Intellia Announces First Clinical Evidence from Ongoing Phase 1 Study that Nexiguran Ziclumeran (nex-z), an In Vivo CRISPR/Cas9-Based Gene Editing Therapy, May Favorably Impact Disease Progression in Transthyretin (ATTR) Amyloidosis

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- *Consistently rapid, deep and durable reduction in serum TTR accompanied by evidence of disease stabilization or improvement after a one-time treatment of nex-z, supporting the hypothesis that greater TTR reduction may lead to a greater clinical benefit in ATTR amyloidosis*
- *Favorable trends consistently observed across multiple markers of cardiac disease progression at month 12 compared to baseline in an ATTR-CM population with a high proportion of advanced heart failure patients*
- *Consistent trend observed to date in ATTRv-PN arm, with stability or improvement of neuropathy as measured by multiple clinical measures of disease progression compared to baseline*
- *Persistently deep levels of serum TTR reductions following a single infusion remain virtually unchanged after two or more years of follow-up in over 25 patients*
- *Favorable safety and tolerability profile observed*
- *ATTR-CM data presented at the 2024 AHA Scientific Sessions and published in the* New England Journal of Medicine
- *Intellia to host investor webcast today, November 16 at 11:00 a.m. CT / 12:00 p.m. ET*

CAMBRIDGE, Mass., Nov. 16, 2024 (GLOBE NEWSWIRE) -- Intellia Therapeutics, Inc. (NASDAQ:NTLA), a leading clinical-stage gene editing company focused on revolutionizing medicine with CRISPR-based therapies, today announced positive new clinical data from the ongoing Phase 1 trial of nexiguran ziclumeran (nex-z, also known as NTLA-2001) in patients with transthyretin (ATTR) amyloidosis. Nex-z is an investigational *in vivo* CRISPR-based gene editing therapy in development as a one-time treatment for ATTR amyloidosis. Development and commercialization of nex-z is led by Intellia as part of a multi-target collaboration with Regeneron.

The Phase 1 trial is an open-label, two-part study evaluating the safety and activity of nex-z in patients with either ATTR amyloidosis with cardiomyopathy (ATTR-CM) or hereditary ATTR amyloidosis with polyneuropathy (ATTRv-PN). New results from the Phase 1 study were as of the data cut-off date of August 21, 2024. The data from the ATTR-CM arm of the Phase 1 study were presented in a late-breaking oral presentation at the 2024 American Heart Association (AHA) Scientific Sessions in Chicago, Illinois, and published online in the *New England Journal of Medicine*.

“The Phase 1 data presented today offer compelling evidence that deep and persistently low levels of TTR reduction achieved with nex-z, an investigational *in vivo* CRISPR-based gene editing therapy, may favorably impact disease progression for people living with ATTR amyloidosis,” said Intellia President and Chief Executive Officer John Leonard, M.D. “The stability or improvement observed after a single dose of nex-z in multiple markers of cardiac disease progression is remarkable, especially considering the high proportion of patients with cardiomyopathy who had advanced heart failure. We observed similarly positive and consistent trends, indicative of a disease-modifying effect, in patients with hereditary ATTR amyloidosis with polyneuropathy. These results from the ongoing Phase 1 study increase our belief in the likelihood of success of our active Phase 3 studies based on our hypothesis that greater TTR reduction may lead to greater clinical benefit.”

ATTR-CM Arm Results

- **Rapid, Deep and Durable Serum TTR Reduction:** Across all patients (n=36), a single dose of nex-z led to consistently rapid, deep and sustained serum TTR reduction, regardless of baseline levels, through the latest follow-up. At month 12, the mean serum TTR reduction was 90%, and the mean absolute residual serum TTR concentration was 17 µg/mL. With 11 patients who have reached 24 months of follow-up, all patients continued to show a sustained response with no evidence of a waning effect over time. The consistently low levels of serum TTR are anticipated to reduce the rate of ongoing amyloid formation and potentially allow for amyloid clearance and improvement in cardiac function.

