NTLA-2001 for ATTR Amyloidosis: Interim Clinical Results from Ongoing Phase 1 Trial

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

Intellia THERAPEUTICS

February 28, 2022

Agenda

Welcome

Introduction

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

Review of NTLA-2001 Interim Phase 1 Clinical Trial Data

Ed Gane, MBChB, MD, FRACP, MNZM
Professor of Medicine, University of Auckland, New Zealand, Chief Hepatologist, Transplant Physician, Deputy Director, New Zealand Liver Transplant Unit, Auckland City Hospital; Investigator for Intellia's Phase 1 Study of NTLA-2001 in New Zealand

NTLA-2001 Clinical Development Plans

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

Closing Remarks and Q&A Session

Intellia THERAPEUTICS

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This presentation contains "forward-looking statements" of Intellia Therapeutics, Inc. ("Intellia", "we" or "our") within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements include, but are not limited to, express or implied statements regarding Intellia's beliefs and expectations regarding the safety, efficacy and advancement of our clinical program for NTLA-2001 for the treatment of transthyretin amyloidosis, including the expected timing of data releases, regulatory filings, and the initiation and completion of clinical trials; our ability to successfully secure additional clinical studies authorizations, such as investigational new drug applications ("IND") and clinical trial applications ("CTA"); our belief that NTLA-2001 can be approved as a single-dose therapy, that it can halt and reverse ATTR progression or that it leads to deep, durable serum TTR reduction; our plans to present data at upcoming scientific conferences; the advancement, expansion and acceleration of our CRISPR/Cas9 technology and *in vivo* pipeline to develop breakthrough genome editing treatments for people living with severe diseases; ability to demonstrate and leverage our platform's modularity to advance a pipeline of CRISPR-based investigational therapies across a variety of indications and replicate or apply results achieved in preclinical or clinical studies, including those in our ATTR program, in any future studies; our ability to optimize the impact of our collaborations on our development programs, including but not limited to our collaboration with Regeneron Pharmaceuticals, Inc. ("Regeneron"); statements regarding the timing of regulatory filings and clinical trial execution, including dosing of patients, regarding our development programs; and potential commercial opportunities, including value and market, for our product candidates.

Any forward-looking statements in this presentation are based on management's current expectations and beliefs of future events, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: risks related to our ability to protect and maintain our intellectual property position; risks related to our relationship with third parties, including our licensors and licensees; risks related to the ability of our licensors to protect and maintain their intellectual property position; uncertainties related to regulatory agencies' evaluation of regulatory filings and other information related to our product candidates; uncertainties related to the authorization, initiation and conduct of studies and other development requirements for our product candidates; risks related to the development and/or commercialization of any of Intellia's or its collaborators' product candidates, including that they may not be successfully developed and commercialized; risks related to the results of preclinical studies or clinical studies, including that they may not be positive or predictive of future results in connection with future studies; and the risk that our collaborations with Regeneron or our other collaborations will not continue or will not be successful. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause Intellia's actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in Intellia's most recent annual report on Form 10-K as well as discussions of potential risks, uncertainties, and other important factors in Intellia's other filings with the Securities and Exchange Commission ("SEC"). All information in this presentation is as of the date of the release, and Intellia undertakes no duty to update this information unless required by law.

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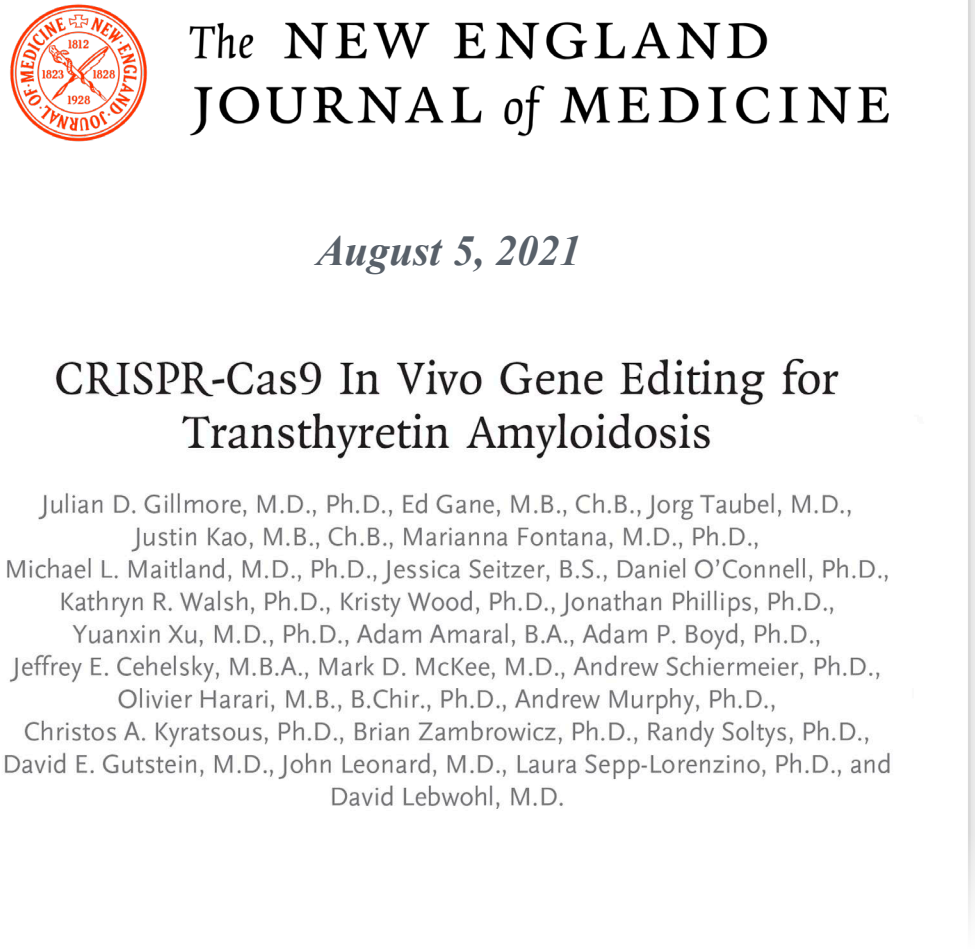
In Vivo Leader: First to Demonstrate Systemic CRISPR Gene Editing in Humans



The NEW ENGLAND JOURNAL of MEDICINE

August 5, 2021

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B., Marianna Fontana, M.D., Ph.D., Michael L. Maitland, M.D., Ph.D., Jessica Seitzer, B.S., Daniel O'Connell, Ph.D., Kathryn R. Walsh, Ph.D., Kristy Wood, Ph.D., Jonathan Phillips, Ph.D., Yuanxin Xu, M.D., Ph.D., Adam Amaral, B.A., Adam P. Boyd, Ph.D., Jeffrey E. Cehelsky, M.B.A., Mark D. McKee, M.D., Andrew Schiermeier, Ph.D., Olivier Harari, M.B., B.Chir., Ph.D., Andrew Murphy, Ph.D., Christos A. Kyratsous, Ph.D., Brian Zambrowicz, Ph.D., Randy Soltys, Ph.D., David E. Gutstein, M.D., John Leonard, M.D., Laura Sepp-Lorenzino, Ph.D., and David Lebwohl, M.D.

