Integrated Analysis of Lonvoguran Ziclumeran Phase 1/2/3 Studies in Hereditary Angioedema: Efficacy, Safety, and Tolerability

Aleena Banerji,[1] Danny M. Cohn,[2] Paula J. Busse,[3] Jonny Peter,[4] Marc A. Riedl,[5] Markus Magerl,[6,7] Adele Golden,[8] David Maag,[8] Catherine R. Miller,[8] Padmalal Gurugama[9]

[1]Massachusetts General Hospital, Boston, MA, and Harvard Medical School, Boston, MA; [2]Amsterdam Cardiovascular Sciences, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands; [3]The Mount Sinai Hospital, New York, NY; [4]Groote Schuur Hospital, University of Cape Town and Allergy and Immunology Unit, University of Cape Town Lung Institute, Cape Town, South Africa; [5]University of California San Diego, San Diego, CA; [6]Charité-Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [7]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany; [8]Intellia Therapeutics, Cambridge, MA; [9]Cambridge University Hospitals, NHS Foundation Trust, Cambridge, UK

Poster R071

Introduction

- Hereditary angioedema due to C1 inhibitor deficiency (HAE-C1INH) is caused by an imbalance in the kallikrein-kinin system, which leads to excess bradykinin production and debilitating swelling attacks[1]
- Targeting kallikrein to inhibit bradykinin production is a clinically proven strategy for the prevention of HAE attacks[2,3]
- Lonvoguran ziclumeran (lonvo-z) is an investigational, *in vivo* CRISPR-based one-time treatment designed to permanently inactivate the *KLKB1* gene to reduce kallikrein production with the goal of treating HAE-C1INH[4,5]
- Lonvo-z has been investigated in adults with HAE-C1INH in 3 studies: a completed Phase 1/2 study (NCT05120830), an ongoing Phase 3 HAELO study (NCT06634420), and an ongoing long-term follow-up study (LTFU; NCT06262399)[4-6]

Objective

- To evaluate the efficacy and safety of a single 50 mg infusion of lonvo-z in an integrated analysis of the Phase 1/2, Phase 3 HAELO, and LTFU studies

Methods

Phase 1/2 (last patient last visit: June 26, 2026)

- Phase 1: Open-label, dose-escalation, multicenter study; long-term prophylaxis (LTP) permitted
- Phase 2: Randomized, placebo-controlled, double-blind study; LTP permitted after Week 16

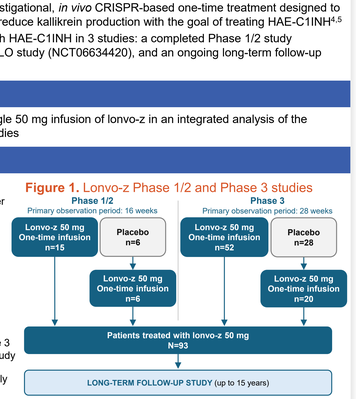
Phase 3 HAELO (data cutoff: Feb 10, 2026)

- Patients with HAE-C1INH were randomly assigned to receive lonvo-z 50 mg or placebo, with an optional, blinded crossover at Week 28; LTP permitted after Week 28

LTFU study (data cutoff: July 10, 2026)

- Once patients completed the Phase 1/2 or Phase 3 studies, they were invited to enroll in the LTFU study
- The current analysis excludes patients who initially received lonvo-z 25 mg or 75 mg

Figure 1. Lonvo-z Phase 1/2 and Phase 3 studies



Results: Patient baseline characteristics were generally representative of the HAE-C1INH population[7]

- A total of 93 patients were treated with lonvo-z 50 mg in the Phase 1/2 and Phase 3 HAELO studies
- The median (range) duration of follow-up was 7.6 (0.3-46.5) months
  - Most patients (n=67; 72%) had ≥6 months of follow-up (**Table 2**)
- Nearly all patients remain on study and in follow-up (n=92; 99%)

Table 1. Demographics and baseline characteristics

Parameter	Lonvo-z 50 mg (N=93)
Age, median (range), years	42 (18-76)
Female, n (%)	62 (67)
Hereditary angioedema type, n (%)	
Type 1	84 (90)
Type 2	9 (10)
Historical attack severity, n (%)	
Mild	13 (14)
Moderate	61 (66)
Severe	19 (20)
Prior use of LTP at study entry, n (%)	
Any	62 (67)
Lanadelumab	34 (37)
Berotralstat	8 (9)
C1 inhibitor	11 (12)
Other[a]	10 (11)
Baseline monthly attack rate, mean (SD)[b]	3.3 (2.0)

[a]Includes tranexamic acid, danazol, and stanozolol. [b]Baseline is defined as the screening period (50 mg initial dose) or for placebo to 50 mg as the time from informed consent to 50 mg infusion or start of any LTP, whichever occurred first. In the Phase 1 trial, a washout period was not required, and 3 patients used LTP at baseline.
LTP, long-term prophylaxis.

Table 2. Duration of follow-up

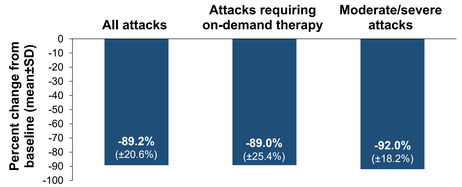
Duration of follow-up after one-time lonvo-z 50 mg,[a] n (%)				
<6 months	≥6 months	≥1 year	≥2 years	≥3 years
26 (28)	67 (72)	22 (24)	15 (16)	7 (8)

[a]Duration of follow-up as of last contact.

