Intellia is Leading the Gene Editing Revolution

Corporate Overview

November 2024

MILTON
Living with ATTR amyloidosis
with cardiomyopathy

Intellia Therapeutics’ Legal Disclaimer

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 about Intellia’s beliefs and expectations regarding: our ability to build a world-class gene editing toolbox to develop an unsurpassed gene editing pipeline; the safety, efficacy and advancement of our clinical programs for NTLA-2001, also known as nexiguran ziclumeran or “nex-z”, for the treatment of transthyretin (“ATTR”) amyloidosis, NTLA-2002 for the treatment of hereditary angioedema (“HAE”) and NTLA-3001 for the treatment of alpha-1 antitrypsin deficiency (“AATD”)-associated lung disease pursuant to our clinical trial applications (“CTA”) and investigational new drug (“IND”) submissions, including the expected timing of data releases, regulatory filings, and the initiation and completion of clinical trials, such as initiating the Phase 3 study for the treatment of ATTR amyloidosis with polyneuropathy in 2024, presenting updated data from the ongoing Phase 1 study of NTLA-2001 in 2024, and dosing the first patient in the Phase 1 study of NTLA-3001 in 2024; the execution of its strategic priorities for 2024-2026, including the completion of patient enrollment for pivotal studies of NTLA-2001 and NTLA-2002, the planned BLA submission for NTLA-2002 for HAE in 2026, demonstrating human proof-of-concept for targeted *in vivo* gene insertion, initiating clinical development for its allogeneic *ex vivo* program, demonstrating preclinical proof-of-concept of editing in tissues outside the liver, and advancing DNA writing technology; the ability to generate data to initiate clinical trials and the timing of CTA and IND submissions; the advancement, expansion and acceleration of our CRISPR/Cas9 technology and related technologies, including DNA writing, base editing, manufacturing and delivery technologies, to advance and develop additional candidates and treatments; our ability to demonstrate our platform’s modularity and replicate or apply results achieved in preclinical studies, including those in its NTLA-2001, NTLA-2002 and NTLA-3001 programs, in any future studies, including human clinical trials; our ability to optimize the impact of our collaborations on our development programs, including, but not limited to, collaborations with Regeneron Pharmaceuticals, Inc. (“Regeneron”), including our co-development programs for ATTR amyloidosis and hemophilia A, with AvenCell Therapeutics, Inc. (“AvenCell”) for the development of universal CAR-T cell therapies, with SparingVision SAS (“SparingVision”) for the development of ophthalmic therapies, with ReCode Therapeutics, Inc. (“ReCode”) for the development of novel genomic medicines for the treatment of cystic fibrosis, with Kyverna Therapeutics, Inc. (“Kyverna”) for the development of KYV-201, and with ONK Therapeutics Ltd. (“ONK”) for the development of engineered NK cell therapies; the potential commercial opportunities, including value and market, for our product candidates, including the potential of NTLA-2001, NTLA-2002 and NTLA-3001 to be a single-dose treatment, the potential of NTLA-2001 to halt and reverse disease and result in lifelong, stable TTR reduction, the potential of NTLA-2002 to eliminate significant treatment burden; and the potential of NTLA-3001 to achieve normal human levels of alpha-1 antitrypsin protein and halt progression of lung disease; and our use of capital and other financial results.

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 valid third party intellectual property; 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, including uncertainties related to regulatory approvals to conduct clinical trials; 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 or clinical studies, including that they may not be positive or predictive of future results; risks related to the development of novel platform capabilities, including technologies related to editing in tissues outside the liver, base editing and DNA writing; risks related to Intellia’s reliance on collaborations, including that its collaborations with Regeneron, AvenCell, SparingVision, ReCode, Kyverna, ONK or its 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 and Quarterly Report on Form 10-Q as well as discussions of potential risks, uncertainties, and other important factors in Intellia’s other filings with the Securities and Exchange Commission. All information in this presentation is as of the date on its cover page, and Intellia undertakes no duty to update this information unless required by law.

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Intellia is Leading a New Era of Medicine

Turning Nobel-Prize-Winning Science into Medicine

- Poised to bring first-ever *in vivo* CRISPR therapy to market
- Initiated first-ever, pivotal Phase 3 program for an *in vivo* CRISPR therapy
- Three active Phase 3 studies expected by the end of 2024

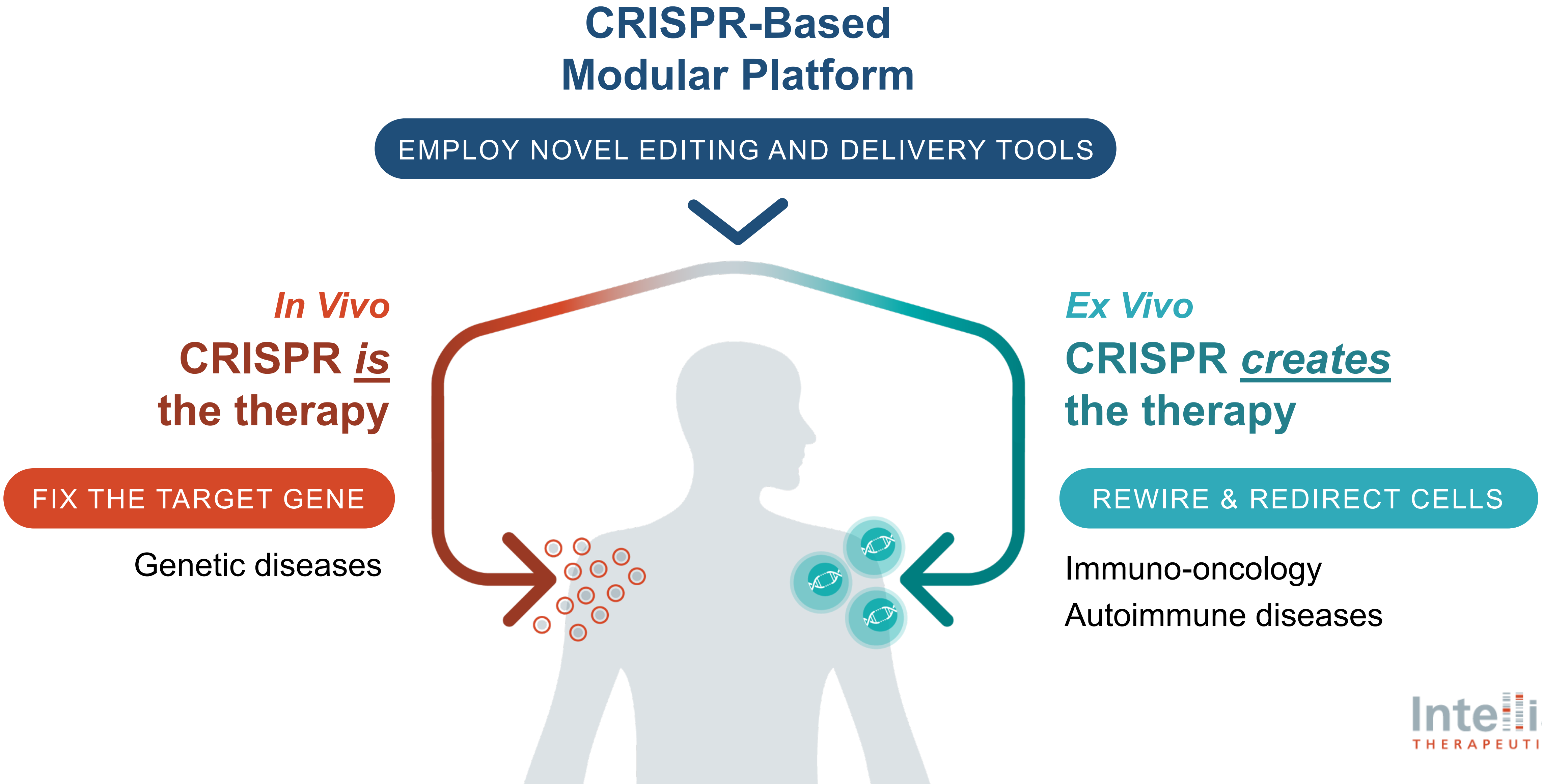
150+ patients
dosed with Intellia's investigational *in vivo* CRISPR-based therapies

Robust pipeline of *in vivo* and *ex vivo* programs

Comprehensive gene editing toolbox

Intellia THERAPEUTICS

Advancing a Full-Spectrum Genome Editing Company



Intellia is Developing Potentially Curative Gene Editing Treatments to Transform the Lives of Patients

Full-Spectrum Strategy

Pipeline of *in vivo* and *ex vivo* CRISPR-based therapies for life-threatening diseases with high unmet need

Clinically Validated Modular Platform

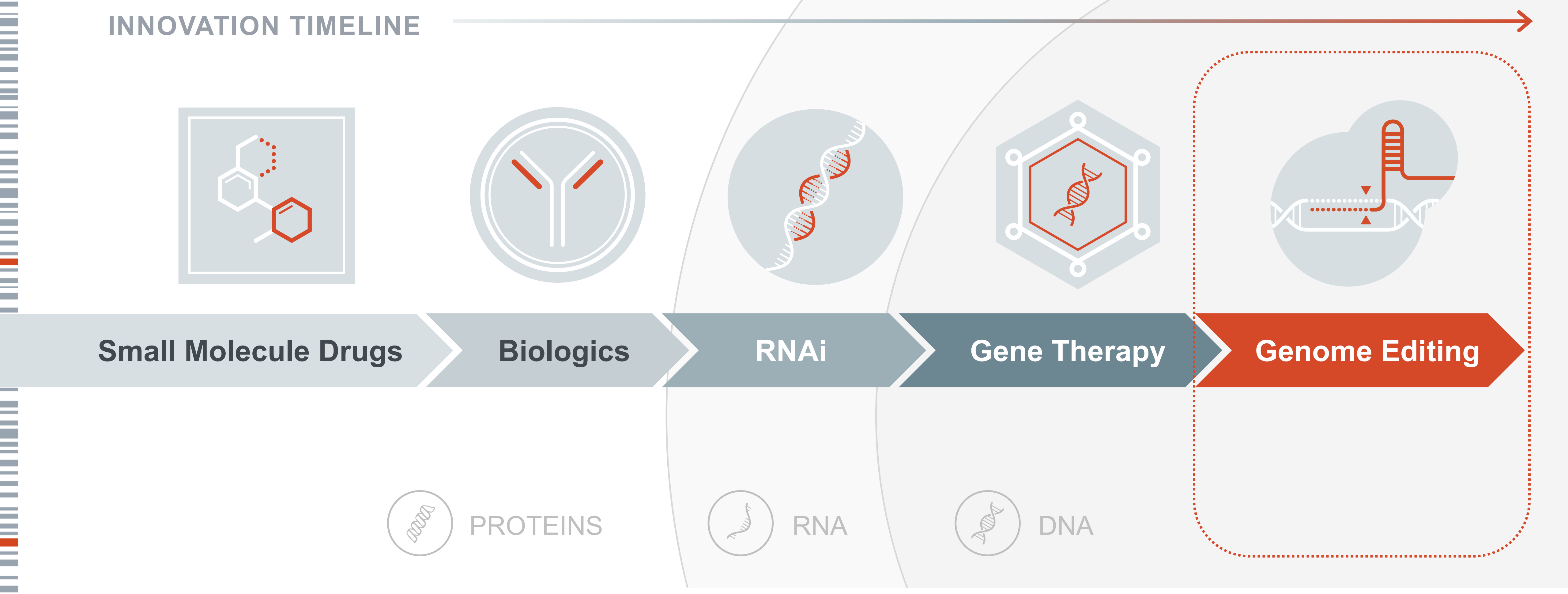
Modular technology enables a reproducible path to drug discovery and development

Deploying Novel Tools

Continued innovation across editing and delivery modalities for future therapeutic applications

Intellia THERAPEUTICS

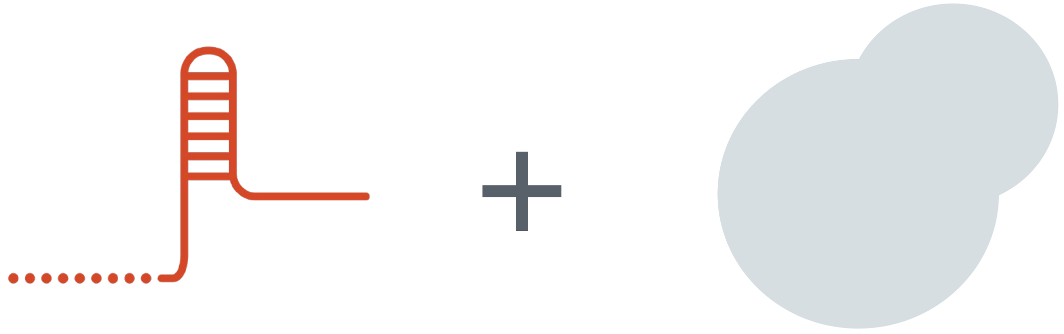
Therapeutic Strategies to Treat Life-Threatening Diseases Have Advanced Over Time



Intellia THERAPEUTICS

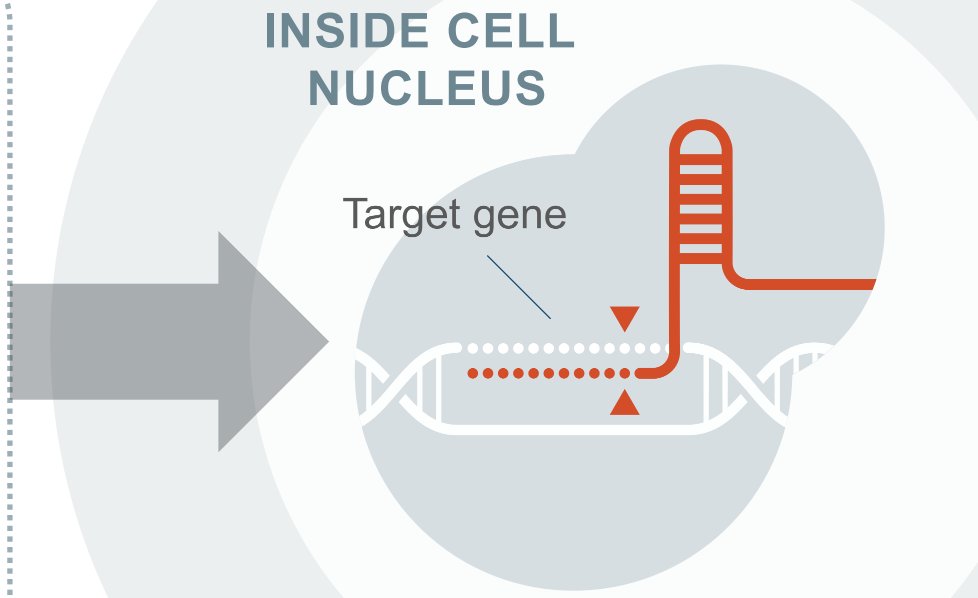
Gene Editing Starts with CRISPR/Cas9, a Two-Part, Programmable System

FOUNDATIONAL CRISPR MACHINERY



1 **Guide RNA (gRNA)**
Identifies genetic target

2 **Cas Protein**
Responsible for the targeted DNA editing and provides platform for other enzymatic activities

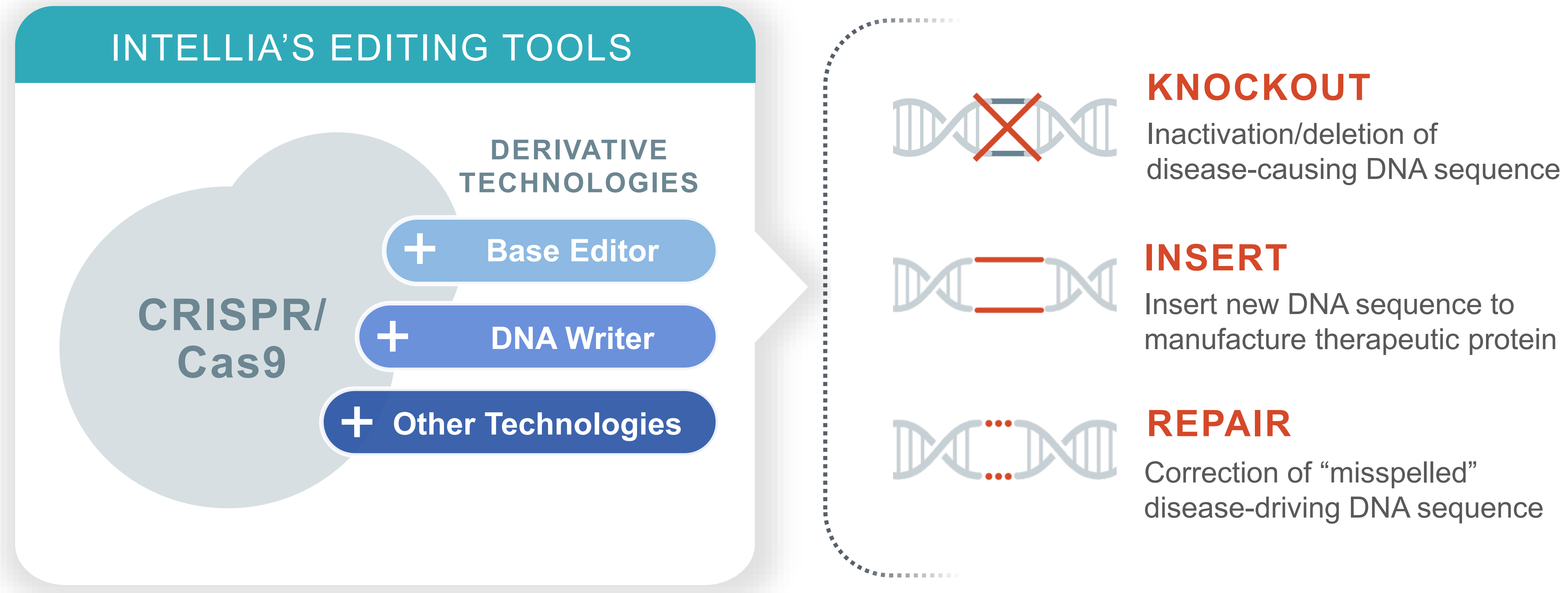


KEY FEATURES OF CRISPR/CAS9 SYSTEM

✓ Selectivity ✓ High potency ✓ Address any site ✓ Target multiple DNA sites

Intellia THERAPEUTICS

CRISPR/Cas9 and Derivative Gene Editing Technologies Can Be Used to Make Any Type of Edit



INTELLIA SELECTS THE BEST TOOL FOR EACH THERAPEUTIC APPLICATION

A Tailored Approach to Maximize the Reach of Gene Editing Across Multiple Tissues

INTELLIA'S DELIVERY TOOLS

LNP: Liver-targeted

LNP: Bone marrow-targeted

AAV

Other technologies

TARGET TISSUES*

LNPs are well-suited for delivery to the liver and blood cells

Liver

Bone Marrow

AAV and other technologies are well-suited for delivery to other tissues

CNS/PNS

Eye

Muscle

* This is a representative list of target tissues and does not include all future opportunities.

