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

Welcome

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

NTLA-2001 Interim Clinical Data Review
David Lebwohl, M.D.
*Chief Medical Officer*, Intellia Therapeutics

Closing Remarks and Q&A Session
NTLA-2001 Expanded Phase 1 Study

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

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

**PART I**
- ATTRv-PN patients
  - Single-Ascending Dose Escalation Cohorts

**PART II**
- ATTR-CM patients
  - Single-Ascending Dose Escalation Cohorts
- Single Dose Expansion Cohort
  - Administer dose derived from Part I data

Clinicaltrials.gov ID: NCT04601051
NTLA-2001 Phase 1 Study: Polyneuropathy Arm

Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN)

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

**SECONDARY OBJECTIVES**
Evaluate efficacy on clinical measures of neurologic function
- Neuropathic impairment endpoints include NIS (Part 1 and 2) and mNIS+7 (Part 2 only)

**PART I – DOSING COMPLETE**
Single-Ascending Dose
- 1.0 mg/kg (n=6)
- 0.7 mg/kg (n=3)
- 0.3 mg/kg (n=3)
- 0.1 mg/kg (n=3)

**PART II – ONGOING**
Single Dose Expansion Cohort
- N = 8 subjects
- Administer 80 mg fixed dose
NTLA-2001 Was Generally Well Tolerated Across All Dose Levels Through The Follow-up Period

- Across all dose levels, the most frequent adverse events* were headache, infusion-related reactions, back pain, rash† and nausea
  - Majority of adverse events were mild in severity with 73% (n=11) of patients reporting a maximal adverse event severity of Grade 1
  - All infusion-related reactions were considered mild, resolving without clinical sequelae
  - All patients received a complete study dose of NTLA-2001

- A single possibly-related Grade 3 event (SAE) of vomiting was reported at the 1.0 mg/kg dose in a patient with underlying gastroparesis
  - 1.0 mg/kg dose level expanded per protocol to 6 patients to further characterize safety and PD

- No clinically significant laboratory findings observed
  - Transient Grade 1 liver enzyme elevations observed

- Maximally tolerated dose was not reached

Data Cut Off: May 16, 2022
Median follow-up for all subjects is 10 months
* Related and unrelated events in more than 2 patients
† Date of onset D6–D145; all mild in severity
PD, pharmacodynamics; SAE, serious adverse event
This slide includes data for investigational products not yet approved by regulatory authorities
Dose-dependent Reductions in Serum TTR, Reaching a Mean Reduction of 93% at 1.0 mg/kg

Mean (SE) % TTR reduction by dose level at Day 28

- 0.1 mg/kg: -52% (n=3)
- 0.3 mg/kg: -87% (n=3)
- 0.7 mg/kg: -86% (n=3)
- 1.0 mg/kg: -93% (n=6)

Dashed line represents the targeted minimum reduction

SE, standard error; TTR, transthyretin

This slide includes data for investigational products not yet approved by regulatory authorities
Higher Doses Demonstrated Rapid and Deep Serum TTR Reduction Sustained Through 6-12 Months

Mean (SE) % TTR reduction by dose level

-100 -90 -80 -70 -60 -50 -40 -30 -20 -10 0 10

TTR reduction (%)

0 1 2 4 6 9 12

Months

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

This slide includes data for investigational products not yet approved by regulatory authorities.
Simulations Identified NTLA-2001 80mg as the Fixed Dose Equivalent to 1.0 mg/kg

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

Interim model
This slide includes data for investigational products not yet approved by regulatory authorities
Deep, Consistent, and Durable TTR Reductions Following Single Administration of *in vivo* CRISPR-based Gene Editing

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

These data further support and extend early findings from this pioneering trial demonstrating the promise of CRISPR-based *in vivo* gene editing in humans
Intellia is Opening a New Era of Medicine

**KEY TAKEAWAYS**

Growing body of evidence

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

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

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

**NEXT STEPS**

- Complete enrollment of Phase 1 study of NTLA-2001 for both ATTRv-PN and ATTR-CM in 2022
- Present interim clinical data from cardiomyopathy arm in 2022
- Engage with regulatory agencies, including U.S. FDA, to discuss a potential pivotal trial design
Q&A

NTLA-2001 Interim Phase 1 Clinical Data