Science JOURNALS AAAS — *"CRISPR injected into the blood treats a genetic disease for the first time"*

FT FINANCIAL TIMES — *"CRISPR gene-editing 'revolution' treats internal organ for first time"*

USA TODAY — *"'It's a wow': New CRISPR gene-editing success holds promise for treating many genetic diseases with a single dose"*

nature — *"Landmark CRISPR trial shows promise against deadly disease"*

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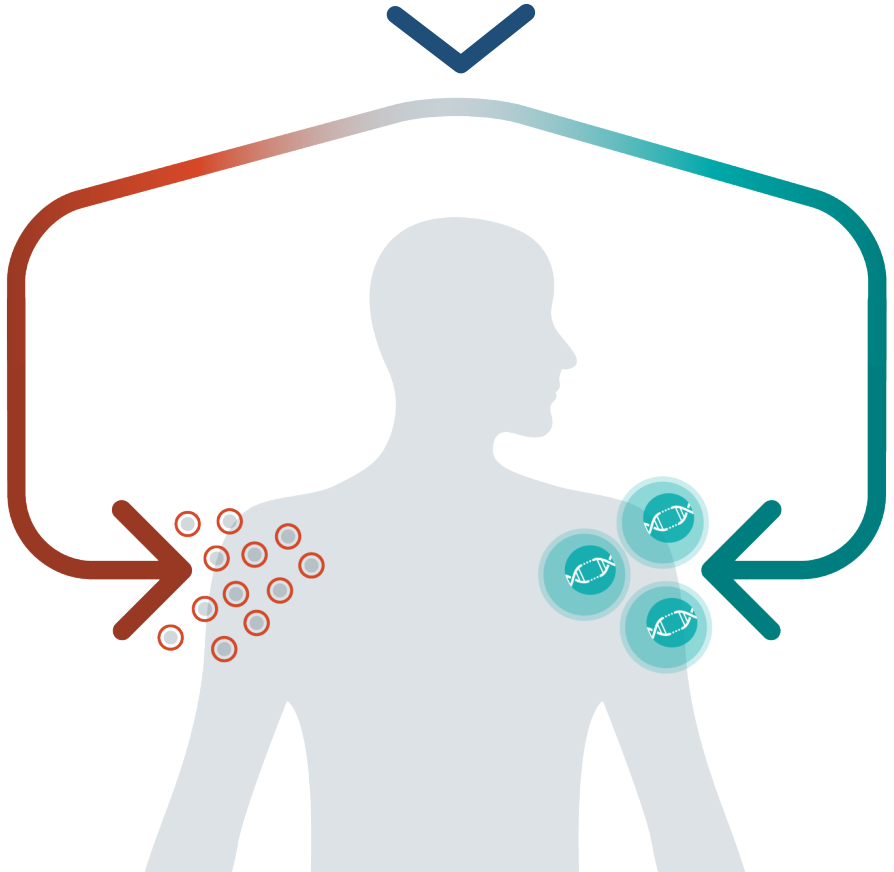
Building a Full-Spectrum Genome Editing Company

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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In Vivo Development Pipeline Fueled by Robust Research Engine

PROGRAM	APPROACH	Research	IND-Enabling	Early-Stage Clinical	Late-Stage Clinical	PARTNER
***In Vivo:* CRISPR is the therapy**						
NTLA-2001: Transthyretin Amyloidosis	Knockout					LEAD Intellia* THERAPEUTICS REGENERON
NTLA-2002: Hereditary Angioedema	Knockout					Intellia THERAPEUTICS
NTLA-2003: AATD-Liver Disease	Knockout					Intellia THERAPEUTICS
NTLA-3001: AATD-Lung Disease	Insertion					Intellia THERAPEUTICS
Hemophilia B	Insertion					Intellia THERAPEUTICS LEAD REGENERON*
Hemophilia A	Insertion					Intellia THERAPEUTICS LEAD REGENERON*
Research Programs	Knockout, Insertion, Consecutive Edits					Intellia THERAPEUTICS
Research Programs	Various					Intellia THERAPEUTICS REGENERON** SPARINGVISION

*Lead development and commercial party **Rights to certain *in vivo* targets

AATD: Alpha-1 Antitrypsin Deficiency

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Ex Vivo Development Pipeline Fueled by Robust Research Engine

PROGRAM	APPROACH	Research	IND-Enabling	Early-Stage Clinical	Late-Stage Clinical	PARTNER
***Ex Vivo:* CRISPR creates the therapy**						
OTQ923 / HIX763: Sickle Cell Disease	HSC					Intellia*** THERAPEUTICS, NOVARTIS
NTLA-5001: Acute Myeloid Leukemia	WT1-TCR					Intellia THERAPEUTICS
NTLA-6001: CD30+ Lymphomas	Allo CAR-T					Intellia THERAPEUTICS
Solid Tumors	WT1-TCR					Intellia THERAPEUTICS
Allo Undisclosed	Undisclosed					Intellia THERAPEUTICS
Research Programs	Allo Universal CAR-T					Intellia THERAPEUTICS, AVENCELL
Other Novartis Programs	CAR-T, HSC, OSC	Undisclosed				Intellia*** THERAPEUTICS, NOVARTIS

***Milestones & royalties only

CAR-T: Chimeric Antigen Receptor T Cells **HSC:** Hematopoietic Stem Cells **OSC:** Ocular Stem Cells **TCR:** T Cell Receptor

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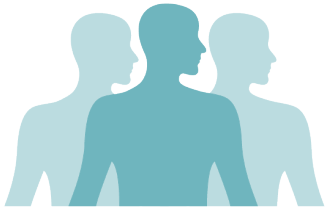
Key Principles of Our Genome Editing Strategy

GENOME EDITING STRATEGY

Precision editing

Safety and specificity



Consistency

Durability

Intellia THERAPEUTICS

Ed Gane, MBChB, MD, FRACP, MNZM

Professor of Medicine, University of Auckland, Deputy Director NZ Liver Transplant Unit

