UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): November 2, 2023

INTELLIA THERAPEUTICS, INC.
(Exact name of Registrant as Specified in Its Charter)

Delaware	**001-37766**	**36-4785571**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

40 Erie Street, Suite 130 **Cambridge, Massachusetts**	**02139**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's Telephone Number, Including Area Code: (857) 285-6200

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, par value $0.0001 per share	NTLA	The Nasdaq Global Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01. Regulation FD Disclosure.

On November 2, 2023, Intellia Therapeutics, Inc. ("Intellia") issued a press release titled "Intellia Presents New Interim Data from the Ongoing Phase 1 Study of NTLA-2001 at the 4th International ATTR Amyloidosis Meeting." A copy of the press release is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

Additionally, Intellia presented clinical data from its ongoing Phase 1 Study of NTLA-2001 at the 4th International ATTR Amyloidosis Meeting. The presentation materials are attached to this Current Report on Form 8-K as Exhibit 99.2.

The information under this Item 7.01, including Exhibits 99.1 and 99.2 hereto, are being furnished herewith and shall not be deemed "filed" for the purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall such information be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 8.01. Other Events.

Updated Interim Clinical Data of NTLA-2001

On November 2, 2023, Intellia presented additional interim results from its ongoing Phase 1 study of NTLA-2001, an investigational, *in vivo* CRISPR/Cas9 genome editing therapy in development as a single-dose treatment for transthyretin (ATTR) amyloidosis, at the 4th International ATTR Amyloidosis Meeting in Madrid, Spain. The data presented today, with a cutoff date of May 11, 2023, are from the initial 65 out of 72 patients dosed in the Phase 1 study, which has now completed enrollment. In the newly reported dose-expansion portion, administration of NTLA-2001 at the 55 mg and 80 mg dose led to deep serum TTR reductions consistent with the results previously reported from patients in the dose-escalation portion who received the corresponding weight-based dose, 0.7 mg/kg and 1.0 mg/kg, respectively.

Across all patients who received a dose of 0.3 mg/kg or higher (n=62), the median serum TTR reduction was 91% and the median absolute residual serum TTR concentration was 17 µg/mL at day 28. The reduction of serum TTR compared to baseline was sustained through the latest follow-up. With 29 patients now reaching at least 12 months of follow-up, all patients continued to show a long-lasting response with no evidence of loss in activity over time.

NTLA-2001 was generally well tolerated across all patients and at all dose levels tested. The most commonly reported adverse events were infusion-related reactions, which occurred in 38% of patients. The majority of adverse events, including infusion-related reactions, were Grade 1 or 2 in severity, transient and resolved spontaneously. Other adverse events that were reported in greater than 10% of patients included headache, diarrhea and back pain, and were all Grade 1 or 2. All patients received a full dose of NTLA-2001 and remain on study. No dose-limiting toxicities were observed. Based on the safety and activity of NTLA-2001, the 55mg dose has now been selected to be evaluated in the upcoming pivotal Phase 3 study.

Forward Looking Statements.

This Current Report on Form 8-K and certain of the materials furnished or filed herewith contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended. The words "may," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "estimate," "predict," "project," "potential," "continue," "target" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These forward-looking statements include, but are not limited to, express or implied statements regarding Intellia's beliefs and expectations regarding: the safety, efficacy and advancement of its clinical program for NTLA-2001 for the treatment of transthyretin ("ATTR") amyloidosis pursuant to its 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 its ability to initiate a global pivotal Phase 3 trial by year-end; its ability to generate data to demonstrate NTLA-2001 as a potential single-dose treatment for ATTR amyloidosis; its ability to maintain and expand its related intellectual property portfolio, and avoid or acquire rights to valid intellectual property of third parties; and the timing of regulatory filings and clinical trial execution, including enrollment and dosing of patients.

Any forward-looking statements in this press release 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 the initiation and conduct of a global pivotal Phase 3 study for NTLA-2001 for the treatment of ATTR-CM and that the results of such Phase 3 study may not be positive; risks related to Intellia's ability to protect and maintain its intellectual property position; risks related to the authorization, initiation and conduct of studies and other development requirements, including manufacturing, for NTLA-2001; the risk that any one or more of Intellia's product candidates, including NTLA-2001, will not be successfully developed and commercialized; the risk that the results of preclinical studies or clinical studies, including for NTLA-2001, will not be predictive

of future results in connection with future studies; and the risk that Intellia will not be able to demonstrate its platform's modularity and replicate or apply results achieved in preclinical studies to develop additional product candidates, including to apply its proprietary CRISPR/Cas9 technology platform successfully to additional product candidates. 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 press release is as of the date of the release, and Intellia undertakes no duty to update this information unless required by law.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Press Release, dated November 2, 2023.
99.2	Clinical Data Presentation at 4th International ATTR Amyloidosis Meeting on November 2, 2023.
104	104 Cover Page Interactive Data File (embedded within the Inline XBRL document).

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Intellia Therapeutics, Inc.

