First-in-Human *in vivo* CRISPR/Cas9 Editing of the *TTR* Gene by NTLA-2001 in Patients with Transthyretin (ATTR) Amyloidosis with Cardiomyopathy

Julian D. Gillmore, Jörg Täubel, Ed Gane, Björn Pilebro, Michael L. Maitland, Mark Stroh, Yuanxin Xu, Adam Boyd, Jeffrey Cehelsky, David E. Gutstein, Tina Ho, Alison Sonderfan, Liron Walsh, David Lebwohl, and Mariana Fontana

American Heart Association® Scientific Sessions 2022
05 November 2022

Clinical Trial Registration # NCT04601051
This study and medical writing support for this presentation is funded by Intellia Therapeutics

Disclosures

- Dr. Gillmore receives consultancy fees from Alnylam, Ionis, AstraZeneca, Pfizer, Intellia, ATTRalus and NovoNordisk

- Dr. Gillmore has received grant support from Alnylam Pharmaceuticals

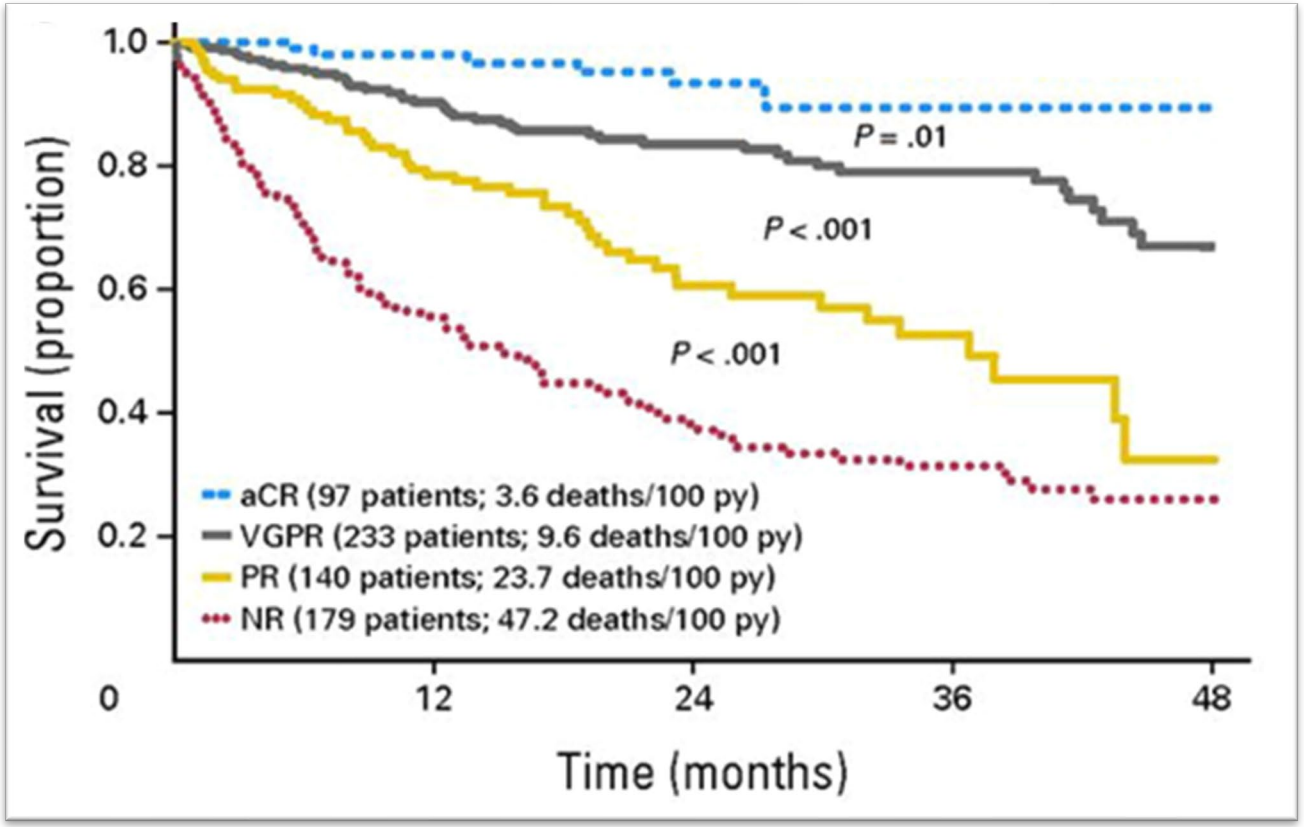
Transthyretin (ATTR) amyloidosis is a progressive and fatal disease