- Research interests: early phase development for new therapies for inherited and acquired liver diseases and liver cancer
- Published over 600 articles in peer-reviewed journals including *Nature Medicine*, *New England Journal of Medicine*, *Hepatology*, *Journal of Hepatology*, *Gastroenterology*, *Gut*, and *The Lancet*
- In 2012, received NZHRC Beaven Medal for best research project and in 2014, the NZHRC Liley Medal for outstanding contribution to health and medical sciences
- In 2011, awarded Member of the Order of New Zealand for Services to Medicine
- In 2017, named New Zealand Innovator of the Year
- In 2018, elected to the Royal Society of Medicine (NZ)

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

Ed Gane, MBChB, MD, FRACP, MNZM

New Zealand Clinical Research, Auckland, New Zealand
University of Auckland, Auckland, New Zealand

Disclosures

I disclose the following financial relationships with a commercial interest:

- **Member of scientific advisory boards:**
  AbbVie, Aligos, AlloVir, Arbutus, Arrowhead, Assembly, Avalia, Clear B, Dicerna, DrugFarm, Gilead, GlaxoSmithKline, Invictus, Janssen, Merck, Novartis, Roche, Silverback, Surrozen, Venatorx, Vir Bio, Virion

- **Research grant:** AbbVie

- **Speaker:** Abbott, AbbVie, Gilead, Intellia, Roche

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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

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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

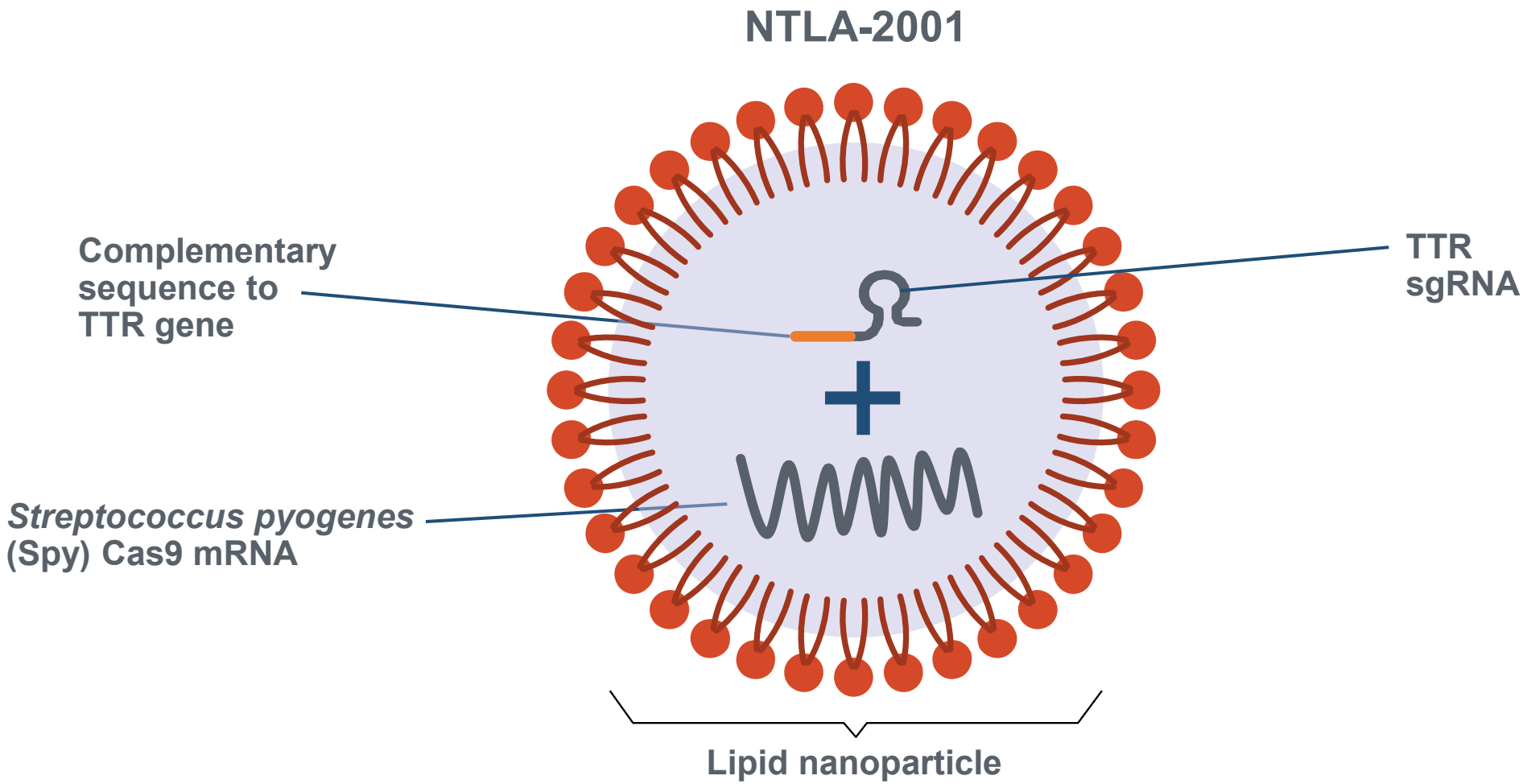
NTLA-2001 is being studied as a potential one-time treatment to permanently knockout the *TTR* gene