CRISPR-Based Editing Technologies are a Promising New Therapeutic Modality

Potential of CRISPR-Based Editing Technologies

Treat patients
at the **root cause**
of their disease

Single dose
treatment with potential
lifelong benefit

Reduce burden
to the healthcare system
over a patient's lifetime

Intellia THERAPEUTICS

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.

The NEW ENGLAND JOURNAL of MEDICINE

January 31, 2024

CRISPR-Cas9 In Vivo Gene Editing of *KLKB1* for Hereditary Angioedema

H.J. Longhurst, K. Lindsay, R.S. Petersen, L.M. Fijen, P. Gurugama, D. Maag, J.S. Butler, M.Y. Shah, A. Golden, Y. Xu, C. Boiselle, J.D. Vogel, A.M. Abdelhady, M.L. Maitland, M.D. McKee, J. Seitzer, B.W. Han, S. Soukamneuth, J. Leonard, L. Sepp-Lorenzino, E.D. Clark, D. Lebwohl, and D.M. Cohn

The NEW ENGLAND JOURNAL of MEDICINE

October 24, 2024

CRISPR-Based Therapy for Hereditary Angioedema

Danny M. Cohn, M.D., Ph.D., Padmalal Gurugama, M.D., Markus Magerl, M.D., Constance H. Katelaris, M.B., B.S., Ph.D., F.R.A.C.P., David Launay, M.D., Ph.D., Laurence Bouillet, M.D., Ph.D., Remy S. Petersen, M.D., Karen Lindsay, M.B., Ch.B., Emel Aygören-Pürsün, M.D., David Maag, Ph.D., James S. Butler, Ph.D., Mrinal Y. Shah, Ph.D., Adele Golden, Ph.D., Yuanxin Xu, M.D., Ph.D., Ahmed M. Abdelhady, Ph.D., David Lebwohl, M.D., and Hilary J. Longhurst, Ph.D., F.R.A.C.P.

N Engl J Med 2021; 385:493-502; DOI: 10.1056/NEJMoa2107454
N Engl J Med 2024; 390:432-441; DOI: 10.1056/NEJMoa2309149
N Engl J Med 2024; DOI: 10.1056/NEJMoa2405734

Intellia THERAPEUTICS

Intellia's Strategic Priorities for 2024 – 2026

1 Execute pivotal trials for first two *in vivo* CRISPR-based therapies

- Complete patient enrollment for pivotal studies of NTLA-2001, also known as nexiguran ziclumeran (nex-z), and NTLA-2002
- Planned BLA submission for NTLA-2002 for HAE in 2026

2 Launch next wave of *in vivo* and *ex vivo* clinical programs

- Demonstrate human proof-of-concept for targeted *in vivo* gene insertion
- Initiate clinical development for first allogeneic *ex vivo* program

3 Deploy new gene editing and delivery modalities

- Demonstrate preclinical proof-of-concept of editing in tissues outside the liver
- Advance DNA writing technology

Upcoming 2024 Key Clinical Program Milestones

NTLA-2001 (nex-z) **ATTR**	✓ (completed)	Dose first patient in pivotal Phase 3 MAGNITUDE trial for ATTR-CM in Q1 2024
	✓ (completed)	Continue to open new sites and enroll patients
	○	Initiate a pivotal Phase 3 study for ATTRv-PN by year-end
	○	Present updated data from the ongoing Phase 1 study in 2H 2024
NTLA-2002 **HAE**	✓ (completed)	Present updated data from the Phase 1 portion in 2024
	✓ (completed)	Initiate the Phase 3 study in 2H 2024
	✓ (completed)	Present data from the Phase 2 portion in 2H 2024
NTLA-3001 **AATD**	○	Dose first patient in Phase 1 study of NTLA-3001 by year-end 2024

Intellia THERAPEUTICS

Broad Development Pipeline Fueled by Robust Research Engine

PROGRAM	APPROACH	Research and Preclinical	Early-Stage Clinical	Late-Stage Clinical	PARTNERS
***In Vivo*: CRISPR is the therapy**					
NTLA-2001 (nexiguran ziclumeran*): Transthyretin Amyloidosis	Knockout				LEAD Intellia Therapeutics; Regeneron
NTLA-2002: Hereditary Angioedema	Knockout				Intellia Therapeutics
NTLA-3001: AATD-Lung Disease	Insertion				Intellia Therapeutics
Hemophilia A / B***	Insertion				Intellia Therapeutics; Regeneron LEAD
Research Programs	Knockout, insertion or repair				Intellia Therapeutics
Research Programs	Tissues outside the liver				Intellia Therapeutics**; ReCode; Regeneron; SparingVision
***Ex Vivo*: CRISPR creates the therapy**					
Research Programs	Allogeneic and other				Intellia Therapeutics**; AvenCell; kyverna; ONK Therapeutics

Lead refers to lead development and commercial party.
* NTLA-2001 is also known as nexiguran ziclumeran (nex-z)
** Intellia is advancing both wholly owned and partnered programs.
*** Hemophilia A program is in the research stage; Hemophilia B is being advanced by Regeneron – Intellia is eligible for milestones and royalties.

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In Vivo

CRISPR is the therapy

GENETIC DISEASES

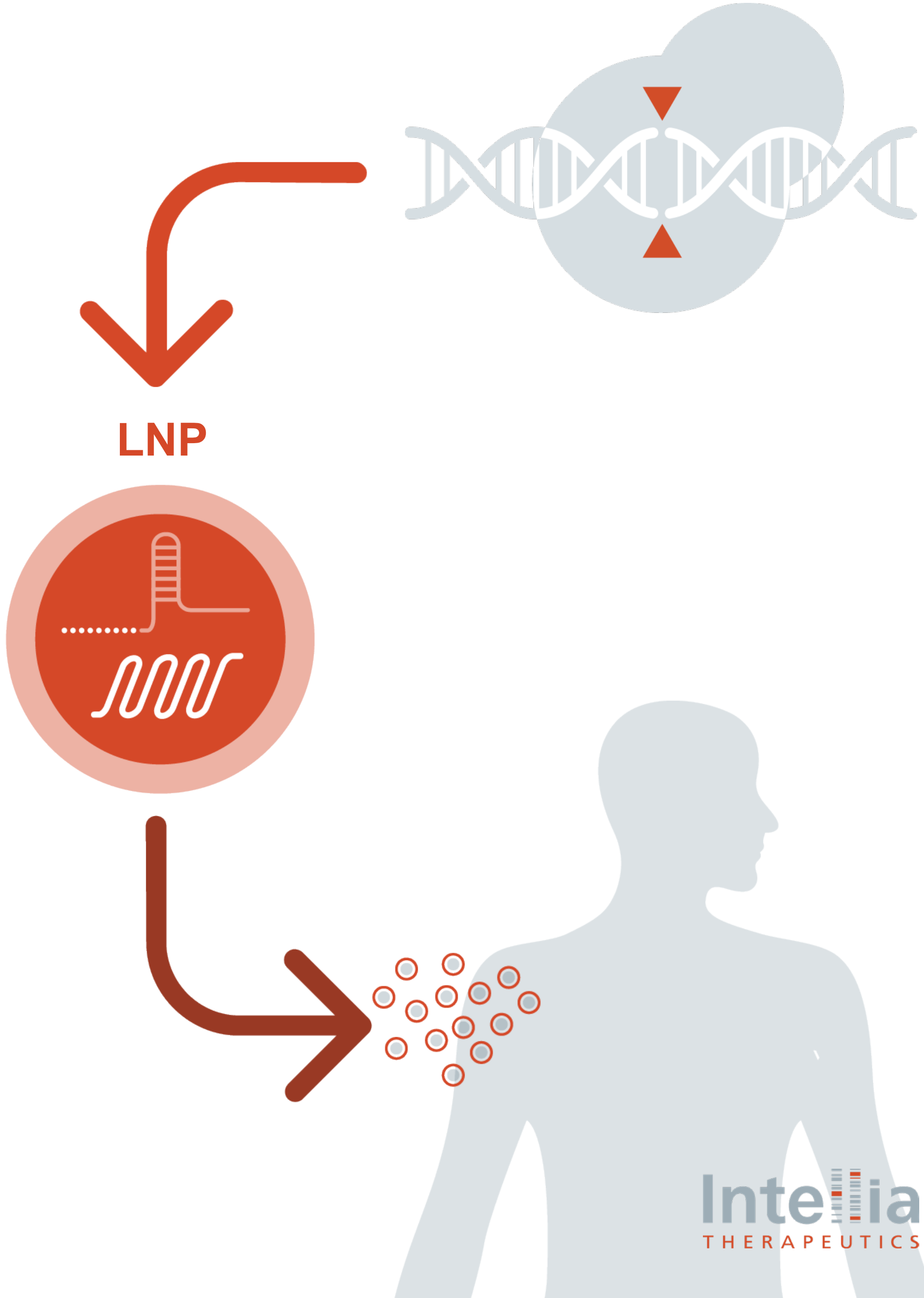
Strategic Advantages:

Potential curative therapy from a single dose

Systemic non-viral delivery of CRISPR/Cas9 provides transient expression and potential safety advantages

Potential for permanent gene knockout or gain of function by targeted insertion

Capable of delivering to multiple tissue types for various therapeutic applications



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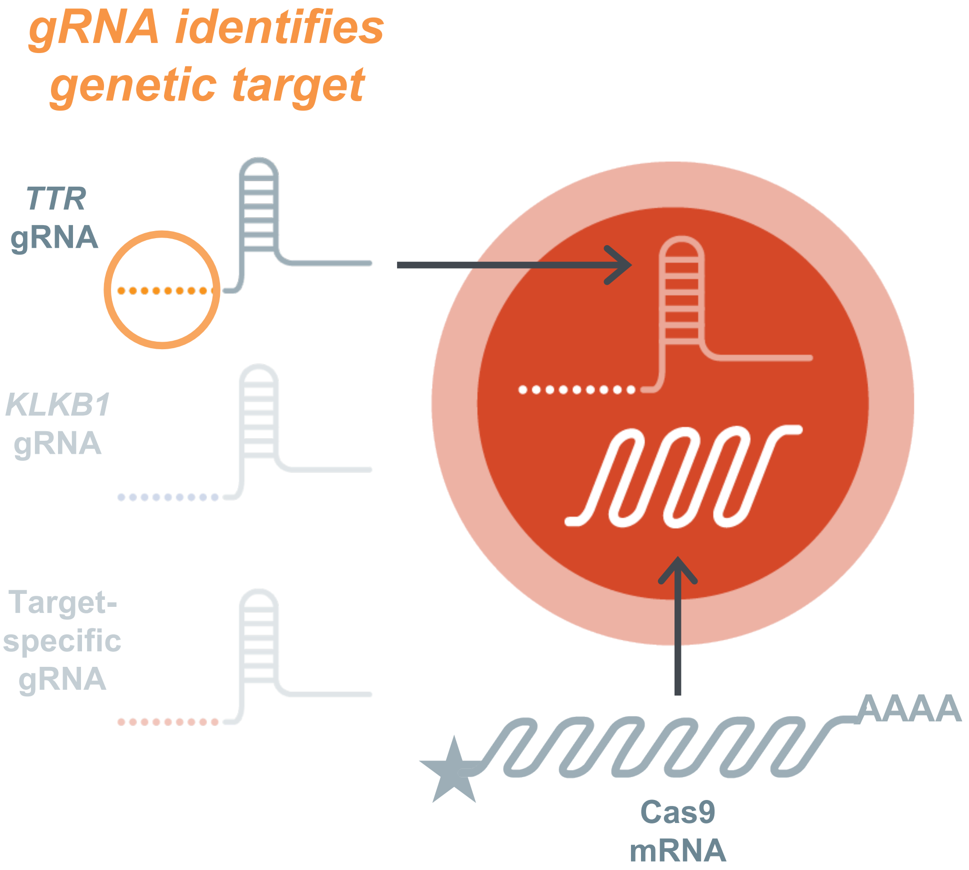
Modular Delivery Platform Enables Rapid and Reproducible Path to Clinical Development

LNP Delivery System:



Key Advantages of LNP Delivery

- Clinically-proven delivery to liver
- Large cargo capacity
- Transient expression
- Biodegradable
- Low immunogenicity
- Well-tolerated
- Redosing capability
- Scalable synthetic manufacturing
- Tunable to other tissues

Intellia THERAPEUTICS

NTLA-2001 (nex-z*) for Transthyretin (ATTR) Amyloidosis

About ATTR Amyloidosis

- Caused by accumulation of misfolded TTR protein
- Primarily affects the nerves and/or the heart
- Chronic dosing is required with current treatment options

Our Approach

Knock out *TTR* gene with a single-dose CRISPR-based treatment

- Reduces wild-type and mutant TTR protein
- Aims to address polyneuropathy and cardiomyopathy

Key Advantages Includes Potential to:

- Halt and reverse disease with deep and consistent TTR reduction
- Be a single-dose treatment
- Expect lifelong, stable TTR reduction

* NTLA-2001 is also known as nexiguran ziclumeran (nex-z)

REGENERON Intellia THERAPEUTICS

ATTR Amyloidosis:
Large Commercial Opportunity with Significant Unmet Need

NTLA-2001 (nex-z)

Potential to be the best-in-class TTR reduction agent and only single-dose treatment

Prevalence[1,2]	**50,000** ATTRv patients worldwide	**~200-500K** ATTRwt patients worldwide
Life Expectancy[3]	**2-7 years** after diagnosis for ATTR-CM patients	**10+ years** after diagnosis for ATTRv-PN patients
Disease Burden[4]	Patients experience **highly burdensome symptoms**, including heart failure, shortness of breath, muscle weakness and sensory deficits	
Commercial Opportunity[5,6]	**$11B+** global market size expected by 2029	**$450K+** average annual cost of TTR reduction treatment in the U.S.

