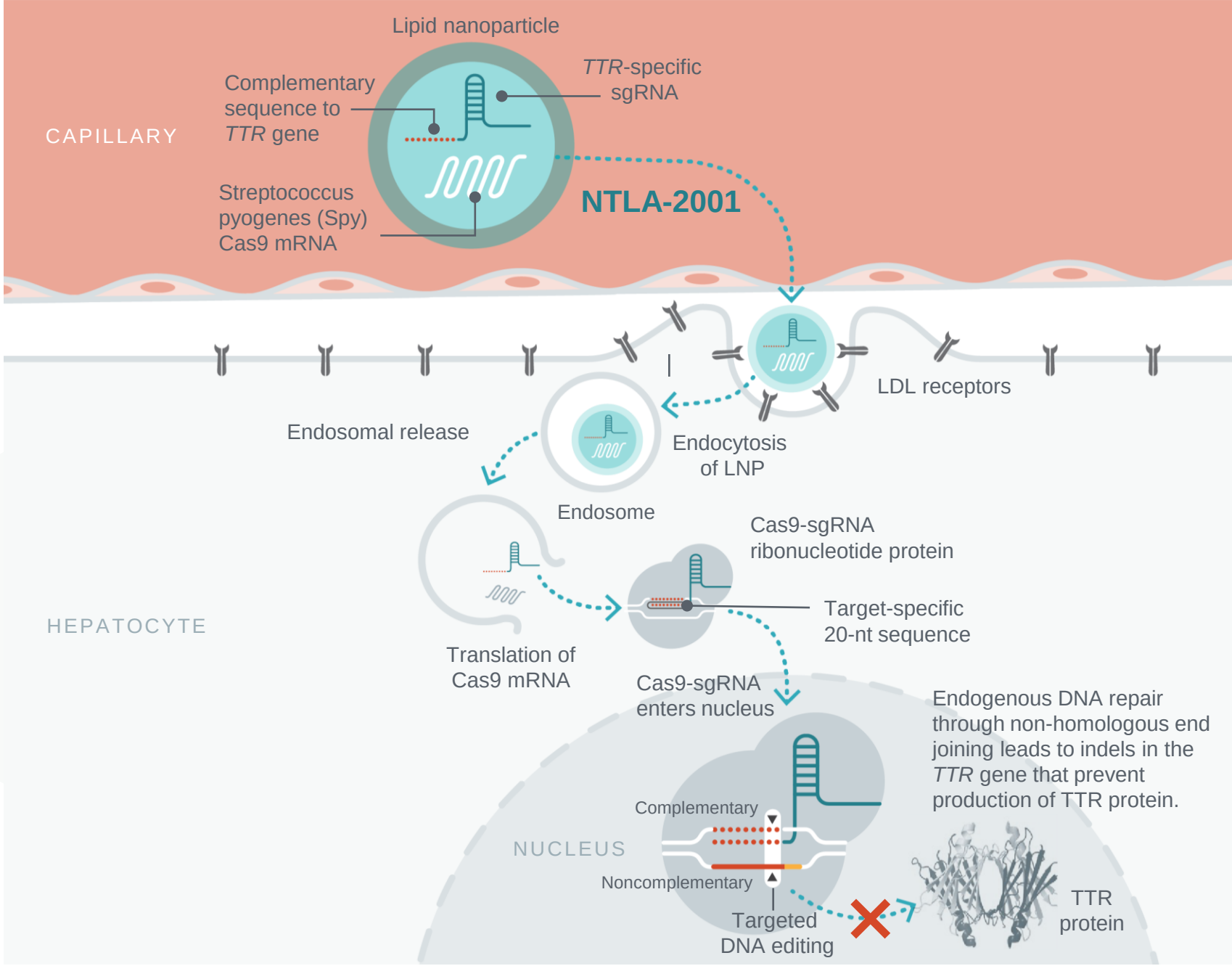
ATTRv, hereditary ATTR amyloidosis; TTR, transthyretin

