CRISPR-Cas9 Gene Editing with Nexiguran Ziclumeran for ATTR Cardiomyopathy

Marianna Fontana, M.D., Ph.D., Scott D. Solomon, M.D., Jessica Kachadourian, PharmD., Liron Walsh, M.D., Ricardo Rocha, M.D., David Lebwohl, M.D., Derek Smith, M.S., Jörg Täubel, M.D., Edward J. Gane, M.B., Ch.B., Björn Pilebro, M.D., David Adams, M.D., Ph.D., Yousuf Razvi, M.B., Ch.B., Joy Olbertz, Ph.D., PharmD., Alexandra Haagensen, M.D., M.B.A., Peijuan Zhu, Ph.D., Yuanxin Xu, M.D., Ph.D., Adia Leung, M.S., Alison Sonderfan, M.S., R.D., David E. Gutstein, M.D., and Julian D. Gillmore, M.D., Ph.D.

From National Amyloidosis Centre, Division of Medicine, University College London, London, United Kingdom (M.F, Y.R., J.D.G.); Brigham and Women's Hospital, Boston, MA (S.D.S); Intellia Therapeutics, Cambridge, MA (J.K., L.W. R.R, D.L., D.S., J.O., A.H., P.Z., Y.X., A.L., A.S.); Richmond Pharmacology, London, UK (J.T.); University of Auckland, Auckland, New Zealand (E.J.G.); Umea University, Umea, Sweden (B.P.); CHU de Bicêtre, AP-HP, University Paris-Saclay, Le Kremlin-Bicêtre, France (D.A.); Regeneron Pharmaceuticals, Tarrytown, NY (D.E.G.)

Dr. Fontana can be contacted at m.fontana@ucl.ac.uk or at Royal Free London NHS Foundation Trust, Cardiology. Pond Street London, UK NW3 2QG

ABSTRACT

BACKGROUND: ATTR amyloidosis with cardiomyopathy (ATTR-CM) is a progressive, often fatal disease with limited approved therapies. Nexiguran ziclumeran (nex-z or NTLA-2001) is an investigational, *in vivo*, clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease (CRISPR-Cas9)-based therapy targeting the transthyretin gene (*TTR*).

METHODS: In this phase 1, ongoing, open-label trial, patients with ATTR-CM received a single intravenous infusion of nex-z. Primary objectives included the assessment of the effect of nex-z on safety and pharmacodynamics (serum TTR). Secondary endpoints included its effect on NT-proBNP, hs-Troponin-T, 6-minute walk test (6MWT) distance and change in New York Heart Association [NYHA] class.

RESULTS: Thirty-six patients (50% NYHA class III; 31% variant ATTR-CM) were dosed with nex-z and completed at least 12 months of follow-up. Adverse events were reported in 34 patients, including 5 patients with infusion-related reactions and 2 patients with AST elevations, all of which were transient. Serious adverse events were reported in 14 patients. Mean (95% confidence interval [CI]) percent change from baseline in serum TTR levels at day 28 and month 12 were -89% (-92 to -87) and -90% (-93 to -87), respectively. Geometric mean (95% CI) fold change from baseline to month 12 in NT-proBNP and hs-Troponin-T were 1.02 (0.88, 1.17) and 0.95 (0.89, 1.01), respectively. Median (IQR) change from baseline to month 12 in 6MWT distance was +5 meters (-33 to +49). 92% of patients experienced no change or improvement in NYHA class.

CONCLUSIONS: In this phase 1 study in patients with ATTR-CM, treatment with a single dose of nex-z led to consistently deep, rapid and durable reductions in serum TTR and was associated with transient infusion-related reactions. A phase 3 study of nex-z to treat ATTR-CM has been initiated (Funded by Intellia Therapeutics and Regeneron Pharmaceuticals; ClinicalTrials.gov number, NCT04601051.)