[1] Hawkins et al. *Ann Med*. 2-15; 47(8): 625–638
[2] Compiled from various sources.
[3] Luigetti et al. *Ther Clin Risk Manag*. 2020; 16:109-123
[4] Griffin et al. *JACC* 2021; Intellia Patient Survey 2022
[5] GlobalData 2023
[6] Redbook 2023

REGENERON Intellia THERAPEUTICS

NTLA-2001 (nexiguran ziclumeran) Phase 1 Study in ATTR Amyloidosis

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

Intervention: Single-dose CRISPR/Cas9-based gene editing therapy administered via an intravenous (IV) infusion

	PART I: Single-Ascending Dose Escalation		PART II: Dose Expansion		
ATTRv-PN patients (n=36)	**0.1 mg/kg** (n=3) **0.3 mg/kg** (n=3) **0.7 mg/kg** (n=3) **1.0 mg/kg** (n=6)	**N=15**	**55 mg** (n=16) **80 mg** (n=5)	**N=21**	**N=72**
ATTR-CM patients (n=36)	**0.7 mg/kg NYHA Class I/II** (n=3) **0.7 mg/kg NYHA Class III** (n=6) **1.0 mg/kg NYHA Class I/II** (n=3)	**N=12**	**55 mg NYHA Class I/II** (n=12) **55 mg NYHA Class III** (n=12)	**N=24**	

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: NCT04601051
* NTLA-2001 is also known as nexiguran ziclumeran (nex-z)

Most Frequent Treatment-Emergent Adverse Events

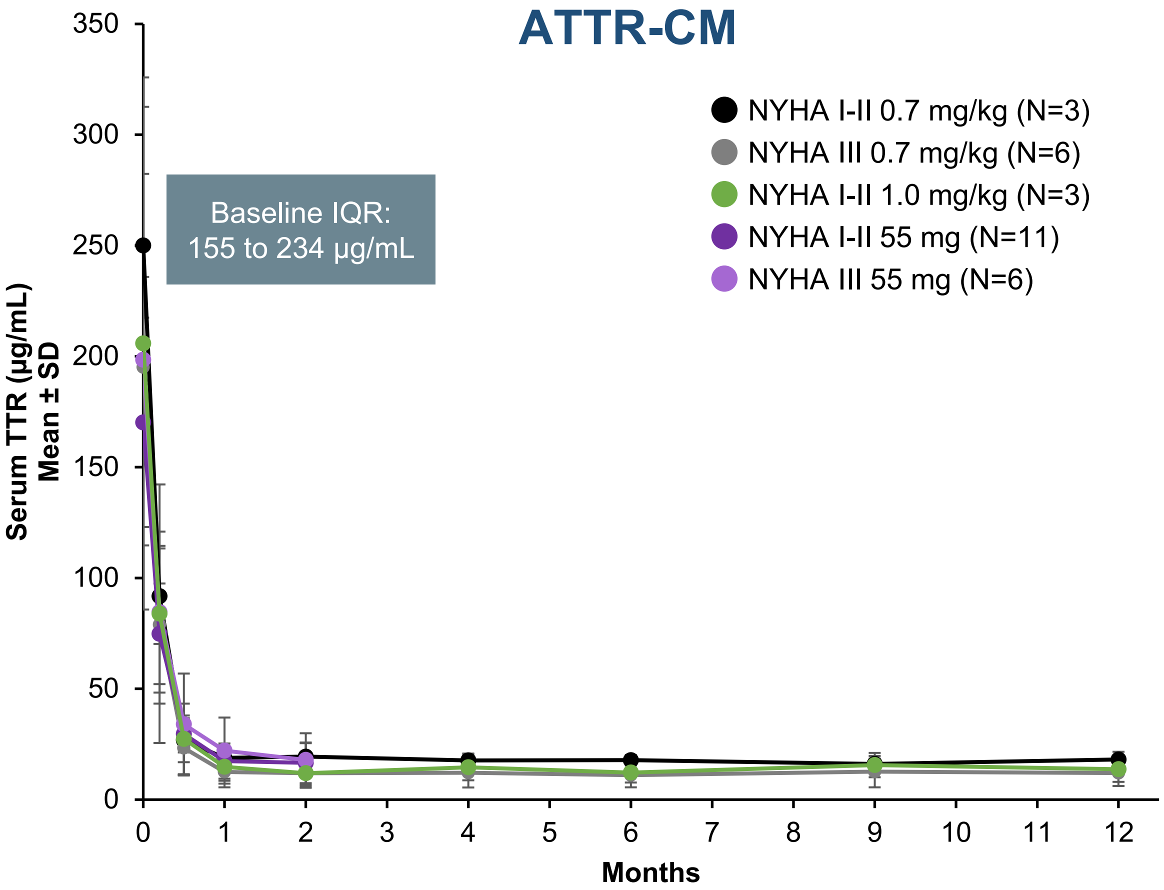
TEAEs by Maximum Toxicity Grade and Preferred Term Reported in >5% of All ATTRv-PN and ATTR-CM Patients (N=65)

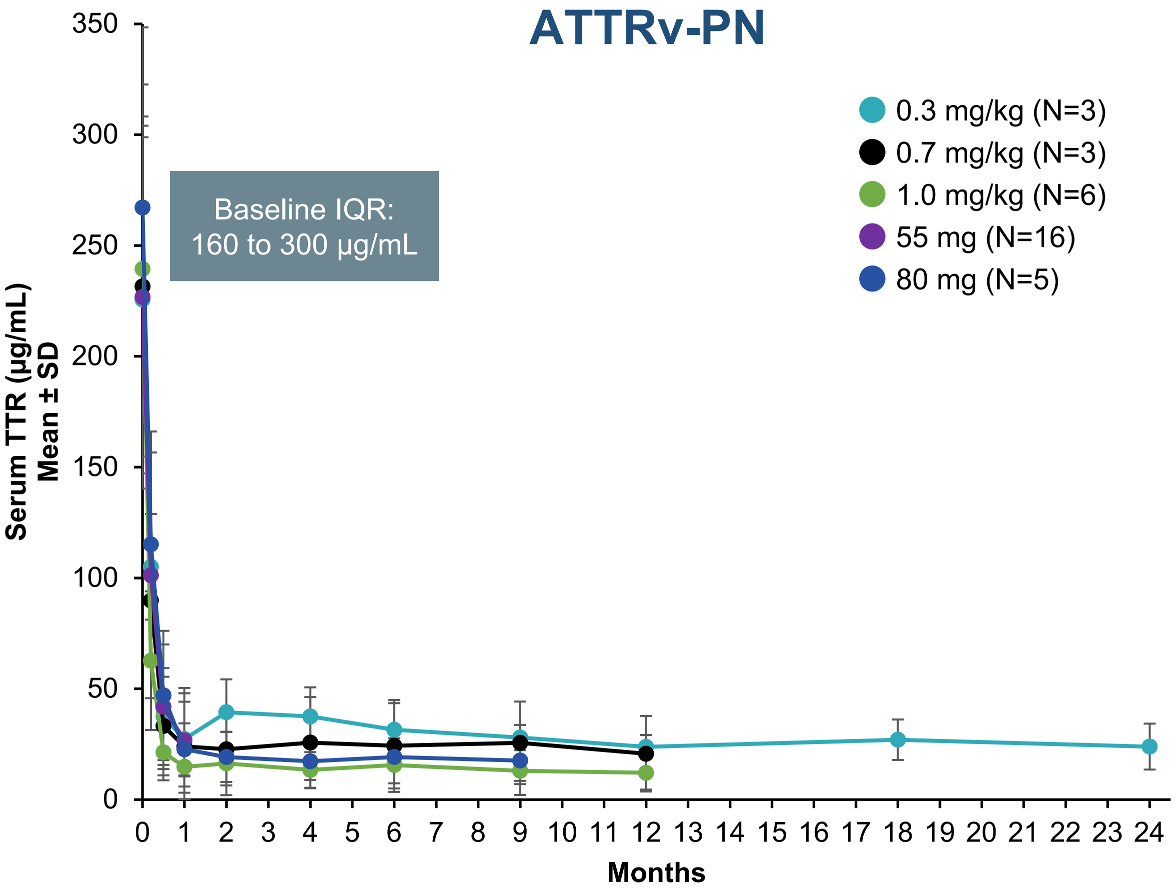
AE, Preferred Term, n (%)	Any Grade	Grade 1	Grade 2	Grade ≥3
Infusion-related reaction	25 (38)	10 (15)	14 (22)	1 (2)
Headache	12 (18)	12 (18)		
Diarrhea	11 (17)	10 (15)	1 (2)	
Back pain	7 (11)	7 (11)		
COVID-19 infection	6 (9)	5 (8)	1 (2)	
Cardiac failure	6 (9)	2 (3)	2 (3)	2 (3)
Upper respiratory tract infection	6 (9)	6 (9)		
AST increased	5 (8)	3 (5)	1 (2)	1 (2)
Dizziness	5 (8)	5 (8)		
Fatigue	5 (8)	5 (8)		
Muscle spasms	5 (8)	4 (6)	1 (2)	
Vision blurred	5 (8)	5 (8)		
Atrial flutter	4 (6)		1 (2)	3 (5)
Constipation	4 (6)	2 (3)	2 (3)	
Rash	4 (6)	4 (6)		

- This includes all reported events, including those unrelated to NTLA-2001 (nex-z) (e.g., atrial flutter and cardiac failure hospitalizations)
- Infusion-related reactions were most common; nearly all were considered mild, and all resolved without sequelae, and all patients received the complete, planned dose
- Any liver enzyme elevations resolved spontaneously, were asymptomatic, and required no intervention (e.g., steroids) or hospitalization

Data cutoff May 11, 2023.
Patients reporting more than one AE related to NTLA-2001 (nex-z) are counted only once using the maximum toxicity grade. AEs coded to preferred term using Medical Dictionary for Regulatory Activities (MedDRA), version 23.0 for PN and version 24.0 for CM. Interim data presented are from the initial 65 of 72 patients dosed. Results from the final 7 patients enrolled after the data cutoff will be reported at a future date.

Regardless of Baseline TTR Levels, NTLA-2001 (nex-z) Led to Consistently Low and Sustained Absolute Serum TTR in All Patients





Median (IQR) Serum TTR at Day 28 (n=62)		
	Residual absolute TTR concentration at day 28	17 µg/mL (11 to 24 µg/mL)
	% Change from baseline in serum TTR at day 28	-91% (-88 to -94%)

Data cutoff May 11, 2023.
Figure notes: Results for each dose level are shown out to the last time point with complete follow-up for the entire cohort. Interim data presented excludes the 0.1 mg/kg cohort from the dose-escalation of the polyneuropathy arm. The three patients in the 0.1 mg/kg cohort have been re-dosed at 55 mg and results will be shared in a future presentation. The 55 mg and 80 mg doses are the fixed doses corresponding to 0.7 mg/kg and 1.0 mg/kg, respectively.

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MAGNITUDE CLINICAL TRIAL

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate NTLA-2001 (nexiguran ziclumeran*) in Patients with ATTR Amyloidosis with Cardiomyopathy (ATTR-CM)

N = ~765

Randomization 2:1

nexiguran ziclumeran*
Single 55 mg IV infusion

Placebo

Primary Endpoint

- Composite endpoint of CV-related mortality and CV-related events

Key Secondary Endpoints

- Serum TTR
- KCCQ-OS score

Key Eligibility Criteria:

- Adult patients with diagnosis of either hereditary or wild-type ATTR-CM
- NYHA Class I – III
- NT-proBNP baseline ≥ 1000 pg/mL

Stratification:

- NAC stage
- TTR genotype: wild-type vs. mutant
- Concomitant tafamidis use vs. no tafamidis

Study Duration:

- Dependent on occurrence of pre-specified number of CV events and a minimum of 18 months follow-up
- Majority of patients are expected to have ≥ 30 months of follow-up for the primary analysis

Clinicaltrials.gov ID: NCT06128629
* NTLA-2001 is also known as nexiguran ziclumeran (nex-z)

REGENERON Intellia THERAPEUTICS

MAGNITUDE-2
CLINICAL TRIAL

A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate NTLA-2001 (nexiguran ziclumeran*) in Patients with Hereditary ATTR Amyloidosis with Polyneuropathy (ATTRv-PN)

N = 50

Randomization 1:1

nexiguran ziclumeran*
Single 55 mg IV infusion

Placebo

Crossover option following month 18 for all participants

Primary Endpoints

- Change from baseline in mNIS+7 at month 18 and serum TTR at day 29

Key Secondary Endpoints

- Change from baseline in Norfolk QOL-DN, mBMI and serum TTR and absolute serum TTR at month 18

Key Eligibility Criteria:

- Adult patients with diagnosis of ATTRv-PN
- NIS 10 – 130
- PND score of ≤ 3B
- Naïve to silencers; washout of stabilizers

Stratification:

- NIS score <50 vs. ≥ 50
- *TTR* genotype: early onset V30M vs others

Study Duration:

- All patients have completed the month 18 visit

Clinicaltrials.gov ID: NCT06672237
* nexiguran ziclumeran (nex-z, also known as NTLA-2001)

REGENERON Intellia THERAPEUTICS

NTLA-2002 for Hereditary Angioedema (HAE)

About HAE

- Genetic disease characterized by recurring, severe and unpredictable swelling in various parts of the body
- Despite availability of existing therapies, significant unmet need persists
- Chronic dosing is required with current treatment options

Our Approach

Knock out *KLKB1* gene with a single-dose CRISPR-based treatment

- Reduce kallikrein activity to prevent attacks

Key Advantages Includes Potential to:

- Be a single-dose treatment
- Provide extensive and continuous reduction in kallikrein activity
  - Intended to minimize the risk of breakthrough attacks
- Eliminate significant treatment burden

HAE: Large Commercial Opportunity with Significant Unmet Need

NTLA-2002

Potential to be the best-in-class HAE prophylaxis agent and only single-dose treatment

Prevalence[1]	**150,000+** HAE patients worldwide	
Diagnosis[2]	**20 years old** average age of diagnosis	Symptom onset typically occurs by 12 years old
Disease Burden[3]	**50-60%** patients continue to have HAE attacks despite existing therapies	• Attacks can result in hospitalizations • Patients subject to lifetime of attack risk and chronic treatment
Commercial Opportunity[4,5]	**$6B+** global market size expected by 2029	**$500K+** annual U.S. cost of leading prophylactic treatment

[1] Zuraw BL. Clinical practice. Hereditary angioedema. N Engl J Med. 2008 Sep 4;359(10):1027-36. doi: 10.1056/NEJMcp0803977. PMID: 18768946.
[2] Farkas et al. Allergy. 2017. 72;300-313
[3] Banjerii et al. Ann Allergy Asthma Immunol. 2020. 124;600-607
[4] GlobalData 2023
[5] Redbook 2023

NTLA-2002 Phase 1/2 Trial Design

International, multicenter study to assess safety, tolerability, PK, PD and effect of NTLA-2002 on attacks in adults with Type I or Type II HAE

Total Enrollment:

Up to 55 patients, age 18 and older

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

PHASE 1
Open-Label, Single-Ascending Dose

- 75 mg (n=3)
- 50 mg (n=4)
- 25 mg (n=3)

PHASE 2
Expansion study to confirm recommended dose

Randomized

- 50 mg (n=10)
- 25 mg (n=10)
- Placebo arm (n=5)

KEY ENDPOINTS

- Evaluate safety and tolerability
- Change in plasma kallikrein protein and activity levels
- Change in attack rates (Phase 2)

Clinicaltrials.gov ID: NCT05120830

Phase 2 Study: NTLA-2002 Continues to Be Well Tolerated Across All Dose Levels

TEAEs in ≥2 Patients After NTLA-2002 Administration (pooled), n (%)	NTLA-2002 25 mg (n=10)	NTLA-2002 50 mg (n=11)	Placebo (n=6)
Any TEAE	10 (100)	11 (100)	6 (100)
Headache	4 (40)	4 (36)	1 (17)
Fatigue	3 (30)	3 (27)	2 (33)
Nasopharyngitis	3 (30)	3 (27)	2 (33)
Back pain	3 (30)	2 (18)	0
Upper respiratory tract infection	3 (30)	2 (18)	1 (17)
Cough	3 (30)	1 (9)	0
Infusion-related reaction	1 (10)	3 (27)	1 (17)
COVID-19	2 (20)	1 (9)	1 (17)
Ear infection	2 (20)	0 (0.0)	0
Epistaxis	0	2 (18)	1 (17)
Influenza-like illness	1 (10)	1 (9)	0
Oropharyngeal pain	1 (10)	1 (9)	1 (17)
Pyrexia	0	2 (18.2)	0
Sinusitis	1 (10)	1 (9)	0