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

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



NTLA-2001 Uptake in Hepatocytes



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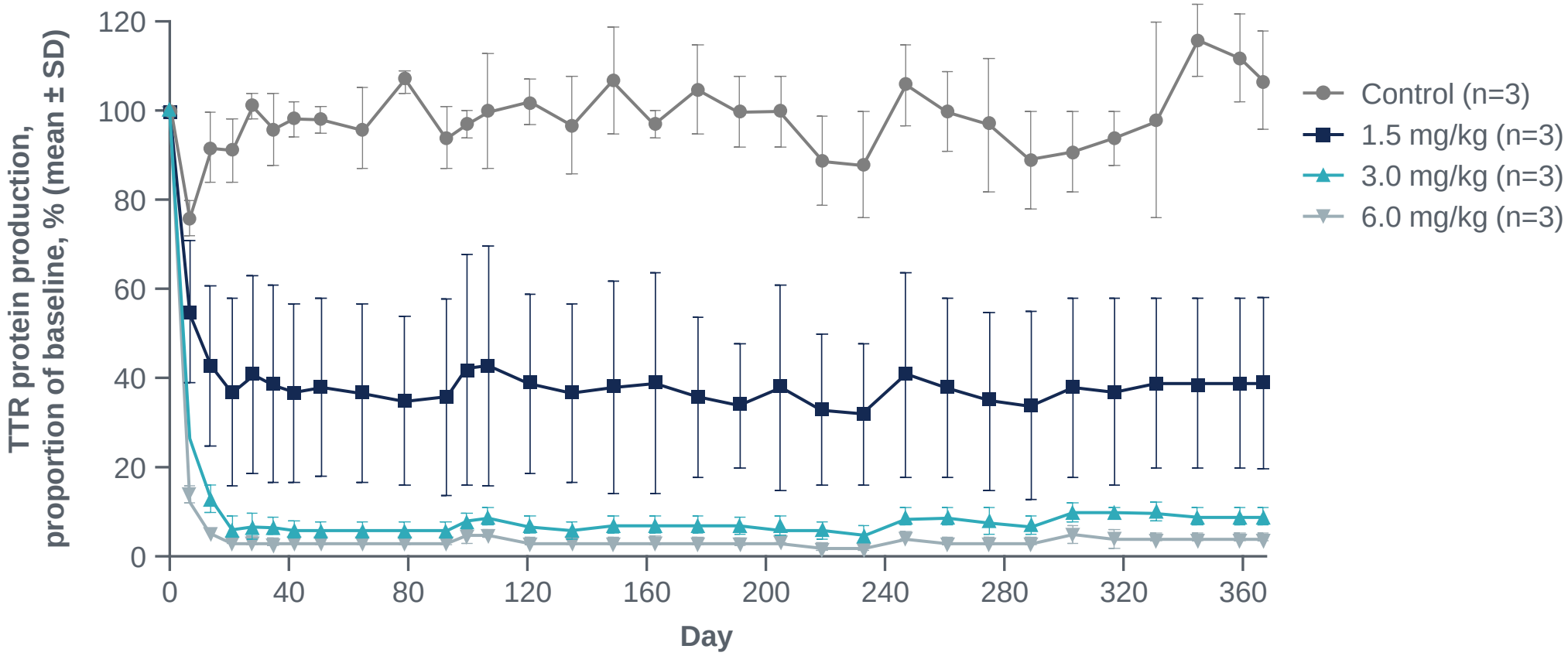
LNP; lipid nanoparticle; sgRNA; single guide RNA; TTR, transthyretin

Non-human primates: Durable, >95% TTR reduction after single dose of NTLA-2001



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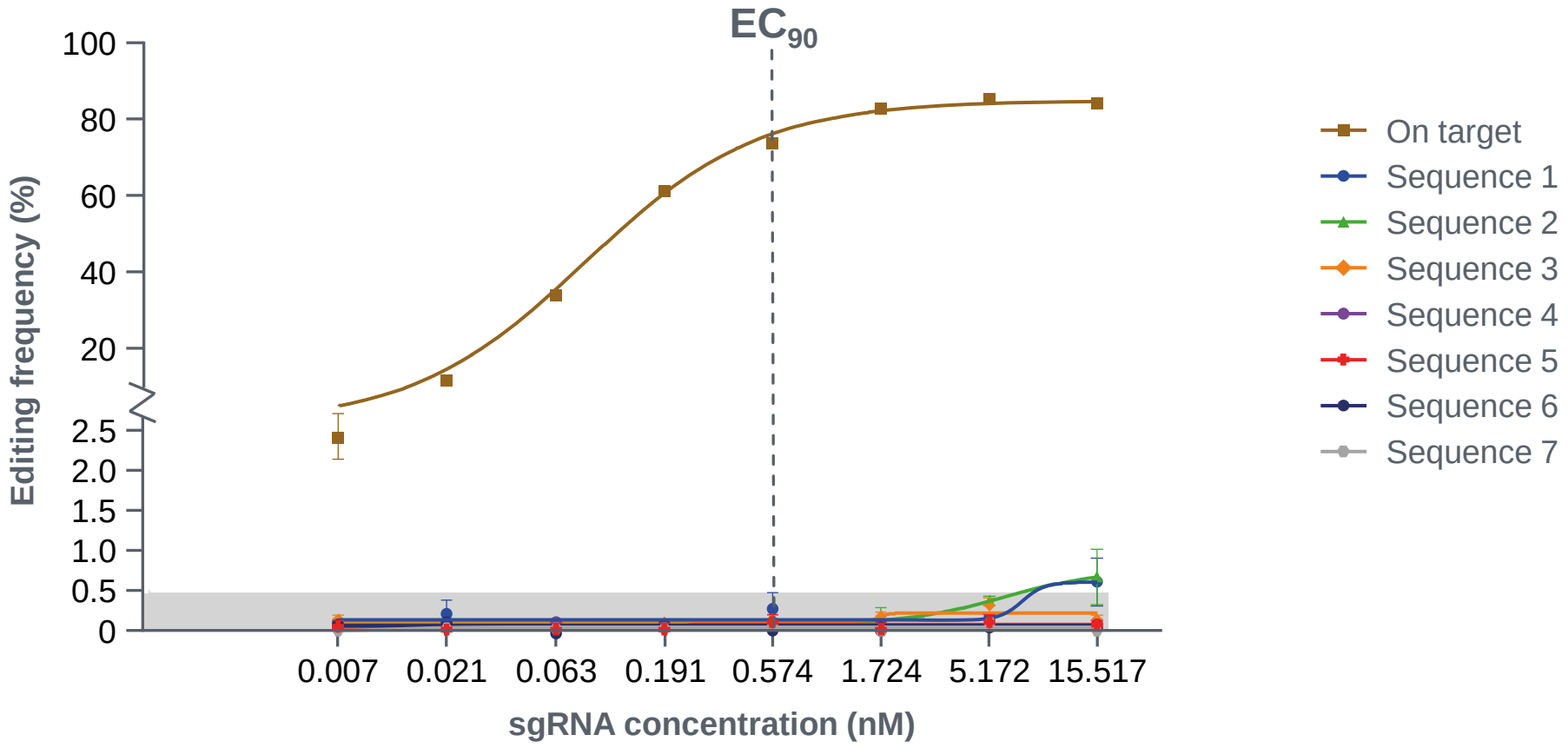
TTR, transthyretin