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

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



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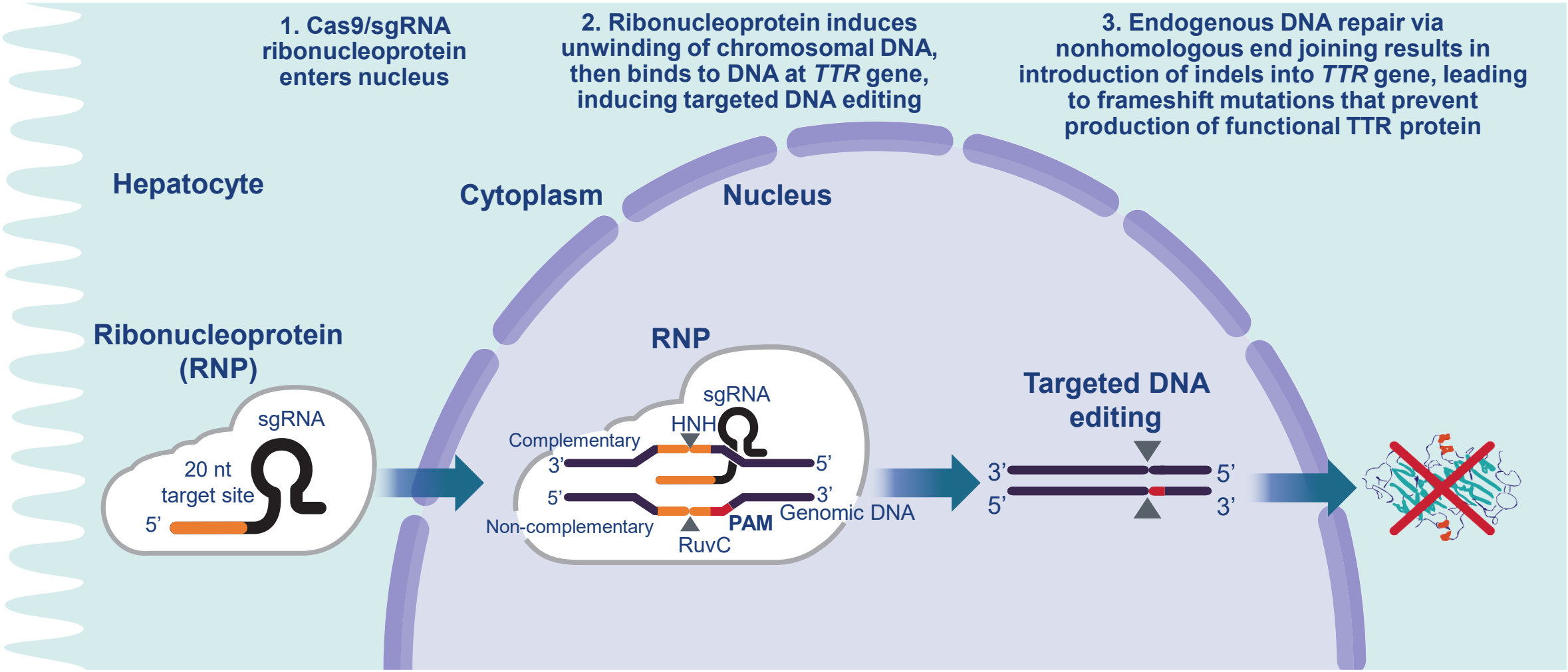
sgRNA, single guide RNA; TTR, transthyretin

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



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

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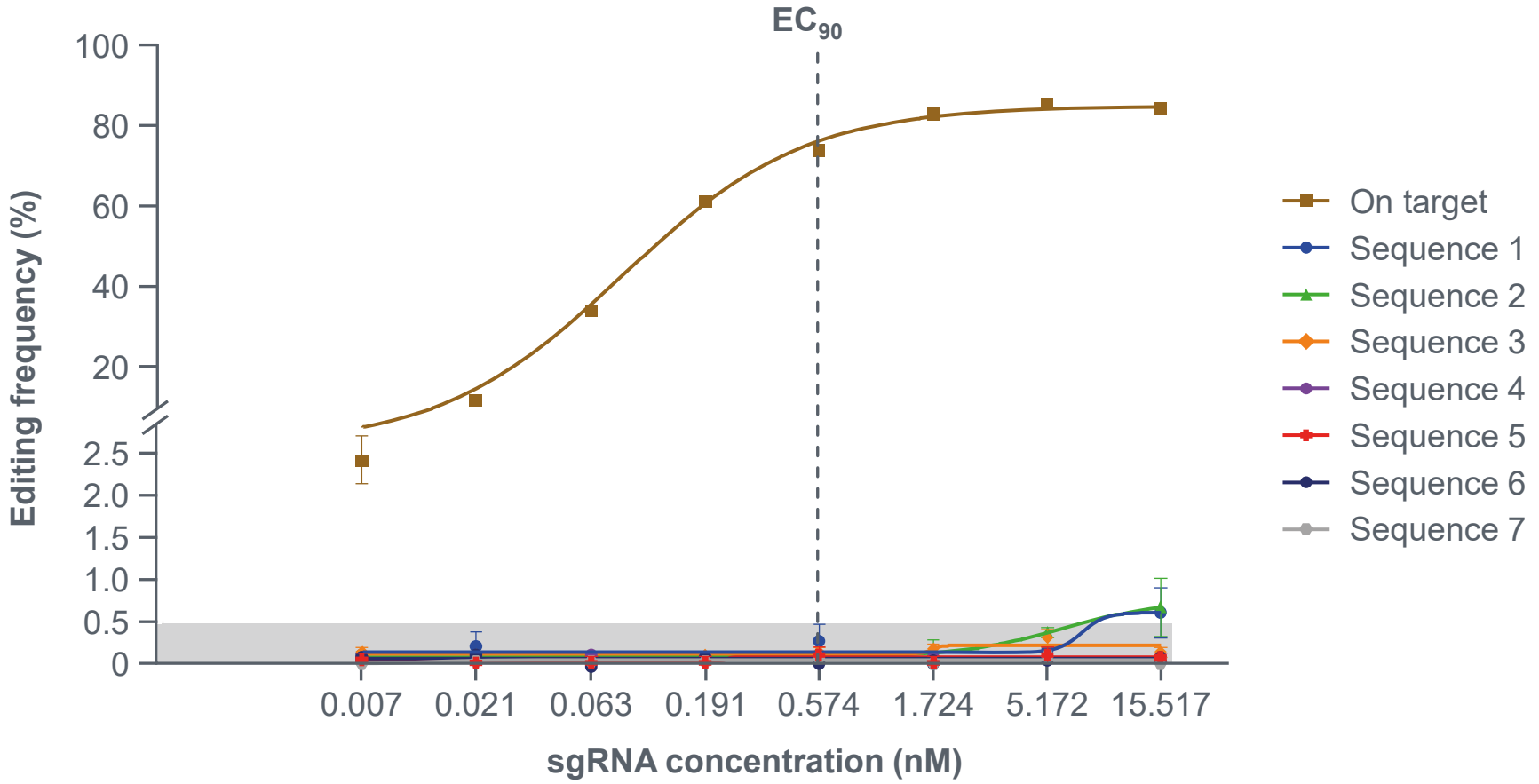
In vitro: No detectable off-target editing with pharmacologic concentrations of sgRNA



