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Long-Term Durability, Outcomes, and Safety of Nexiguran Ziclumeran Gene Editing in Hereditary Transthyretin Amyloidosis With Polyneuropathy

Julian D. Gillmore,[1] Ed Gane,[2] Jörg Täubel,[3] Björn Pilebro,[4] Justin Kao,[5] William J. Litchy,[6] Liron Walsh,[7] Derek Smith,[7] Ana Camejo,[7] Michael Levine,[7] David E. Gutstein,[8] Andoni Echaniz-Laguna[9]

[1]University College London, London, UK; [2]University of Auckland, Auckland, New Zealand; [3]Richmond Pharmacology, London, UK; [4]Umea University, Umea, Sweden; [5]Auckland City Hospital, Auckland, New Zealand; [6]Mayo Clinic, Rochester, MN, USA; [7]Intellia Therapeutics, Cambridge, MA, USA; [8]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [9]CHU de Bicêtre, AP-HP, Université Paris-Saclay, Le Kremlin-Bicêtre, France

Conclusions

- A one-time treatment with nex-z resulted in rapid, deep, and durable reductions in serum TTR through Year 4 in participants with ATTRv-PN
- Nex-z was well tolerated, with a favorable safety profile (median exposure 3.5 years)
- Untreated patients with ATTRv-PN experience disease progression over time, but one-time treatment with nex-z provided long-term stability or improvements in disease-relevant measures, including NIS, mNIS+7, and Norfolk QOL-DN
- Nex-z is being evaluated in participants with ATTRv-PN in the ongoing Phase 3 MAGNITUDE-2 study (NCT06672237)

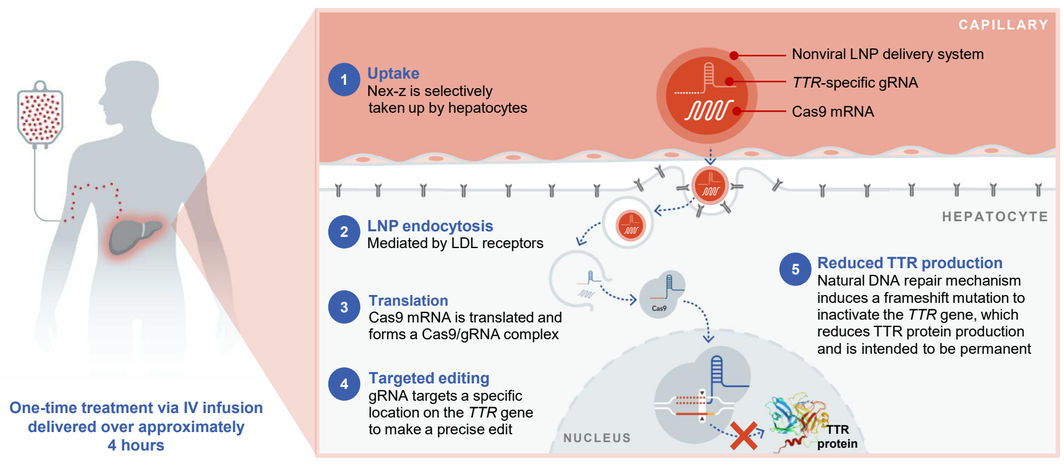
KEY TAKEAWAY

A one-time treatment with nex-z provided long-term stability or improvements in neuropathy and QOL scores in participants with ATTRv-PN

Introduction

- ATTRv-PN is a progressive, multisystem disease caused by variants of the *TTR* gene, resulting in TTR misfolding, amyloid deposits in peripheral nerves, progressive disability, and death[1]
- Approved therapies can slow disease progression of ATTRv-PN, but patients require lifelong treatment and may continue to experience disease progression[2]
- Nex-z is an investigational, *in vivo,* CRISPR-based, one-time gene editing therapy designed to achieve lifelong suppression of hepatic TTR production (**Figure 1**)[3,4]

Figure 1. Nex-z mechanism of action



On average, >99% of each component of nex-z is eliminated within 2 weeks of dosing

