Nancy and her father, Il Hyung, both living with ATTR amyloidosis

Intellia is Leading the Genome Editing Revolution

Corporate Overview
November 2023
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 genome editing toolbox to develop an unsurpassed genome editing pipeline; the safety, efficacy and advancement of our clinical programs for NTLA-2001 for the treatment of transthyretin ("ATTR") amyloidosis and NTLA-2002 for the treatment of hereditary angioedema ("HAE") 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; the advancement of our development candidates, including NTLA-3001 for the treatment of alpha-1 antitrypsin deficiency ("AATD")-associated lung disease, NTLA-2003 for AATD-associated liver disease, and NTLA-6001 for CD30+ lymphomas; the ability to generate data to initiate clinical trials and the timing of CTA and IND submissions; our ability to consistently deliver high-quality, readily available and persistent allogeneic cell products; 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 maintain and expand our related intellectual property portfolio, and avoid or acquire rights to valid intellectual property of third parties; 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, NTLA-2003, NTLA-3001, and NTLA-6001 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, hemophilia A and hemophilia B, 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 Kyverna Therapeutics, Inc. ("Kyverna") for the development of KYV-201, and with ONK Therapeutics Ltd. ("ONK") for the development of engineered NK cell therapies; and the potential timing and receipt of future milestones and royalties, or profits, as applicable, based on our license, collaboration and, if applicable, co-development agreements with Regeneron, Novartis Institutes for Biomedical Research, AvenCell, SparingVision, Kyverna, and ONK; the timing of regulatory filings and clinical trial execution, including dosing of patients, regarding its development programs; the potential commercial opportunities, including value and market, for our product candidates; our use of capital and other financial results; and our ability to fund operations beyond the next 24 months.

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 that the acquisition of ReWrite Therapeutics, Inc. may not result in additional platform capabilities; risks related to Intellia’s reliance on collaborations, including that its collaborations with Regeneron, AvenCell, SparingVision, 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 of the release, and Intellia undertakes no duty to update this information unless required by law.
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Appendix
Intellia is Leading a New Era in Medicine

**FIRST AND ONLY COMPANY**
to demonstrate successful systemic CRISPR gene editing in humans

80+ patients have been dosed with Intellia’s *in vivo* CRISPR-based therapies in ongoing clinical trials, with durability data beyond two years in earliest patients

**3 CLINICAL PROGRAMS**
achieved human proof-of-concept: NTLA-2001, NTLA-2002 and SCD*

Positioned to bring forth first-ever pivotal study for an *in vivo* CRISPR-based therapy

**10+**
*in vivo* and *ex vivo* programs for diseases with high unmet need**

**6**
collaborations with leading biotech and pharma partners

**BROADEST AND DEEPEST GENOME EDITING TOOLBOX**
underpins platform innovation and research engine

* Novartis-led sickle cell disease (SCD) program that utilized Intellia’s *ex vivo* genome editing technology.
** Both wholly owned and partnered programs.
Advancing a Full-Spectrum Genome Editing Company

CRISPR-based Modular Platform

**EMPLOY NOVEL EDITING AND DELIVERY TOOLS**

**In Vivo**
CRISPR *is* the therapy

**Ex Vivo**
CRISPR *creates* the therapy

**REWIRE & REDIRECT CELLS**

- Genetic diseases
- Immuno-oncology
- Autoimmune diseases

*REWIRE & REDIRECT CELLS*
Intellia is Developing Potentially Curative Genome 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
Therapeutic Strategies to Treat Life-Threatening Diseases Have Advanced Over Time
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
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. Kyriatsos, 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.
Intellia’s Core Strategic Priorities for 2023 – 2024

- Global pivotal studies planned for the treatment of transthyretin amyloidosis and hereditary angioedema
- First-in-human trial for lead in vivo insertion program for alpha-1 antitrypsin deficiency
- First allogeneic ex vivo CRISPR-based clinical program
- Base editing and DNA writing technologies
- Extend in vivo platform beyond liver targets
# Key Near-Term Milestones for Intellia

<table>
<thead>
<tr>
<th>NTLA-2001</th>
<th>Received IND clearance to begin pivotal study of NTLA-2001 for ATTR-CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATTR</td>
<td>Presented additional clinical data from the ongoing Phase 1 study by year end</td>
</tr>
<tr>
<td>NTLA-2002</td>
<td>Initiated the Phase 2 portion of the ongoing Phase 1/2 study</td>
</tr>
<tr>
<td>HAE</td>
<td>Received Intellia’s first IND clearance for an <em>in vivo</em> CRISPR-based candidate</td>
</tr>
<tr>
<td>NTLA-3001</td>
<td>Submit a Clinical Trial Application (CTA) filing in Q1 2024</td>
</tr>
<tr>
<td>AATD</td>
<td>Advanced novel gene editing technologies, including DNA writing, and delivery to other tissues outside the liver*</td>
</tr>
</tbody>
</table>

* Achieved research milestone for DNA writing technology in January 2023.