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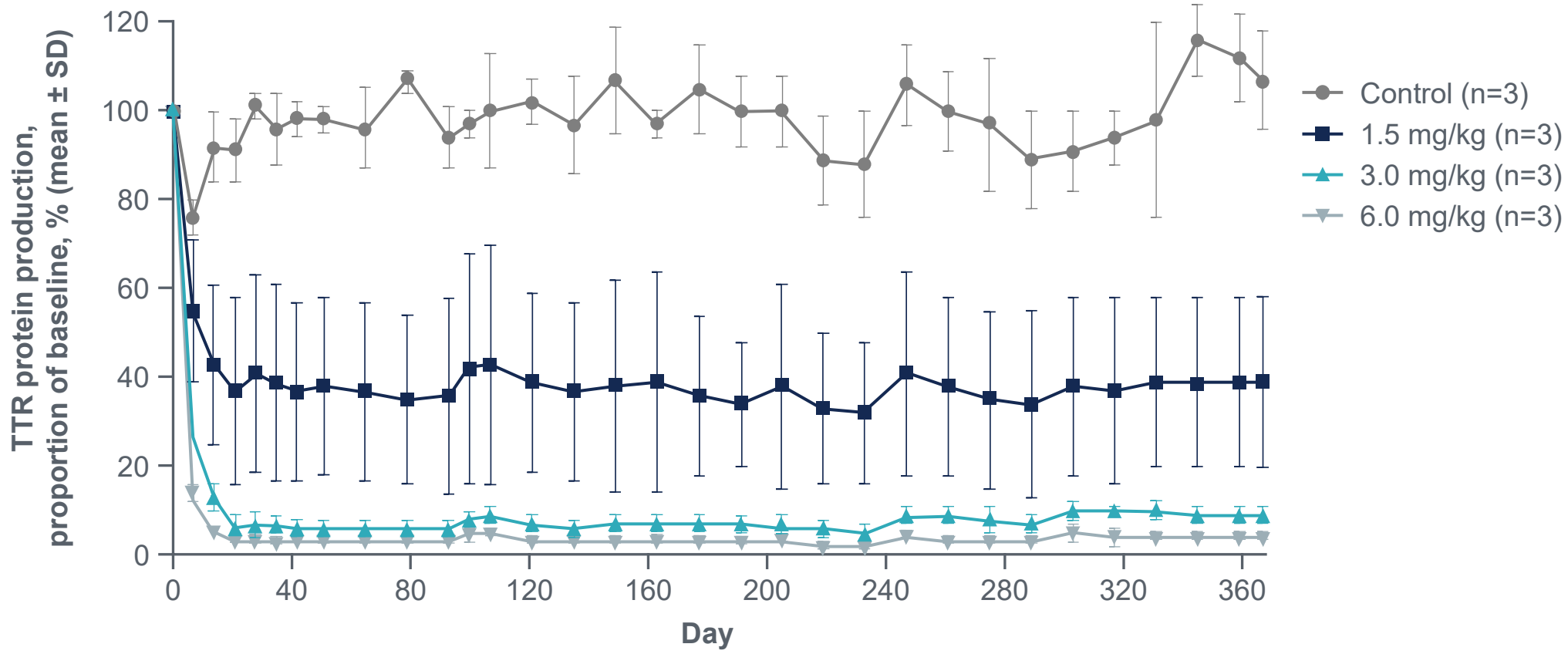
EC_{90}, concentration inducing 90% of maximal effect; sgRNA, single guide RNA

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



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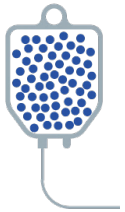
TTR, transthyretin

Two-part phase 1 first-in-human study of NTLA-2001 in ATTRv-PN

Today's interim data presentation covers patients across all four dose levels*

Population
Adults with ATTRv with polyneuropathy



Intervention
Single dose administered via an intravenous infusion

Part I
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
Single-dose expansion cohort

Administer recommended dose selected from Part I

Primary objectives:

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

* Data as of January 20, 2022
† Expanded to 6 patients per protocol to further characterize safety and PD
ATTRv, hereditary ATTR amyloidosis; PD, pharmacodynamics; PK, pharmacokinetics

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

Patient demographics

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%)
Self-reported race, n (%)					
White or Caucasian	1 (33%)	3 (100%)	2 (67%)	4 (67%)	10 (67%)
Western European	2 (67%)	–	–	1 (17%)	3 (20%)
Asian	–	–	–	1 (17%)	1 (7%)
Native Hawaiian / other Pacific Islander	–	–	1 (33%)	–	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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Baseline 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
***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%)
Clinical scores, n (%)					
PN disability score					
1	3 (100%)	3 (100%)	3 (100%)	4 (67%)	13 (87%)
2	0	0	0	2 (33%)	2 (13%)
NYHA Classification					
I	3 (100%)	3 (100%)	3 (100%)	4 (67%)	13 (87%)
II	0	0	0	1 (17%)	1 (7%)
No diagnosis of HF	0	0	0	1 (17%)	1 (7%)
NT-proBNP (ng/L)*, median (min, max)	127 (89, 596)	118 (<50, 359)	58 (<50, 195)	112 (<50, 544)	118 (<50, 596)

* NT-ProBNP ULN = 125 ng/L

HF, heart failure; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PN, peripheral neuropathy; TTR, transthyretin; ULN, upper limit of normal

NTLA-2001 was generally well tolerated across all dose levels

- **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 patients received a complete study dose of NTLA-2001
  - All infusion-related reactions were considered mild, resolving without clinical sequelae
- **A single 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
- **No clinically significant laboratory findings observed**
  - Transient Grade 1 liver enzyme elevations observed
- **Maximally tolerated dose was not reached**

Median follow-up for all subjects is 6 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 mg/kg n=6			All 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	–	–	4	–	–	7	–	–
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 (SAE) of COVID-19 pneumonia
† Related Grade 3 (SAE) of vomiting in a patient with concomitant medical history of gastroparesis