- **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
- **Transthyretin amyloid cardiomyopathy (ATTR-CM)**
  - Amyloid deposits cause impaired systolic/diastolic function and conduction disorders
  - Fatal within 3 to 10 years in the absence of treatment
  - Remains under-diagnosed
- **Unmet medical need in ATTR-CM**
  - Progressive heart failure leads to poor QoL, high morbidity and mortality
  - Current treatment only slows disease progression and requires lifelong administration
  - Limited access to approved therapies

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

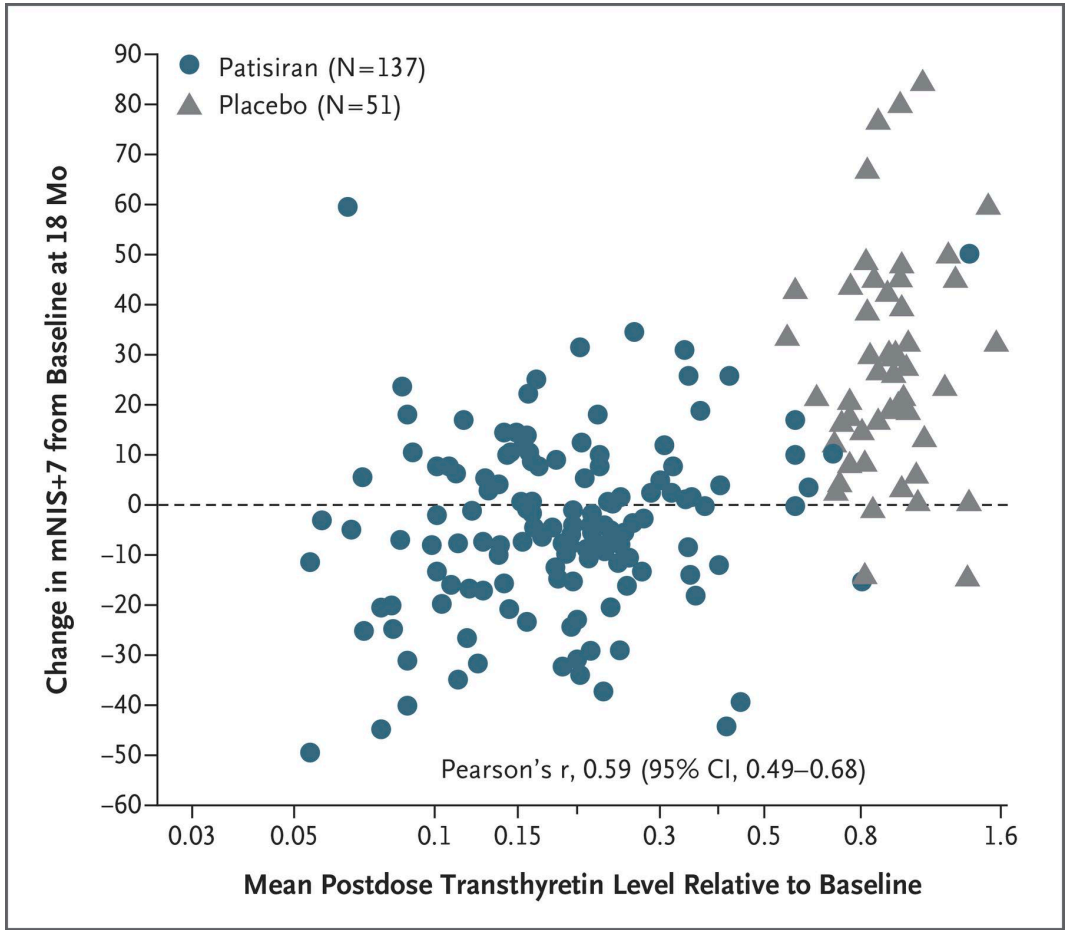
Magnitude of precursor protein knockdown is associated with survival in AL amyloidosis