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



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

NTLA-2001 Phase 1 Study: Polyneuropathy Arm

Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN)

Today's interim data presentation covers longer-term safety, PD and PK data across all four dose levels in Part I

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

PART I – DOSING COMPLETE
Single-Ascending Dose

- 1.0 mg/kg (n=6)
- 0.7 mg/kg (n=3)
- 0.3 mg/kg (n=3)
- 0.1 mg/kg (n=3)

PART II – ONGOING
Single Dose Expansion Cohort

N = 8 subjects
Administer 80 mg fixed dose

KEY ELIGIBILITY CRITERIA

- ATTRv with clinical PN
- Polyneuropathy Disability Score ≤ 3b
- Weight ≥ 45kg

PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK and PD

- *Measure serum TTR levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of neurologic function

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Clinicaltrials.gov ID: NCT04601051 PK; Pharmacokinetics PD; Pharmacodynamics

Patient demographics & characteristics

Parameter	0.1 mg/kg n=3	0.3 mg/kg n=3	0.7 mg/kg n=3	1.0 mg/kg n=6	All patients n=15
Age, years median (min, max)	54 (50, 63)	53 (46, 64)	51 (19, 58)	61 (49, 70)	55 (19, 70)
Sex, n (%)					
Male	1 (33%)	3 (100%)	2 (67%)	3 (50%)	9 (60%)
Female	2 (67%)	–	1 (33%)	3 (50%)	6 (40%)
***TTR* genotype, n (%)**					
p.H110D	0	1 (33%)	0	0	1 (7%)
p.S97Y	1 (33%)	1 (33%)	0	0	2 (13%)
p.E94G	0	0	1 (33%)	0	1 (7%)
p.T80A	2 (67%)	1 (33%)	1 (33%)	2 (33%)	6 (40%)
p.S70R	0	0	0	1 (17%)	1 (7%)
p.E62D	0	0	1 (33%)	2 (33%)	3 (20%)
p.V50M	0	0	0	1 (17%)	1 (7%)
Weight, kg median (min, max)	82 (70, 89)	84 (83, 90)	87 (62, 98)	75 (59, 111)	83 (59, 111)

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Data Cut Off : 16th May 2022

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

- **Across all dose levels, the most frequent adverse events* were headache, infusion-related reactions, back pain, rash† and nausea**
  - Majority of adverse events were mild in severity with 73% (n=11) of patients reporting a maximal adverse event severity of Grade 1
  - All infusion-related reactions were considered mild, resolving without clinical sequelae
  - All patients received a complete study dose of NTLA-2001
- **A single possibly-related Grade 3 event (SAE) of vomiting was reported at the 1.0 mg/kg dose in a patient with underlying gastroparesis**
  - 1.0 mg/kg dose level expanded per protocol to 6 patients to further characterize safety and PD
- **Maximally tolerated dose was not reached**

Data Cut Off : 16th May 2022
Median follow-up is 10 months
* Related and unrelated events in more than 2 patients
† Date of onset D6–D145; all mild in severity
PD, pharmacodynamics; SAE, serious adverse event

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Majority of adverse events were mild in severity

	0.1 mg/kg n=3			0.3 mg/kg n=3			0.7 mg/kg n=3			1.0 mg/kg n=6			All Patients n=15		
Parameter	**Gr. 1**	**Gr. 2**	**Gr. 3**	**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	3	–	–	3	–	–	2	–	1*	3	2	1†	11	2	2
Headache	2	–	–	–	–	–	2	–	–	3	–	–	7	–	–
Infusion-related reaction	1	–	–	–	–	–	2	–	–	3	–	–	6	–	–
Back pain	1	–	–	–	–	–	2	1	–	1	–	–	4	1	–
Rash	1	–	–	–	–	–	–	–	–	3	–	–	4	–	–
Nausea	1	–	–	–	–	–	1	–	–	1	–	–	3	–	–