INTRODUCTION

Transthyretin amyloidosis (ATTR) is an infiltrative cardiomyopathy (ATTR-CM) caused by the deposition of misfolded transthyretin (TTR) protein, in the form of amyloid fibrils, within the myocardium. ATTR-CM is characterized by progressive decline in cardiac structure and function with associated deterioration in functional capacity and quality of life (QOL), symptomatic heart failure, frequent hospitalization, and death. Therapeutic approaches that have been tested in cardiac outcomes trials and have shown to have clinical benefit focus on either stabilization of the tetrameric form of TTR (a TTR stabilizer) or inhibition of TTR protein synthesis by means of degradation of TTR messenger RNA (a TTR silencer). Nevertheless, patients remain at risk of cardiac events or death as observed in recent studies, especially patients with more advanced disease.[1-3] Additionally, these therapies require lifelong administration, adding to the overall disease burden for patients.

Nexiguran ziclumeran (nex-z, also known as NTLA-2001) is a clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease (CRISPR-Cas9) investigational therapy packaged in a proprietary lipid nanoparticle (LNP) delivery system with liver tropism. Nex-z was designed as a one-time therapy to induce a rapid, deep, and durable reduction in serum TTR and carries two components: the single-guide RNA that precisely targets the *TTR* and the human-codon–optimized mRNA sequence of *Streptococcus pyogenes* Cas9 protein. The LNP formulation was developed for efficient delivery to hepatocytes, the main source of circulating TTR protein. Unlike gene therapies that utilize adeno-associated virus for delivery, the LNP formulation utilized in nex-z allows for broad administration across patients and is rapidly cleared following administration.[4] We previously reported that a single intravenous dose of nex-z resulted in marked decreases in serum TTR protein concentrations through targeted knockout of TTR in six patients with variant ATTR amyloidosis with polyneuropathy (PN).[4]

Here, we report the safety of nex-z and its effects on TTR levels, functional capacity, QOL, and cardiac imaging and biomarkers of disease progression in patients with ATTR-CM.

METHODS

Study Design and Oversight

This phase 1 trial is an ongoing, single-arm, open-label, two-part, single-dose escalation (part 1) and single-dose expansion (part 2) study, assessing the safety, pharmacodynamic, and clinical effects of nex-z in patients with ATTR amyloidosis. The present report includes data from 36 patients with ATTR-CM in parts 1 and 2 of the study.

The trial was sponsored by Intellia Therapeutics, Inc. and Regeneron Pharmaceuticals, Inc. The study concept and design were developed by the sponsor in collaboration with investigators. Study oversight was provided by an independent data and safety monitoring committee. Data for the ATTR-CM cohort were collected by investigators at the National Amyloidosis Centre in the United Kingdom (UK) in partnership with Richmond Pharmacology (UK), analyzed by the sponsors, and interpreted jointly by the sponsors and the authors. The first and last authors prepared the first draft of the manuscript. The authors employed by the sponsor had direct access to the data and vouch for the accuracy and completeness of the data and analyses. All authors vouch for the fidelity of the trial to the protocol. All authors contributed to the review, editing, and approval of the manuscript for publication and participated in the decision to submit for publication. The protocol was reviewed by national and institutional ethics and regulatory bodies, including expert committees for assessment of new studies of gene therapy, including gene editing (UK: Gene Therapy Advisory Committee of the Medicines and Healthcare Products Regulatory Agency). The study has been conducted in accordance with the Declaration of Helsinki and International Council

for Harmonization Good Clinical Practice guidelines, and all patients provided written informed consent.

Patients

Eligible patients were 18 to 90 years of age with diagnosis of variant ATTR-CM (ATTRv) or wild-type ATTR-CM (ATTRwt), had at least 1 prior hospitalization for heart failure and/or clinical evidence of heart failure New York Heart Association (NYHA) class I, class II, or class III, and levels of N-terminal pro–B-type natriuretic peptide (NT-proBNP) greater than 600 pg/mL (or, if patient has known diagnosis of atrial fibrillation, NT-proBNP >1,000 pg/mL). Patients with other types of amyloidosis or known leptomeningeal amyloidosis were excluded. Full eligibility criteria are listed in the protocol, available at NEJM.org.