**ATTR-CM**: ATTR amyloidosis with cardiomyopathy; **ATTRv-PN**: hereditary ATTR amyloidosis with polyneuropathy; **AATD**: alpha-1 antitrypsin deficiency
# Broad Development Pipeline Fueled by Robust Research Engine

<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>APPROACH</th>
<th>Research</th>
<th>IND- Enabling</th>
<th>Early-Stage Clinical</th>
<th>Late-Stage Clinical</th>
<th>PARTNER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In Vivo: CRISPR is the therapy</strong></td>
<td></td>
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<tr>
<td>NTLA-2001: Transthyretin Amyloidosis</td>
<td>Knockout</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LEAD/REGENERON</td>
</tr>
<tr>
<td>NTLA-2002: Hereditary Angioedema</td>
<td>Knockout</td>
<td></td>
<td></td>
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<td></td>
<td>Intellia Therapeutics</td>
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<tr>
<td>NTLA-2003: AATD-Liver Disease</td>
<td>Knockout</td>
<td></td>
<td></td>
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<td>Intellia Therapeutics</td>
</tr>
<tr>
<td>NTLA-3001: AATD-Lung Disease</td>
<td>Insertion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intellia Therapeutics</td>
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<tr>
<td>Hemophilia B</td>
<td>Insertion</td>
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<td></td>
<td></td>
<td>LEAD/REGENERON</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>Insertion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intellia Therapeutics</td>
</tr>
<tr>
<td>Research Programs</td>
<td>Knockout, Insertion, Consecutive Edits</td>
<td></td>
<td></td>
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<td></td>
<td>Intellia Therapeutics</td>
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<tr>
<td>Research Programs</td>
<td>Various</td>
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<td>Intellia Therapeutics</td>
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<tr>
<td><strong>Ex Vivo: CRISPR creates the therapy</strong></td>
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<tr>
<td>NTLA-6001: CD30+ Lymphomas</td>
<td>Allo CAR-T</td>
<td></td>
<td></td>
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<td>Intellia Therapeutics</td>
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<tr>
<td>Acute Myeloid Leukemia / Solid Tumors</td>
<td>Allo WT1-TCR</td>
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<td>Research Programs</td>
<td>Allo – Undisclosed</td>
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<td>Various</td>
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<td></td>
<td>Intellia Therapeutics</td>
</tr>
<tr>
<td>Novartis Programs</td>
<td>CAR-T, HSC, OSC</td>
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<td></td>
<td></td>
<td>Intellia Therapeutics</td>
</tr>
</tbody>
</table>

Lead refers to lead development and commercial party; * Rights to certain in vivo targets; ** Milestones & royalties only

AATD: alpha-1 antitrypsin deficiency; CAR-T: chimeric Antigen Receptor T Cells; HSC: hematopoietic stem cells; OSC: ocular stem cells; TCR: T cell receptor
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**In Vivo**

CRISPR is the therapy

**GENETIC DISEASES**

**Strategic Advantages:**

- Potential curative therapy from 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

LNP: lipid nanoparticle
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

LNP Delivery System:

- gRNA identifies genetic target
- LNP: lipid nanoparticle; gRNA: guide RNA; mRNA: messenger RNA
NTLA-2001 for Transthyretin (ATTR) Amyloidosis

About ATTR Amyloidosis

• Caused by accumulation of misfolded transthyretin (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

Potential to:

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

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

• Reduces wild-type and mutant TTR protein
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Potential to:

• Halt and reverse disease with deep and consistent TTR reduction
• Be a single-dose treatment
• Expect lifelong, stable TTR reduction
ATTR Amyloidosis: Large Commercial Opportunity with Significant Unmet Need

**Prevalence**

2. Compiled from various sources.

**Life Expectancy**


**Disease Burden**

4. Griffin et al. JACC 2021; Intellia Patient Survey 2022

**Commercial Opportunity**

5. GlobalData 2022

6. Redbook 2022

**NTLA-2001**

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

<table>
<thead>
<tr>
<th></th>
<th>ATTRv patients worldwide</th>
<th>ATTRwt patients worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>50,000</td>
<td>~200-500K</td>
</tr>
<tr>
<td><strong>Life Expectancy</strong></td>
<td>2-7 years</td>
<td>~10 years</td>
</tr>
<tr>
<td><strong>Disease Burden</strong></td>
<td>Patients experience highly burdensome symptoms, including heart failure, shortness of breath, muscle weakness and sensory deficits</td>
<td></td>
</tr>
<tr>
<td><strong>Commercial Opportunity</strong></td>
<td>$11B+</td>
<td>$450K+</td>
</tr>
</tbody>
</table>