Adverse events reported in more than 2 patients
Patients counted once per row, per dose level, as highest grade reported
* Unrelated Grade 3 SAEs of COVID-19 pneumonia (study day 121) and chest pain (study day 296) in the same patient
† Possibly related Grade 3 SAE of vomiting in a patient with concomitant medical history of gastroparesis

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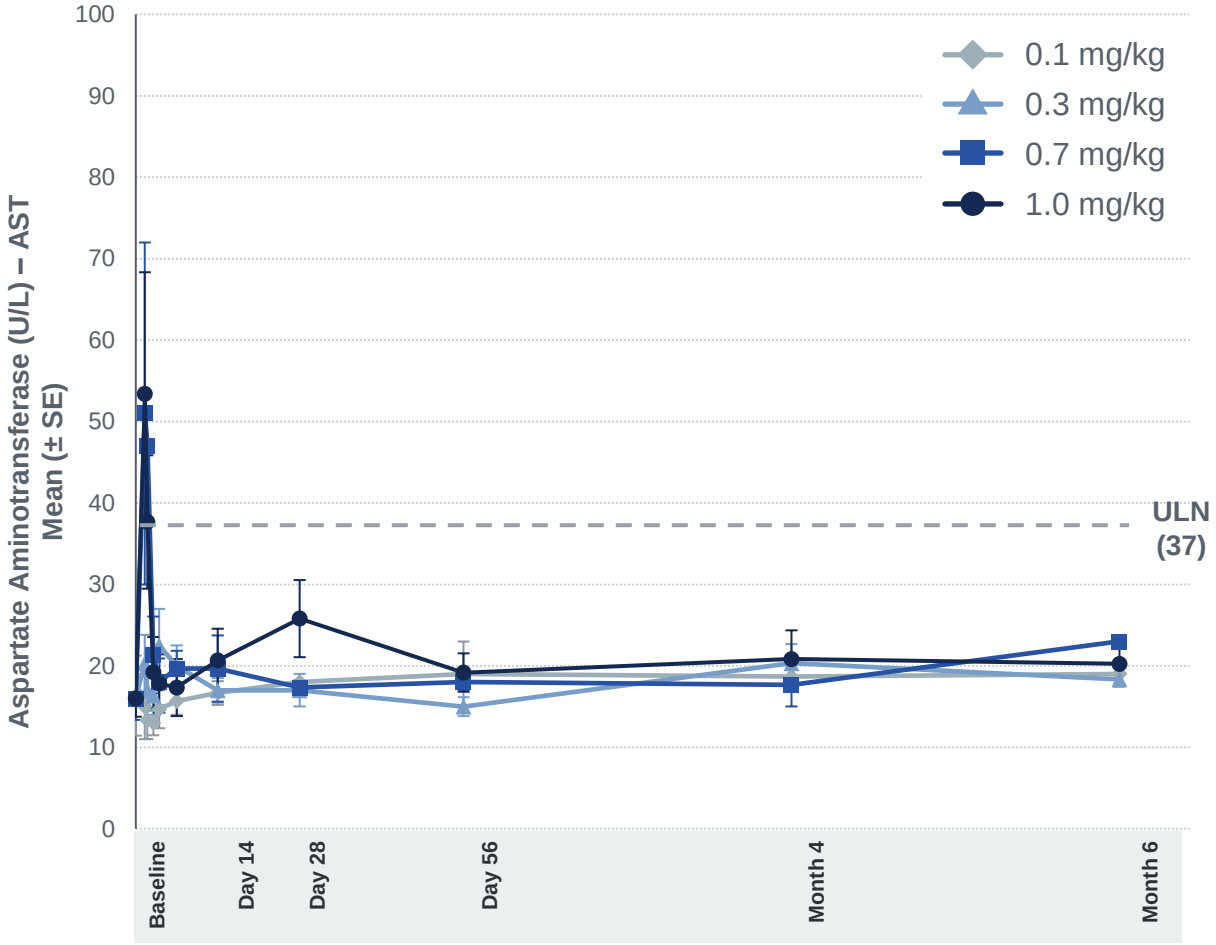
Data Cut Off: 16th May 2022
Gr., Grade; SAE, serious adverse events; TEAE, treatment-emergent adverse event