Treatment

In the dose-finding portion of the study (part 1), patients received a dose of either 0.7 mg/kg (N=9) or 1 mg/kg (N=3). Following this, in the part 2 expansion portion of the study, patients received treatment with nex-z at a dose of 55 mg (N=24), the fixed dose equivalent of 0.7 mg/kg **(Supplementary Fig. 1)**. The planned duration of infusion was over a minimum of 2 hours. To mitigate the risk of infusion-related reactions (IRRs), patients received a pretreatment regimen consisting of one dose of oral dexamethasone 8 mg or equivalent administered between 8 and 24 hours before the infusion of nex-z and one dose each of a glucocorticoid, an H_1 receptor antagonist, and an H_2 receptor antagonist administered approximately 1 hour before the infusion. All patients are being followed for at least 24 months. Details about the dose selection for part 1 and part 2 are provided in the **Supplementary Appendix**.

Clinical Assessments

Samples for pharmacodynamic analyses (serum TTR, analyzed as previously reported[4]) and assessment of efficacy measures were obtained at study visits in accordance with the schedule of

activities provided in the protocol. Vital signs were measured, clinical history was obtained, and physical examinations and laboratory tests were performed before the infusion and at prespecified intervals over the course of the study. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Study End Points

The primary objectives of the study were to evaluate the safety, tolerability, and pharmacodynamics of nex-z. Serum TTR levels was the primary measure of pharmacodynamics. Secondary endpoints included assessments in change in NT-proBNP, hs-Troponin-T, NYHA class, quality of life based on the Kansas City Cardiomyopathy Questionnaire (KCCQ), measurements of cardiac remodelling by echocardiogram and cardiac magnetic resonance (CMR),[5] and changes in functional capacity as measured by 6-Minute Walk Test (6MWT) and cardio-pulmonary exercise testing (CPET).[6] All available data was reported, which included out to 27 months of safety and 24 months for TTR. Secondary and exploratory analysis were reported out to 12 months, the study visit reached by all study patients by the data cutoff date.

Statistical Analysis

For this phase 1 study, data were analyzed descriptively, and no formal statistical hypotheses were tested. The analysis reported here is interim and was unplanned; we carried it out because each of the participants had completed at least 12 months of follow-up. Safety summaries include all patients who received nex-z, while pharmacodynamic and disease marker summaries include all those who received nex-z and had at least one post-baseline assessment. Safety and serum TTR results include all available data for the 36 patients. Change from baseline in disease markers was reported out to month 12, the study visit reached by all study patients. The results were summarized for the overall ATTR-CM population, which combined patients across all dose levels in part 1 and part 2 portions of the study.

Geometric mean fold-change from baseline and the corresponding confidence intervals (CIs) for NT-proBNP and hs-Troponin-T were calculated from the natural-log transformed difference, which was back-transformed for presentation. Reported 95% CIs are based on a t-distribution, and CI widths have not been adjusted for multiplicity and should not be used for hypothesis testing. Post hoc exploratory analyses included assessment of the frequency of worsening or stability in several prognostic markers of disease progression in ATTR-CM as follows: as previously reported, progression of 6MWT distance was defined as a greater than 35 m decrease compared with baseline, progression of NT-proBNP was defined as an increase from baseline that was both greater than700 ng/L and more than 30%, and progression of hs-Troponin-T was defined as an increase from baseline that was both greater than 10 ng/L and more than 20%.[7,8] For NYHA Class, improvement or worsening was defined as a change of at least one class level at 12 months relative to baseline.

Treatment emergent adverse events (TEAEs) were defined as any adverse event that occurred during or following nex-z administration through the data cutoff date. The hospitalization rate for cardiovascular events was estimated using a negative binomial model. Cardiovascular events analyzed included hospitalizations for serious adverse events (SAEs) associated with cardiac failure (i.e., heart failure), arrhythmia, or stroke.

RESULTS

Patients

A total of 36 patients were enrolled as of August 21, 2024 (data cutoff) and the median follow-up was 18 months (range, 12 to 27). Baseline data provided were representative of the global population of patients with ATTR-CM including those with advanced disease (**Table 1, Table S1**). 31% of patients had ATTRv-CM with five different pathogenic TTR variants including seven

patients (19%) with the p.Val142Ile gene variant (two of whom were homozygous). At baseline, median NT-proBNP was 2052 ng/L (range, 851 to 19624) and 50% of the participants had NYHA class III disease. Patients in this study were not on baseline TTR stabilizer therapies due to lack of availability in the UK during the time when the study was initiated. Information about concomitant medication use at baseline and at 12 months is provided in **Table 1** and **Table S2**. One patient was initiated on tafamidis on study day 363.