Date: November 2, 2023

By: /s/ John M. Leonard
Name: John M. Leonard
Title: Chief Executive Officer and President

PRESS RELEASE

Intellia Presents New Interim Data from the Ongoing Phase 1 Study of NTLA-2001 at the 4th International ATTR Amyloidosis Meeting

- *Updated data from over 60 patients showed consistent, deep and durable serum TTR reduction achieved with a single dose of NTLA-2001, including in 29 patients who have now reached 12 months or more of follow-up*
- *NTLA-2001 was generally well-tolerated across both polyneuropathy and cardiomyopathy arms at all dose levels tested*
- *55 mg dose of NTLA-2001 selected for further evaluation in the global pivotal Phase 3 trial expected to begin by year-end*

CAMBRIDGE, Mass., Nov. 2, 2023 – Intellia Therapeutics, Inc. (NASDAQ:NTLA), a leading clinical-stage genome editing company focused on developing potentially curative therapies leveraging CRISPR-based technologies, today presented additional interim results from its ongoing Phase 1 study of NTLA-2001, an investigational, *in vivo* CRISPR/Cas9 genome editing therapy in development as a single-dose treatment for transthyretin (ATTR) amyloidosis. Results were presented in an oral presentation at the 4th International ATTR Amyloidosis Meeting, held Nov. 2–3 in Madrid, Spain.

“With 65 patients reported from the Phase 1 study, this update represents the largest clinical dataset for an *in vivo* CRISPR-based investigational therapy. These positive interim results add to the growing body of data that demonstrates deep and durable reductions of serum TTR after a single dose of NTLA-2001. The consistent and profound levels of reduction in all patients bolster our confidence that NTLA-2001 could potentially reset the standard of care for ATTR amyloidosis — both for treating the disease and how response is evaluated,” said Intellia President and Chief Executive Officer John Leonard, M.D. “We have also observed early signals of clinical activity in the initial cohorts and look forward to presenting the first clinical data beyond serum TTR levels once we have longer follow-up across all cohorts.”

The Phase 1 trial is a two-part study evaluating NTLA-2001 in patients with either ATTR amyloidosis with cardiomyopathy (ATTR-CM) or hereditary ATTR amyloidosis with polyneuropathy (ATTRv-PN). The data presented today, with a cutoff date of May 11, 2023, are from the initial 65 out of 72 patients dosed in the Phase 1 study, which has now completed enrollment. The results from the final seven patients dosed, who were enrolled after the data cutoff, will be reported at a future date.

In the newly reported dose-expansion portion, administration of NTLA-2001 at the 55 mg and 80 mg dose led to deep serum TTR reductions consistent with the results previously reported from patients in the dose-escalation portion who received the corresponding weight-based dose, 0.7 mg/kg and 1.0 mg/kg, respectively.

Across all patients who received a dose of 0.3 mg/kg or higher (n=62), the median serum TTR reduction was 91% and the median absolute residual serum TTR concentration was 17 µg/mL at day 28. The persistently low levels of TTR concentration are expected to reduce the rate of ongoing amyloid formation and hold the possibility for amyloid clearance to reverse the symptoms of the disease. If clinically validated, the use of absolute residual TTR concentration levels could become a new benchmark for evaluating ATTR amyloidosis.

The reduction of serum TTR compared to baseline was sustained through the latest follow-up. With 29 patients now reaching at least 12 months of follow-up, all patients continued to show a long-lasting response with no evidence of loss in activity over time.

NTLA-2001 was generally well tolerated across all patients and at all dose levels tested. The most commonly reported adverse events were infusion-related reactions, which occurred in 38% of patients. The majority of adverse events, including infusion-related reactions, were Grade 1 or 2 in severity, transient and resolved spontaneously. Other adverse events that were reported in greater than 10% of patients included headache, diarrhea and back pain, and were all Grade 1 or 2. All patients received a full dose of NTLA-2001 and remain on study. No dose-limiting toxicities were observed. Based on the safety and activity of NTLA-2001, the 55mg dose has now been selected to be evaluated in the upcoming pivotal Phase 3 study.

These data support NTLA-2001's continued development as a potential one-time treatment to permanently inactivate the *TTR* gene and reduce the disease-causing protein in people living with ATTR amyloidosis. As previously announced, Intellia recently received IND clearance from the FDA to begin a Phase 3 trial of NTLA-2001 for ATTR-CM and expects to initiate the global pivotal trial by the end of this year. Additionally, the Company is actively preparing for a Phase 3 trial for ATTRv-PN.

About NTLA-2001

Based on Nobel Prize-winning CRISPR/Cas9 technology, NTLA-2001 could potentially be the first single-dose treatment for ATTR amyloidosis. NTLA-2001 is the first investigational CRISPR therapy candidate to be administered systemically, or through a vein, to edit genes inside the human body. Intellia's proprietary non-viral platform deploys lipid nanoparticles to deliver to the liver a two-part genome editing system: guide RNA specific to the disease-causing gene and messenger RNA that encodes the Cas9 enzyme, which carries out the precision editing. Robust preclinical and clinical data, showing deep and long-lasting transthyretin (TTR) reduction following *in vivo* inactivation of the target gene, supports NTLA-2001's potential as a single-administration therapeutic. Intellia leads development and commercialization of NTLA-2001 as part of a multi-target discovery, development and commercialization collaboration with Regeneron. The global Phase 1 trial is

an open-label, multi-center, two-part study of NTLA-2001 in adults with hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) or transthyretin amyloidosis with cardiomyopathy (ATTR-CM). The Phase 1 trial is now closed for enrollment. Visit clinicaltrials.gov (NCT04601051) for more details.