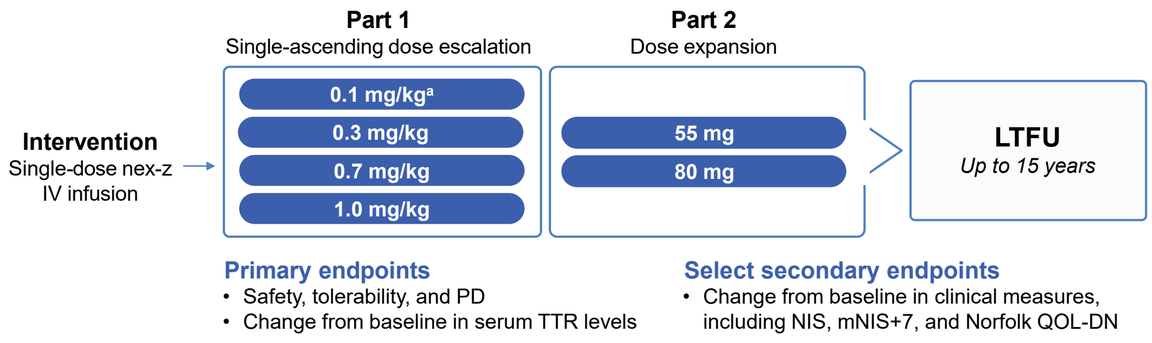
Objective

- To report LTFU safety, pharmacodynamics, and efficacy outcomes of participants with ATTRv-PN who received a single dose of nex-z in a Phase 1 study (NCT04601051)

Methods

- Nex-z was evaluated in a 2-part, open-label, Phase 1 study (**Figure 2**)
- After ≥24 months of follow-up, all participants were eligible to enter the LTFU study (NCT05697861)
- Safety outcomes, including AESIs and SAEs, and change from baseline in serum TTR, NIS, mNIS+7, and Norfolk QOL-DN are reported in all participants who received a single dose of nex-z ≥0.3 mg/kg

Figure 2. Nex-z Phase 1 and LTFU study design



[a]Participants who received nex-z 0.1 mg/kg in Part 1 were redosed with nex-z 55 mg after 24 months of follow-up.

Results

- A total of 33 participants have been treated with a single dose of nex-z ≥0.3 mg/kg in the Phase 1 study (**Table 1**), and 31 participants have entered the LTFU study
- The median duration of nex-z exposure was 3.5 (range, 0.7-5.1) years

Table 1. Demographics and baseline characteristics

Parameter	All participants (N=33)[a]
Median age (range), years	61.0 (19-75)
Male, n (%)	25 (76)
Race, n (%)	
Asian	1 (3)
Black or African American	0
Native Hawaiian or Other Pacific Islander	1 (3)
White or Caucasian	15 (45)
Multiple	1 (3)
Not reported	15 (45)
NIS, mean (SD)	33 (27.7)
mNIS+7, mean (SD)[b]	48 (34.1)
Norfolk QOL-DN, mean (SD)	38 (31.8)
NYHA class	
No heart failure	12 (36)
I	16 (48)
II	5 (15)
III/IV	0

Data cutoff: June 29, 2026.
[a]Includes all participants who received a single dose of nex-z ≥0.3 mg/kg. [b]mNIS+7 is reported in participants from Part 2 (n=21).