Pharmacodynamics

Serum TTR protein concentrations rapidly declined from baseline, with mean (95% CI) absolute serum concentrations achieved at days 28 and month 12 of 18.9 (15.4 to 22.5) and 16.5 (13.4 to 19.7) ug/mL, corresponding to a mean (95% CI) percent change of -89% (-92 to -87) at day 28 and -90% (-93 to -87) at 12 months (**Fig. 1**). Deep and sustained reductions in serum TTR levels were observed in all patients, regardless of baseline TTR level, dose received, or genotype, with every patient reaching steady levels of serum TTR below 50 ug/mL by day 28 of whom 78% were <25 ug/mL. The observed effects on serum TTR reduction was sustained to month 24 in all 11 patients who have completed 2 years of follow-up at the time of the present report.

Secondary Endpoints

At month 12, the geometric mean (95% CI) fold change from baseline in NT-proBNP and hs-Troponin-T was 1.02 (0.88 to 1.17) and 0.95 (0.89 to 1.01), respectively. The median (interquartile range) change from baseline to month 12 in 6MWT distance was +5 meters (-33 to 49). The median change in the overall KCCQ score was +8 points (-0.5 to 15), with 61% of patients having at least a 5-point increase. (**Fig. 2, Table 2**). (KCCQ scores range from 0 to 100, with 0 representing the worst health status and 100 representing the best with a 5-point change considered to be clinically meaningful.[9]) With respect to NYHA class, 47% had an improvement of at least one class, 44% remained stable, and 8% worsened at 12 months. Measurements of cardiac remodeling

at 12 months with either echocardiography or CMR, including quantification of myocardial extracellular volume, a marker of cardiac amyloid load, consistently showed a similar pattern of stability (**Table S4, Figures S2 and S3**). CPET measurements of cardiopulmonary response to exercise at 12 months (**Table S4, Figure S4**) showed a median (interquartile range) change from baseline in peak VO_2 of -0.3 (-2.3, 1.4) and in VE/VCO2 slope of -0.6 (-5.6, 1.2) at month 12.

Post-hoc Analyses

We carried out two post-hoc exploratory analyses. An evaluation of disease progression based on prognostic markers (NT-proBNP, hs-Troponin-T, or 6MWT) showed that 66% (83% of NYHA class I/II patients and 47% of NYHA class III patients) had no worsening in any marker by 12 months **(Fig. S5A, Table S3)**. Evaluation of the individual disease markers at 12 months showed stability in NT-proBNP, hs-Troponin-T, and 6MWT in 81%, 94%, and 77% of patients, while worsening was observed in 19%, 6%, and 23%, respectively (**Fig. S5B**).

Safety

All patients received the intended dose of nex-z and no patient required permanent discontinuation of the infusion. Thirty-four patients reported at least one TEAE with the most common being cardiac failure (n=13, 36%), upper respiratory tract infection (n=7, 19%), Covid-19 (n=7, 19%), atrial fibrillation (n=6, 17%), urinary tract infection (n=6, 17%), and infusion-related reactions (IRRs) (n=5, 14%) (**Table 3)**. Adverse events assessed as related to nex-z by the investigators were limited to IRRs in five participants (14 (%) and increased levels of aspartate aminotransferase (AST) in two participants (6%) , whose peak AST levels were approximately 3 x upper limit of normal within the first month after dosing. Both events resolved within approximately 10 days without medical intervention. The AST and alanine aminotransferase levels measured throughout

the initial 12 months are presented in **Figures S6** and **S7**. Two additional mild adverse events associated with elevations in liver enzymes were observed on Day 252 and Day 730. Adverse events were generally similar across ATTRv-CM and ATTRwt-CM patients.