About Transthyretin (ATTR) Amyloidosis

Transthyretin amyloidosis, or ATTR amyloidosis, is a rare, progressive and fatal disease. Hereditary ATTR (ATTRv) amyloidosis occurs when a person is born with mutations in the *TTR* gene, which causes the liver to produce structurally abnormal transthyretin (TTR) protein with a propensity to misfold. These damaged proteins build up as amyloid in the body, causing serious complications in multiple tissues, including the heart, nerves and digestive system. ATTRv amyloidosis predominantly manifests as polyneuropathy (ATTRv-PN), which can lead to nerve damage, or cardiomyopathy (ATTRv-CM), which can lead to heart failure. Some individuals without the genetic mutation produce non-mutated, or wild-type TTR proteins that become unstable over time, misfolding and aggregating in disease-causing amyloid deposits. This condition, called wild-type ATTR (ATTRwt) amyloidosis, primarily affects the heart. There are an estimated 50,000 people worldwide living with ATTRv amyloidosis and between 200,000 and 500,000 people with ATTRwt amyloidosis.

About Intellia Therapeutics

Intellia Therapeutics, a leading clinical-stage genome editing company, is developing novel, potentially curative therapeutics leveraging CRISPR-based technologies. To fully realize the transformative potential of CRISPR-based technologies, Intellia is pursuing two primary approaches. The company's *in vivo* programs use intravenously administered CRISPR as the therapy, in which proprietary delivery technology enables highly precise editing of disease-causing genes directly within specific target tissues. Intellia's *ex vivo* programs use CRISPR to create the therapy by using engineered human cells to treat cancer and autoimmune diseases. Intellia's deep scientific, technical and clinical development experience, along with its robust intellectual property portfolio, have enabled the company to take a leadership role in harnessing the full potential of genome editing to create new classes of genetic medicine. Learn more at intelliatx.com. Follow us on X (formerly known as Twitter) @intelliatx.

Forward-Looking Statements

This press release contains "forward-looking statements" of Intellia Therapeutics, Inc. ("Intellia" or the "Company") within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements include, but are not limited to, express or implied statements regarding Intellia's beliefs and expectations regarding: the safety, efficacy and advancement of its clinical program for NTLA-2001 for the treatment of transthyretin ("ATTR") amyloidosis pursuant to its 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 its ability to initiate a global pivotal Phase 3 trial by year-end; its ability to generate data to demonstrate NTLA-2001 as a potential single-dose treatment for ATTR amyloidosis to permanently inactivate the *TTR* gene and reduce the disease-causing protein in people living with ATTR amyloidosis; its beliefs concerning observed early signals of clinical activity in the initial cohorts; its

belief that NTLA-2001 may reduce the rate of ongoing amyloid formation, reverse the symptoms of ATTR amyloidosis, including possible amyloid clearance, and reset the standard of care for ATTR amyloidosis; its belief that the use of absolute residual TTR concentration levels could become a new benchmark for evaluating ATTR amyloidosis, if clinically validated; its ability to develop its modular platform and full-spectrum approach to advance its complex genome editing capabilities, including to apply its proprietary CRISPR/Cas9 technology platform to additional product candidates; its ability to maintain and expand its related intellectual property portfolio, and avoid or acquire rights to valid intellectual property of third parties; its ability to demonstrate its platform's modularity and replicate or apply results achieved in preclinical studies and clinical studies, including those in its NTLA-2001 program, in any future studies, including human clinical trials; and the timing of regulatory filings and clinical trial execution, including enrollment and dosing of patients.

Any forward-looking statements in this press release 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 the initiation and conduct of a global pivotal Phase 3 study for NTLA-2001 for the treatment of ATTR-CM and that the results of such Phase 3 study may not be positive; risks related to Intellia's ability to protect and maintain its intellectual property position; risks related to the authorization, initiation and conduct of studies and other development requirements, including manufacturing, for NTLA-2001; the risk that any one or more of Intellia's product candidates, including NTLA-2001, will not be successfully developed and commercialized; the risk that the results of preclinical studies or clinical studies, including for NTLA-2001, will not be predictive of future results in connection with future studies; and the risk that Intellia will not be able to demonstrate its platform's modularity and replicate or apply results achieved in preclinical studies to develop additional product candidates, including to apply its proprietary CRISPR/Cas9 technology platform successfully to additional product candidates. 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 press release 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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# # #

4TH INTERNATIONAL ATTR Amyloidosis meeting for patients and doctors

November 2-3, 2023 • MADRID

AMYLOIDOSIS ALLIANCE
THE VOICE OF PATIENTS

Hospital Universitario Puerta de Hierro Majadahonda

Enabling the development of serum [TTR] as a biomarker for treatment of ATTR amyloidosis

Julian D. Gillmore

National Amyloidosis Centre, Division of Medicine, University College London
on behalf of:

Jörg Täubel,[2] Ed Gane,[3] Björn Pilebro,[4] Michael L. Maitland,[5] Ricardo Rocha,[5] Joy Olbertz,[5] Adia Leung,[5] Derek Smith,[5] Michael D. Pickard,[5] Carri Boiselle,[5] Yuanxin Xu,[5] Peijuan Zhu,[5] David Gutstein,[6] Liron Walsh,[5] David Adams[7]

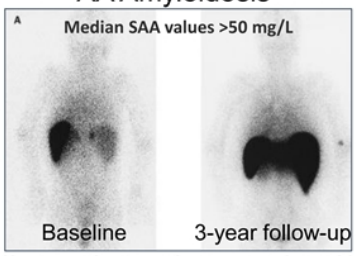
[2]Richmond Pharmacology, St. George's University of London, London, UK
[3]New Zealand Clinical Research, Auckland, New Zealand
[4]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden
[5]Intellia Therapeutics, Cambridge, MA, USA
[6]Regeneron Pharmaceuticals, Tarrytown, NY, USA
[7]Department of Neurology, CHU Bicetre, University Paris Saclay, AP-HP, Le Ktremin-Bicetre, France

Disclosures

- Adviser for Alnylam, AstraZeneca, Attralus, BridgeBio, Ionis, Pfizer, and Intellia

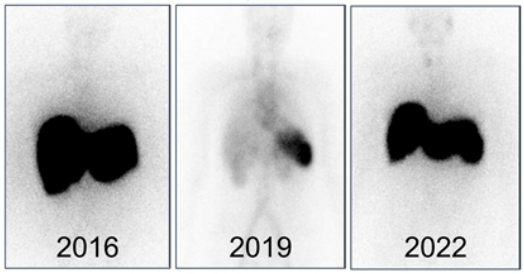
Treatment outcomes in systemic amyloidosis associate with the residual concentration of the amyloid precursor protein[1,2]

AA Amyloidosis[1]



Unresponsive to methotrexate and steroids

AL Amyloidosis[a]



Hematologic response Hematologic relapse

- More amyloid = worse outcomes
  Less amyloid = better outcomes
- "Natural" clearance of *in vivo* amyloid deposits occurs slowly
- Clearance of amyloid occurs at different rates in different organs
  Liver vs heart
- The rate of amyloid clearance varies between individuals
  A 75% reduction in fibril precursor protein concentrations may be sufficient to permit amyloid regression in one patient but may result in amyloid accumulation in another

Reprinted from *The Lancet*, Gillmore JD, et al, volume 358, Amyloid load and clinical outcome in AA amyloidosis in relation to circulating concentration of serum amyloid A protein, pages 24-29, copyright 2001, with permission from Elsevier.

AA, amyloid A; AL, amyloid light chain; SAA, serum amyloid A.

1. Gillmore JD, et al. *Lancet.* 2001;358(9275):24-29.
2. Lachmann HJ, et al. *Br J Haematol.* 2003;122(1):78-84.

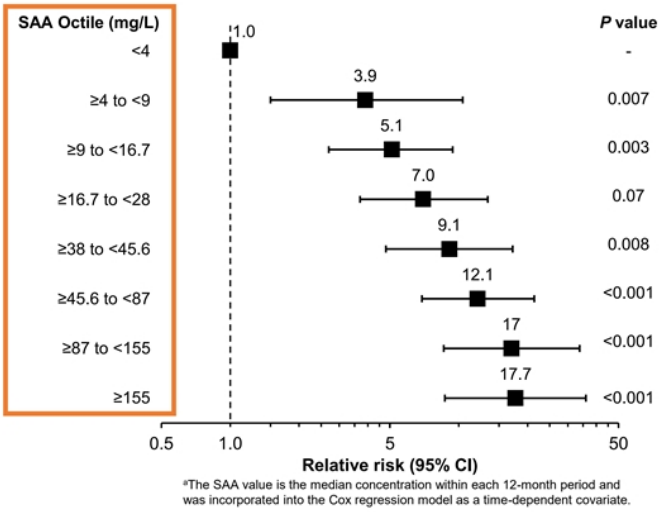
[a]Unpublished.

Our community has incorporated this information to advance therapy in AA and AL amyloidosis

Specific concentration thresholds inform outcomes

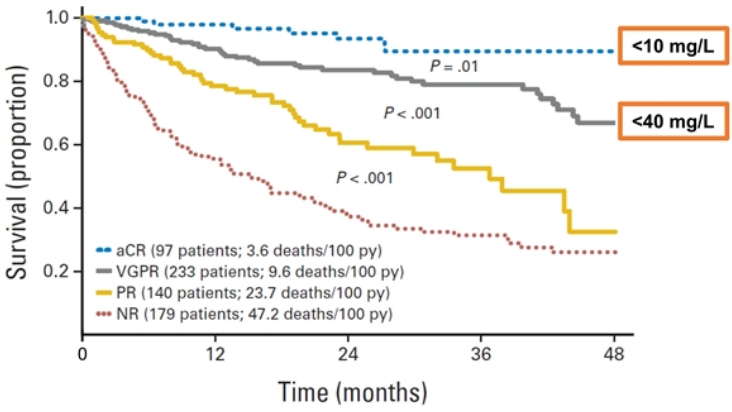
AA amyloidosis[1]

Unadjusted relative risk of death associated with the most recent median annual SAA concentration during follow-up[a]



[a]The SAA value is the median concentration within each 12-month period and was incorporated into the Cox regression model as a time-dependent covariate.