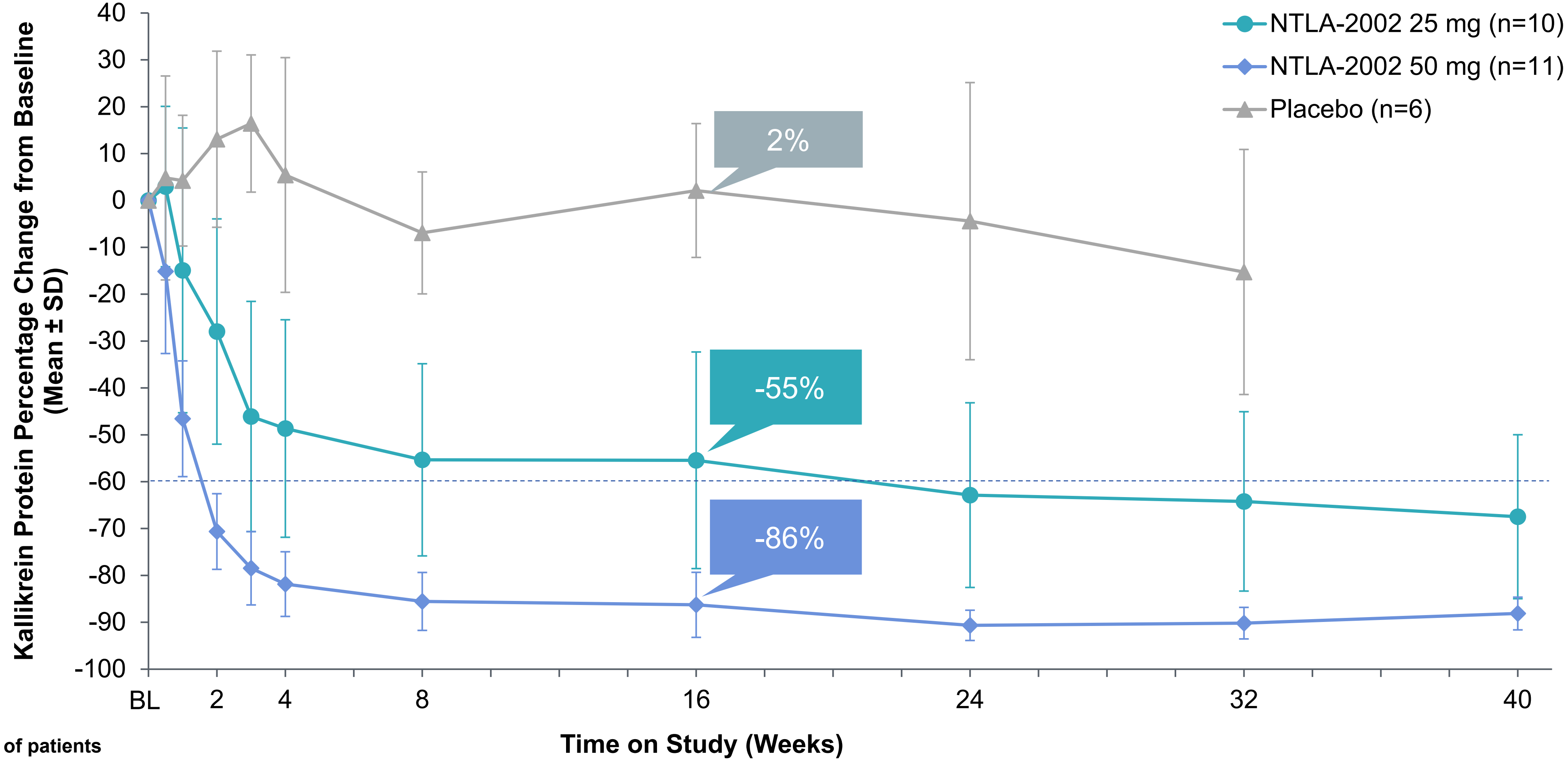
- All TEAEs were Grade 1 or 2*
- No SAEs in patients treated with NTLA-2002
- 4 IRRs with NTLA-2002; 2 led to temporary interruption of study drug
  - Each instance resolved without sequelae and both patients received the full dose
- No clinically significant laboratory abnormalities
  - 1 patient had transient Grade 2 increase in ALT on Day 22

ALT, alanine aminotransferase; IRR, infusion-related reaction; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
*Common Terminology Criteria for Adverse Events (CTCAE) Grading

This presentation includes data for an investigational product not yet approved by regulatory authorities. Data cutoff date: 04Apr2024.

Intellia THERAPEUTICS

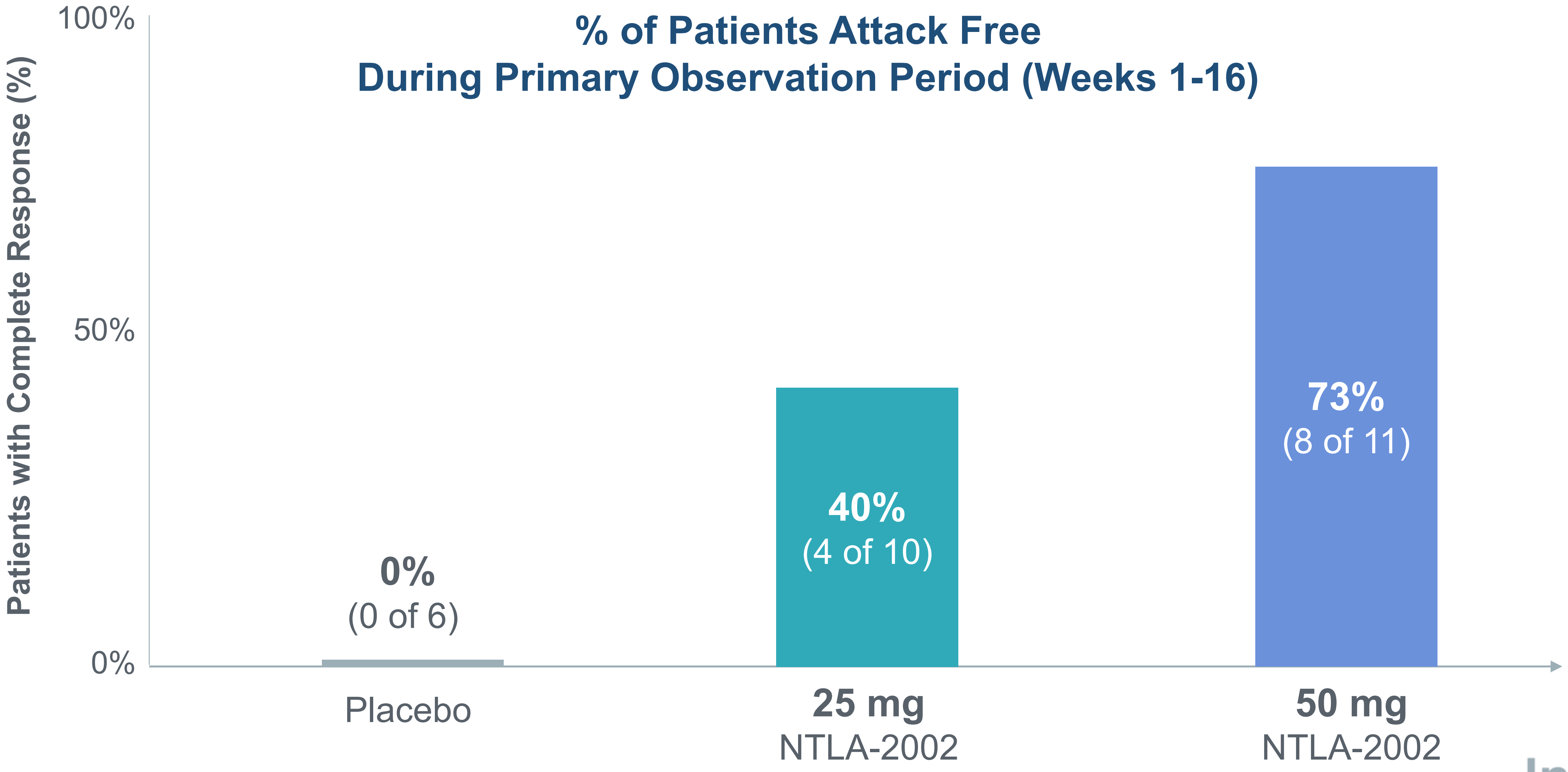
Phase 2 Study: A Single Dose of NTLA-2002 Showed Dose-Dependent and Durable Reductions in Plasma Kallikrein Protein Over Time



Number of patients	BL	2	4	8	16	24	32	40
NTLA-2002 25 mg	10	10	10	10	10	6	6	4
NTLA-2002 50 mg	11	11	11	11	10	5	5	3
Placebo	6	6	6	5	5	4	3	

For post-baseline assessments, only scheduled visits completed by at least 3 patients in each arm are presented. Dashed line represents targeted minimum reduction.
BL, baseline; SD, standard deviation.
This presentation includes data for an investigational product not yet approved by regulatory authorities. Data cutoff date: 04Apr2024.

Phase 2 Study: Eight of 11 Patients Receiving a Single 50 mg Dose Experienced a Complete Response – Attack-Free and No Subsequent Treatment Required



This presentation includes data for an investigational product not yet approved by regulatory authorities. Data cutoff date: 04Apr2024.

Intellia THERAPEUTICS

Phase 1/2 Data Demonstrated the Potential of a Single Dose of NTLA-2002 to Be a Functional Cure for Patients With HAE

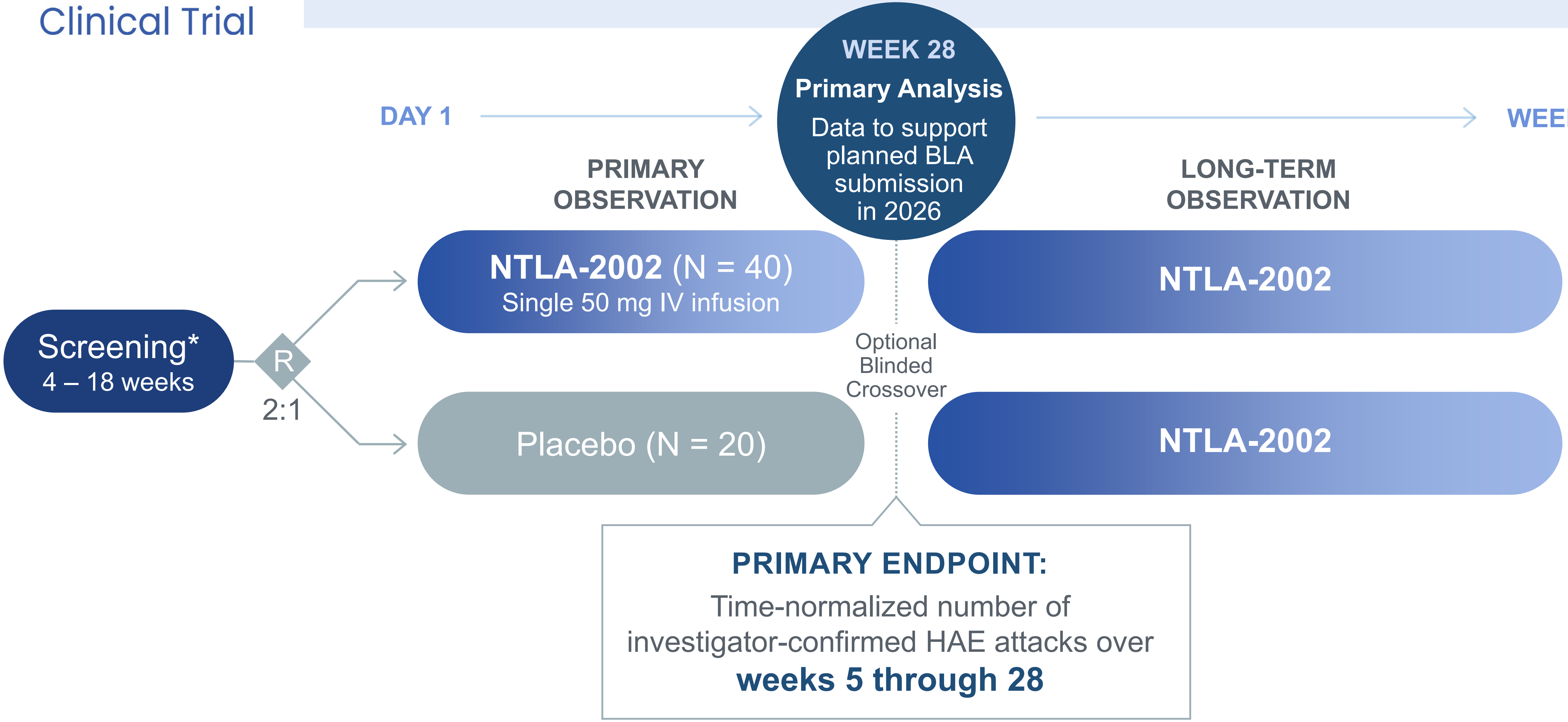
Key Takeaways

- Single 50 mg dose led to majority of patients (12/15) achieving complete elimination of attacks through the latest follow-up
- Robust and durable attack reductions observed in all patients
- Dose-dependent and durable reductions in plasma kallikrein protein achieved
- Highly encouraging safety and tolerability profile observed

50 mg dose selected for Phase 3 study

HAELO Clinical Trial

A Phase 3, Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of NTLA-2002 in Patients with Hereditary Angioedema (HAE)



Clinicaltrials.gov ID: NCT06634420

* Patients on long-term prophylaxis are required to wash out of therapy prior to the run-in period of screening.

NTLA-3001 for Alpha-1 Antitrypsin Deficiency (AATD)-Associated Lung Disease

About AATD

- Genetic disorder leading to progressive lung and/or liver disease[1]
- >60K AATD patients in the U.S.[2*]
- ~250K AATD patients globally[3*]

Our Approach

Targeted insertion of a functional *SERPINA1* gene into the albumin locus

- Continuous expression of functional AAT protein at normal levels

Key Advantages

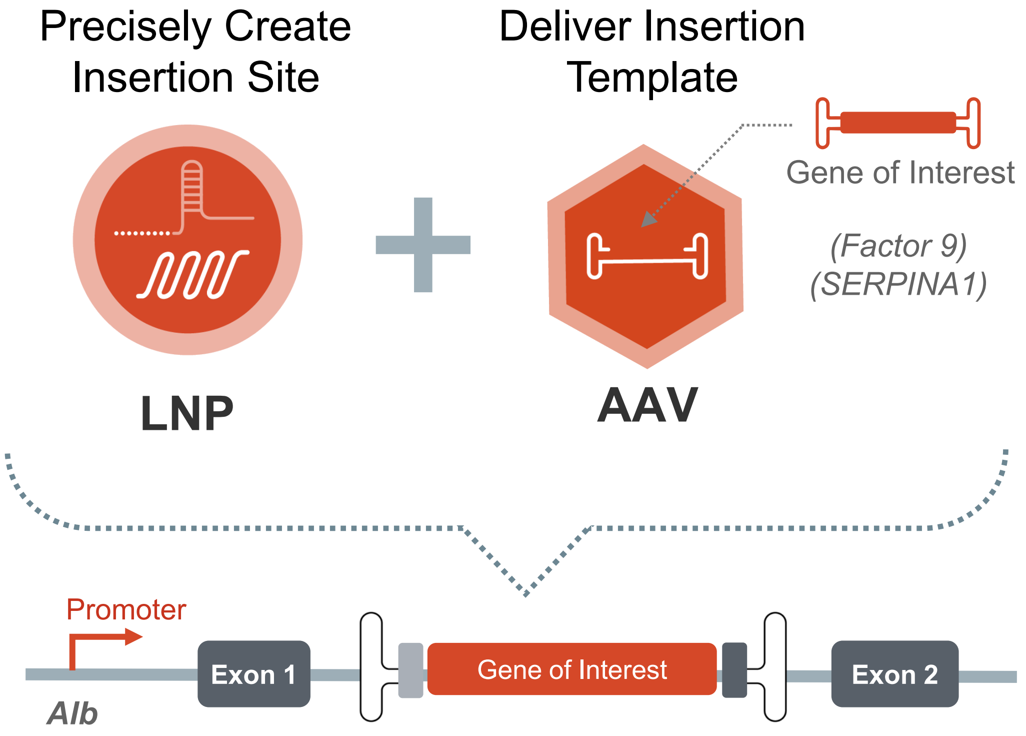
- Designed to be a single-dose treatment
- Aims to achieve normal human levels of AAT protein and halt progression of lung disease

[1] Remih et al. Curr Opin Pharmaco 2021; 59:149-156
[2] Brantly M. *Clin Chem*. 2006; 52:2180-2181
[3] Blanco et al. *Int J Chron Obstruct Pulmon Dis*. 2017; 12:561-569
* In severe AATD patients defined as individuals with Pi*ZZ genotype.

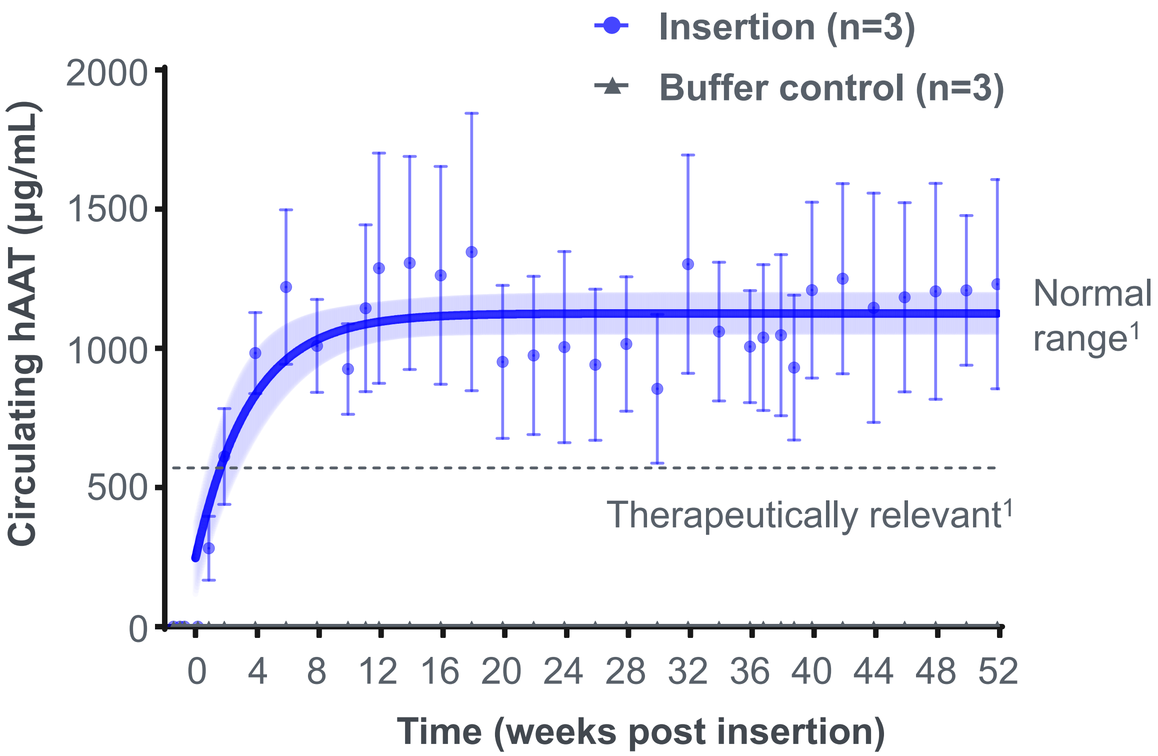
Intellia THERAPEUTICS

Durable Production of Physiologic Levels of hAAT Through One Year in NHP

Insertion Platform Enables Targeted, Stable Gene Insertion in the Albumin Locus



Human AAT (hAAT) Expression



[1] Stoller & Aboussouan. *The Lancet*, 2005
Normal range: ~1000-2700 μg/mL, or 20-53 μM; Therapeutically relevant: 571 μg/mL, or 11 μM
This presentation includes data for an investigational product not yet approved by regulatory authorities.