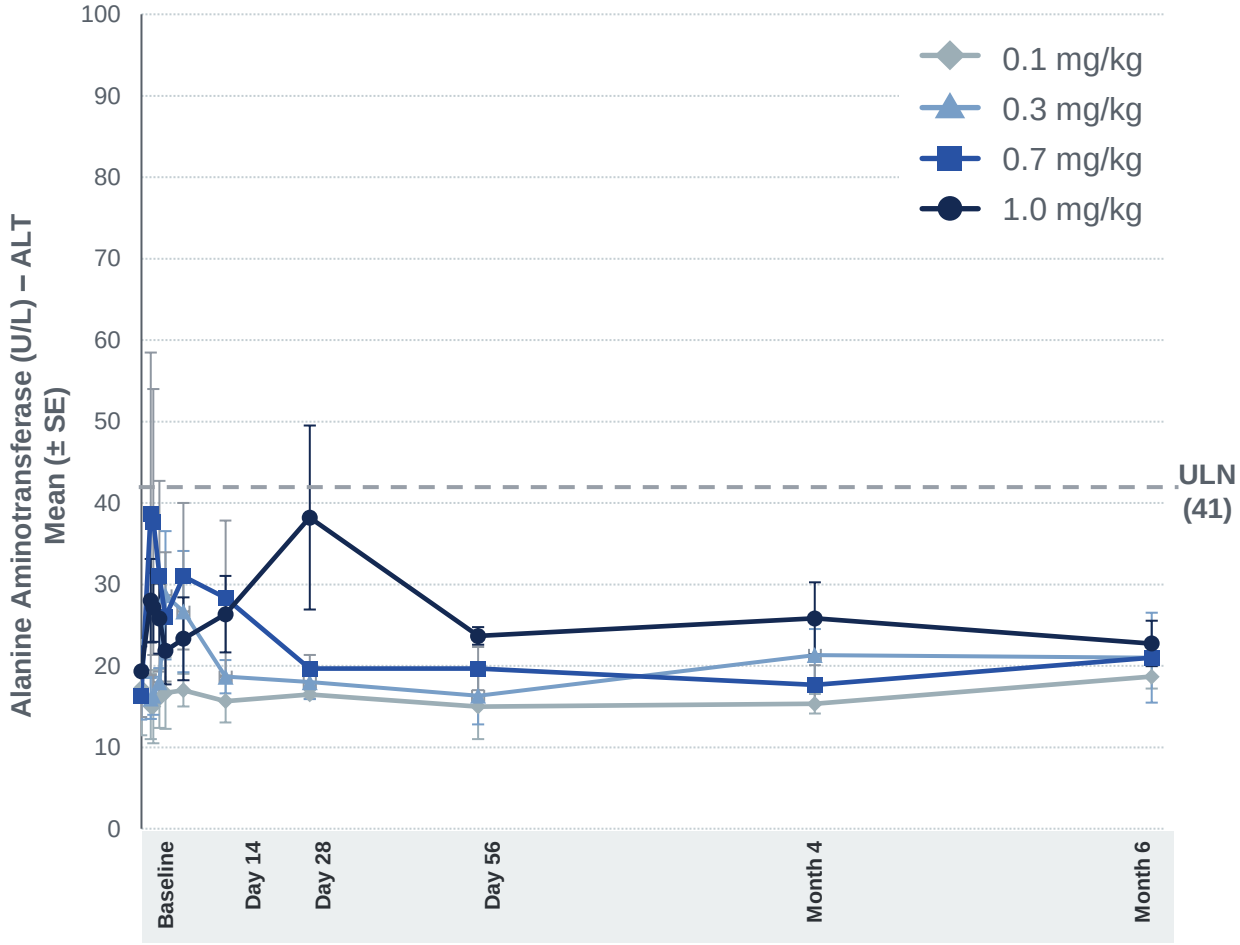
Minor, transient changes in AST and ALT levels observed post NTLA-2001 infusion

AST Levels Over 6 Months



	Baseline	Day 14	Day 28	Day 56	Month 4	Month 6
0.1 mg/kg (n):	3	3	2	2	3	3
0.3 mg/kg (n):	3	3	3	3	3	3
0.7 mg/kg (n):	3	3	3	3	3	1
1.0 mg/kg (n):	6	6	5	6	6	4

ALT Levels Over 6 months



	Baseline	Day 14	Day 28	Day 56	Month 4	Month 6
0.1 mg/kg (n):	3	3	2	2	3	3
0.3 mg/kg (n):	3	3	3	3	3	3
0.7 mg/kg (n):	3	3	3	3	3	1
1.0 mg/kg (n):	6	6	5	6	6	4