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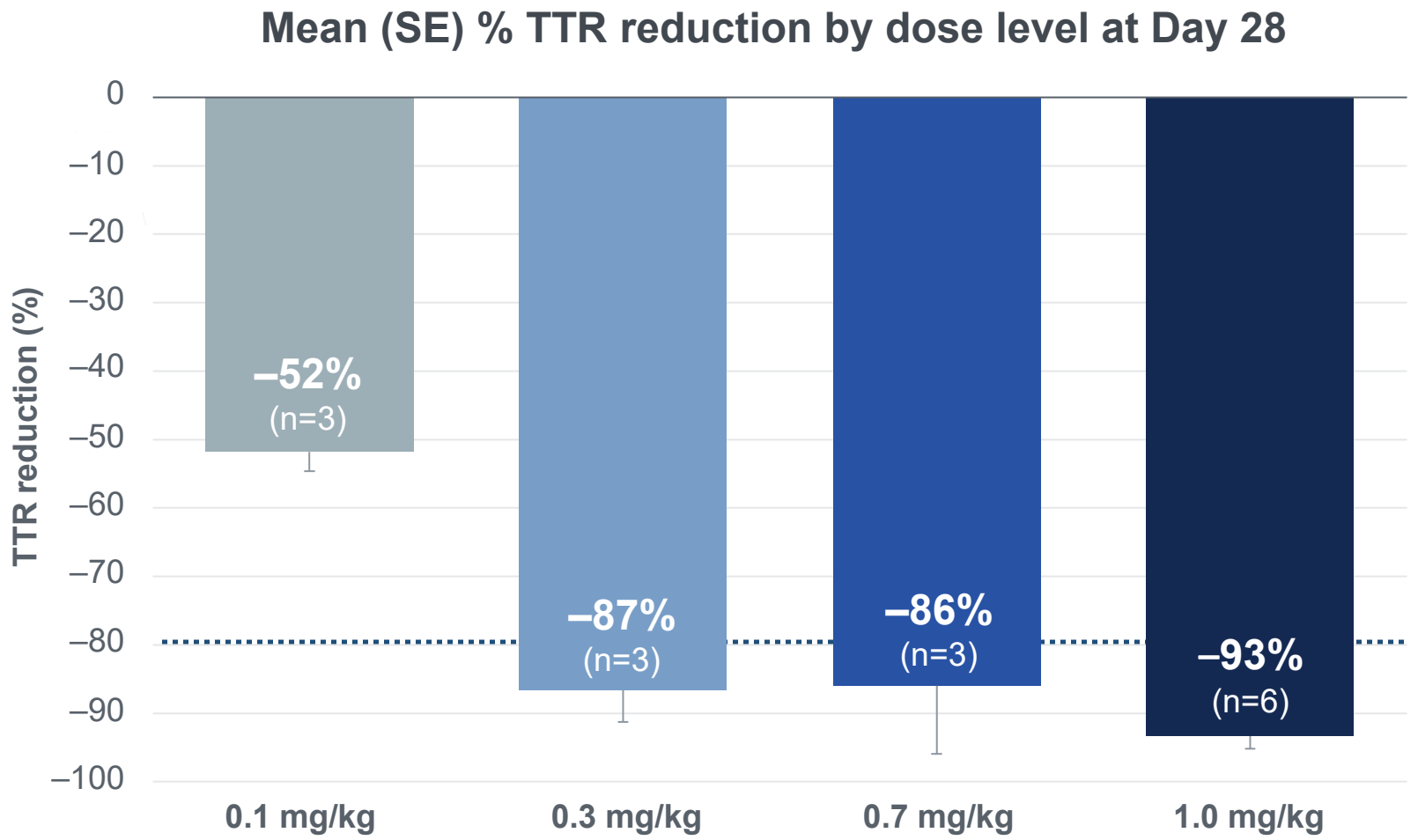
Gr., Grade; SAE, serious adverse events; TEAE, treatment-emergent adverse event

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



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

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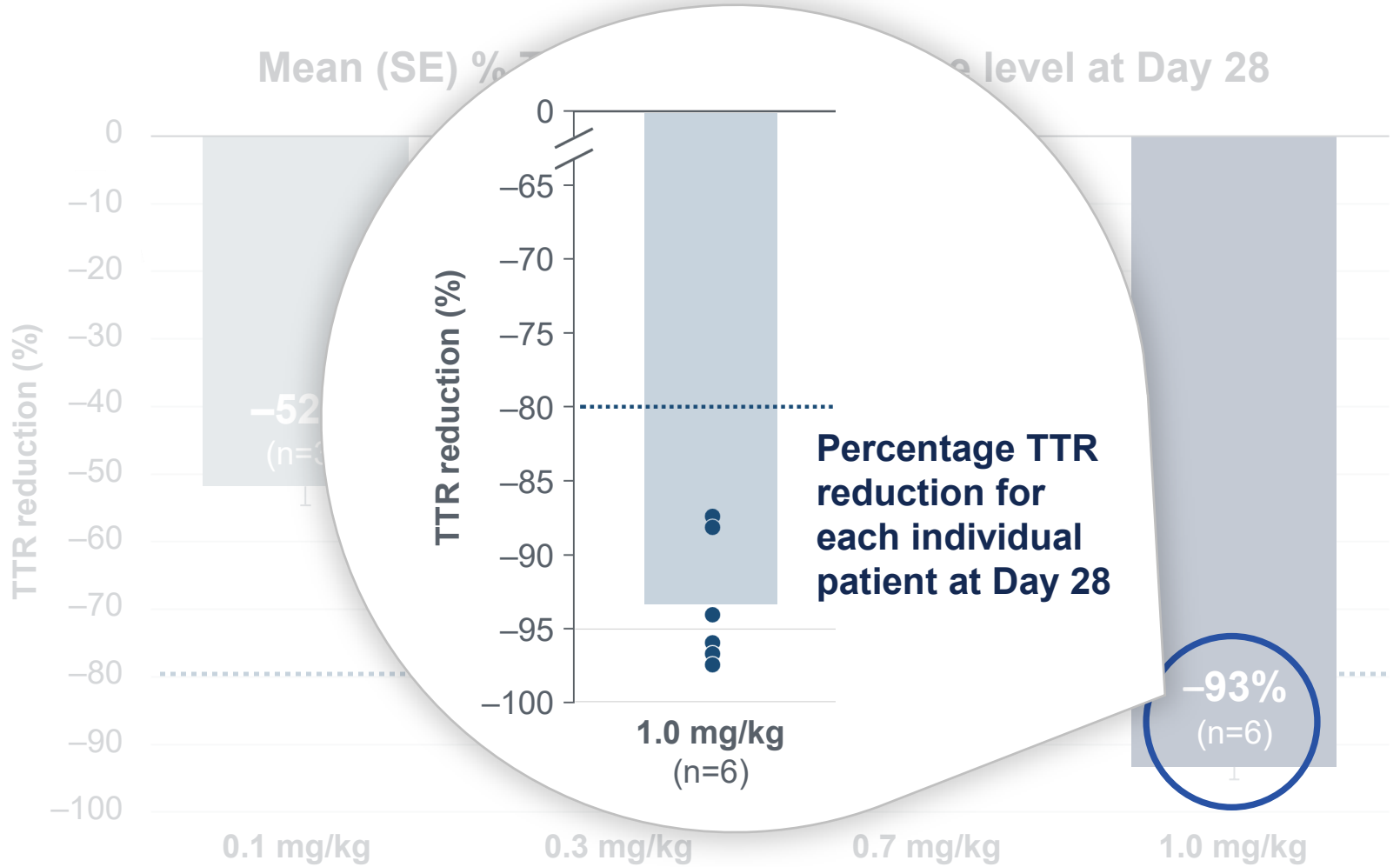
Consistent reductions in serum TTR at 1.0 mg/kg