AL amyloidosis[2]



1. Lachmann HJ, et al. *N Engl J Med.* 2007;356(23):2361-2371.
2. Palladini G, et al. *J Clin Oncol.* 2012;30(36):4541-4549.

From Palladini G, et al, New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes, *Journal of Clinical Oncology*, volume 30, issue 36, pages 4541-4549, DOI: 10.1200/JCO.2011.37.7614, with permission from Wolters Kluwer Health.

AA, amyloid A; aCR, amyloidosis complete response; AL, amyloid light chain; CI, confidence interval; NR, no response; PR, partial response; py, person years;SAA, serum amyloid A; VGPR, very good partial response.

There is an equilibrium between circulating amyloid fibril precursor protein concentration and change in amyloid burden

Precursor protein

Amyloid clearance

Amyloid formation

Amyloid

Reduce supply of amyloid precursor protein

- **Chemotherapy in AL**
- **Anti-inflammatory therapy in AA**
- **Gene "silencers" and gene editing in ATTR**

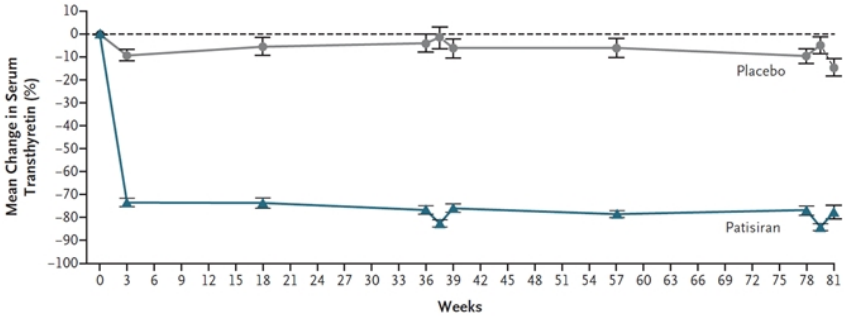
Stabilise amyloid-forming proteins
- β sheet breakers

Reduce supply of amyloid precursor protein
- Immunotherapy
- SAP depletion

AA, amyloid A; AL, amyloid light chain; ATTR, transthyretin amyloidosis; SAP, serum amyloid P component.

Percent reduction in serum [TTR] is associated with clinical benefit in ATTR amyloidosis

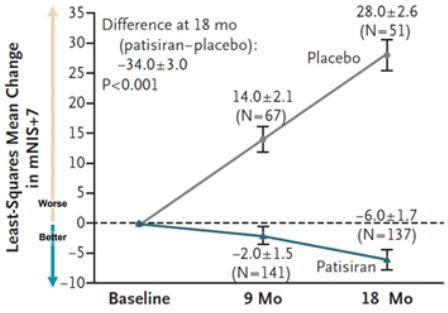
Pharmacodynamics: % change in serum TTR over 18 months[1]



Median reduction in serum TTR in the patisiran group was 81% (range, -38% to 95%) and was similar across age, sex, or genotype[1]

In a post hoc analysis of the cardiac subpopulation (n=126), there was **an approximate 45% reduction** in the **composite rate of cardiac hospitalization and all-cause mortality**[2]

Primary endpoint: mNIS+7 neuropathy score[1]



56% vs 4%
of patisiran- and placebo-treated patients, respectively, experienced a **halting or reversal of disease progression** (change <0 point mNIS+7)[1]

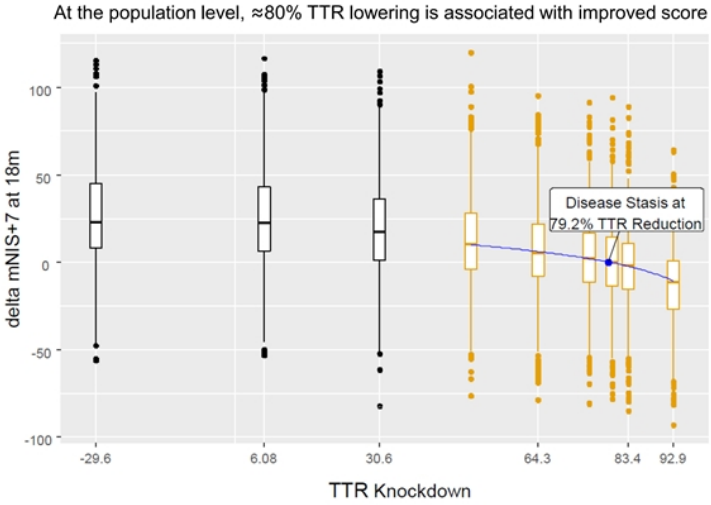
1. Adams D, et al. *N Engl J Med*. 2018;379(1):11-21.
2. Solomon SD, et al. *Circulation*. 2019;139(4):431-443.