Four of five IRRs were considered mild or moderate and occurred within 3 hours of the infusion. One IRR was graded as severe and an SAE; it occurred in a patient with NYHA class III who became hypotensive, leading to overnight observation in the hospital. Hypotension was treated with 500 mL IV saline administration. No additional treatment was required. The most frequent symptoms associated with IRRs were pyrexia, headache, hypotension, and back pain, which were predominantly mild to moderate in intensity. Paracetamol was the most common treatment for IRRs, and all IRRs resolved within median (range) 14 (0.2 to 38) hours.

Based on the TTR protein function to transport vitamin A and thyroid hormone, changes in laboratory values and associated adverse events were closely monitored after nex-z administration. As expected, vitamin A levels declined and remained low throughout follow-up. No clinically relevant changes in thyroid-stimulating hormone levels were observed and there were no clinical findings associated with vitamin A deficiency or abnormalities of thyroid function.

Fourteen (39%) patients experienced an SAE. One SAE, the IRR described above, was judged by investigators to be treatment-related. Of the 14 patients who experienced SAEs, seven were reported to have had an SAE requiring hospitalization associated with cardiac failure (n=4) or arrhythmia (n=2) or both (n=1). The observed rate of these cardiac events was 0.16/pt/yr (95% CI: 0.08 to 0.36). To date, there has been one death in the study (ischemic heart disease, not treatment-related), which occurred on study day 505 in a 77-year-old male patient who, in addition to ATTR-CM (NYHA class II, p.Val142Ile mutation, baseline NT-proBNP 19,624 ng/L), had a history of ischemic heart disease.

DISCUSSION

Administration of a single dose of nex-z to 36 patients with ATTR-CM resulted in deep reductions in serum TTR. Adverse events were reported in 34 patients, including 5 patients with infusion-related reactions and 2 patients experienced transient AST elevations. Serious adverse events were reported in 14 patients. . Serial measurements of serum total TTR concentration after nex-z administration confirmed the durability and consistency of the TTR knockdown across all patients, with TTR levels remaining low and virtually unchanged through 24 months after dosing. Notably, the deep and sustained reductions in serum TTR levels appeared to be accompanied in most patients by evidence of disease stabilization at 12 months, based on multiple markers of disease progression. There was no concurrent use of other ATTR-CM disease-modifying therapies.

Data from completed studies of TTR-lowering agents, which require repeat administration, have shown that long-term reduction in serum TTR is safe and translates into meaningful clinical benefits relative to placebo.[3,10-12] The reduction in TTR levels following administration of nex-z were -89% (-92 to -87) and -90% (-93 to -87) at day 28 and month 12. An RNA-targeted TTR-lowering therapy showed mean TTR reductions of approximately 80% after 6 months of treatment.[3] It has not been confirmed that more intensive, consistent, and sustained reductions in serum TTR levels would lead to greater clinical benefits in ATTR-CM. However, a positive association between the magnitude of TTR protein reduction and the clinical benefit has been demonstrated in patients with ATTR-PN,[11] analogous to the case in amyloid A protein (AA) and immunoglobulin light chain amyloidosis, in which greater suppression of circulating serum AA protein and immunoglobulin light chain protein, respectively, is associated with improved survival.[13-17]

When untreated, patients with ATTR-CM experience disease progression, as evidenced by worsening of NT-proBNP and troponin, oral diuretic intensification, and 6MWT, which is typically evident within 12 months in recent studies.[3,7,8,18] Even in patients receiving treatment, there is still a residual risk of disease progression and cardiovascular events.[2,3,18] In post-hoc analyses, we

observed evidence of limited disease progression over the initial 12-month period following nex-z administration as shown by the apparent general stability in cardiac biomarkers and 6MWT, known to be associated with poor prognosis in ATTR-CM.[7,8] Similar evidence was observed in imaging measurements of cardiac structural remodelling at 12 months, as well as in functional capacity as measured by CPET, which is known to worsen over a short period of time in this population.[19] Although patients with less severe disease seem to remain more stable over the 12 months, changes in markers consistent with stability were observed in some patients with more advanced disease (**Table 2**, **Table S5**). Moreover, TTR suppression was similar across all patients regardless of disease severity.

