NTLA-2001 and Transthyretin (ATTR) Amyloidosis

NTLA-2001 is the first investigational CRISPR-based therapy candidate to be administered systemically to edit genes inside the human body.

Transthyretin (ATTR) Amyloidosis

ATTR amyloidosis is a rare, progressive and fatal disease that occurs when a protein called TTR becomes malformed and is deposited in various parts of the body. When it is inherited, known as hereditary ATTR (ATTRv), a person is born with mutations in the gene that encodes the TTR protein. When it occurs spontaneously, known as wild-type ATTR (ATTRwt), the protein becomes malformed for reasons other than a genetic mutation.

Abnormal TTR proteins most commonly form deposits in the heart and peripheral nerves, causing conditions known as cardiomyopathy and polyneuropathy. Cardiomyopathy limits the heart’s ability to pump blood; polyneuropathy causes nerve damage throughout the body, especially in the extremities.

**ATTR AMYLOIDOSIS** leads to deposits of misfolded TTR protein throughout the body, resulting in diverse complications, often fatal, including: cardiomyopathy and polyneuropathy.

**NTLA-2001 IS DESIGNED TO INACTIVATE THE GENE THAT LEADS TO TTR PROTEIN PRODUCTION TO TREAT ALL FORMS OF ATTR AMYLOIDOSIS.**

50K

Patients worldwide

caused by inherited mutation

200K to 500K

Patients worldwide

arises spontaneously
NTLA-2001 is an investigational therapy for ATTR amyloidosis. It is in development by Intellia Therapeutics and based on Nobel prize-winning CRISPR/Cas9 genome editing technology. It is the first CRISPR therapeutic candidate to be administered systemically, to edit genes inside the human body. NTLA-2001 is designed to be a single-dose treatment that greatly reduces production of the TTR protein by inactivating the TTR gene, whether mutated or not. Its goal is to halt or even reverse TTR accumulation in the body, with the potential of arresting the disease.

What is CRISPR/Cas9?

CRISPR/Cas9 was developed in part by Intellia co-founders, including Nobel prize winner Jennifer Doudna. It can make a permanent, precisely targeted edit to a person’s DNA to treat an underlying genetic mutation that contributes to disease. The CRISPR/Cas9 genome editing system consists of two parts: guide RNA, which targets the medicine to the disease-causing gene, and genetic instructions to assemble the Cas9 enzyme, which are switched on once the guide RNA binds in the proper location and helps create the edit.

NTLA-2001 encapsulates the CRISPR/Cas9 genome editing system in lipid nanoparticles (LNPs), which are similar in chemical composition to cell membranes and introduced to the body via intravenous infusion. The LNPs are designed to migrate to the liver, where the TTR gene is active.
NTLA-2001 Phase 1 Study Design

**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)

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

**PART I – DOSING COMPLETE**
Single-Ascending Dose

<table>
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<th>Dose (mg/kg)</th>
<th>Subjects (n)</th>
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**PART II – INITIATE IN Q1 2022**
Single Dose Expansion Cohort

N=8 subjects
Administer dose selected from Part I

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**NTLA-2001 Phase 1 Study: Cardiomyopathy Arm**
Hereditary transthyretin amyloidosis with cardiomyopathy (ATTRv-CM) or wild-type cardiomyopathy (ATTRwt-CM), NYHA Class I – III

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

**Secondary Objectives**
Evaluate efficacy on clinical measures of cardiac disease
- Cardiac imaging, biomarkers, cardiopulmonary exercise test, 6MWT

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

**PART I**
Single-Ascending Dose

<table>
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**PART II**
Single Dose Expansion Cohort

N=12 subjects
Administer dose selected from Part I

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*3 to 6 subjects per cohort        Clinicaltrials.gov ID: NCT04601051         NYHA: New York Heart Association        PK: Pharmacokinetics        PD: Pharmacodynamics        6MWT: 6 Minute Walk Test

Intellia is continuing to enroll patients in the cardiomyopathy arm of the study. Visit [clinicaltrials.gov](https://clinicaltrials.gov) (NCT04601051) for more details.

To learn more about the interim clinical data presented by Intellia on February 28, 2022, please see our Investor’s page [https://ir.intelliatx.com/press-releases](https://ir.intelliatx.com/press-releases)
Looking Ahead

These are the first clinical data in history that have demonstrated significant and durable reduction of disease-causing proteins with a single-dose infusion of CRISPR genome editing therapy. This has implications for in vivo CRISPR therapies that are being developed for other diseases. Intellia is working to advance its pipeline to extend the benefits of this technology to broader patient populations. With these early clinical data, Intellia has opened a new era in medicine by showing the full potential of genome editing can be harnessed for human health.

More information about the data is available at www.intelliatx.com