NTLA-3001 Phase 1/2 Study Design

International, multi-center, open-label study to evaluate NTLA-3001 in adults with alpha-1 antitrypsin deficiency (AATD)-associated lung disease

Total Enrollment:
Up to 30 patients, age 18-75 years with AATD-associated lung disease

Key Eligibility:

- ZZ or Z/null genotype
- < 11 µM AAT serum concentration
- FEV1 ≥ 35% to ≤ 65%

Intervention:
Single administration of intravenous (IV) AAV and LNP infusions

PHASE 1
Single-Ascending Dose

N = Up to 18 patients*

AAV	LNP
Dose 1 / Dose 2 / Dose 3 — **Up to 3 dose-escalation** cohorts	**Fixed dose** (50 mg)

PHASE 2
Expansion study

N = ~12 patients

Administer dose selected from Phase I

KEY ENDPOINTS

- Evaluate safety, tolerability
- Measure change in serum AAT levels

* Minimum of 3 patients per cohort

Significant Opportunities to Unlock Full Potential of *In Vivo* Platform

CRITERIA USED TO SELECT POTENTIAL FUTURE CANDIDATES:

Unmet need • Population size • Technical feasibility

Potential Liver Development Programs*

RARE DISEASES**

- Blood disorders
- Lysosomal storage diseases
- Metabolic diseases

PREVALENT DISEASES**

- Chronic viral diseases
- Dyslipidemia
- Hypertension
- NASH

Unlocking Full Potential of Genome Editing

TARGET TISSUES

- Bone marrow
- CNS/PNS**
- Eye***
- Heart
- Muscle**
- Lung ****

Expansion into tissue-specific diseases

* This is a selection of potential liver targets and does not represent all future opportunities.
** Individual targets could be developed by Intellia, Regeneron or through collaborations.
*** In collaboration with SparingVision
**** In collaboration with ReCode

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Intellia THERAPEUTICS

Ex Vivo

CRISPR creates the therapy

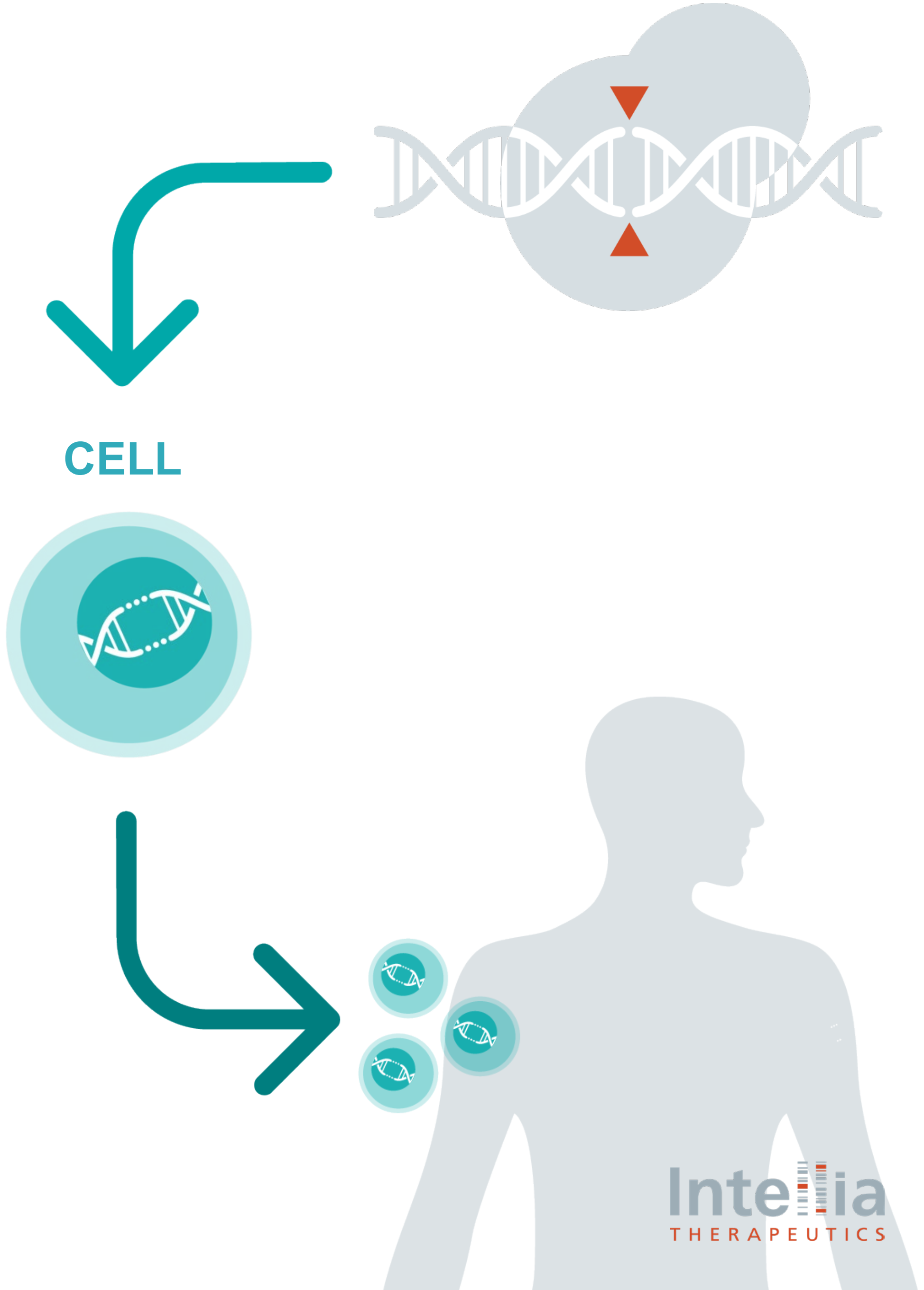
IMMUNO-ONCOLOGY / AUTOIMMUNE DISEASES

Strategic Advantages:

Utilizing proprietary CRISPR engineering platform to create differentiated cell therapies for IO and AI diseases

Targeting modalities, such as TCR, with broad potential in multiple indications

Focused on reproducing natural cell physiology for potential improvements to safety and efficacy in immuno-oncology



Intellia THERAPEUTICS

Proprietary Engineering Platform to Power Next-Generation Engineered Cell Therapies

LNP-BASED CELL ENGINEERING PLATFORM

Highly efficient sequential editing | Optimal cell performance | Scalable manufacturing process

ENABLES VERSATILE SOLUTIONS BY "MIXING AND MATCHING," INCLUDING:

Cell Type

HSCs, T cells

NK cells, Macrophages

Targeting Modality

TCRs

CAR-Ts, Universal CARs

Rewiring Instructions

Immune-enhancing edits

Novel targets

Differentiated Approach to Cell Therapy Genome Engineering

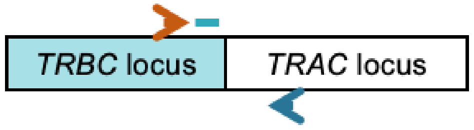
		Intellia THERAPEUTICS	Other Approaches	
Gene Editing Approach	Delivery	**LNP**	Electroporation	Electroporation
	Editing Mode	**Sequential**	Simultaneous	Simultaneous
	Knockout (KO)	**Cleavase or Base Editor**	Cleavase	Base Editor
	Insertion	**CRISPR insertion**	Lenti/Retroviruses	Lenti/Retroviruses
Key Questions From Preclinical Data	Minimize random DSB?	✓	✗	✗
	Minimize random insertion?	✓	✗	✗
	Minimize genotoxicity risk?	✓	✗	✗

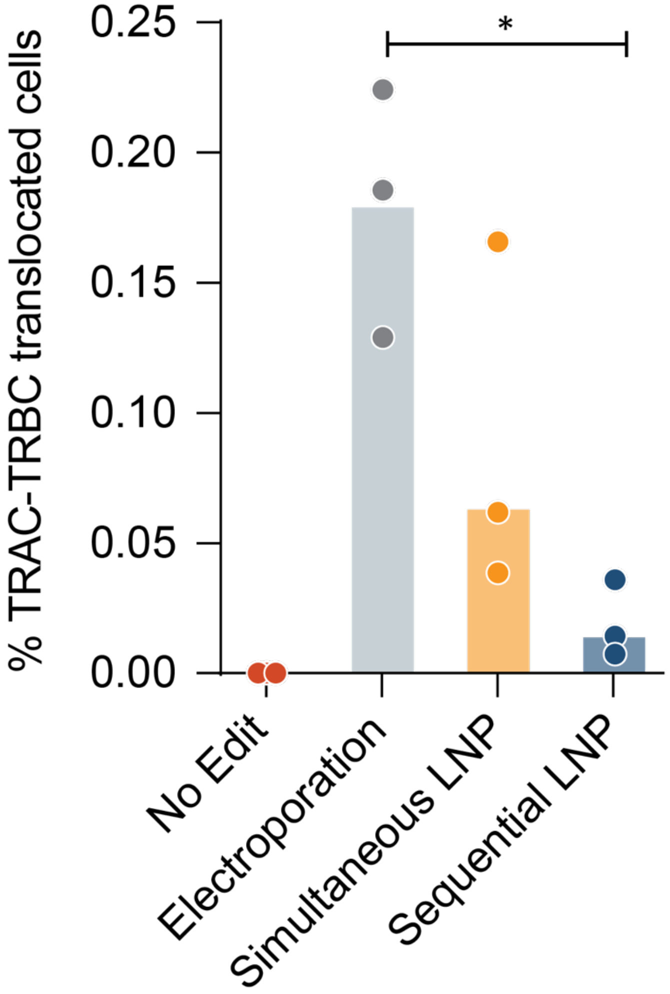
Intellia THERAPEUTICS | **LNP-based, sequential process** + **Precise CRISPR KOs & insertion(s)** = **Quality cell product**

Slide based on preclinical data disclosed by Intellia. Intellia's cell product to be further explored in additional preclinical and clinical studies.

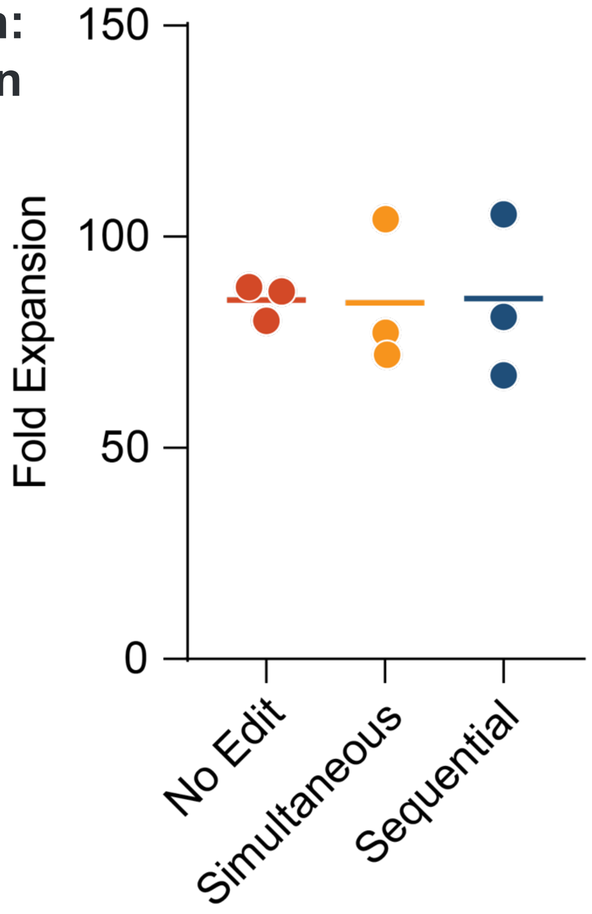
Sequential Editing with LNP Approach Minimizes Translocations While Retaining Robust Cell Viability and Expansion

ddPCR assay to detect *TRAC-TRBC* translocations



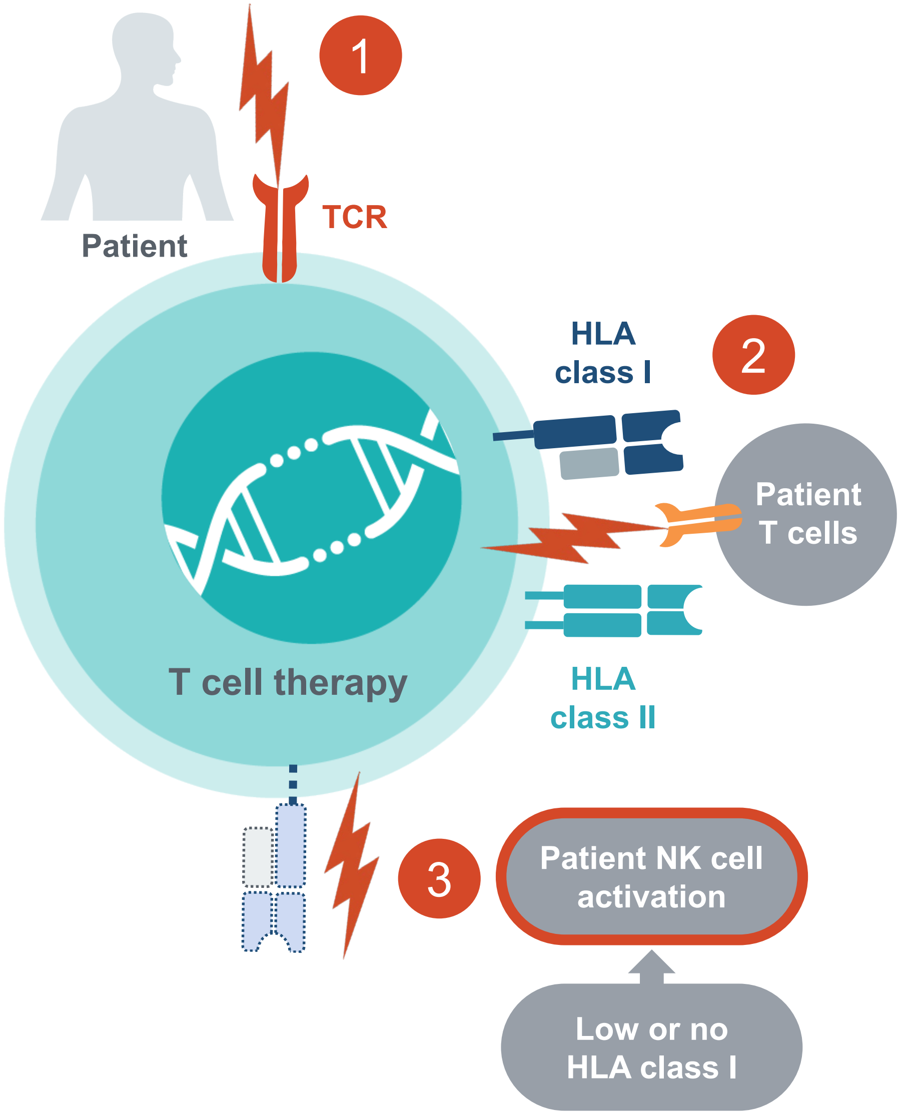


LNP Approach: Cell Expansion at D10



Intellia THERAPEUTICS

Three Immune Concerns Must Be Addressed by Allogeneic Cell Therapies



1 Graft-versus-host disease (GvHD)

T cell receptor (TCR) from allogeneic T cells recognizes and kills recipient (host) cells.