Graphs from *The New England Journal of Medicine*, Adams D, et al, Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis, volume 379, pages 11-21, copyright 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

ATTR, transthyretin amyloidosis; mNIS+7, modified neuropathy impairment score +7; TTR, transthyretin.

Serum [TTR] is typically expressed as % reduction from baseline – should we be using residual absolute serum [TTR] instead?

% serum TTR reduction vs ΔmNIS+7 by nonile in APOLLO A



Polydefkis M, et al. Presented at ISA. Mar 26-29, 2018; Kumamoto, Japan. Graph used with permissions from first author.

Same % serum TTR reduction can mean different risk for ongoing fibril formation

	80% knockdown	
	Patient 1	Patient 2
Predose [TTR] (μg/mL)	350	150
Postdose [TTR] (μg/mL)	70	30

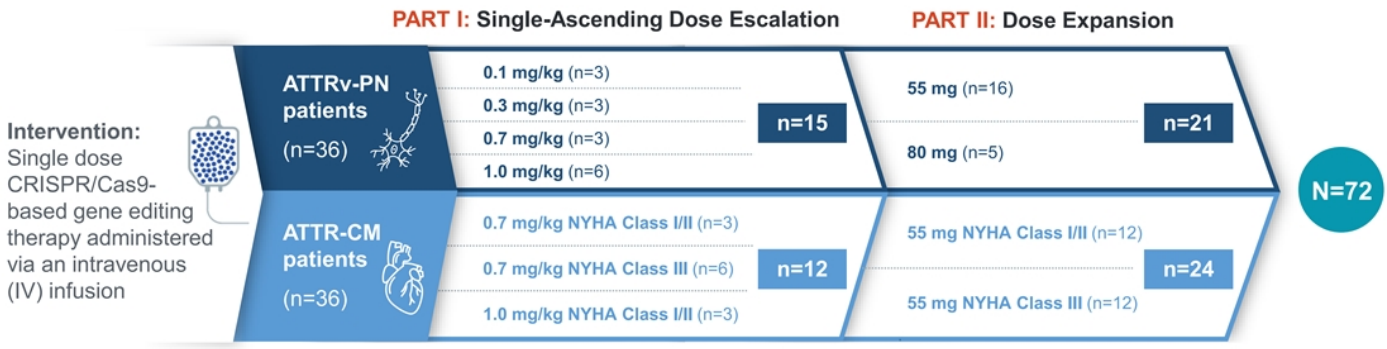
Both represent 80% knockdown, but >2× available substrate for ongoing amyloid formation in Patient 1 post-treatment

Should we be using residual absolute serum [TTR] instead?

ΔmNIS+7, change in modified neuropathy impairment score +7; TTR, transthyretin.

The NTLA-2001 phase 1 study in ATTR amyloidosis has completed enrollment (N=72)

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



PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK, and PD

- *Measure serum TTR levels*

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of:

- *Neurologic function in patients with ATTRv-PN*
- *Cardiac disease in patients with ATTR-CM*

Clinicaltrials.gov ID: NCT0460105.

4TH INTERNATIONAL ATTR Amyloidosis meeting

ATTR, transthyretin amyloidosis; Cas, CRISPR-associated protein; CRISPR, clustered regularly interspaced short palindromic repeats; NYHA, New York Heart Association; PD, pharmacodynamics; PK, pharmacokinetics.

AMYLOIDOSIS ALLIANCE

Patient demographics and characteristics

Characteristic		PN Patients (N=36)	CM Patients (N=29)	All Patients (N=65)
Age, years	Median (min, max)	61 (19, 75)	78 (46, 86)	68 (19, 86)
Sex, n (%)	Male	26 (72)	28 (97)	54 (83)
Weight, kg	Median (min, max)	77 (55, 117)	82 (63, 115)	81 (55, 117)
***TTR* genotype, n (%)**	p.V50M	11 (31)	0	11 (17)
	p.V142I	1 (3)	6 (21)	7 (11)
	p.T80A	7 (19)	1 (3)	8 (12)
	p.S97Y	7 (19)	0	7 (11)
	p.E62D	4 (11)	0	4 (6)
	Other	6 (17)	2 (7)	8 (12)
	WT	0	20 (69)	20 (31)
NYHA Class, n (%)	No diagnosis of heart failure	12 (33)	0	12 (18)
	I	19 (53)	3 (10)	22 (34)
	II	5 (14)	14 (48)	19 (29)
	III	0	12 (41)	12 (18)
NT-proBNP, ng/L	Median (min, max)	127 (<50, 1878)	1845 (851, 19,624)	757 (<50, 19,624)

Data cutoff May 11, 2023.
Interim data presented are for the first 65 (dosed and reached at least 28 days post-infusion by the data cutoff) of 72 patients dosed. Results from the final 7 patients will be reported at a future date. CM, cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PN, polyneuropathy; TTR, transthyretin.

