Phase 3 Trials of Intellia's Nex-z CRISPR Therapy Resume after the Clinical Holds are Lifted

Intellia Therapeutics recently announced that the U.S. Food and Drug Administration (FDA) has lifted the hold on its clinical trial for the investigational CRISPR-based gene-editing therapy, nexiguran ziclumeran, also known as nex-z or NTLA-2001.

The four-month hold was implemented after a patient in the MAGNITUDE study experienced severe liver toxicity, specifically elevated liver transaminases and increased total bilirubin, in a patient who had received a dose of nex-z. The patient died following hospitalization, which Intellia attributes to complicating comorbidities and not just the therapy. A hold was also placed on the related MAGNITUDE-2 Phase 3 trial, which was lifted in late January.

The MAGNITUDE study is testing a research medicine to help people with transthyretin amyloidosis, also called ATTR, a rapidly progressive and ultimately fatal disease caused by misfolded transthyretin proteins. Specifically, MAGNITUDE is designed for ATTR-CM, a heart-related form of transthyretin amyloidosis, while MAGNITUDE-2 is for hereditary transthyretin amyloidosis (ATTRv-PN) with polyneuropathy, a nerve-related form. Both are multinational, double-blind, placebo-controlled trials with treatment consisting of a single 55mg intravenous infusion of nex-z or placebo. Patients between the ages of 18 and 90 are eligible for the MAGNITUDE study if they've been diagnosed with heart failure due to ATTR and have experienced it in the past year; women are eligible if they can no longer have children.

At the time of the hold, over 650 patients were enrolled in MAGNITUDE and 47 in MAGNITUDE-2, with over 450 of these patients estimated to have already been dosed with nex-z. The FDA's lifting of the hold on the MAGNITUDE trials comes after Intellia agreed to

several safety measures, including enhanced monitoring of liver laboratory tests; guidance on short-term steroid treatment if liver enzymes are elevated shortly after dosing; and exclusion of patients with certain liver issues, and those with a recent history of cardiovascular instability.

“We are very pleased to have aligned with the FDA on the path forward for our Magnitude clinical trial, with measures designed to further enhance patient safety and allow us to continue to investigate nex-z in a broad ATTR-CM population,” Intellia President and CEO John Leonard, M.D., said in the press release.

Following the lifts, Leonard states that Intellia, in partnership with Regeneron, is now focused on completing enrollment in both ongoing trials.

Analysts from Evercore ISI say the safety adjustments are modest and that the hold was lifted relatively quickly, likely causing little disruption to the clinical timeline. The regulatory developments are significant given nex-z's potential to provide a one-time treatment for such a devastating disease.

Transthyretin amyloidosis (ATTR): a progressive and often fatal disease

Transthyretin amyloidosis (ATTR) is caused by misfolded transthyretin proteins. As these proteins break down into amyloid fibrils and accumulate in organs, they can cause irreversible damage and lead to premature death. When amyloid deposits amass in the heart, the walls can become stiff and cause cardiomyopathy, a condition that makes it difficult for the heart to pump blood. As the disease progresses, eventually the heart is unable to adequately do its job and heart failure occurs.

Patients with Transthyretin amyloidosis (ATTR) have a median survival rate of two to six years after diagnosis. Unfortunately, most patients remain undiagnosed and untreated while experiencing symptoms that mimic other conditions, like heart failure caused by high blood pressure, hypertension, or hypertrophic cardiomyopathy. Other symptoms can include shortness of breath even while resting or with little exertion, lower extremity swelling, increased heart rate, abnormal heart rhythms, confusion or difficulty thinking, carpal tunnel syndrome and pain and numbness in the hands and feet, known as peripheral neuropathy.

However, ATTR does not affect all patients in the same way, and the disease can be put into two major categories: hereditary ATTR-CM (hATTR), which affects approximately 50,000 people worldwide, and wild-type ATTR-CM (wtATTR), which affects approximately 200,000 to 300,000 people worldwide. In hereditary ATTR-CM, a mutation in the transthyretin gene can cause amyloid deposits in the heart, nerves, and potentially other organs. Symptoms usually appear later in life but can start as early as 30. Wild-type ATTR-CM occurs without a transthyretin gene mutation and does not run in families, typically presenting much later in life.

Given the progressive and often fatal nature of ATTR, nex-z aims to address the disease by targeting the root cause: production of the transthyretin protein.

Nexiguran ziclumeran — nex-z: a one-time treatment

Nexiguran ziclumeran (formerly known as NTLA-2001 and now known as nex-z) is an investigational in vivo CRISPR-Cas9-based gene-editing therapy. The drug is designed to help those with ATTR, in which misfolded TTR proteins form amyloid deposits that damage organs — primarily the heart or peripheral nerves. Nex-z uses a lipid nanoparticle platform to deliver CRISPR components that inactivate the *TTR* gene in the liver, permanently reducing transthyretin (TTR) protein production. The therapy is designed to be a one-time treatment for ATTR-CM and ATTRv-PN and has positive Phase 1 data showing durable TTR reductions of 89-90% maintained at 24 months, as well as stable and improved cardiac biomarkers, and a manageable safety profile.