Incremental improvements in precursor protein reduction led to improved clinical outcomes

aCR, amyloid complete response; **AL**, amyloid light chain
NR, no response**; PR**, partial response
VGPR, very good partial response
Palladini G *et al*, JCO 2012;30:4541-4549

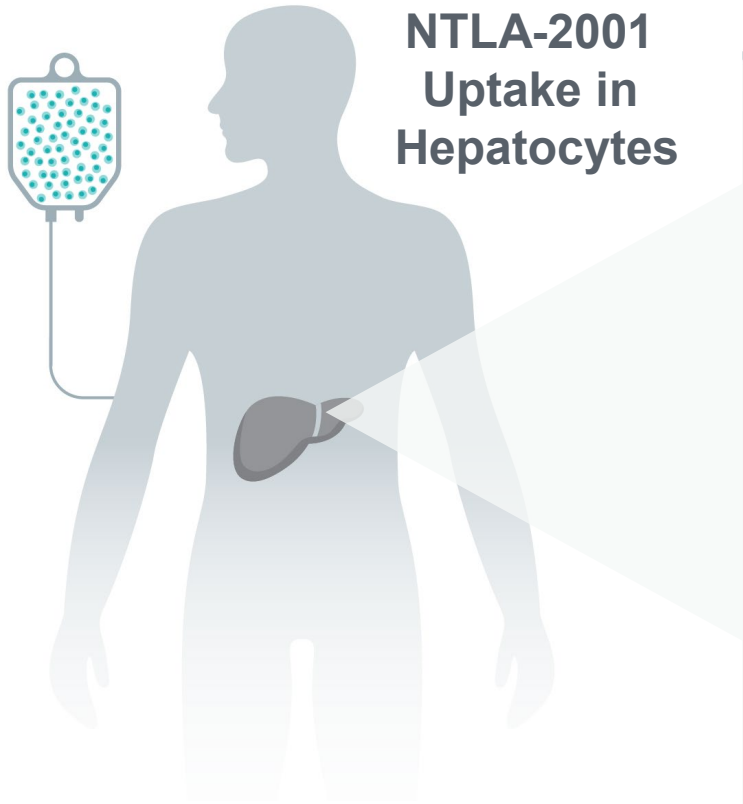
Greater TTR knockdown associated with clinical improvements in ATTR amyloidosis