Most frequent treatment emergent adverse events

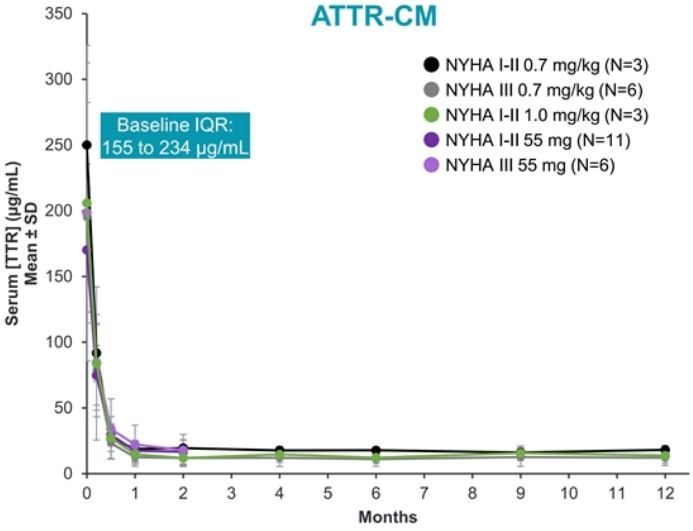
TEAEs by Maximum Toxicity Grade and Preferred Term Reported in >5% of All ATTRv-PN and ATTR-CM Patients (N=65)

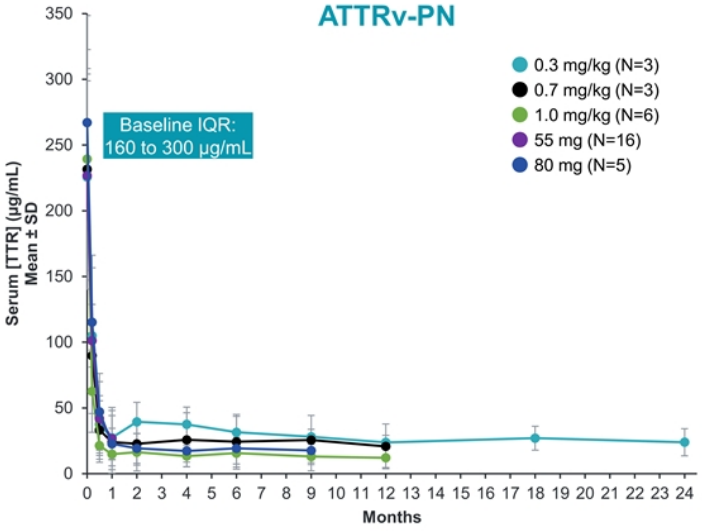
AE, Preferred Term, n (%)	Any Grade	Grade 1	Grade 2	Grade ≥3
Infusion-related reaction	25 (38)	10 (15)	14 (22)	1 (2)
Headache	12 (18)	12 (18)		
Diarrhea	11 (17)	10 (15)	1 (2)	
Back pain	7 (11)	7 (11)		
COVID-19 infection	6 (9)	5 (8)	1 (2)	
Cardiac failure	6 (9)	2 (3)	2 (3)	2 (3)
Upper respiratory tract 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 (e.g., atrial flutter and cardiac failure hospitalizations)
- Infusion-related reactions were most common; nearly all were considered mild and 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; CM, cardiomyopathy; PN, polyneuropathy; TEAE, treatment-emergent adverse event.

Regardless of baseline TTR levels, NTLA-2001 led to consistently low and sustained absolute serum [TTR] in all patients





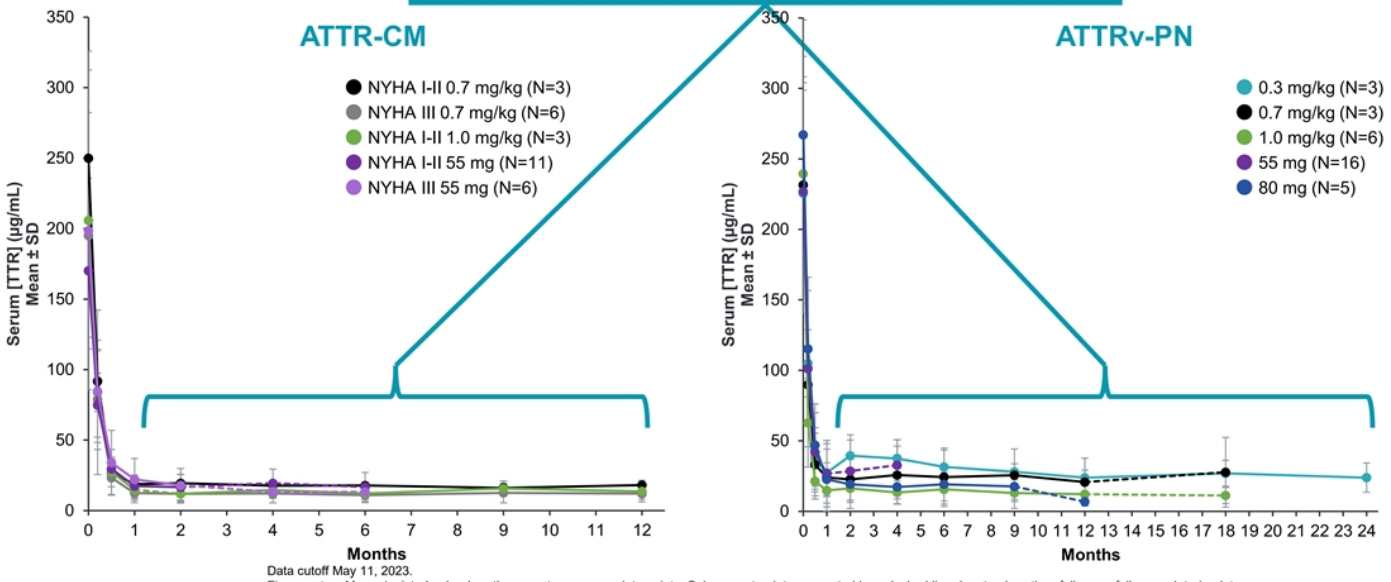
Median (IQR) Serum [TTR] at Day 28 (n=62)	Residual absolute TTR concentration at day 28	17 µg/mL (11 to 24)
	% Change from baseline in serum TTR at day 28	-91% (-88 to -94)