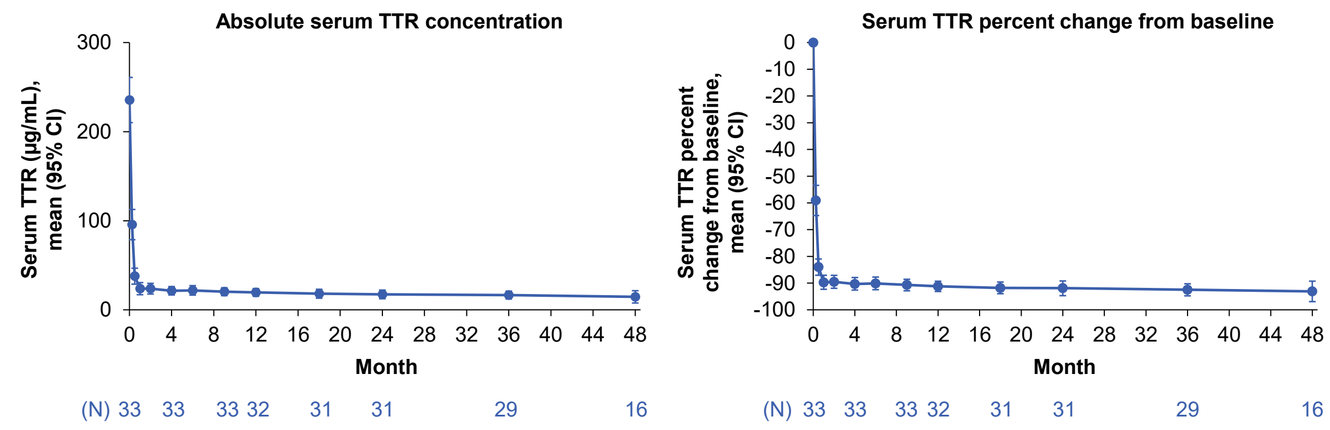
Table 2. AESIs and SAEs in the LTFU

Event, n (%)	All participants (N=31)[a]
Any AESI[b] or SAE	9 (29)
Mild	0
Moderate	4 (13)
Severe	5 (16)
Any AESI[b]	6 (19)
Treatment-related AESI	0
Any SAE[c]	8 (26)
Treatment-related SAE	1 (3)
AESI or SAE leading to death	1 (3)[d]

Data cutoff: June 29, 2026. Adverse events in LTFU were limited to AESIs and SAEs.
[a]Includes all participants who received a single dose of nex-z ≥0.3 mg/kg and entered the LTFU.
[b]AESI categories reported included new incidence or exacerbation of preexisting neurologic disorder, new incidence of a hematologic disorder, new incidence or exacerbation of a prior rheumatologic or autoimmune disorder, and severe infection.
[c]No hepatic-related SAEs have been observed in the LTFU.
[d]SAE of esophageal adenocarcinoma deemed by the investigator to be possibly related to treatment. This participant also had risk factors of Barrett's esophagus, alcohol use, and smoking.

- One-time treatment with nex-z led to deep, consistent, and durable reductions in serum TTR (**Figure 3**)
- Mean serum TTR was 16.6 µg/mL at Month 36 and 14.6 µg/mL at Month 48, and mean change from baseline was -92.5% and -93.1%, respectively

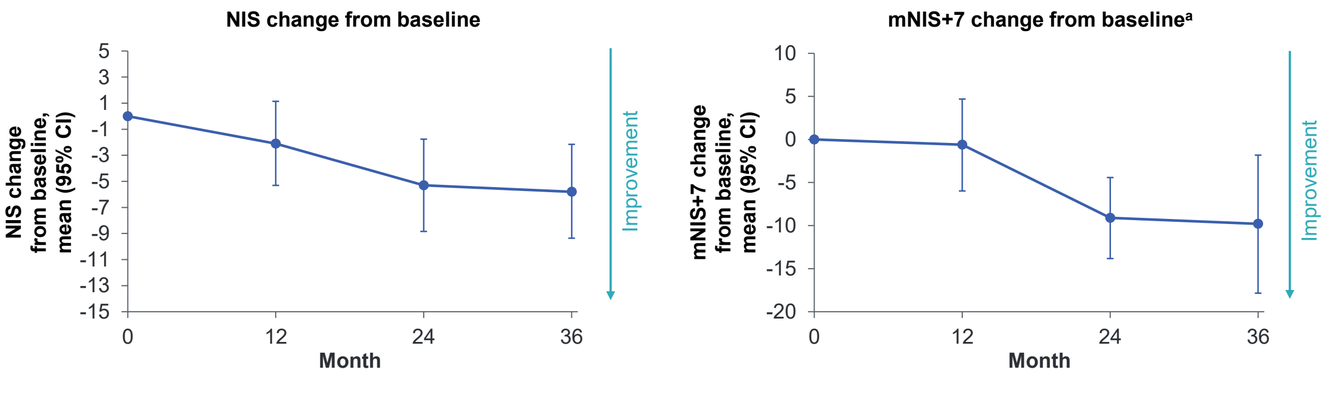
Figure 3. Changes in serum TTR levels



Data cutoff: June 29, 2026. Baseline defined as the average of the visits within 42 days prior to the start of study intervention.