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

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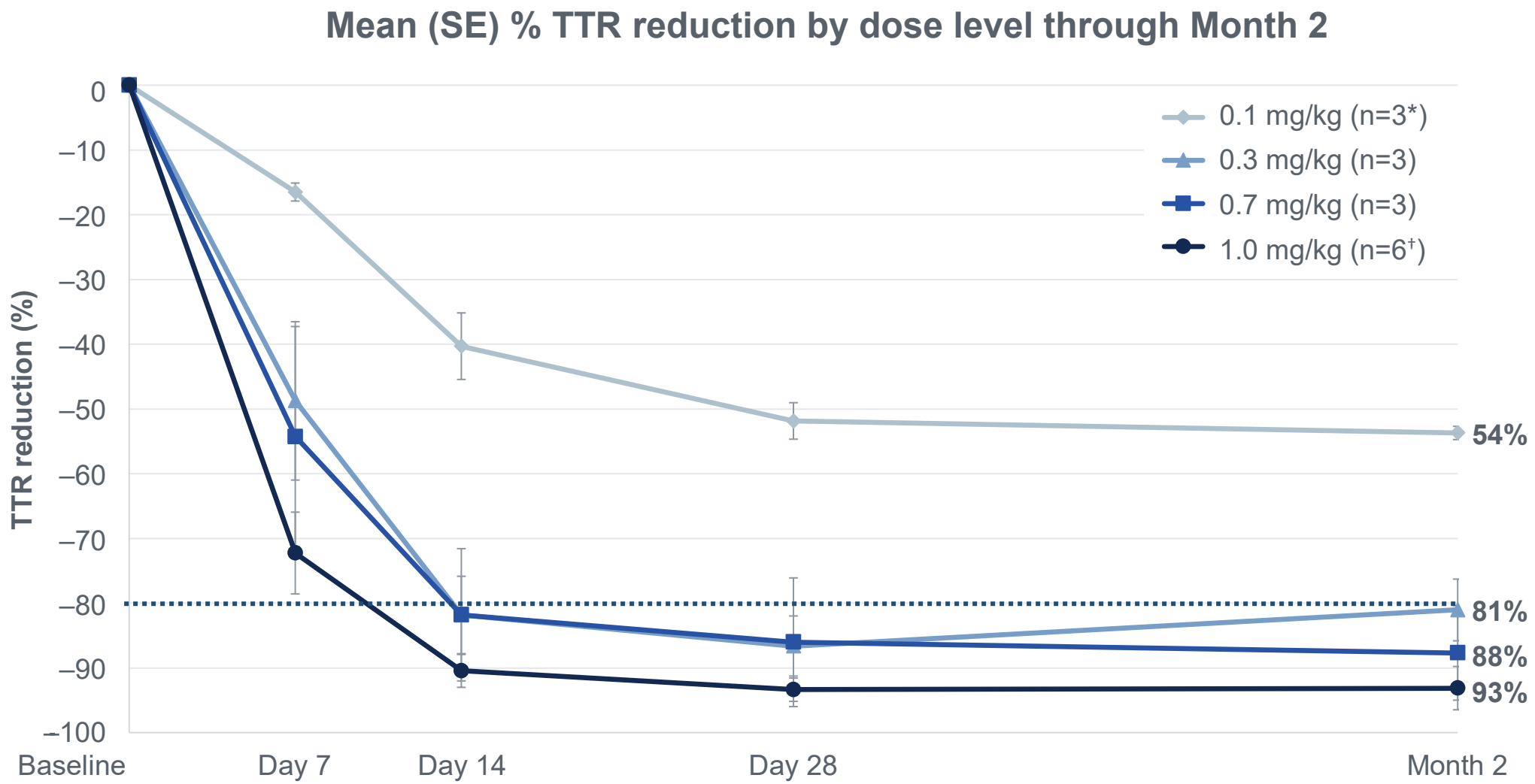
Rapid reductions in serum TTR, achieving nadir by Day 28



* n=2 at Month 2; † n=5 at Month 2
Dashed line represents the targeted minimum reduction
SE, standard error; TTR, transthyretin

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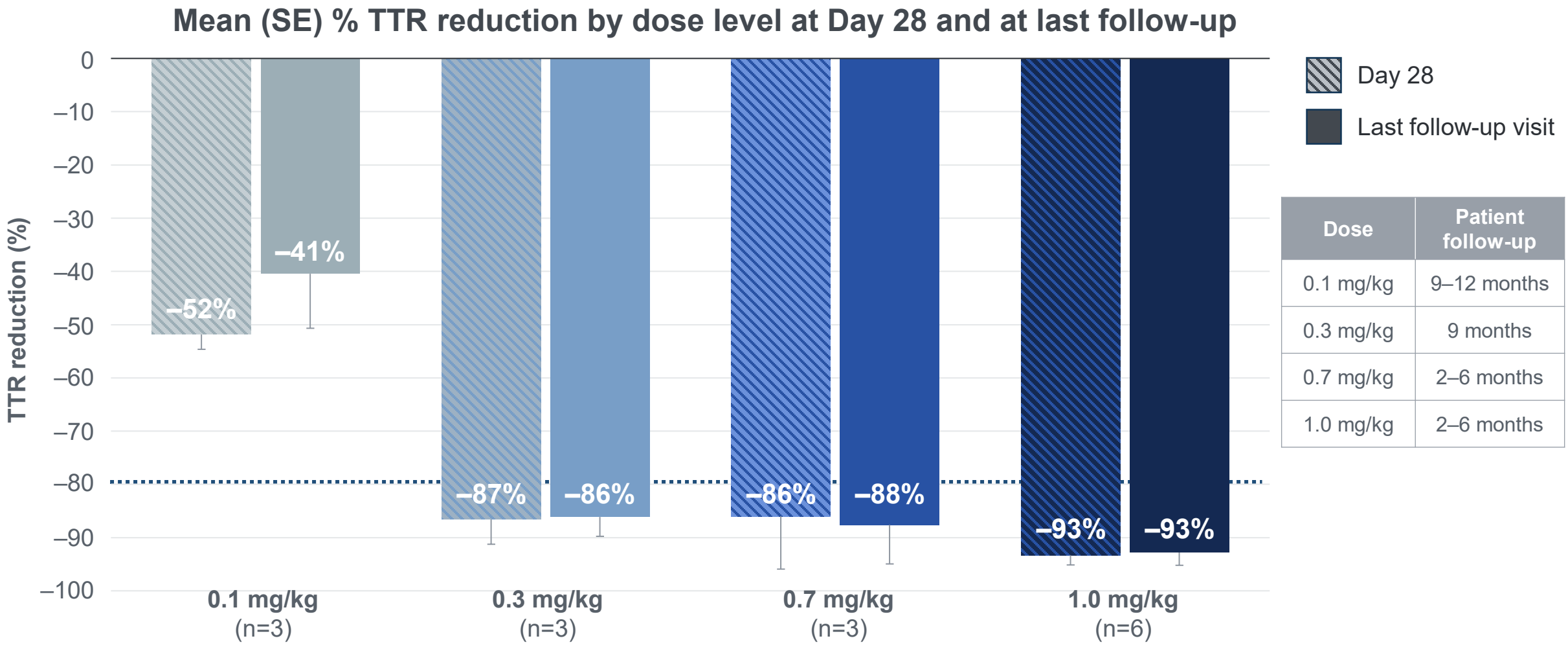
Durable reductions in serum TTR were observed over the follow-up period