2. Compiled from various sources.  
4. Griffin et al. JACC 2021; Intellia Patient Survey 2022  
5. GlobalData 2022  
6. Redbook 2022

ATTRv: hereditary ATTR amyloidosis; ATTRwt: wild-Type ATTR amyloidosis

ATTR-CM: ATTR amyloidosis with cardiomyopathy; ATTRv-PN: hereditary ATTR amyloidosis with polyneuropathy
NTLA-2001 Phase 1 Study in ATTR Amyloidosis

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

PART I: Single-Ascending Dose Escalation

- 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)

- 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)

PART II: Dose Expansion

- 55 mg (n=16)
- 80 mg (n=5)

- 55 mg NYHA Class I/II (n=12)
- 55 mg NYHA Class III (n=12)

SECONDARY OBJECTIVES
Evaluate efficacy on clinical measures of:
- Neurologic function in subjects with ATTRv-PN
- Cardiac disease in subjects with ATTR-CM

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

Clinicaltrials.gov ID: NCT04601051

PK: pharmacokinetics; PD: pharmacodynamics
## 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)

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

- This includes all reported events, including those unrelated to NTLA-2001 (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 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.

AE: adverse event; AST: aspartate transaminase; TEAE: treatment-emergent adverse event.
Regardless of Baseline TTR Levels, NTLA-2001 Led to Consistently Low and Sustained Absolute Serum TTR in All Patients

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.

ATTR-CM: transthyretin amyloidosis with cardiomyopathy; ATTRv-PN: hereditary transthyretin amyloidosis with polyneuropathy; IQR: interquartile range; NYHA: New York Heart Association; SD: standard deviation; TTR: transthyretin.
A Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate NTLA-2001 in Patients with ATTR Amyloidosis with Cardiomyopathy (ATTR-CM)

Randomization 2:1

**NTLA-2001**
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

CV: cardiovascular; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire-Overall Summary
NAC: National Amyloidosis Centre; NYHA: New York Heart Association; NT-proBNP: N-terminal-prohormone of brain natriuretic peptide
NTLA-2002 for Hereditary Angioedema (HAE)

Shanna and their sons, Oren and Damian, all living with HAE
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
  - Reduce kallikrein activity to prevent attacks

**Key Advantages**
- 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

### Prevalence

<table>
<thead>
<tr>
<th>Prevalence&lt;sup&gt;1&lt;/sup&gt;</th>
<th>&gt;15,000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In U.S. and EU</td>
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</table>

### Diagnosis

<table>
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<tr>
<th>Diagnosis&lt;sup&gt;2&lt;/sup&gt;</th>
<th>20 years old</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Average age of diagnosis</td>
</tr>
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</table>

### Disease Burden

<table>
<thead>
<tr>
<th>Disease Burden&lt;sup&gt;3&lt;/sup&gt;</th>
<th>50-60%</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Patients continue to have HAE attacks despite existing therapies</td>
</tr>
<tr>
<td></td>
<td>• Attacks can result in hospitalizations</td>
</tr>
<tr>
<td></td>
<td>• Patients subject to lifetime of attack risk and chronic treatment</td>
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</table>

### Commercial Opportunity

<table>
<thead>
<tr>
<th>Commercial Opportunity&lt;sup&gt;4,5&lt;/sup&gt;</th>
<th>$4B+</th>
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<tbody>
<tr>
<td>Projected global market size for HAE therapies in 2026</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>$500K+</th>
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<tr>
<td>Annual U.S. cost of leading prophylactic treatment</td>
<td></td>
</tr>
</tbody>
</table>

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2 Farkas et al. Allergy. 2017. 72:300-313
4 GlobalData 2022
5 Redbook 2022
NTLA-2002 Phase 1/2 Trial Design

International, multi-center 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
- 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)
NTLA-2002 Was Generally Well Tolerated Across All Dose Levels Evaluated

<table>
<thead>
<tr>
<th>Adverse events occurring in ≥ 2 patients</th>
<th>25 mg n = 3</th>
<th>50 mg n = 4</th>
<th>75 mg n = 3</th>
<th>All patients N = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr. 1</td>
<td>Gr. 2</td>
<td>Gr. 1</td>
<td>Gr. 2</td>
</tr>
<tr>
<td>Any TEAE (max grade)</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>2</td>
<td>–</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>–</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>COVID-19</td>
<td>3</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Headache</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

No clinically significant laboratory findings observed.
No treatment-emergent SAEs or ≥ Grade 3 TEAEs were observed.
Median duration of follow-up for all patients was 9.0 months (range, 5.6-14.1 months).