Largely solved with knockout (KO) of endogenous TCR

2 Rejection via host T cells

Human leukocyte antigen (HLA) molecules must match between donor and recipient to prevent rejection from:

- Host CD8 (HLA class I) T cells
- Host CD4 (HLA class II) T cells

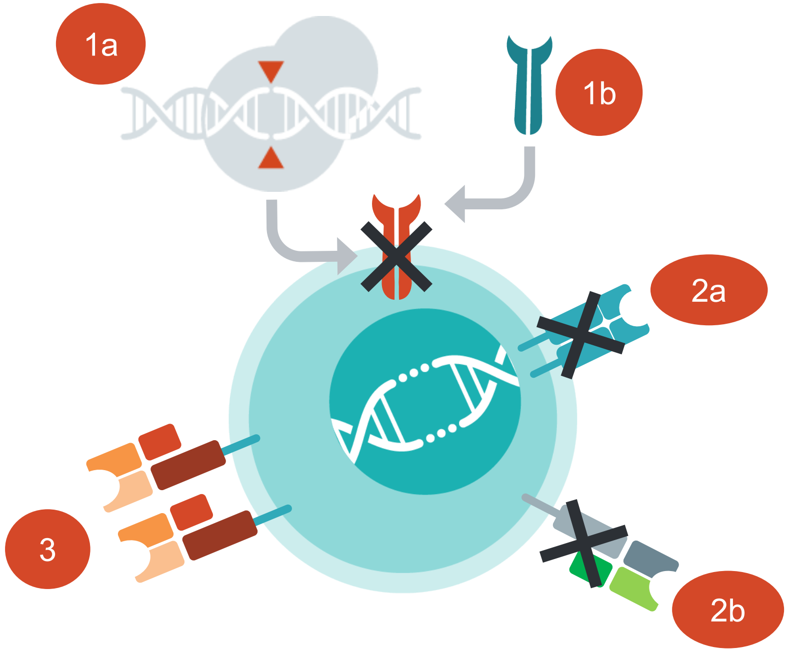
3 Rejection via host natural killer (NK) cells

NK cells will attack cells that lack HLA-I expression or have low HLA-I.

No validated solution yet

Intellia THERAPEUTICS

Intellia's Differentiated Allogeneic Approach Aims to Address All Three Immune Concerns



Key Potential Advantages

- ✓ Approach is applicable to CAR and TCR
- ✓ Solves for host NK and T cell rejection
- ✓ Avoids long-term immunosuppression

	Intellia's Editing Strategy	Main Objective of Edit
1a	Knockout endogenous TCR	**Prevent Graft-versus-Host Disease (GvHD)**
1b	Insert target CAR or TCR	**Direct T cell for tumor killing**
2a	Knockout HLA Class II	**Prevent CD4-mediated rejection**
2b	Knockout HLA-A only	**Prevent CD8-mediated rejection**
3	Partial HLA Class I match	**Block NK cell activation and avoid NK-mediated rejection**

Realizing the Promise of Gene Editing

At Intellia, we innovate every day to make CRISPR-based medicines a reality for patients.

This is just the beginning of the gene editing revolution.

Intellia
THERAPEUTICS

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Intellia THERAPEUTICS

Re-dosing with Intellia's LNP Delivery Platform

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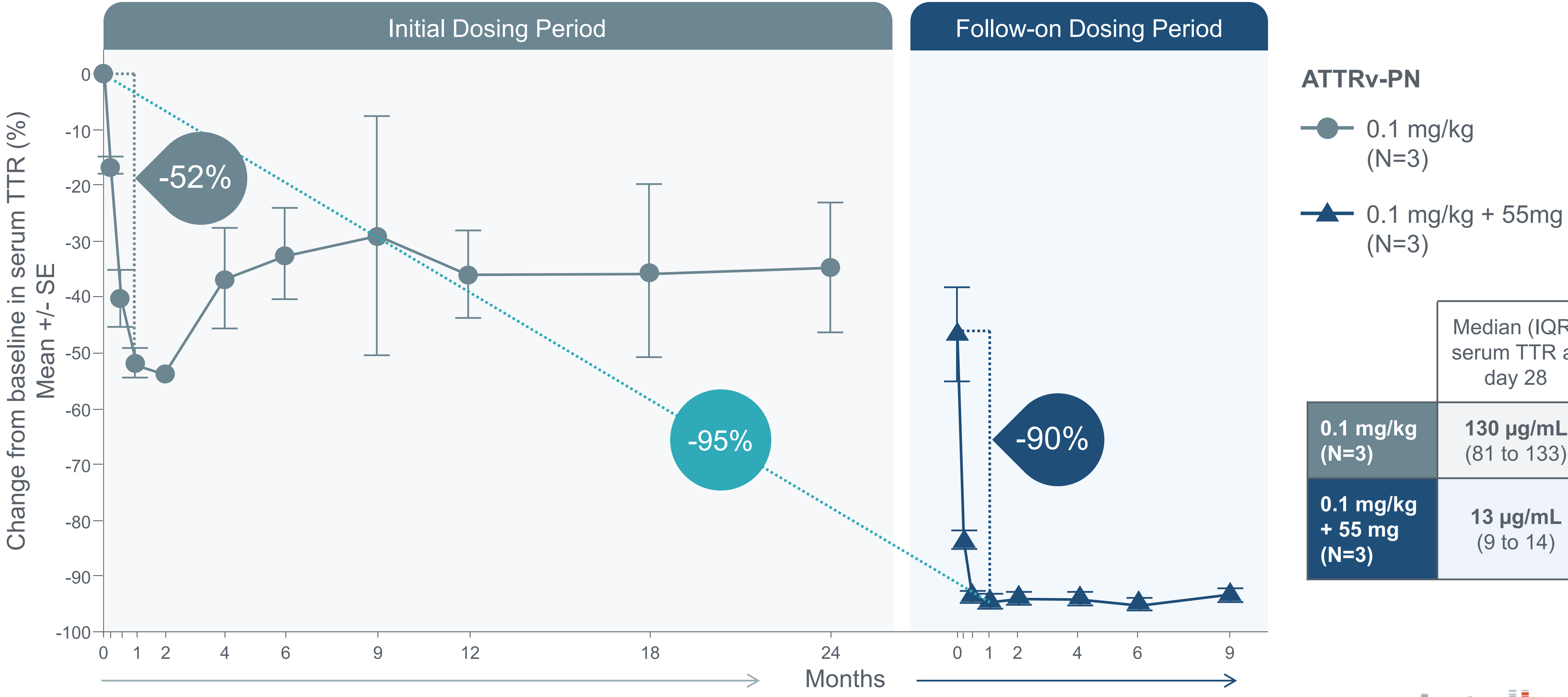
Clinical Proof-of-Concept that Redosing with Intellia's LNP-Delivered Gene Editing Technology Led to a Targeted Additive Pharmacodynamic Effect



	Median (IQR) serum TTR at day 28
0.1 mg/kg (N=3)	**130 µg/mL** (81 to 133)
0.1 mg/kg + 55 mg (N=3)	**13 µg/mL** (9 to 14)

Intellia THERAPEUTICS

Data cutoff April 12, 2024.
This presentation includes data for an investigational product not yet approved by regulatory authorities.

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

- 8 – 12 months of follow-up for patients who received a follow-on dose
- No clinically significant changes in liver enzymes, platelets or coagulation parameters

Data cutoff April 12, 2024. Note: For each preferred term, patients 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.
This presentation includes data for an investigational product not yet approved by regulatory authorities.

Intellia THERAPEUTICS

Persistence of *In Vivo* Edits

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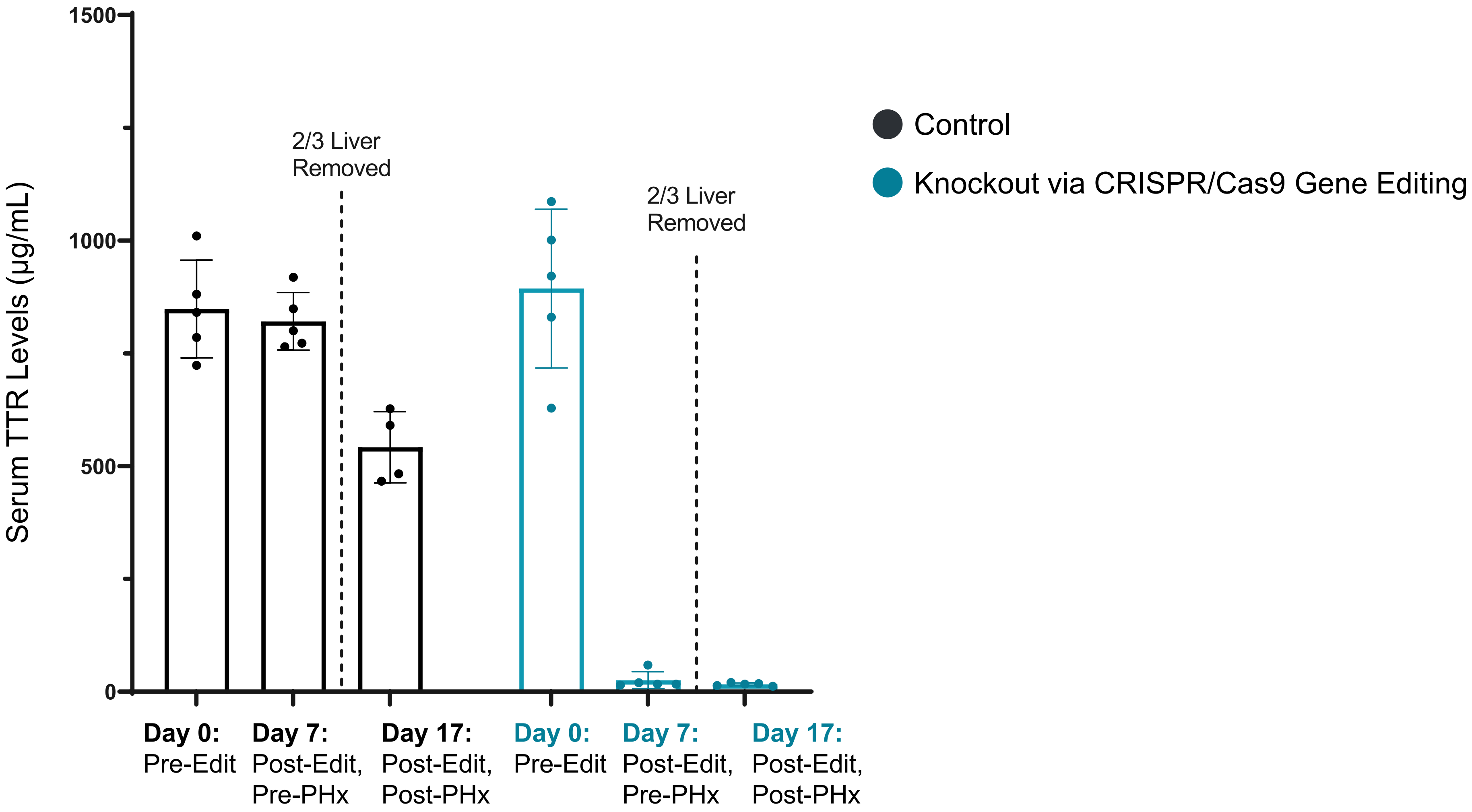
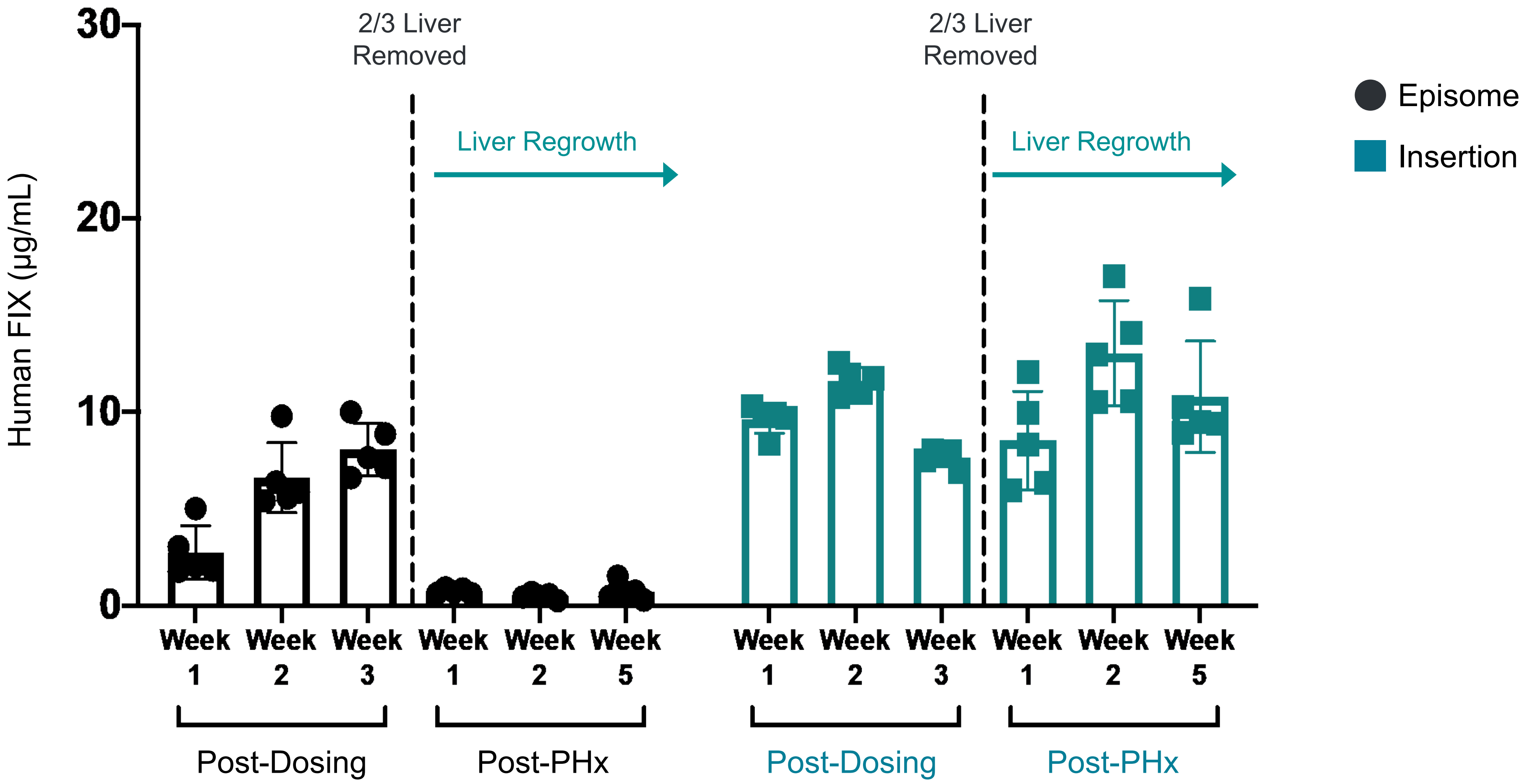
Protein Reduction Remains Unchanged Following PHx Murine Model of Liver Regeneration



* Similar results obtained for control and LNP when sham surgery was performed.
Next generation sequencing (NGS) analysis to evaluate the frequency of insertion and deletion events (edits)

REGENERON Intellia THERAPEUTICS

Gene Insertion Provides a Durability Advantage Over Conventional AAV Episomes in a PHx Murine Model of Rapid Liver Growth



REGENERON

Intellia THERAPEUTICS

In Vivo Editing of Hematopoietic Stem Cells

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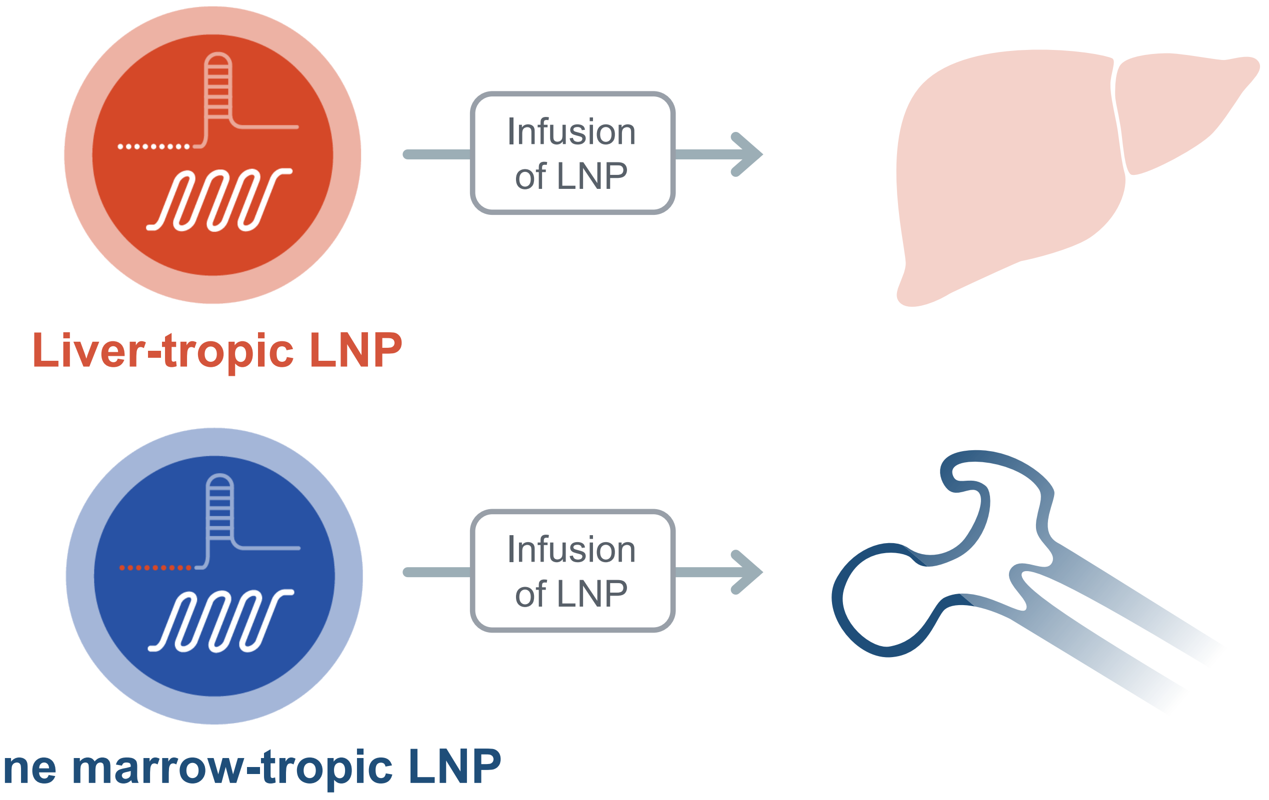
Intellia THERAPEUTICS