IRRs, the most common treatment-related adverse event, were predominantly mild, self-limiting, and did not require permanent discontinuation of the infusion in any patient. Liver enzyme elevations were mild and not indicative of liver injury. In addition, the rate of cardiac events (0.16/pt/yr; 95% CI: 0.08 to 0.36) appears to be low in comparison to observations from a recent interventional study in a contemporaneous population of patients with ATTR-CM.[2]

Limitations of this study include the lack of a control group, a small sample size and limited duration of observation period: 27 months. As a new therapeutic modality, longer-term surveillance of safety effects will be needed. Consistent with regulatory guidance for cell and gene therapies, patients will be followed for 15 years after treatment. This study was carried out at a single site. Because the trial was open label, NYHA class and KCCQ, and 6MWT results are subject to bias and should be interpreted with caution. Indeed, the design of the study precludes assessment of clinical efficacy of nex-z in patients with ATTR-CM. In addition, patients were receiving other heart failure therapies such as SGLT2 inhibitors and mineralocorticoid receptor antagonists which could have affected some of the secondary outcomes. That said, the observed pattern of biomarker and functional response is consistent with modification of natural history in ATTR-CM. Although

the trial population is thought to be representative of a typical ATTR-CM patient group, including those with more severe and variant disease, the small sample size may limit generalizability.

A single dose of nex-z appeared to be safe and was associated with consistently deep, rapid, and durable reductions in serum TTR, accompanied by evidence of limited disease progression during the initial 12 months after treatment. The effect of nex-z treatment on clinical outcomes is being further evaluated in the phase 3 MAGNITUDE trial,[20] a global, randomized, placebo-controlled study in patients with ATTR-CM.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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FIGURES

Figure 1. Serum TTR Protein Concentration Reductions Following Single Intravenous Infusion of nex-z.

Panel A shows the mean (95% CI) percent change in TTR following a single intravenous infusion of nex-z. Mean (95% CI) percent change at day 14, day 28, and month 12 was -83% (-86 to -80), -89% (-92 to -87), and -90% (-93 to -87), respectively. Panel B shows the corresponding mean (95% CI) absolute serum TTR concentrations, where mean (95% CI) concentration at day 14, day 28, and month 12 was 31.4 (26.0 to 36.8) µg/mL, 18.9 (15.4 to 22.5) µg/mL, and 16.5 (13.4 to 19.7) µg/mL, respectively. Confidence interval widths have not been adjusted for multiplicity and should not be used for hypothesis testing.

TTR, transthyretin.

Figure 2. Change from Baseline for NT-proBNP, hs-Troponin-T, KCCQ, and 6MWT.

Change from baseline in NT-proBNP (Panel A), hs-Troponin-T (Panel B), KCCQ Overall Score (Panel C), and 6MWT distance (Panel D). The horizontal dashed lines provide a reference for baseline. Confidence intervals widths have not been adjusted for multiplicity and should not be used for hypothesis testing.

6MWT, 6-Minute Walk Test; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, pro–B-type natriuretic peptide.

TABLES

Table 1. Patient Baseline Characteristics.

	All Subjects (N=36)
Age, y, median (min, max)	78.0 (46, 90)
Sex, male, no. (%)	35 (97)
Race, no. (%)	
Black or African American	8 (22)
White or Caucasian	28 (78)
Weight, kg, median (min, max)	81.8 (53.9, 114.6)
NT-proBNP, ng/L, median (min, max)	2052 (851, 19624)
hs-Troponin-T, ng/L, median (min, max)	56 (15, 204)
6-Minute Walk Distance, m, median (min, max)	331 (178, 580)
eGFR,* mL/min/1.73 m^2, median (min, max)	65.1 (32.7, 96.3)
Peak VO_2 † mL/kg/min, median (Q1, Q3)	12.7 (11, 15.2)
VE/VCO_2 slope†	34 (31, 39.8)
Years since diagnosis, median (min, max)	1 (0, 8)
TTR genotype, no. (%)	

Wild type	25 (69)
p.Val142Ile‡	7 (19)
p.Thr80Ala	1 (3)
p.Gly73Glu	1 (3)
p.Glu62Lys	1 (3)
p.Ile88Leu	1 (3)
NYHA class, no. (%)	
I	3 (8)
II	15 (42)
III	18 (50)
NAC stage§	
I	23 (64)
II	9 (25)
III	4 (11)
Heart failure medications, no. (%)	
Loop diuretics	32 (89)
MRAs	20 (56)
SGLT2i	9 (25)
ACE inhibitors	10 (28)
ARBs	6 (17)
Beta-blockers	22 (61)

Percentages may not total 100 because of rounding.