Patients counted once per row with highest grade reported.
Gr., Grade (NCI-CTCAE version 5.0); SAE, serious adverse event; TEAE, treatment-emergent adverse event.
NTLA-2002 Resulted in Dose-dependent and Durable Reductions in Plasma Kallikrein Protein

Data are mean values with standard deviation. Dashed line represents targeted minimum reduction. Mean percentage reduction callout on graph refers to last measurement as of the data cutoff date.
Robust and Durable HAE Attack Reductions Observed in all Patients After a Single Dose of NTLA-2002

Historic monthly attack rate prior to screening (months)

SCREENING PERIOD PRIMARY OBSERVATION PERIOD POST-PRIMARY OBSERVATION PERIOD

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Historic Monthly Attack Rate</th>
<th>Administration of NTLA-2002</th>
<th>ATTACK SEVERITY:</th>
<th>PROPHYLAXIS WITHDRAWAL:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.9</td>
<td>25 mg</td>
<td>Mild</td>
<td>Berotralstat withdrawn at day 94</td>
</tr>
<tr>
<td>2</td>
<td>14.0</td>
<td>75 mg</td>
<td>Moderate</td>
<td>Berotralstat withdrawn at day 113</td>
</tr>
<tr>
<td>3</td>
<td>2.2</td>
<td>50 mg</td>
<td>Severe</td>
<td>No concomitant prophylaxis</td>
</tr>
</tbody>
</table>

ATTACK SEVERITY:
- Mild
- Moderate
- Severe

PROPHYLAXIS WITHDRAWAL:
- Berotralstat withdrawn at day 94
- Berotralstat withdrawn at day 113
- Danazol withdrawn at day 151
- Stanozolol withdrawn at day 74

Longest attack free duration post NTLA-2002 (months):

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Historic Monthly Attack Rate</th>
<th>Administration of NTLA-2002</th>
<th>Longest Attack Free Duration Post NTLA-2002 (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.9</td>
<td>25 mg</td>
<td>12.3</td>
</tr>
<tr>
<td>2</td>
<td>14.0</td>
<td>75 mg</td>
<td>11.5</td>
</tr>
<tr>
<td>3</td>
<td>2.2</td>
<td>50 mg</td>
<td>13.0</td>
</tr>
<tr>
<td>1</td>
<td>16.8</td>
<td>75 mg</td>
<td>7.5</td>
</tr>
<tr>
<td>2</td>
<td>1.9</td>
<td>25 mg</td>
<td>10.1</td>
</tr>
<tr>
<td>3</td>
<td>4.4</td>
<td>50 mg</td>
<td>8.9</td>
</tr>
<tr>
<td>1</td>
<td>1.9</td>
<td>50 mg</td>
<td>5.9</td>
</tr>
<tr>
<td>2</td>
<td>0.9</td>
<td>50 mg</td>
<td>6.1</td>
</tr>
<tr>
<td>3</td>
<td>0.9</td>
<td>50 mg</td>
<td>6.0</td>
</tr>
<tr>
<td>4</td>
<td>0.9</td>
<td>50 mg</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Days:
-56 -42 -28 -14 0 14 28 42 56 70 84 98 112 140 168 196 224 252 280 308 336 364 392 420 448

Weeks 1-16

Months 4-16
Across All Patients, a Single Dose of NTLA-2002 Led to a 95% Mean Reduction in Monthly HAE Attack Rate Through the Latest Follow-up

<table>
<thead>
<tr>
<th>Week</th>
<th>25 mg ( n = 3 )</th>
<th>50 mg ( n = 4 )</th>
<th>75 mg ( n = 3 )</th>
<th>All patients ( N = 10 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1-16</td>
<td>-91% (16%)</td>
<td>-97 (5%)</td>
<td>-80% (30%)</td>
<td>-89 (19%)</td>
</tr>
<tr>
<td>Week 5-16</td>
<td>-89% (19%)</td>
<td>-100% (0%)</td>
<td>-87% (23%)</td>
<td>-92% (16%)</td>
</tr>
<tr>
<td>Week 1-24</td>
<td>-94% (11%)</td>
<td>-98% (3%)</td>
<td>-86% (20%)</td>
<td>-93% (13%)</td>
</tr>
<tr>
<td>On-study period</td>
<td>-95% (4%)</td>
<td>-98% (3%)</td>
<td>-93% (11%)</td>
<td>-95% (6%)</td>
</tr>
</tbody>
</table>