Editing HSCs *In Vivo* Requires LNPs with Bone Marrow Tropism

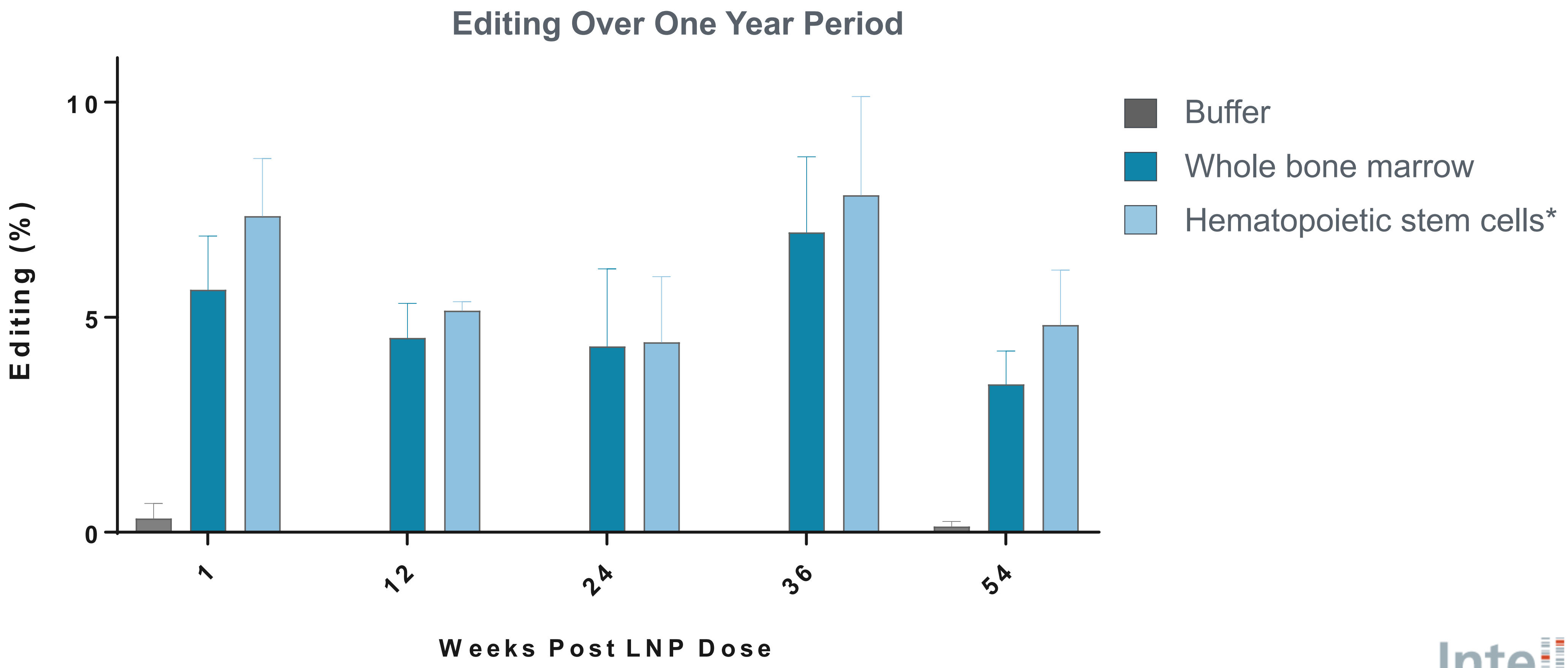
LNPs designed, formulated and tested *in vivo* to identify compositions with enhanced delivery to bone marrow and HSCs



Intellia THERAPEUTICS

Editing of Mouse Bone Marrow and HSCs is Durable Through At Least One Year

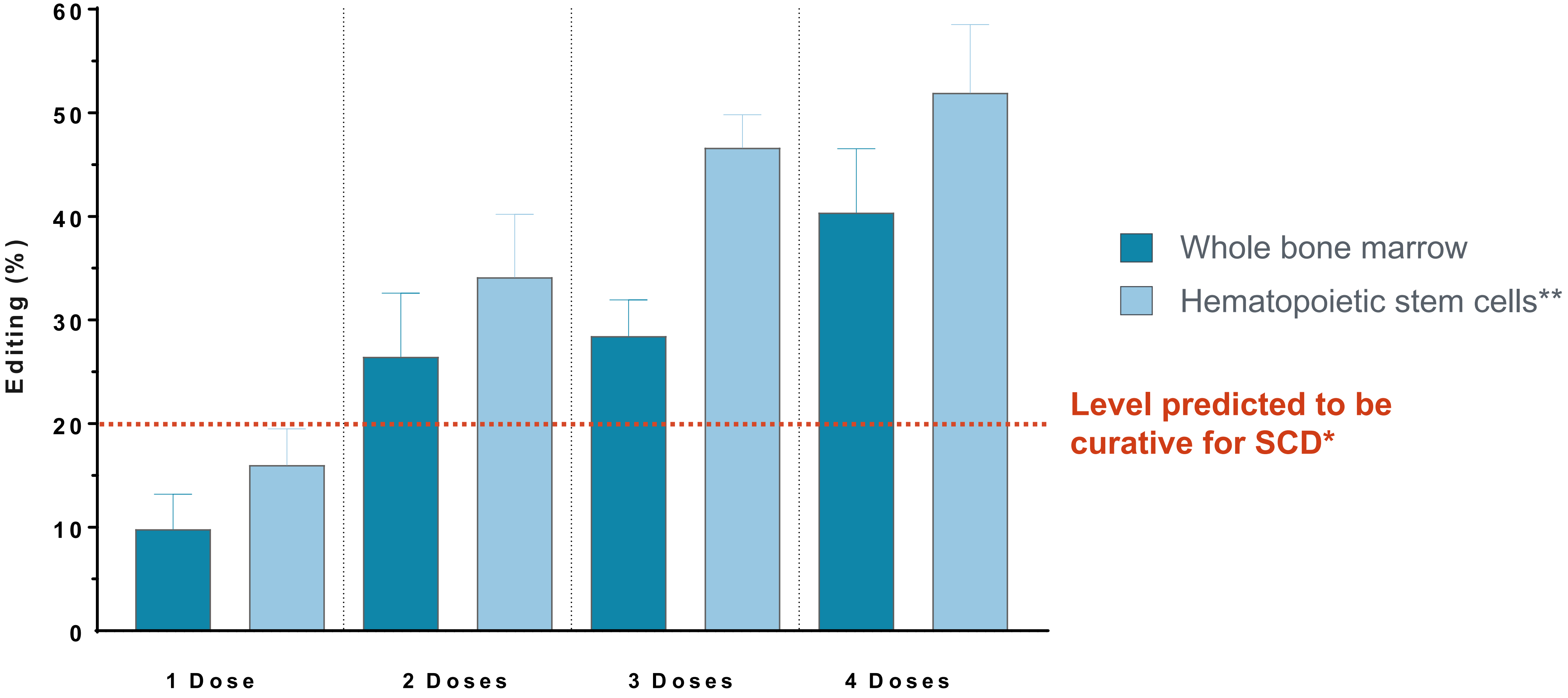
- Editing was similar across all time points assessed, in both whole bone marrow and HSCs populations
- Results highlight the potential for a single-course, long-lasting therapy



* Lin-Sca-1+c-Kit+CD34-Flk2- cell population

Editing of Mouse Bone Marrow and HSCs Increases with Multidosing

- Non-immunogenic LNP delivery platform may enable stepwise “treat-to-target” approach



* Blood. 2017;130(17):1946-1948
** Lin-Sca-1+c-Kit+CD34-Flk2- cell population

Intellia THERAPEUTICS

Intellia’s Allogeneic Solution

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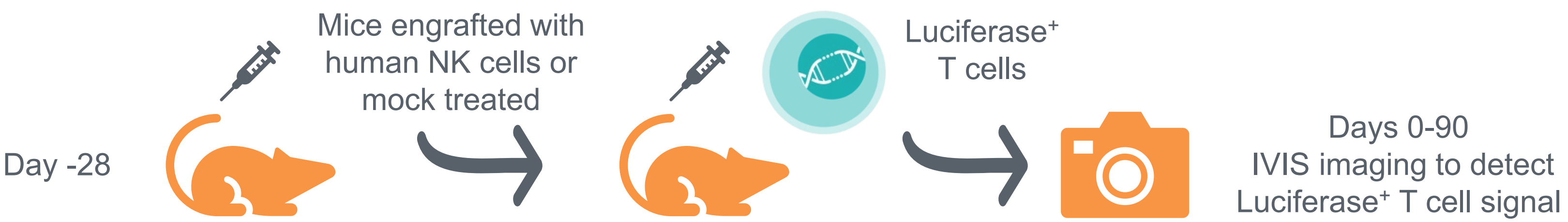
Immune Concerns Unaddressed by Current Allogeneic Solutions

Approach	Employ intense lymphodepletion regimen	Knockout (KO) HLA-I (B2M)	KO HLA-I & express NK inhibitor (HLA-E)	Intellia's Approach: KO HLA-II & partial HLA Class I match
Avoid rejection of cell therapy by host CD8 T cells	✓	✓	✓	✓
Avoid rejection of cell therapy by host CD4 T cells	✓	✗	✗	✓
Avoid rejection of cell therapy by host NK cells	✓	✗	✗ (faded)	✓
Avoid profound immunosuppression	✗	✓	✓	✓

Slide based on preclinical data disclosed by Intellia. Intellia's cell product to be further explored in additional preclinical and clinical studies.

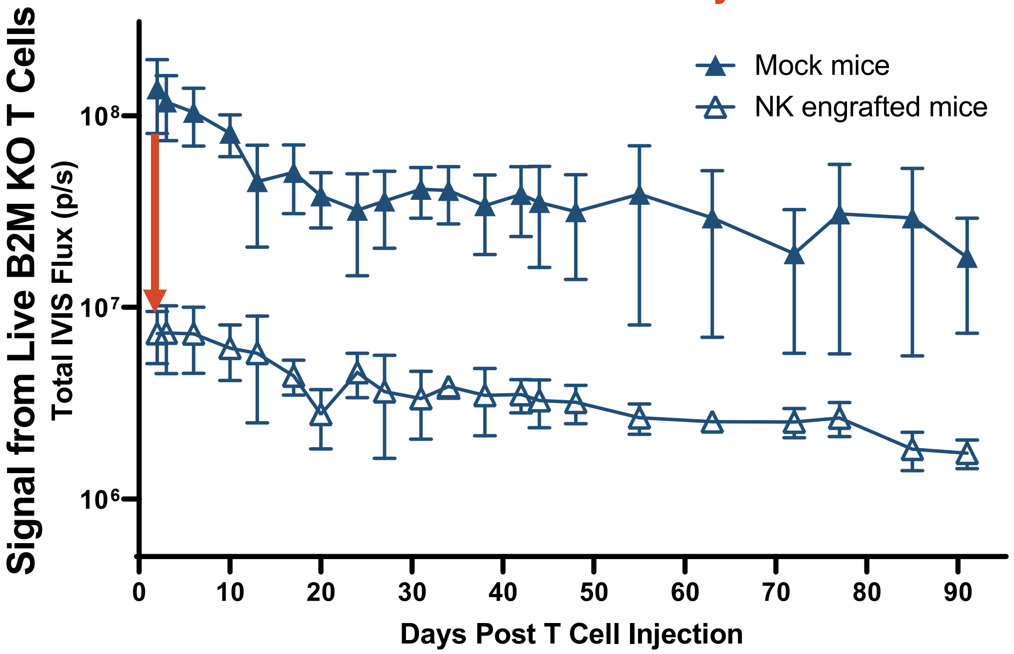
Intellia THERAPEUTICS

Allo TCR-T Cells Resist NK Cell Killing for at Least 90 Days *In Vivo*



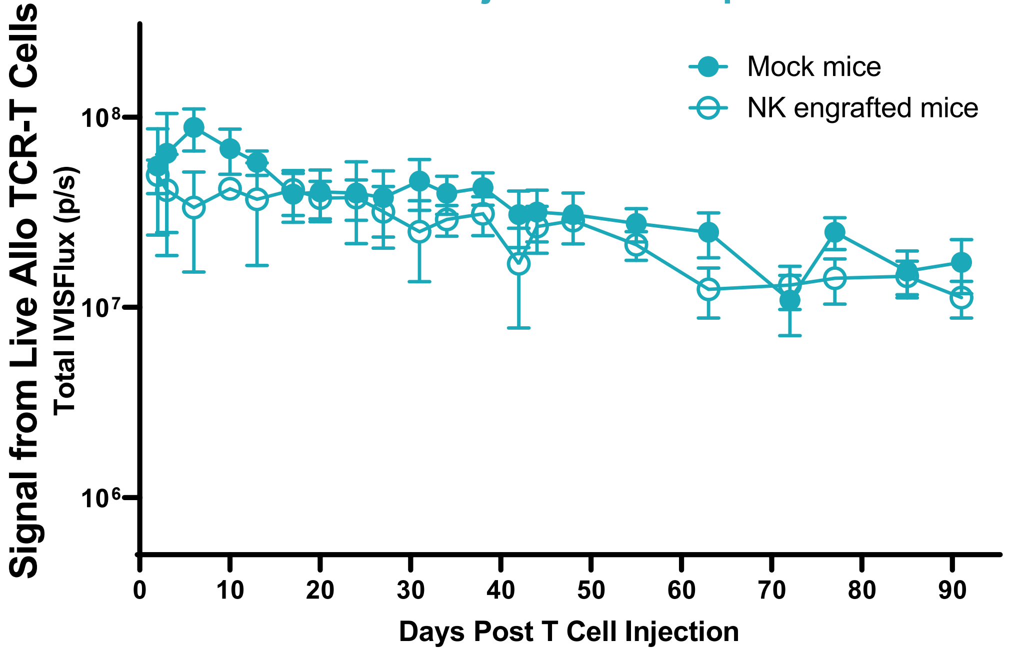
B2M Knockout T cells

>90% B2M KO T cells killed by NKs within 24h



Allo TCR-T Cells

Minimal Allo T cell rejection in the presence of NK cells



Intellia THERAPEUTICS

Platform: Identifying Potent and Highly Specific Guide RNAs

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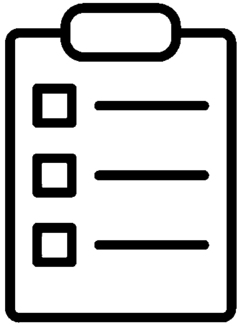
Comprehensive gRNA Specificity Assessment: An Off-Target Workflow

1: Discovery of Potential Off-Target Edits

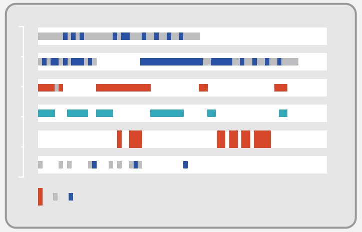
- Computational prediction
- \+ SITE-Seq Genomic DNA digest
- \+ GUIDE-seq Cell-based DNA repair

Aggregate **ALL** potential off-target genomic loci



2: Cell-based Validation of True Off-Target Edits by Deep Sequencing

- Multiplex panel for NGS
- Targeted Amp-Seq NGS follow-up



Ex Vivo

- Cell drug product

In Vivo

- Edit cells *in vitro* using drug product formulation
- Therapeutically relevant human primary cell type(s) (multiple donors)
- Dose range to exceed projected therapeutic exposure (≥10X)