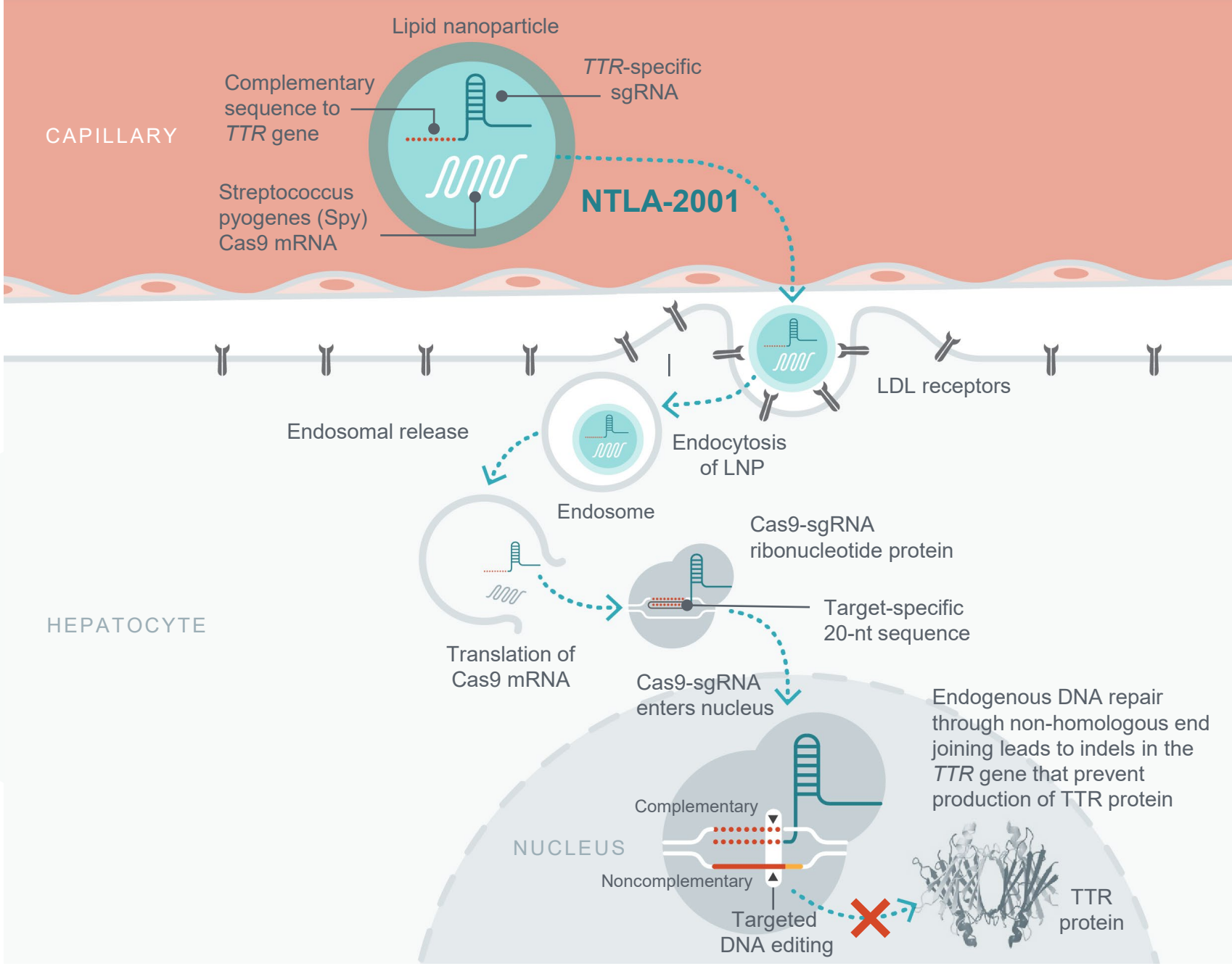
- Greater TTR knockdown is associated with improved neuropathy scores for ATTRv-PN
- Emerging evidence indicates that deep TTR reductions may be clinically beneficial for patients with ATTR-CM

Adams D *et al*, NEJM 2018;379:11–21
Mauer M *et al*, OPLB001; ISA 2022

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



NTLA-2001 Uptake in Hepatocytes



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

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

Rigorous process to select sgRNA for NTLA-2001 to achieve both potent on-target and no detectable off-target editing

1 IDENTIFICATION

Conduct computational analysis to identify potential CRISPR-candidate sites for knockout and then eliminate sites containing *TTR* pathogenic variants, common SNPs and sequences with high off-target potential

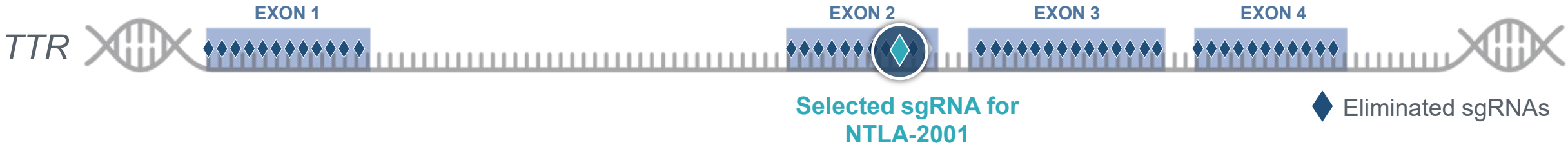
2 CANDIDATE ASSESSMENT

Synthesize pool of initial sgRNAs and test rigorously for knockout efficiency, off-target editing and genotoxicity (including SVs), using human cells and animal models

- Multiple methods: *in silico*, biochemical/cell-based assays and image-based methods