Dose	Patient follow-up
0.1 mg/kg	9–12 months
0.3 mg/kg	9 months
0.7 mg/kg	2–6 months
1.0 mg/kg	2–6 months

Mean % reduction at last follow-up calculated using TTR value from last available follow-up visit for each patient per dose level
Dashed line represents the targeted minimum reduction
SE, standard error; TTR, transthyretin

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First-in-human evidence of deep, consistent, and durable TTR reductions following *in vivo* CRISPR-based gene editing

Single systemic administration of NTLA-2001 resulted in deep reductions in serum TTR

93% mean reduction at 1.0 mg/kg by Day 28

6 out of 6 patients at 1.0 mg/kg achieved >80% reductions in TTR

- Durable reductions in serum TTR observed over follow-up period
  - Consistent with animal data supporting potential lifelong TTR suppression
- Generally well tolerated: predominately mild adverse events
- A fixed dose of 80 mg has been selected for evaluation in Part II

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

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

TTR, transthyretin

Acknowledgments

- We thank the patients who participated in this trial and their families
- We thank our investigators: Jorg Taubel, Björn Pilebro, Julian Gillmore, Justin Kao, and Marianna Fontana
- We acknowledge valuable input in the development of NTLA-2001 from Intellia Therapeutics and Regeneron Pharmaceuticals team members
- 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
- Medical writing support was provided by Spirit Medical Communications Group Limited, and funded by Intellia Therapeutics in accordance with Good Publication Practice 3 (GPP3) guidelines (www.ismpp.org/gpp3)

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ELISA, enzyme-linked immunosorbent assay; PK, pharmacokinetics; TTR, transthyretin

Agenda

Welcome

Introduction

John Leonard, M.D.
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Review of NTLA-2001 Interim Phase 1 Clinical Trial Data

Ed Gane, MBChB, MD, FRACP, MNZM
Professor of Medicine, University of Auckland, New Zealand, Chief Hepatologist, Transplant Physician, Deputy Director, New Zealand Liver Transplant Unit, Auckland City Hospital; Investigator for Intellia's Phase 1 Study of NTLA-2001 in New Zealand

NTLA-2001 Clinical Development Plans

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

Closing Remarks and Q&A Session

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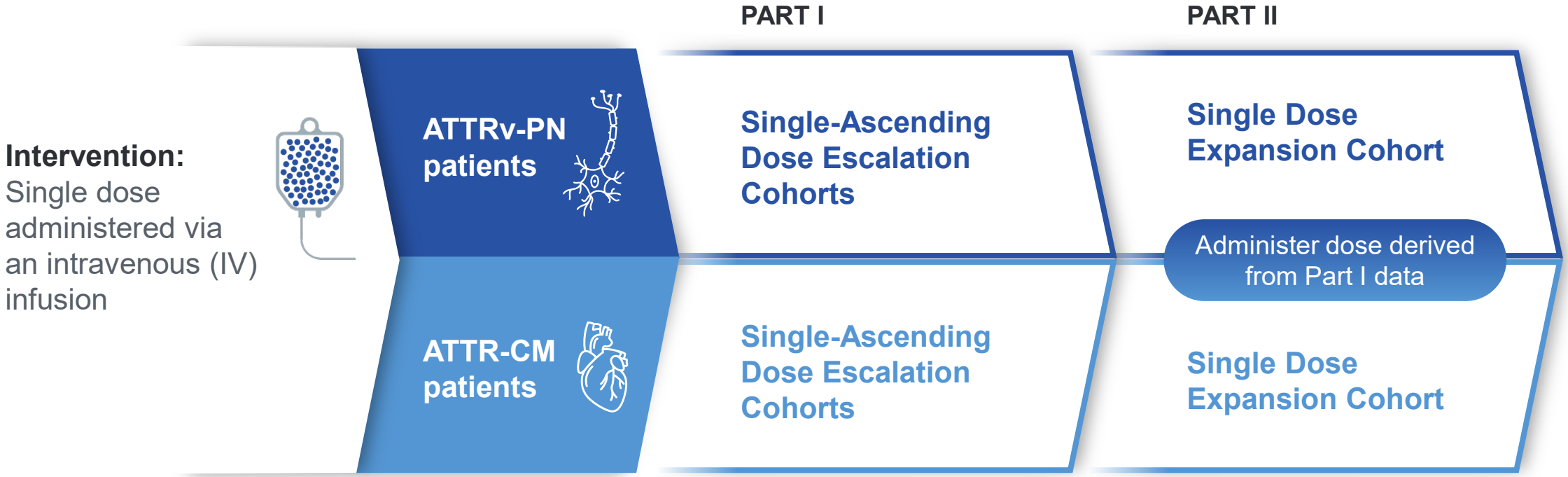
NTLA-2001 Expanded Phase 1 Study

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



Clinicaltrials.gov ID: NCT04601051

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Next Steps for Advancing NTLA-2001 Clinical Evaluation

NTLA-2001 **ATTRv-PN**

- Selected fixed dose of 80 mg to be evaluated in Part 2, a single dose-expansion cohort, pending regulatory feedback
- On track to initiate Part 2 in Q1 2022

NTLA-2001 **ATTR-CM**

- Continue to enroll and dose patients in Part 1
- Evaluate NTLA-2001 at 0.7 mg/kg and 1.0 mg/kg dose levels in ATTR-CM patients in Part 1

Moving Towards Pivotal Studies

- Plan to present additional clinical data from Phase 1 study in 2022 at future medical meeting
- Complete enrollment of Phase 1 study for both ATTRv-PN and ATTR-CM in 2022
- Engage with regulatory agencies, including U.S. FDA, to discuss a potential pivotal trial design

Growing Confidence in NTLA-2001 as Potential Treatment for ATTR Amyloidosis

Key Insights from Ongoing Phase 1 Study	Supported by Interim Data
Generally well-tolerated at all dose levels	✓
Dose-response relationship with deep reductions at higher doses	✓
Consistent reductions in serum TTR across ATTRv-PN patients	✓
Durable response following a single dose	✓

93% mean serum TTR reduction demonstrated at 1.0 mg/kg by Day 28 (n=6)

NTLA-2001 is an investigational product. Safety and efficacy have not been established by any health authority.

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Agenda

Welcome

Introduction

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

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Intellia is Opening a New Era of Medicine

KEY TAKEAWAYS

Growing body of evidence **NTLA-2001 could be a potential single-dose treatment for ATTR amyloidosis** that leads to deep, durable serum TTR reduction based on initial safety and activity data

Plan to **leverage modular platform** to advance a pipeline of CRISPR-based investigational therapies across a variety of indications

Intellia is at the **forefront of genome editing** and is the reference company across the industry for its scientific innovation

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Q&A

NTLA-2001 Interim Phase 1 Clinical Data

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