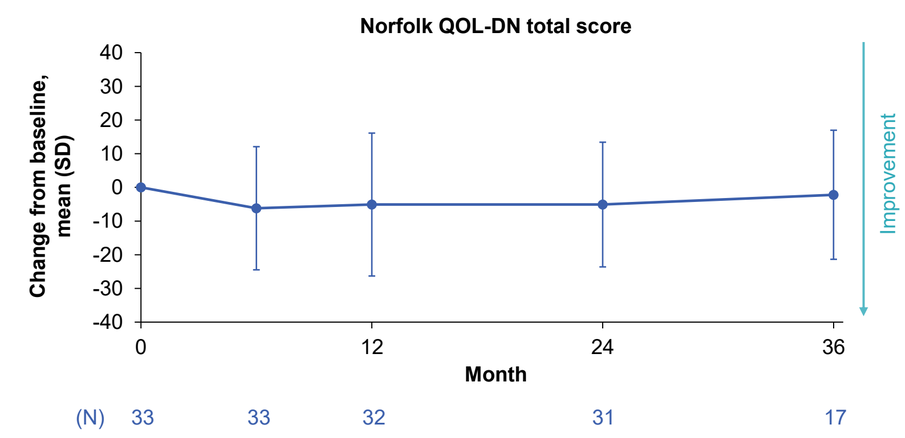
- Long-term improvements in NIS and mNIS+7 were observed following one-time treatment with nex-z (**Figure 4**)
- At Month 36, mean change from baseline was -5.8 for NIS and -9.8 for mNIS+7

Figure 4. Changes from baseline in NIS and mNIS+7



Data cutoff: June 29, 2026. Baseline NIS defined as the last available measurement taken prior to the start of infusion of study drug. Baseline mNIS+7 defined as the average of the visits within 42 days prior to the start of study intervention. NIS ranges from 0 to 244 and mNIS+7 ranges from 0 to 304, with higher values indicating increased impairment.
[a]mNIS+7 is reported in participants from Part 2 (n=21).

Figure 5. Changes from baseline in Norfolk QOL-DN



Data cutoff: June 29, 2026. Baseline defined as the last available measurement taken prior to the start of infusion of study drug.

- Norfolk QOL-DN total scores were generally stable or improved following one-time treatment with nex-z (**Figure 5**)
- At Month 36, mean change from baseline in Norfolk QOL-DN total score was -2.2

This presentation includes data for an investigational product not yet approved by regulatory authorities.

Disclosure: **JDG** reports consultancy agreements with Alnylam, AstraZeneca, Attralus, Alexion Pharmaceuticals, Bayer, BridgeBio, Ionis Pharmaceuticals, Intellia Therapeutics, Lycia Therapeutics, and Pfizer, an institutional grant from Alnylam, and research grants from Alnylam and AstraZeneca.

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References: 1. Adams D, et al. *Nat Rev Neurol.* 2019;15(7):387-404. **2.** Ide T, et al. *Neurol Ther.* 2026;15(5):2341-2358. **3.** Gillmore JD, et al. *N Engl J Med.* 2021;385(6):493-502. **4.** Fontana M, et al. *N Engl J Med.* 2024;391(23):2231-2241.

Abbreviations: AESI, adverse event of special interest; ATTRv-PN, hereditary transthyretin-mediated amyloidosis with polyneuropathy; Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; gRNA, guide RNA; IV, intravenous; LDL, low-density lipoprotein; LNP, lipid nanoparticle; LTFU, long-term follow-up; mNIS+7, modified Neuropathy Impairment Score +7; mRNA, messenger RNA; nex-z, nexiguran ziclumeran; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy Questionnaire; PD, pharmacodynamics; QOL, quality of life; SAE, serious adverse event; TTR, transthyretin.

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