3 VALIDATION AND FINAL SELECTION

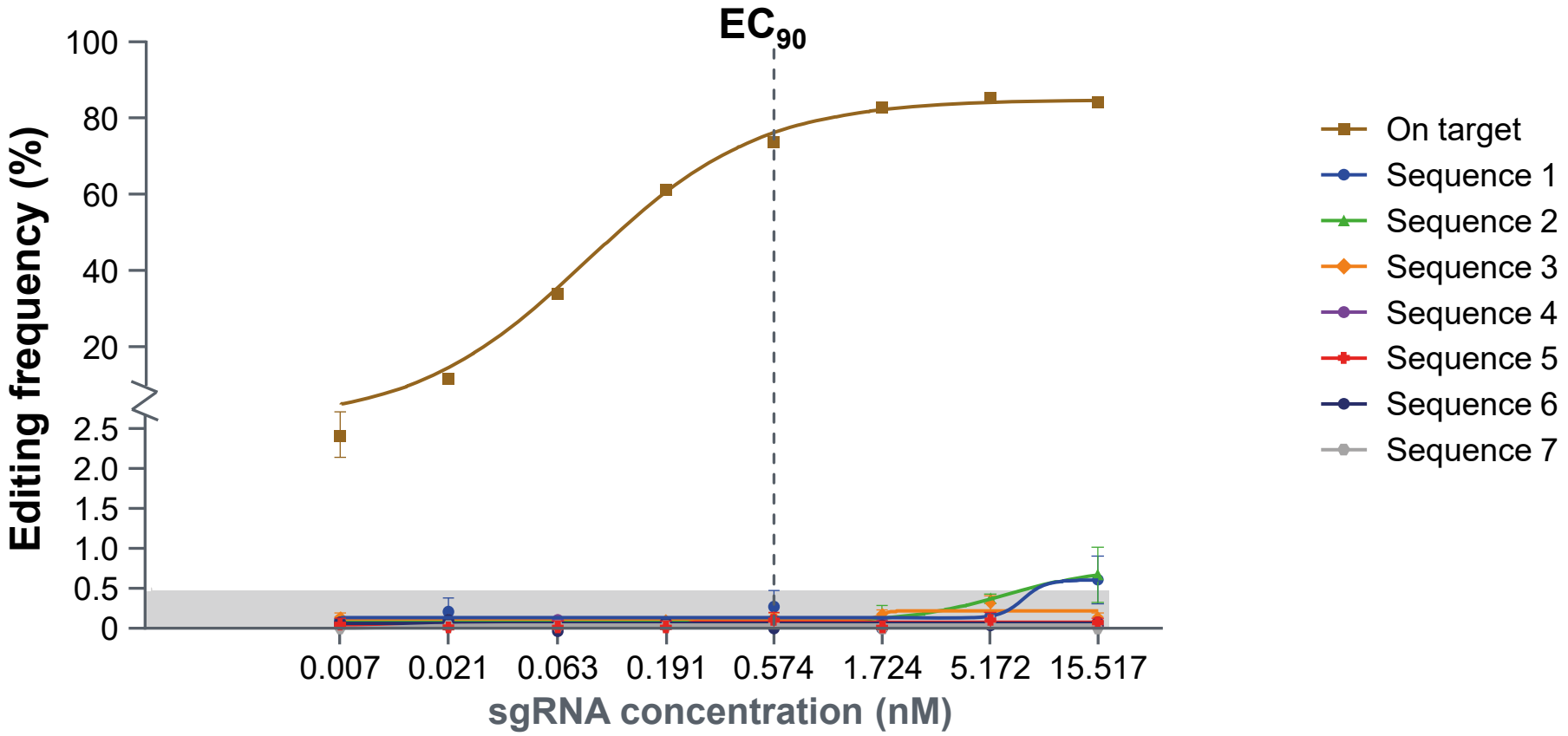
Select sgRNA with the highest on-target knockout efficiency and no detectable off-target potential at multiples of human therapeutic dose



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

sgRNA, single guide RNA; **SNPs**, single nucleotide polymorphisms
SV, structural variants; **TTR**, transthyretin