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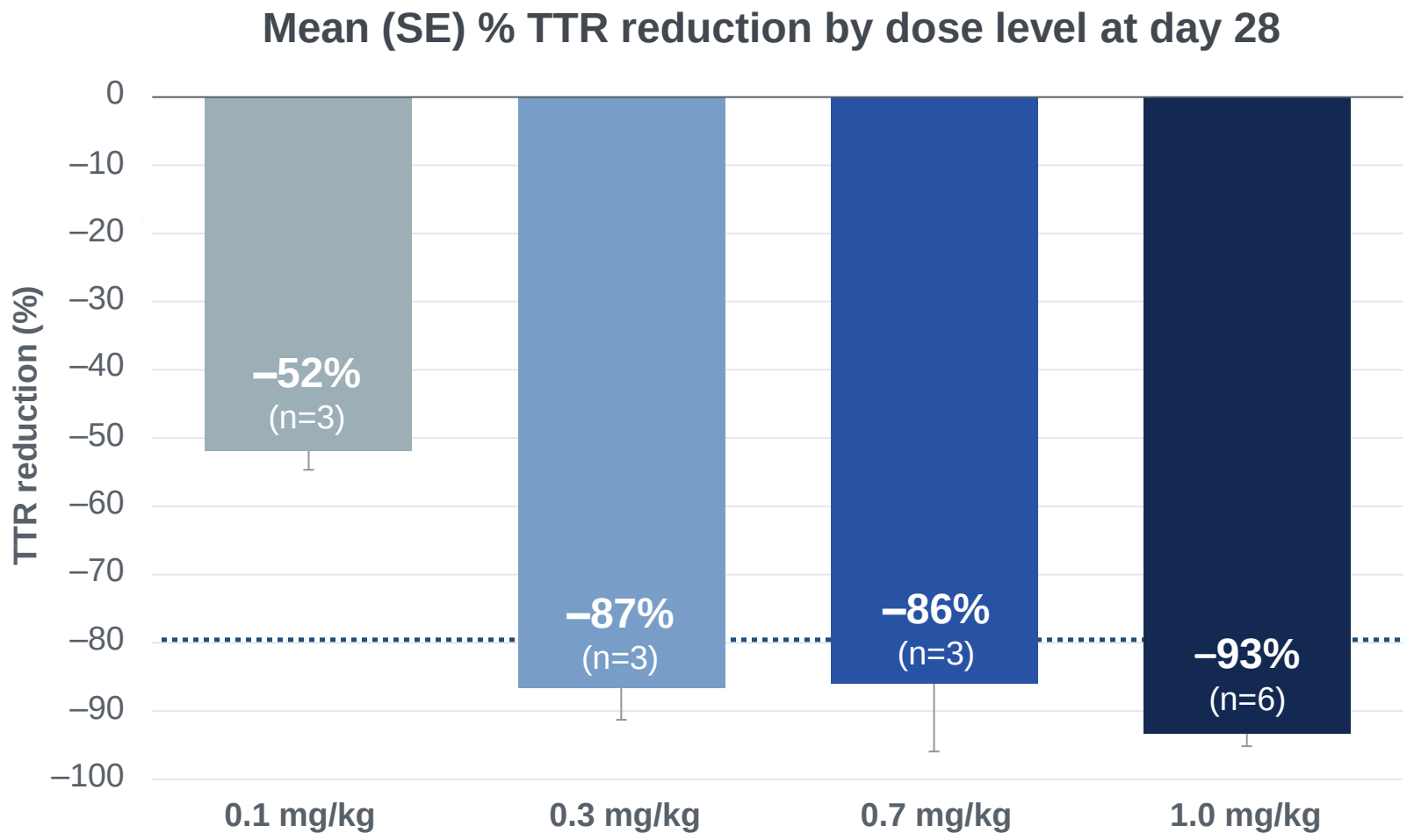
Dose-dependent reductions in serum TTR, reaching a mean reduction of 93% at 1.0 mg/kg



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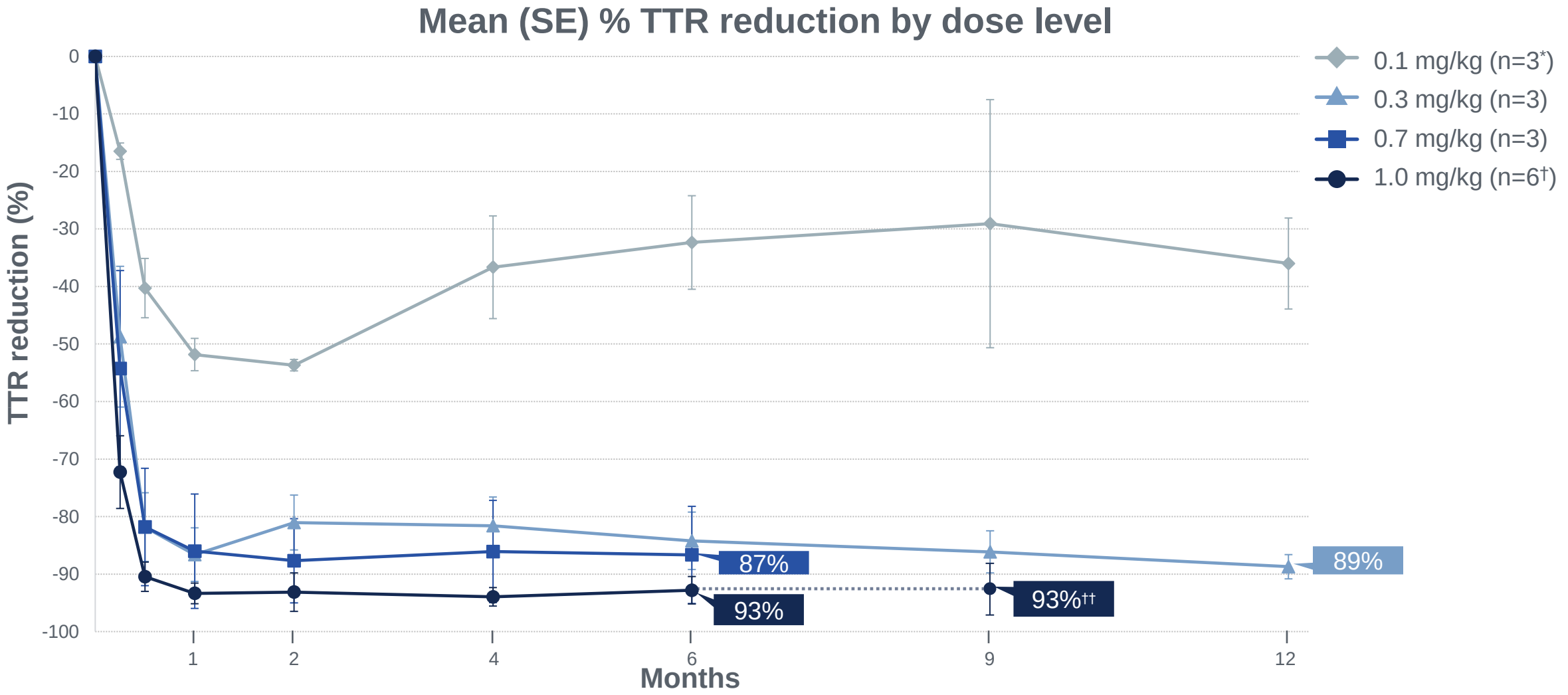
Dashed line represents the targeted minimum reduction
SE, standard error; TTR, transthyretin