Data are mean % change from baseline (standard deviation).
Baseline is defined as up to 42 days screening period prior to the administration of NTLA-2002.
On-study period is defined as the time from the dosing of NTLA-2002 through the last HAE attack assessment as of the data cutoff date.
For the 50 mg cohort, one of four patients was not evaluable as they reported zero attacks during the screening period.
Beyond Gene Inactivation, Intellia is Also Advancing Targeted Insertion Programs

CRISPR-Enabled Targeted Insertion Approach Offers Significant Advantages Over Alternate Gene Therapy Approaches

High Levels of Protein Expression

Potential to Revolutionize Gene Replacement

Durable Protein Expression
NTLA-3001 for Alpha-1 Antitrypsin Deficiency (AATD)

About AATD

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

Our Approach

NTLA-3001: Targeted insertion of a functional SERPINA1 gene
- Continuous expression of functional A1AT protein at normal levels
- Address AATD-associated lung disease

Key Advantages

- Designed to be a single-dose treatment
- NTLA-3001: Aims to achieve normal human levels of A1AT 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
* In severe AATD patients defined as individuals with PiZZ genotype.
Durable Production of Physiologic Levels of hA1AT Through One Year in NHP

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

Precisely Create Insertion Site

Deliver Insertion Template

Gene of Interest

(Factor 9)
(SERPINA1)

LNP

AAV

Circulating hA1AT (µg/mL)

Therapeutically relevant

Normal range

0 4 8 12 16 20 24 28 32 36 40 44 48 52

Time (weeks post insertion)

Circulating hA1AT (µg/mL)

Insertion (n=3)

Buffer control (n=3)

1 Stoller & Aboussouan. The Lancet, 2005
Normal range: ~1000-2700 µg/mL, or 20-53 µM; Therapeutically relevant: 571 µg/mL, or 11 µM
Clinical Validation of LNP Delivery Platform Supports *In Vivo* Pipeline Acceleration

**Unlock Full Potential**

**Targets Across Multiple Tissues**

**First Wave of Programs**

**Unlock Liver Targets**

**Address diseases with genetically defined targets in the liver**
- ✔ Remove a toxic protein via knockout
- ❏ Restore a functional protein via insertion

**ATTR, HAE, AATD, Hem B**

**Hem A, PH, Undisclosed Indications**

**Modular Platform**

---

**CNS:** central nervous system; **Hem A and B:** hemophilia A and B; **PH:** primary hyperoxaluria; **LNP:** lipid nanoparticle
Significant Opportunities to Unlock Full Potential of *In Vivo* Platform

<table>
<thead>
<tr>
<th>Potential Liver Development Programs*</th>
<th>Unlocking Full Potential of Genome Editing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare Diseases</strong>**</td>
<td><strong>Target Tissues</strong></td>
</tr>
<tr>
<td>• Blood disorders</td>
<td>• Bone marrow</td>
</tr>
<tr>
<td>• Lysosomal storage diseases</td>
<td>• CNS/PNS**</td>
</tr>
<tr>
<td>• Metabolic diseases</td>
<td>• Eye***</td>
</tr>
<tr>
<td><strong>Prevalent Diseases</strong>**</td>
<td>• Heart</td>
</tr>
<tr>
<td>• Chronic viral diseases</td>
<td>• Muscle**</td>
</tr>
<tr>
<td>• Dyslipidemia</td>
<td></td>
</tr>
<tr>
<td>• Hypertension</td>
<td></td>
</tr>
<tr>
<td>• NASH</td>
<td></td>
</tr>
</tbody>
</table>

Criteria Used to Select Potential Future Candidates:
- Unmet need
- Population size
- Technical feasibility

*NASH*: nonalcoholic steatohepatitis; *CNS*: central nervous system; *PNS*: peripheral nervous system

*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 Sparing/Vision*
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Intellia Investment Overview

In Vivo Portfolio

Ex Vivo Portfolio

Appendix
CRISPR creates the therapy

**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
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:**

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Targeting Modality</th>
<th>Rewiring Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSCs, T cells</td>
<td>TCRs</td>
<td>Immune-enhancing edits</td>
</tr>
<tr>
<td>NK cells, Macrophages</td>
<td>CAR-Ts, Universal CARs</td>
<td>Novel targets</td>
</tr>
</tbody>
</table>