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



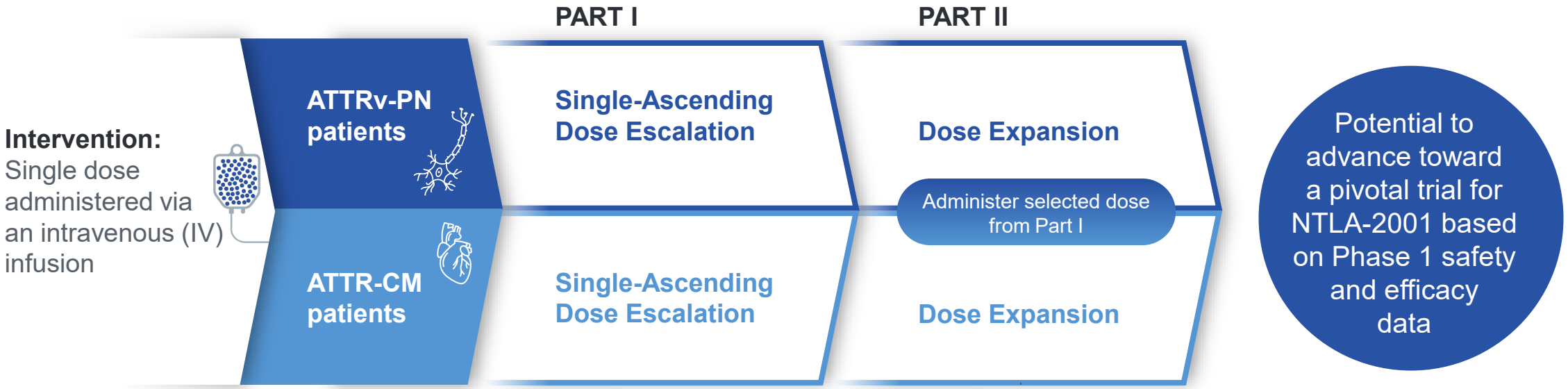
 This presentation includes data for an investigational product not yet approved by regulatory authorities.

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

Gillmore J *et al*. NEJM;2021;385:493-502

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)



PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK and PD

- *Measure serum TTR levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of:

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

Clinicaltrials.gov ID: NCT0460105
PK, Pharmacokinetics; **PD**, Pharmacodynamics

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

- 55 mg

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

NYHA, New York Heart Association; **PK,** Pharmacokinetics; **PD,** Pharmacodynamics; **6MWT**, 6 Minute Walk Test

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: August 25, 2022

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

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**
  - 25% (n=3) of patients reported no AEs and 67% (n=8) reported mild or moderate AEs as their highest severity
  - Infusion-related reactions were reported in 2 patients
  - 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 reported a treatment-related AE higher than Grade 1
- **No clinically significant laboratory findings**
  - Transient Grade 1 liver enzyme elevations observed

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

Data Cut Off: August 25, 2022
Median follow-up for all subjects is 5.5 months
AE, adverse event; **PD**, pharmacodynamics