Higher doses demonstrated rapid and deep serum TTR reduction sustained through 6-12 months



* n=2 at Month 2 (missed visit due to Covid-19 travel restrictions)
† n=5 at Month 2 (missed visit due to Covid-19 travel restrictions)
†† n=3 have reached Month 9 follow-up
SE, standard error; TTR, transthyretin

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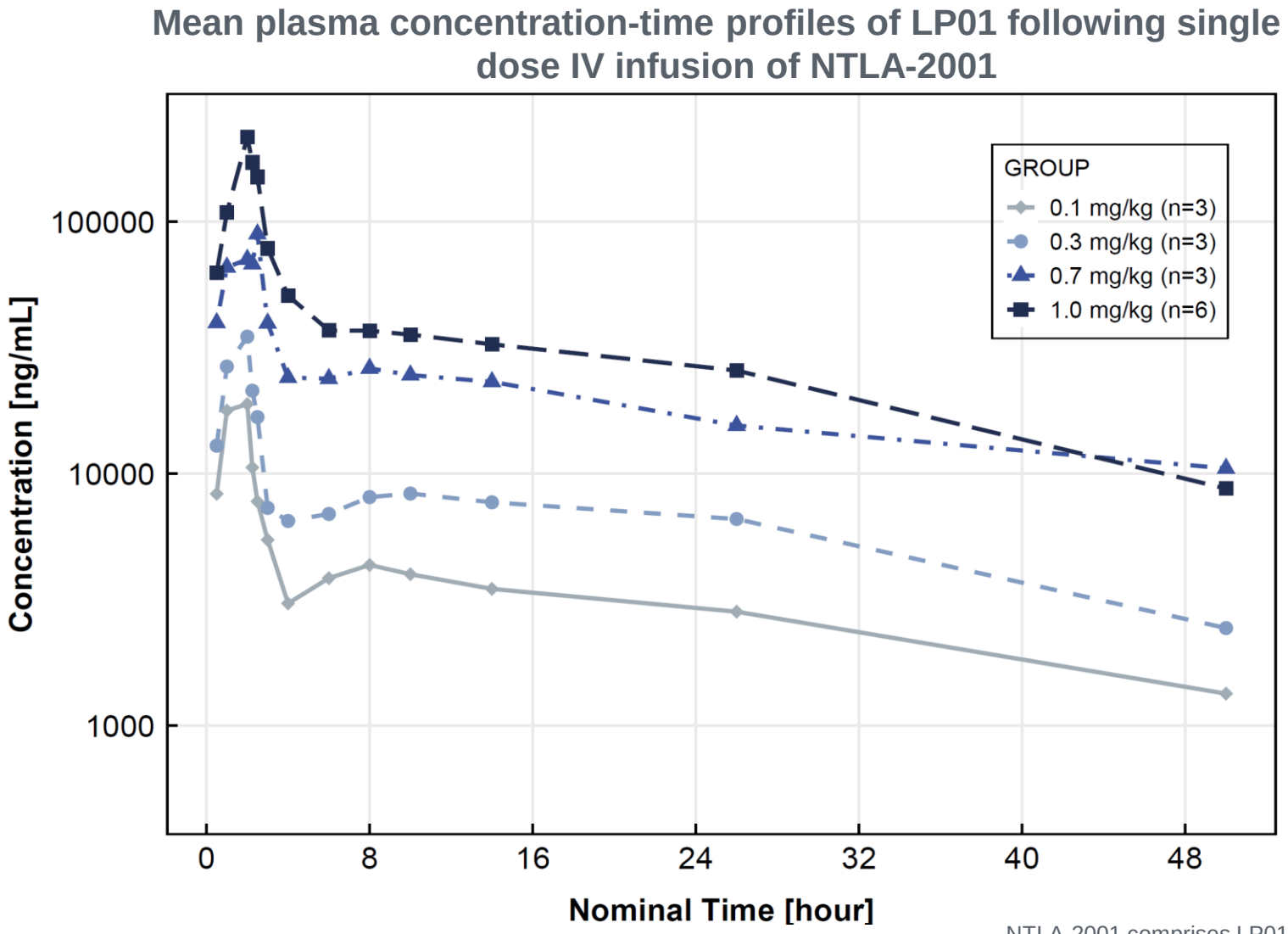
NTLA-2001 declines rapidly from peak and then exhibits a secondary peak and log-linear phase