However, like many gene therapies that act in the liver, nex-z is not the first gene therapy to struggle with liver toxicity concerns. Other pharmaceutical companies that use adeno-associated viruses (AAVs) as vectors rather than lipid nanoparticles have experienced similar issues; for example, uniQure reported in a February press release that two patients receiving an investigational AAV gene therapy for Fabry disease experienced elevations in liver enzymes. Following protocol, the company has halted dosing in the mid- and high-dose groups during further assessment. Both affected patients responded to corticosteroid treatment. Additionally, last year, the FDA limited the label of Sarepta Therapeutics AAV gene therapy, Elevidys, for patients with Duchenne muscular dystrophy (DMD), following three liver-related patient deaths.

While safety remains a central focus for gene therapies, the new safety measures allow the clinical trials of nex-z to continue, and it could potentially enter a rapidly growing competitive field of approved ATTR treatments.

From stabilizers to silencers: the competitive landscape in treating ATTR

The existing landscape for approved ATTR treatments focuses on TTR stabilizers to prevent misfolding or silencers to reduce TTR production. However, both these avenues require ongoing dosing, positioning nex-z's single-dose approach as a breakthrough, should the Phase 3 trial succeed.

Four oral TTR stabilizers are available for ATTR treatment: diflunisal, tafamidis, tolcapone, and acoramidis, but only two — acoramidis and tafamidis — have international approval (1), while diflunisal and tolcapone are considered off-label treatments. Tafamidis, sold under the brand names Vyndaquel and Vyndamax by Pfizer, and Acoramidis, sold as Attruby by BridgeBio Pharma, work by binding to the TTR protein, stabilizing it and slowing its breakdown into the dangerous amyloid deposits. Since the two Tafamidis therapies were approved by the FDA in 2019, the drugs have shown success in reducing mortality and hospitalizations. Acoramidis, approved in late 2024, demonstrated strong Phase 3 clinical data.

TTR gene silencers include inotersen, eplontersen, patisiran, and vutrisiran. Eplontersen, also known as Wainua, received FDA approval in December 2023. The drug, developed by Ionis

Pharmaceuticals in partnership with AstraZeneca, is a GalNAc conjugated antisense oligonucleotide (ASO) for treating hereditary polyneuropathy TTR (hATTR-PN) and is the only treatment for the disease that can be self-administered once a month via an auto-injector.

Ionis Pharmaceuticals also has inotersen (Tegsedi) on the market, which shares the same nucleotide sequence as eplontersen and was approved by the FDA and the EU in 2018 for the treatment of hATTR-PN. The ASO drug, administered subcutaneously weekly, binds both wild-type and mutant *TTR* messenger RNA (mRNA), thereby inhibiting TTR protein expression.

Additionally, Alnylam Pharmaceuticals' Onpattro (patisiran) and Amvuttra (vutrisiran) are approved for the treatment of hATTR. Both drugs are siRNA-based oligonucleotides but differ in their chemical structures. Onpattro, approved in 2018, is an siRNA, encapsulated in a lipid nanoparticle formulation that requires IV administration every three weeks. Amvuttra, approved in 2022, uses an siRNA-GalNAc conjugate with an enhanced stabilization chemistry that, compared to Onpattro, provides greater potency and higher metabolic stability, enabling subcutaneous injection every three months.

These therapies have transformed the field of ATTR treatment, but all require ongoing dosing. Against this competitive and safety-conscious backdrop, the FDA's decision to lift the clinical hold on Intellia's MAGNITUDE and MAGNITUDE-2 trials allows Intellia to resume advancing nexiguran ziclumeran toward a potential one-time CRISPR-based treatment for ATTR. While the recent safety concerns underscore the need for vigilant monitoring of liver toxicity, the protocol changes and resumption of dosing suggest regulators remain confident in the program's potential overall risk-benefit profile. As Intellia and Regeneron work to complete enrollment and generate pivotal Phase 3 data, the results will be closely watched, as they will answer vital questions, including whether the added monitoring will fully prevent liver issues, how well it will work long-term in a broad patient group, and whether there are any off-target effects. As gene editing is permanent, any off-target effects could have lasting consequences. The phase 3 trial results will be critical in determining whether nex-z earns FDA approval. If successful, it will join a competitive market of ATTR therapies, with its one-time treatment offering another option for treating the disease.

References:

1. Judge, D. P. Current available treatment options targeting TTR tetramer stabilization. *European Heart Journal Supplements*. https://doi.org/10.1093/eurheartjsupp/suag010