- **Evidence of Disease Modification Across Multiple Markers of Cardiac Disease Progression:** In newly reported data of multiple markers of disease progression, patients treated with nex-z showed evidence of disease stabilization or improvement at month 12 compared to baseline. This evidence was observed despite the high proportion of patients enrolled with advanced or severe disease, as indicated by 50% classified as New York Heart Association (NYHA) Class III, 31% variant ATTR-CM, as well as elevated baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) and poor functional status. Evaluation of individual disease markers at 12 months showed stability or improvement in NT-proBNP, high sensitivity Troponin T (hs-Troponin T) and 6-minute walk test (6MWT) in 81%, 94% and 77% of patients, respectively; 66% showed stability or improvement across all three markers examined. There also was evidence of benefit in quality of life, based on the Kansas City Cardiomyopathy Questionnaire (KCCQ). Notably, 92% of patients were stable or improved in their NYHA functional classification. All patients with NYHA Class III at baseline (n=18) showed improvement or no change in their NYHA Class at month 12. The month 12 cardiac disease marker results are detailed in the table below.

Consistent with the cardiac disease marker data, assessment of cardiac structure with either echocardiography or MRI, as well as measurements of cardiopulmonary exercise testing also showed a similar pattern of stability at month 12. The hospitalization rate for cardiovascular events among the 36 patients with ATTR-CM was 0.16/patient/year (95% CI: 0.08 to 0.36).

Biomarker of Cardiac Disease	Change from Baseline at Month 12
NT-proBNP, geometric mean fold change (95% CI) (n=36)	1.02 (0.88, 1.17)
hs-Troponin T, geometric mean fold change (95% CI) (n=36)	0.95 (0.89, 1.01)
6MWT, median (Q1, Q3) (n=35)	+5 meters (-33, 49)
KCCQ, median (Q1, Q3) (n=36)	+8 points (-0.5 to 15)

- **Safety:** Nex-z was generally well tolerated across all patients. The most commonly reported treatment-related adverse events were infusion-related reactions (IRRs), which were predominantly mild and moderate in severity, and did not result in any discontinuations.

ATTRv-PN Arm Results

- **Rapid, Deep and Durable Serum TTR Reduction:** Across patients who received a dose of 0.3 mg/kg or higher (n=33), the mean serum TTR reduction was 91% and the mean absolute residual serum TTR concentration was 20 µg/mL at month 12. With 16 patients who have reached 24 months of follow-up, all patients continued to show a sustained response with no evidence of a waning effect over time. It is anticipated that greater TTR reduction may lead to a greater clinical benefit in patients with ATTRv-PN.
- **Evidence of Disease Modification on Clinical Measures:** Favorable trends indicating stability or improvement were observed in patients with ATTRv-PN based on evaluation of multiple clinical measures, including Neuropathy Impairment Score (NIS), modified Neuropathy Impairment Score (mNIS+7) and modified BMI (mBMI). The clinical measure results are detailed in the table below.

Clinical Measures	Change from Baseline at Month 12	Change from Baseline at Month 24
Part 1: Dose-escalation portion (n=15)		
NIS, mean (SD)	-1.9* (5.42)	-4.5 (7.40)
mBMI, mean (SD)	28.2 (93.07)	54.7 (84.58)
Part 2: Dose-expansion portion (n=21)		
mNIS+7, mean (SD)	-0.6† (11.07)	N/A
mBMI, mean (SD)	2.4‡ (94.18)	N/A

*n=14, †n=19, ‡n=20, N/A: Data for this time point is not yet available for the full cohort and will be reported in the future.

- **Safety:** Nex-z was generally well tolerated across all patients and at all dose levels tested. The most commonly reported treatment-related adverse events were IRRs, which were mild or moderate, and did not result in any discontinuations.

Intellia Therapeutics Investor Webcast Information
Intellia will host a live webcast, today, November 16, 2024, at 11:00 a.m. CT / 12:00 p.m. ET to discuss the nex-z Phase 1 data. Joining the Intellia management team will be Marianna Fontana, M.D., Ph.D., Professor of Cardiology and Honorary Consultant Cardiologist, University College London Centre for Amyloidosis, London, UK.