*eGFR was calculated using the MDRD equation.

†Peak VO_2 baseline values were available in only 33 patients

‡Two of these patients were homozygous for p.Val142Ile.

§NAC stages are determined from the levels of the serum biomarkers NT-proBNP and eGFR and are defined as follows: Stage 1, NT-proBNP ≤3000 and eGFR ≥45; Stage 3, NT-proBNP >3000 and eGFR <45; Stage 2, not meeting Stage 1 or Stage 3.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium-glucose co-transporter 2 inhibitor; TTR, transthyretin; NAC, National Amyloidosis Centre.

Table 2. Changes from Baseline at Month 12 for Biomarker, Functional, and KCCQ Endpoints.

	ATTR-CM Population		
Endpoint	**Overall (N=36)**	**NYHA Class I/II (N=18)**	**NYHA Class III (N=18)**
NT-proBNP fold change at month 12			
No.	36	18	18
Geometric mean (95% CI)	1.02 (0.88–1.17)	0.97 (0.82–1.14)	1.06 (0.83–1.35)
hs-Troponin-T mean fold change at month 12			
No.	36	18	18
Geometric mean (95% CI)	0.95 (0.89–1.01)	0.91 (0.84–0.99)	0.98 (0.88–1.09)
6MWT distance change at month 12, m			
No.	35	18	17
Median (Q1, Q3)	5.1 (-32.9, 48.8)	10.6 (-15.6, 48.8)	-14.5 (-73.8, 44.9)
KCCQ overall score			
No.	36	18	18
Median (Q1, Q3)	7.8 (-0.5, 15.4)	5.2 (-3.6, 10.9)	9.0 (0.8, 18.8)
Change in NYHA class at month 12			
No.	36	18	18
Improved	17 (47)	4 (22)	13 (72)
No change	16 (44)	11 (61)	5 (28)
Worsened	3 (8)	3 (17)	0

Confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing.

KCCQ overall score ranges from 0 to 100 with higher scores indicating better health status. A change of at least 5 points in KCCQ is considered to represent a clinically meaningful change.

6MWT, Six-Minute Walk Test; ATTR-CM, ATTR amyloidosis with cardiomyopathy; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association.

Table 3: Safety Summary of 36 Patients with ATTR-CM Treated with Nex-z.

Event	No. (%)
At least one AE*	34 (94)
AEs occurring in ≥15% of patients	
Cardiac failure	13 (36)
COVID-19	7 (19)
Upper respiratory tract infection	7 (19)
Atrial fibrillation	6 (17)
Urinary tract infection	6 (17)
Treatment-related AEs	
Infusion-related reaction	5 (14)
Aspartate aminotransferase increased§	2 (6)
Any serious event†	14 (39)
Serious adverse events occurring in ≥5% of patients	
Cardiac failure	5 (14)
Acute myocardial infarction	3 (8)
Urinary tract infection	3 (8)
Atrial flutter	2 (6)
Pneumonia	2 (6)
Serious AEs of heart failure, arrythmia or stroke	7 (19)
Cardiac failure	5 (14)
Arrhythmia‡	3 (8)
Stroke	0
Any AE leading to treatment discontinuation	0
Any event leading to death	1 (3)

*All adverse events (including SAEs) were graded for severity by National Cancer Institute Common Terminology Criteria for Adverse Events, version 5 (NCI-CTCAE).

†Serious adverse events were defined as AEs that resulted in death, were life-threatening, resulted in inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or clinically significant disability or incapacity, were a congenital anomaly or birth defect, or were important medical events as determined by the investigators.

‡Arrhythmia events included SAEs of atrial flutter and atrioventricular block complete, with one patient experiencing both cardiac failure and arrhythmia on the same day.

§ Two additional mild adverse events associated with elevations in liver enzymes were observed on Day 252 and Day 730.

AE, adverse event; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; SAE, serious adverse event.