**Acronyms:**
- NK: natural killer; TCR: T cell receptor; LNP: lipid nanoparticle; HSC: hematopoietic stem cells; CAR: chimeric antigen receptor
## Differentiated Approach to Cell Therapy Genome Engineering

### Gene Editing Approach

<table>
<thead>
<tr>
<th>Delivery</th>
<th>Lipid Nanoparticle</th>
<th>Electroporation</th>
<th>Electroporation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Editing Mode</td>
<td>Sequential</td>
<td>Simultaneous</td>
<td>Simultaneous</td>
</tr>
<tr>
<td>Knockout (KO)</td>
<td>Cleavase or Base Editor</td>
<td>Cleavase</td>
<td>Base Editor</td>
</tr>
<tr>
<td>Insertion</td>
<td>CRISPR insertion</td>
<td>Lenti/Retroviruses</td>
<td>Lenti/Retroviruses</td>
</tr>
</tbody>
</table>

### 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. DSB: double strand break
Sequential Editing with LNP Approach Minimizes Translocations While Retaining Robust Cell Viability and Expansion

ddPCR assay to detect *TRAC-TRBC* translocations

<table>
<thead>
<tr>
<th>% TRAC-TRBC translocated cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Edit</td>
</tr>
<tr>
<td>Electroporation</td>
</tr>
<tr>
<td>Simultaneous LNP</td>
</tr>
<tr>
<td>Sequential LNP</td>
</tr>
</tbody>
</table>

LNP Approach: Cell Expansion at D10

LNP: lipid nanoparticle; ddPCR: digital droplet polymerase chain reaction
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’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

1a. Knockout endogenous TCR
1b. Insert target CAR or TCR
2a. Knockout HLA Class II
2b. Knockout HLA-A only
3. Match HLA-B and HLA-C

Main Objective of Edit

- Prevent Graft-versus-Host Disease (GvHD)
- Direct T cell for tumor killing
- Prevent CD4-mediated rejection
- Prevent CD8-mediated rejection
- Block NK cell activation and avoid NK-mediated rejection

HLA-I / II: human leukocyte antigen class I / II; TCR: T cell receptor; NK: natural killer
Ex Vivo Pipeline Expansion Strategy

**First Wave of Programs**

**Address a variety of cancers**
- Target new antigens with TCR identification and cell engineering platform
- Allogeneic solution

**Hematological and Solid Tumors**

**Unlock Full Potential**

**Advance cell therapy for cancer and autoimmune diseases**
- Novel immune-enhancing edits

**Prioritize diseases with significant unmet need**

**Immuno-oncology**

**Novel Cell Rewiring for Cancers and Autoimmune Diseases**

**AML, Undisclosed Indications**

TCR: T cell receptor; AML: acute myeloid leukemia
Unlocking the Full Potential of CRISPR
Solving in vivo delivery supports rapid expansion of pipeline to broad patient population

**in vivo**
Genetic diseases
CRISPR is the therapy

- **NTLA-2001**
  Unlock the liver for ATTR, NTLA-2002 for HAE and beyond

- **NTLA-3001 and Factor IX**
  Restore a functional protein via insertion for AATD and Hem B

- Target bone marrow and other tissues

**ex vivo**
Immuno-oncology, autoimmune diseases
CRISPR creates the therapy

- **Rewire T cells to target Acute Myeloid Leukemia**
- **Engineer allogeneic therapies**
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Intellia’s Genome Editing Toolbox

Persistence of In Vivo Edits

In Vivo Editing of Hematopoietic Stem Cells

LNP-Based Editing of T Cells

Intellia’s Allogeneic Solution

Intellia’s Proprietary Base Editor

Platform: Identifying Potent and Highly Specific Guide RNAs

Strategic Collaborations
Intellia’s Genome Editing Toolbox
World-Class Genome Editing Platform Allows for Unsurpassed Capabilities

Proprietary CRISPR-based Modular Platform

<table>
<thead>
<tr>
<th>Editing Tools</th>
<th>Delivery Tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRISPR/Cas9</td>
<td>LNPs</td>
</tr>
<tr>
<td>Spy, HiFi Spy, Nme2</td>
<td></td>
</tr>
<tr>
<td>C&gt;T base editor</td>
<td>AAVs</td>
</tr>
<tr>
<td>DNA writer</td>
<td>Additional modalities</td>
</tr>
</tbody>
</table>

ENABLES SELECTING THE BEST TOOLS FOR EACH THERAPEUTIC APPLICATION:

Applies to *in vivo* or *ex vivo* application

Capable of achieving any editing strategy
- Knockouts, insertions, corrections or deletions
- Multiplicity of edits
Persistence of *In Vivo* Edits
Partial Hepatectomy Model for Investigating Persistence of Knockout Genome Editing

NHP studies demonstrate sustained KO editing and target TTR protein reduction carried through regular cell turnover for 12 months

Key Question: Can editing be carried through tissue regeneration following partial hepatectomy and accelerated cell division?
Protein Reduction Remains Unchanged Following Murine Liver Regeneration

*TTR gene editing rate similarly remains unchanged post-PHx by NGS analysis*

**Similar results obtained for control and LNP when sham surgery was performed.**

1 Next generation sequencing (NGS) analysis to evaluate the frequency of insertion and deletion events (edits)

PHx: partial hepatectomy
Rodent studies show sustained FIX insertion editing through 12 months, demonstrating that editing is carried through normal cell turnover.

**Key Question:** Can insertion editing be carried through tissue regeneration following partial hepatectomy?
Persistent Protein Levels Post-PHx from Targeted Gene Insertion in Murine Model; Significant Loss of Protein Expression with Gene Therapy

Correlating editing rate similarly remains unchanged post-PHx by NGS analysis\(^1\)

Next generation sequencing (NGS) analysis to evaluate the frequency of insertion and deletion events (edits)

<table>
<thead>
<tr>
<th>Event</th>
<th>Circulating hFIX levels (normalized to pre-PHx levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LNP + AAV dose (Day 0)</td>
<td>0</td>
</tr>
<tr>
<td>Post-Edit Pre-PHx</td>
<td>~85% Loss with Episomal Expression</td>
</tr>
<tr>
<td>PHx (Day 40)</td>
<td>~95% Loss with Episomal Expression</td>
</tr>
<tr>
<td>Post-Edit, Post-PHx</td>
<td>~85% Loss with Episomal Expression</td>
</tr>
<tr>
<td>Post-Edit, Necropsy</td>
<td>~95% Loss with Episomal Expression</td>
</tr>
</tbody>
</table>

Episomal AAV Expression
Targeted Insertion via CRISPR/Cas9 Gene Editing

\(^1\) Next generation sequencing (NGS) analysis to evaluate the frequency of insertion and deletion events (edits)
In Vivo Editing of Hematopoietic Stem Cells
Ex vivo SCD Gene Editing Still Has Significant Limitations

Complex cell manufacturing process

Mobilize and harvest cells
Myeloablate the patient
Infuse edited cells & support patient until cells engraft

Conditioning regimen toxicity

- Immunosuppression for > 1 month, predisposing to infection
- Risk of malignancy from chemotherapy drugs, especially leukemia
- Risk of infertility

Implications

- *Ex vivo* gene editing will be limited to highly selected SCD patients with severe disease
- Treatment complexity will limit access for patients in resource-poor settings
**In Vivo Non-Viral SCD Gene Editing Could Overcome These Limitations**

**Potential improved safety and accessibility**
- Avoids myeloablation and associated risks of immunosuppression, malignancy and infertility
  - Approach could become mainstream therapy for SCD
- Avoids need for complex cell manufacturing or extensive supportive care post-treatment
  - Treatment simplicity could expand access to patients in resource-poor settings

**Desired features of *in vivo* approach**
- Provides clinically meaningful, durable HSC editing
- Allows for multidosing to reach therapeutic target
- Preserves regenerative potential of edited cells
- Translatable to human HSC population

**Simplified process**

- Lipid Nanoparticle (LNP)
- Infusion of LNP
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.

- **Liver-tropic LNP**
  - Infusion of LNP

- **Bone marrow-tropic LNP**
  - Infusion of LNP
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

Note: Guide “B” used in this experiment
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
LNP: lipid nanoparticle

Note: Guide “B” used in this experiment
LNP-Based Editing of T Cells
LNP-Based Cell Engineering Technology Optimizes Cell Health and Function

**LNP approach to editing T cells**
- Enables sequential editing
- Reduces safety risks from unwanted breaks caused by EP
- Produces cells with high expansion and performance

**DNA Damage**
- γ-H2AX marker

**Untreated**
- Cell expansion

**Electroporation (EP)**
- Re-stimulation Stress Test

**Intellia’s Process**
- LNP approach to editing T cells

**Cell Expansion**
- Fold Expansion
- Day 10
- Day 14

**Re-stimulation Stress Test**
- OCI-AML3+VLD
- LNP 120 fold expansion
- EP 27 fold expansion

**Legend**
- EP: Electroporation
- LNP: Lipid Nanoparticle
- Untreated
- p < 0.01
Multiplex CRISPR/Cas9 T Cell Editing: 5 Sequential Edits with 2 Insertions