To join the webcast, please visit this link, or the Events and Presentations page of the Investors & Media section of the company's website at www.intelliatx.com. A replay of the webcast will be available on Intellia's website for at least 30 days following the call.

About the MAGNITUDE Study
The pivotal Phase 3 MAGNITUDE clinical trial is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of nex-z in approximately 765 patients with transthyretin amyloidosis with cardiomyopathy (ATTR-CM). The primary endpoint of the study is a composite endpoint of cardiovascular (CV)-related mortality and CV-related events. Adult patients with hereditary or wild type ATTR-CM will be randomized 2:1 to receive a single 55 mg infusion of nex-z or placebo. For more information on MAGNITUDE (NCT06128629), please visit clinicaltrials.gov.

About the MAGNITUDE-2 Study
MAGNITUDE-2 is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of nex-z in 50 adults with ATTRv-PN. Patients will be randomized 1:1 to receive a single 55 mg infusion of nex-z or placebo. Patients randomized to the placebo arm will be eligible for optional crossover to receive nex-z. The primary endpoints are the change from baseline in modified Neuropathy Impairment Score +7 (mNIS+7) at month 18 and serum TTR at day 29. For more information on MAGNITUDE-2 (NCT06672237), please visit clinicaltrials.gov.

About nexiguran ziclumeran (nex-z, also known as NTLA-2001)
Based on Nobel Prize-winning CRISPR/Cas9 gene editing technology, nex-z has the potential to become the first one-time treatment for transthyretin (ATTR) amyloidosis. Nex-z is designed to inactivate the *TTR* gene that encodes for the transthyretin (TTR) protein. Interim Phase 1 clinical data showed the administration of nex-z led to consistent, deep and long-lasting TTR reduction. Intellia leads development and commercialization of nex-z as part of a multi-target discovery, development and commercialization collaboration with Regeneron.

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. There is no known cure for ATTR amyloidosis and currently available medications are limited to slowing accumulation of misfolded TTR protein.

About Intellia Therapeutics
Intellia Therapeutics, Inc. (NASDAQ:NTLA) is a leading clinical-stage gene editing company focused on revolutionizing medicine with CRISPR-based therapies. The company's *in vivo* programs use CRISPR to enable precise editing of disease-causing genes directly inside the human body. Intellia's *ex vivo* programs use CRISPR to engineer human cells outside the body for the treatment of cancer and autoimmune diseases. Intellia's deep scientific, technical and clinical development experience, along with its people, is helping set the standard for a new class of medicine. To harness the full potential of gene editing, Intellia continues to expand the capabilities of its CRISPR-based platform with novel editing and delivery technologies. Learn more at intelliatx.com and follow us @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, success and advancement of its clinical programs for nexiguran ziclumeran or "nex-z" (f/k/a NTLA-2001), for transthyretin ("ATTR") amyloidosis, including the ability to successfully complete our global Phase 3 MAGNITUDE study for ATTR amyloidosis with cardiomyopathy ("ATTR-CM"), to initiate and complete our global Phase 3 MAGNITUDE-2 study for hereditary ATTR amyloidosis with polyneuropathy ("ATTRv-PN") pursuant to our clinical trial applications and investigational new drug submissions; its belief in the success of its MAGNITUDE and MAGNITUDE-2 studies, and its belief that greater TTR reduction may lead to greater clinical benefit.

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 Intellia's ability to protect and maintain its intellectual property position; risks related to valid third party intellectual property; risks related to Intellia's relationship with third parties, including its licensors and licensees; risks related to the ability of its 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, including nex-z; 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, including our ability to initiate or enroll the Phase 3 MAGNITUDE study for ATTR-CM or Phase 3 MAGNITUDE-2 study for ATTRv-PN; the risk that any one or more of Intellia's product candidates, including nex-z, will not be successfully developed and commercialized; the risk that the results of preclinical studies or clinical studies will not be predictive of future results in connection with future studies for the same product candidate or Intellia's other product candidates; and risks related to Intellia's reliance on collaborations, including that its collaboration with Regeneron 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 form 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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