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. 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.

Regardless of baseline TTR levels, NTLA-2001 led to consistently low and sustained absolute serum [TTR] in all patients

The median (IQR) maximum change from day 28 onward (measure of fluctuations) = -1.4 µg/mL (-4.7 to 1.7)



Data cutoff May 11, 2023.

Figure notes: Mean depicted only when there are two or more data points. Subsequent points connected by a dashed line denotes less than full group follow-up. 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.

Summary

- In other systemic amyloidoses, the residual, absolute concentration of the amyloid precursor protein is closely associated with clinical outcomes
- Interim data from 62 patients with ATTR amyloidosis treated with NTLA-2001 continue to show a favorable safety and tolerability profile, with rapid, consistent, and durable reductions of serum [TTR] to low levels in all patients
- For treatments that reduce total serum [TTR], with nonfluctuating steady state measures, the residual absolute serum [TTR] could be a robust biomarker of ATTR amyloidosis therapy outcomes
- With collaboration, this approach to biomarker development has facilitated progress in care and better outcomes in AA and AL amyloidosis

AA, amyloid A; AL, amyloid light chain; ATTR, transthyretin amyloidosis; TTR, transthyretin.

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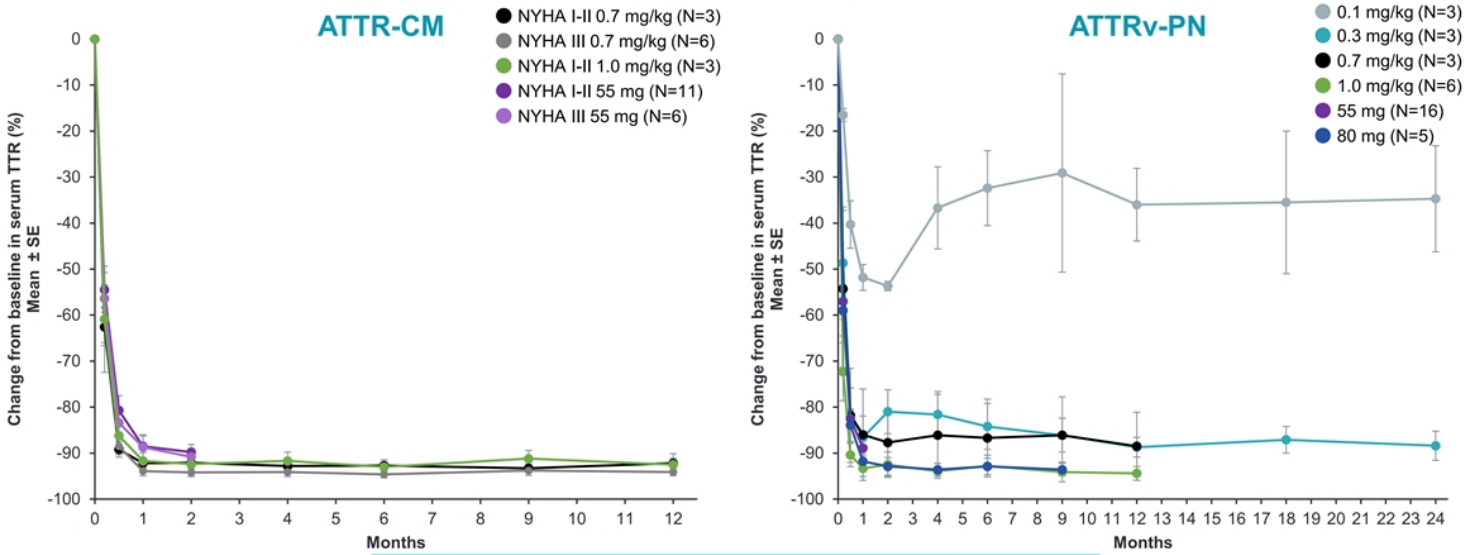
Appendix

Dose-responsive rapid and deep serum TTR reduction sustained across all patients



% Change from baseline in serum TTR at Day 28 (n=62, excludes the 0.1 mg/kg cohort)	
Mean (SE) serum [TTR]	-90% (0.86)
Median (IQR) serum [TTR]	-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.

ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv-PN, hereditary transthyretin amyloidosis with polyneuropathy; NYHA, New York Heart Association; SE, standard error; TTR, transthyretin.