Dual site-specific insertion strategy enables co-expression of CAR/TCR construct and immune enhancing transgene

% Editing Across Loci

- >80% of cells have insertion of both the TCR and GFP transgene
- Cells retained high viability and complete editing of 3 other KO targets
- Modular platform for insertion of T cell supporting transgenes
Intellia’s Allogeneic Solution
### Immune Concerns Unaddressed by Current Allogeneic Solutions

**Intellia’s Approach**

<table>
<thead>
<tr>
<th>Approach</th>
<th>Employ intense lymphodepletion regimen</th>
<th>Knockout (KO) HLA-I (B2M)</th>
<th>KO HLA-I &amp; express NK inhibitor (HLA-E)</th>
<th>KO HLA-II &amp; HLA-A*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid rejection of cell therapy by host CD8 T cells</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Avoid rejection of cell therapy by host CD4 T cells</td>
<td>✔</td>
<td>✗</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td>Avoid rejection of cell therapy by host NK cells</td>
<td>✔</td>
<td>✗</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td>Avoid profound immunosuppression</td>
<td>✗</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

*Slide based on preclinical data disclosed by Intellia. Intellia’s cell product to be further explored in additional preclinical and clinical studies. B2M: beta-2-macroglobulin; HLA-E: human leukocyte antigen class E*
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

Signal from Live B2M KO T Cells

- Mock mice
- NK engrafted mice

Days Post T Cell Injection

Signal from Live Allo TCR-T Cells

- Mock mice
- NK engrafted mice

Days Post T Cell Injection

B2M: beta-2-macroglobulin; NK: natural killer
Intellia’s Proprietary Base Editor
Intellia’s Base Editor is Equipotent to Cas9 for *Ex Vivo* Editing

Intellia’s base editor is highly active with similar activity to Cas9 cleavase

>700 constructs screened for potency
85% of guides gave >90% editing
36% of guides gave >95% C to T purity

**Cas9**

**Base Editor**

![Graph of C>T edits](image)

**Pure C>T edits**
(without indels)

95%

**Pure C>T Editing (%)**

sgRNA

(n = 61)

**sgRNA: single guide RNA**
Simultaneous Knockout with Base Editing **Does Not** Lead to Translocations

1. Isolate primary T cells
2. Deliver base editor + 4 sgRNAs
3. Evaluate editing, receptor KO and translocations

![Graph showing on-target editing and receptor KO and translocations](graph.png)

**On-target editing** (amplicon sequencing)
- TRAC: 98.1%
- TRBC1: 95.9%
- TRBC2: 96.0%
- Gene X: 98.1%
- Gene Y: 92.9%

**Receptor KO** (flow cytometry)
- CD3: 97.3%
- Gene X: 97.3%
- Gene Y: 93.5%

**Interchromosomal Translocations**
- TRAC: ns
- Gene X: ns
- Gene Y: ns

**Locus tested**
- Untreated
- Base Editor
Platform: Identifying Potent and Highly Specific Guide RNAs
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)
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

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
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

**EC$_{90}$** concentration inducing 90% of maximal effect; sgRNA: single guide RNA
Strategic Collaborations
Intellia acquired Rewrite Therapeutics in February 2022

Growing Intellia’s Impact on Patients Through Strategic Collaborations and Business Development

Increasing shareholder value:
- Leveraging our technology while retaining rights to key areas of focus
- Accelerate development of programs outside key areas of focus
- Expand our pipeline with valuable rights in future commercial success
- Access external expertise to enhance our platform

Genetic diseases
- REGENERON

Ophthalmology
- SPARINGVISION

In Vivo
- Ex Vivo

Immuno-oncology (IO)
- VENCCELL

IO (NK Cells)
- ONK THERAPEUTICS

Autoimmune diseases (CD19)
- kyverna

HSC, CAR-T
- NOVARTIS
Foundational Partnerships Provided Access to R&D Capabilities

**REGENERON**

- Up to 15 *in vivo* targets with a mix of co-developed and licensed programs
  - Liver-centric product development
- **ATTR**: First selected Co/Co program
  - Intellia is lead party; Regeneron will share 25% of costs and profits
- **Hemophilia A and B**: Co/Co agreements based on targeted insertion capabilities
  - 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

**NOVARTIS**

- Research collaboration term concluded in December 2019
- Novartis selected various CAR-T, HSC and OSC targets for development
  - Up to $230M in milestone payments per product
  - Mid single-digit royalties

Intellia THERAPEUTICS