NTLA-2001 comprises LP01, an ionizable lipid, additional lipids and the RNA
Available LP01 PK data depicted up to 48 hours post-dose
Estimated mean $t_{1/2}$ ranging 20 - 25 h

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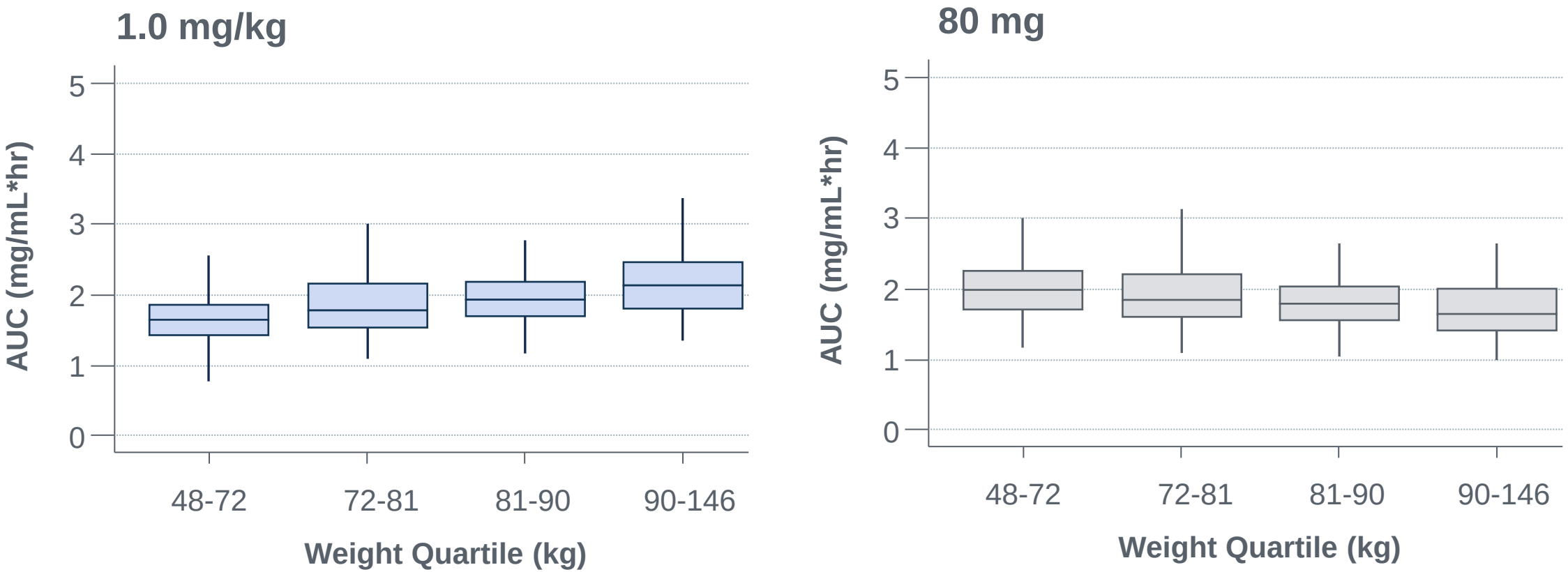
Simulations identified NTLA-2001 80mg as the fixed dose equivalent to 1.0 mg/kg

Model-predicted distribution of NTLA-2001 AUC (mg*h/mL) following 1.0 mg/kg and 80 mg by indicated weight quartile



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Interim model

Deep, consistent and durable TTR reductions following single administration of *in vivo* CRISPR-based gene editing

- Mean TTR reduction sustained at all doses tested through 6-12 months
- At 1.0 mg/kg, mean reduction of 93% at day 28 was sustained through 6 months
- NTLA-2001 was generally well tolerated: the majority of adverse events were mild
- No clinically significant laboratory findings observed
- A dose of 80 mg, the fixed dose equivalent of 1.0 mg/kg, has been selected for evaluation in Part II (ongoing)

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

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TTR, transthyretin

Acknowledgements

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