Intellia THERAPEUTICS

Limited Overlap in Discovered Off-Target Loci by Three Leading Methods

1: Discovery of Potential Off-Target Edits

Computational prediction

+

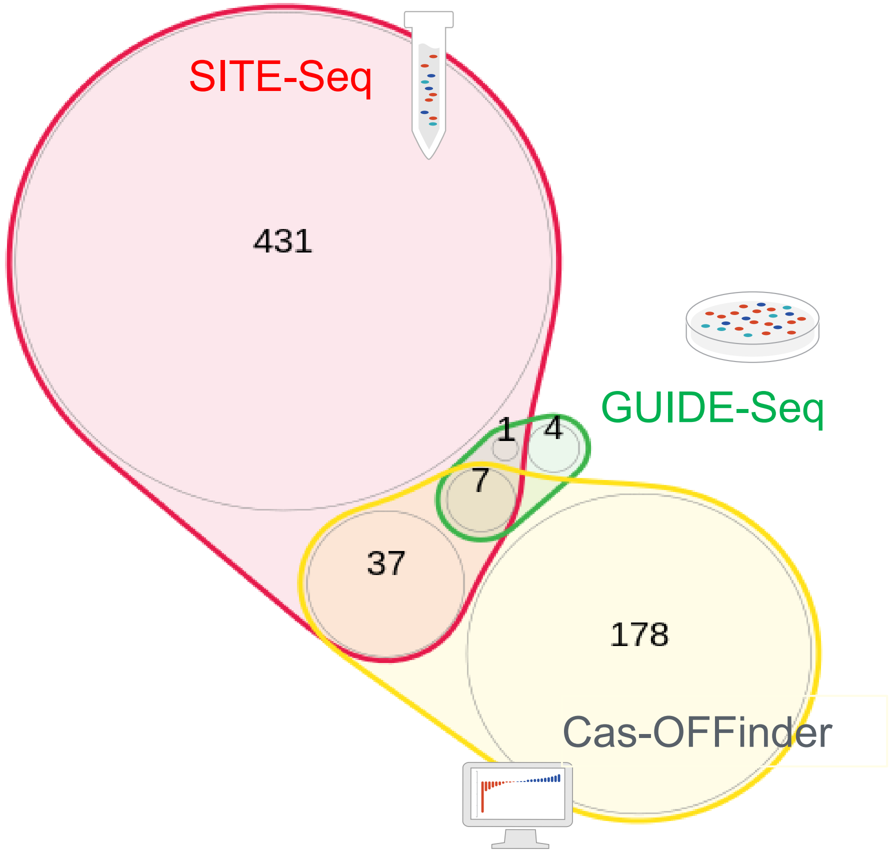
SITE-Seq Genomic DNA digest

+

GUIDE-seq Cell-based DNA repair

Aggregate **ALL** potential off-target genomic loci

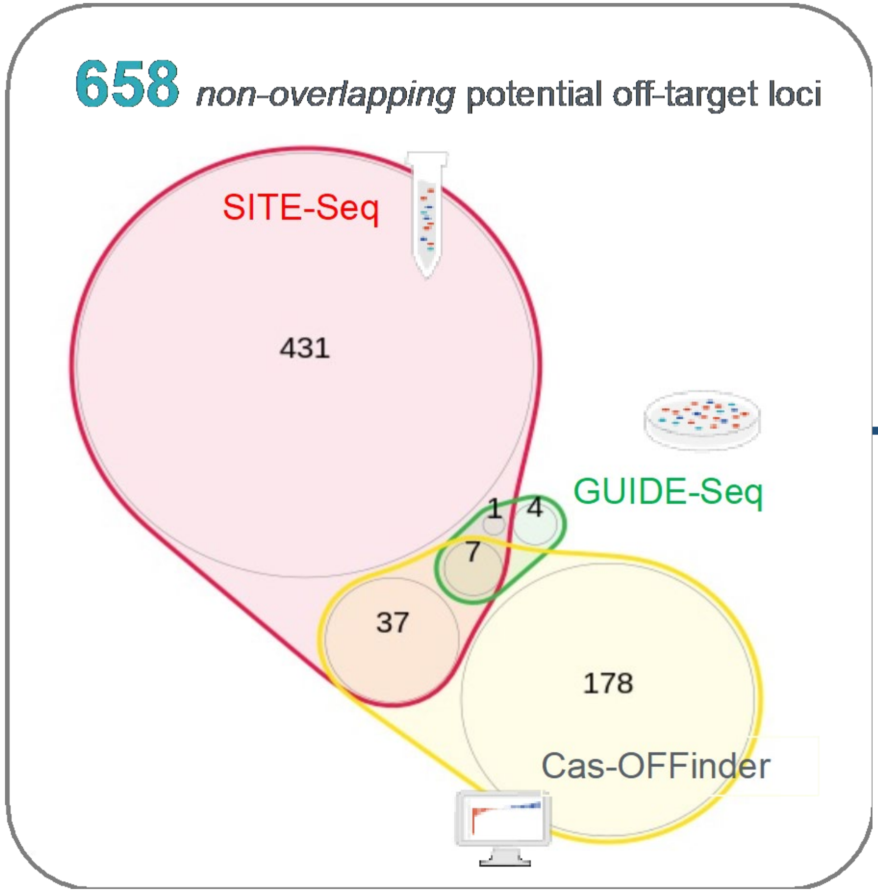
658 *non-overlapping* potential off-target loci



Data above is a representative example

Off-Target Workflow In Practice: Representative Example

1: Discovery of Potential Off-Target Edits



2: Validation of Off-Target Edits in Cells

Multiplex panel for NGS

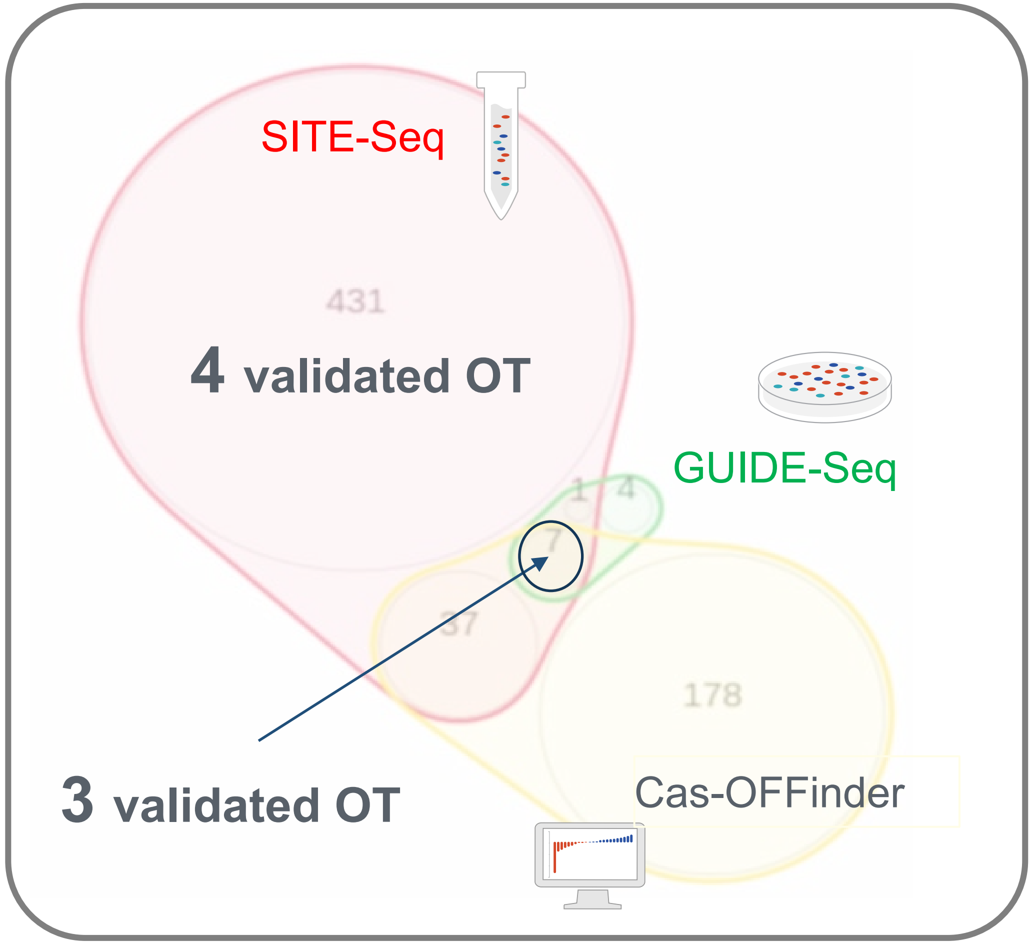
Targeted Amp-Seq NGS follow-up

In Vivo Programs

- Dose responses using drug product formulation
- Therapeutically relevant human primary cell type(s) (2 donors)
- Dose range to exceed projected therapeutic exposure (≥10X)
- Validation: off-target indels detected in edited cells

Data above is a representative example

Validation of Off-Target Editing in Primary Human Hepatocytes at Supersaturating LNP CRISPR Concentrations to Maximize Sensitivity



658 **potential off-target loci**

↓

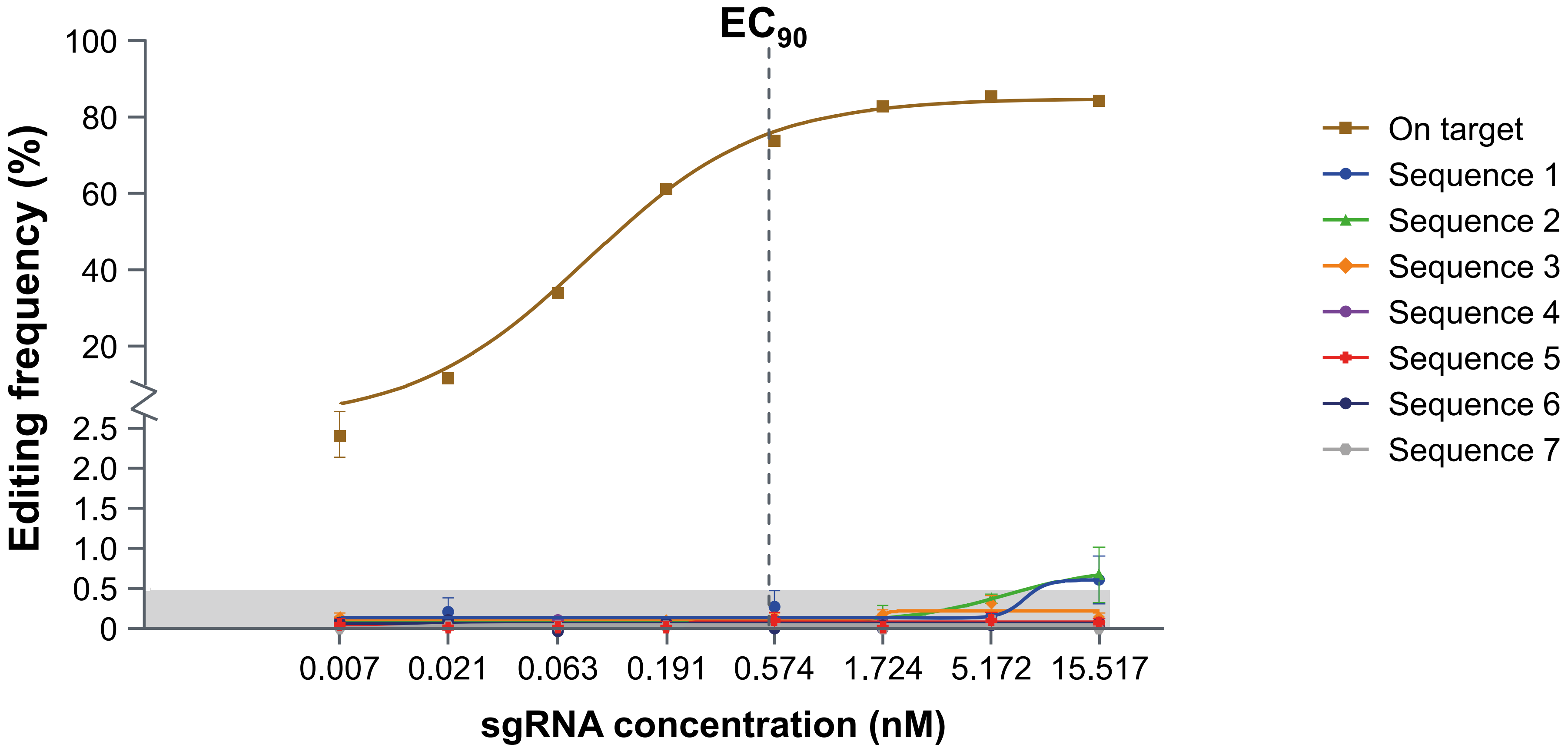
7 **validated off-target (OT) loci**

2 in introns and 5 in intergenic regions

- SITE-Seq discovered **100%**
- GUIDE-Seq and Cas-OFFinder discovered the same 3 out of 7 validated off-target loci **43%**
- Eliminate gRNA with validated off-target indels in regions of the genome associated with cancer

Data above is a representative example

In Vitro: No Detectable Off-Target Editing with Pharmacologic Concentration of sgRNA



Strategic Collaborations

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Intellia
THERAPEUTICS

Growing Intellia's Impact on Patients Through Strategic Collaborations

In Vivo

Genetic diseases

REGENERON

Ophthalmology

SPARINGVISION
GENOMIC MEDICINES FOR OCULAR DISEASES

Cystic Fibrosis

ReCode THERAPEUTICS

Intellia THERAPEUTICS

Ex Vivo

IO (Universal CAR-T)

AVENCELL

Autoimmune diseases (CD19 CAR-T)

kyverna

IO (NK Cells)

ONK THERAPEUTICS

Collaborations Helping to Accelerate the Development of CRISPR-Based Therapies

REGENERON

Collaboration Overview:

- **Up to 15 *in vivo* targets** with a mix of co-developed and licensed programs
  - Liver-centric product development
- **ATTR (*in vivo* knockout):** Intellia is lead party; Regeneron will share 25% of costs and profits
- **Hemophilia A (*in vivo* insertion):** Regeneron is lead party; Regeneron will share 65% of costs and profits
- ***In vivo* targets exclusively developed by Regeneron:**
  - Up to $320M in milestones per target
  - High single to low double-digit royalties
- **Non-exclusive license to certain platform IP** for up to 10 *ex vivo* CRISPR products in defined cell types
- **New research collaboration as of September 2023** to develop treatments for neurological and muscular diseases

Click below to learn more about our other collaborations

AVENCELL

kyverna

ONK THERAPEUTICS

ReCode THERAPEUTICS

SPARINGVISION GENOMIC MEDICINES FOR OCULAR DISEASES

Abbreviations

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Abbreviations

AAT: alpha-1 antitrypsin

AATD: alpha-antitrypsin deficiency

AAV: adeno-associated virus

AE: adverse event

AESI: adverse event of special interest

AI: autoimmune disease

ALT: alanine aminotransferase

AST: aspartate transaminase

ATTR amyloidosis: transthyretin amyloidosis

ATTRv: hereditary ATTR amyloidosis

ATTRwt: wild-type ATTR amyloidosis

ATTR-CM: ATTR amyloidosis with cardiomyopathy

ATTRv-PN: hereditary ATTR amyloidosis with polyneuropathy

B2M: beta-2-microglobulin

BL: baseline

BLA: biologics license application

CAR-T: chimeric antigen receptor T cells

CNS: central nervous system

CTCAE: Common Terminology Criteria for Adverse Events

CV: cardiovascular

ddPCR: digital droplet polymerase chain reaction

DSB: double strand break

GvHD: graft-versus-host disease

EC_{90}: concentration inducing 90% of maximal effect

FEV1: Forced expiratory volume in 1 second

FOD: follow-on dose

Gr: Grade

gRNA: guide RNA

HAE: hereditary angioedema

Hem A/B: hemophilia A/B

HLA-I / II: human leukocyte antigen class I / II

HLA-E: human leukocyte antigen class E

HSC: hematopoietic stem cells

IO: immuno-oncology

IQR: interquartile range

IRR: infusion-related reaction

KCCQ-OS: Kansas City Cardiomyopathy Questionnaire-Overall Summary

KLKB1: kallikrein B1

LNP: lipid nanoparticle

MedDRA: Medical Dictionary for Regulatory Authorities

mRNA: messenger RNA

NAC: National Amyloidosis Centre

NASH: nonalcoholic steatohepatitis

nex-z: nexiguran ziclumeran

NHP: non-human primate

NK: natural killer

NT-proBNP: N-terminal-pro-B-type natriuretic peptide

NYHA: New York Heart Association

PD: pharmacodynamics

PHx: partial hepatectomy

PK: pharmacokinetics

PNS: peripheral nervous system

Pt: patient

SAE: serious adverse event

SE: serious event

SCD: sickle cell disease

SD: standard deviation

sgRNA: single-guide RNA

TCR: T cell receptor

TEAE: treatment-emergent adverse event

TTR: transthyretin

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