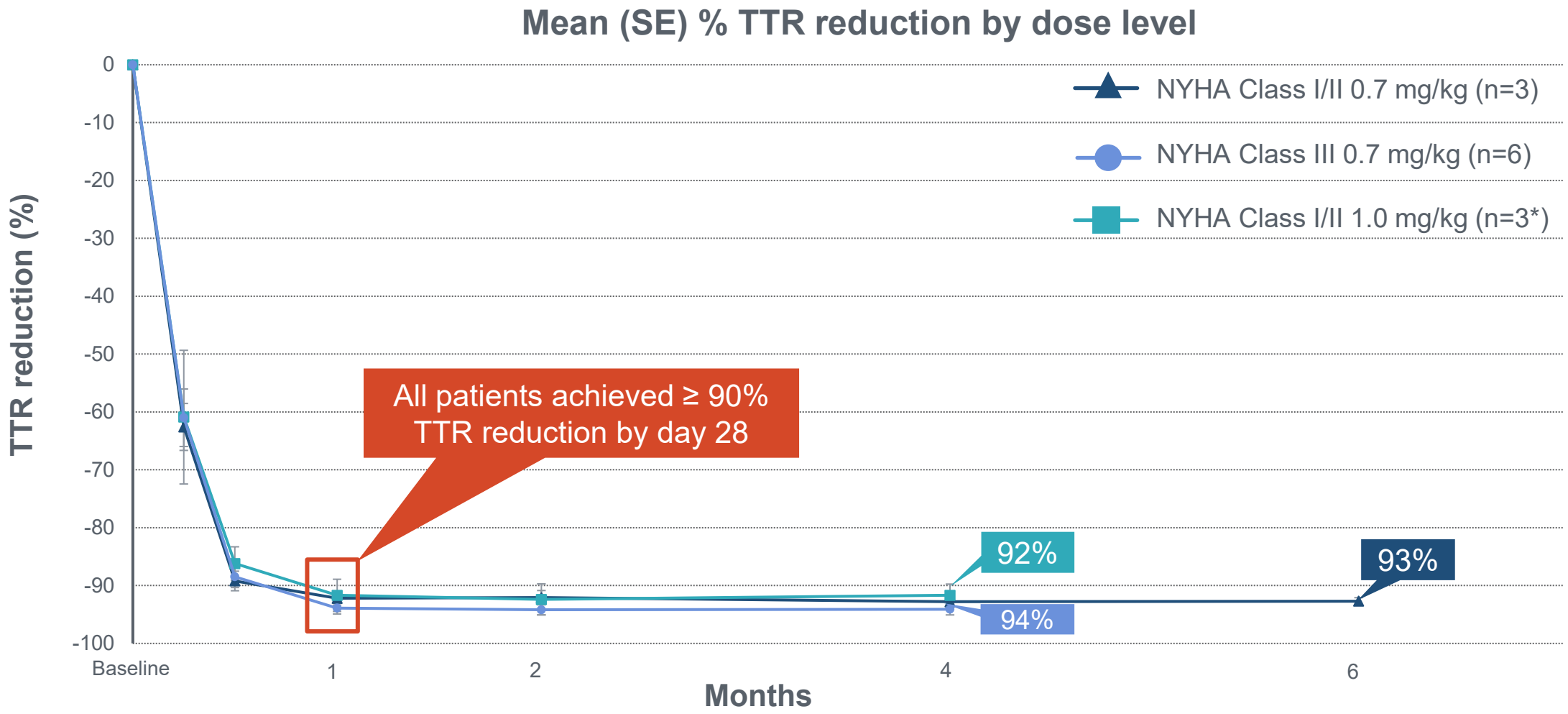
Majority of adverse events were mild in severity

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	1	1†	–	6	2	1
Infusion-related reaction	–	–	–	–	–	1	1	–	–	1	–	1
COVID-19	–	–	–	1	–	–	1	–	–	2	–	–

Data Cut Off: August 25, 2022
TEAEs occurring in ≥ 2 Patients
Patients counted once per row, per dose level, at highest grade reported
*Gr.2 urinary retention and Gr.2 epistaxis in same patient
†Gr.2 herpes zoster and Gr.2 inguinal hernia in same patient
Gr., Grade; **TEAE**, treatment emergent adverse event

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

Rapid and deep serum TTR reduction sustained through 4-6 months across all patients



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

Data Cut Off: August 25, 2022
SE, standard error; **TTR**, transthyretin
*n=2 at Month 2 (missed patient visit)

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 4-6 months (through data cut-off)
- NTLA-2001 was generally well-tolerated at both doses
  - Majority of adverse events were mild
  - No clinically significant laboratory findings observed
- Similar results in patients with either NYHA Class I/II or III heart failure
- 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

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

Acknowledgements

- We express our gratitude to the patients who participated in this study, their families and the research staff at New Zealand Clinical Research, Richmond Pharmacology and Umeå University.
- We thank the Charles River Laboratory, Alta sciences, Precision for Medicine, PPD and QPS for serum TTR, PK and biomarker tests, as well as XP Pharma Consulting, LLC and QuanTx Consulting for their analysis support.
- We acknowledge valuable input in the development of NTLA-2001 from Intellia Therapeutics and Regeneron Pharmaceuticals.