After lonvo-z 50 mg, monthly attack rates decreased by approximately 90% through last assessment

- With up to 4 years of follow-up after lonvo-z 50 mg infusion, patients experienced a mean (SD) of 0.3 (0.7) attacks/month, 0.3 (0.6) attacks/month requiring on-demand therapy, and 0.2 (0.4) moderate or severe attacks/month

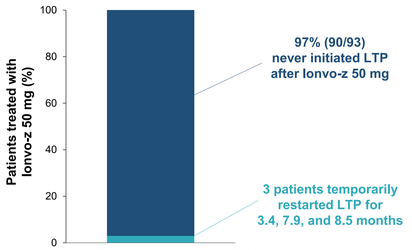
Figure 2. Reductions in attack rate from baseline following lonvo-z 50 mg with up to 4 years of follow-up (N=93)



A month is defined as 28 days. For patients who were taking LTP at the time of lonvo-z 50 mg administration, only data after LTP discontinuation were included in the analysis. For patients who initiated any LTP after receiving lonvo-z 50 mg, data were censored at the time of LTP initiation, and only attacks that started prior to LTP initiation and after LTP discontinuation were included in the analysis.
LTP, long-term prophylaxis.

All (93/93) patients were LTP-free as of last follow-up after one-time infusion of lonvo-z 50 mg

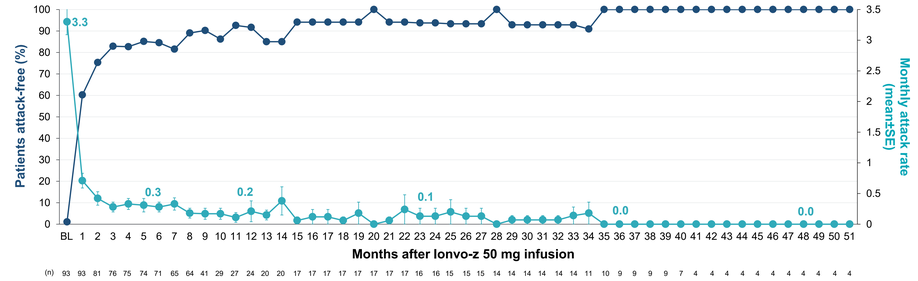
Figure 3. LTP-free status and duration following lonvo-z 50 mg



Six patients continued on prior LTP through lonvo-z infusion and discontinued LTP 0.3-4.1 months after infusion.
LTP, long-term prophylaxis.

After lonvo-z 50 mg, monthly attack rate decreased rapidly and approached zero attacks per month, with durable control observed in patients followed for up to 4 years

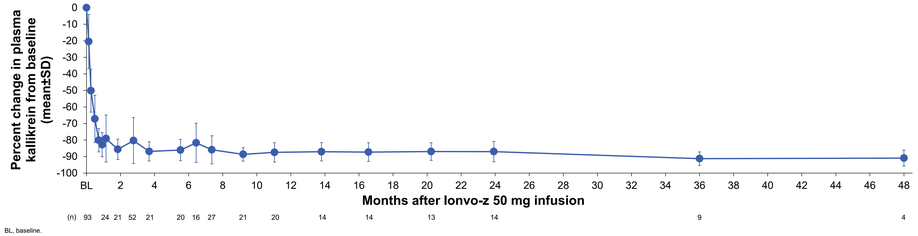
Figure 4. Change in attack rate and attack-free status over time following lonvo-z 50 mg



31/32 patients treated with lonvo-z 50 mg remain in long-term follow-up. N shown represents the number of patients who have reached that time point. One month=28 days. Timepoints with data from ≥3 patients are presented.
BL, baseline.

A one-time treatment with lonvo-z 50 mg led to deep, stable, and durable reductions in plasma kallikrein

Figure 5. Change in kallikrein over time following lonvo-z 50 mg



BL, baseline.

One-time treatment with lonvo-z 50 mg was well tolerated with no long-term risks observed

- The majority of treatment-emergent adverse events after lonvo-z 50 mg infusion were Grades 1 or 2 in severity (**Table 3**)

Table 3. Safety summary[a]

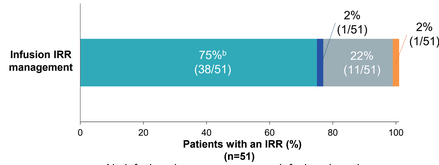
	Lonvo-z 50 mg (N=93) n (%)
Any TEAE	82 (88)
TEAE reported in >10% of patients	
Infusion-related reaction	51 (55)
Headache	18 (19)
Fatigue	17 (18)
Nasopharyngitis	15 (16)
Upper respiratory tract infection	13 (14)
Back pain	12 (13)
Grade ≥3 TEAE	2 (2)
Serious TEAE	2 (2)
Perforated gangrenous appendicitis[b]	1 (1)
Pulmonary embolism[c]	1 (1)
TEAEs leading to study drug discontinuation	1 (1)
Infusion-related reaction	1 (1)[d]
TEAEs leading to death	0

[a]AEs that occurred after each patient received lonvo-z 50 mg are reported. [b]One event of perforated gangrenous appendicitis occurred in 1 patient but was not considered treatment related. [c]The patient had multiple risk factors, which included recent COVID infection, ongoing history of smoking, and obesity. [d]Symptoms of flushing, headache, and lightheadedness lasted 13 minutes total and resolved without treatment.
AE, adverse event; TEAE, treatment-emergent adverse event.

All IRRs resolved; most (75%) without interruption or changes to infusion rate

- To mitigate infusion-related reactions (IRRs), corticosteroid and antihistamine medications were administered the day prior to and the day of infusion per the protocol
- 59% (30/51) of patients with an IRR received a concomitant medication to treat the IRR
  - Medications most commonly utilized (>10% of patients with an IRR) included acetaminophen (37% [19/51]) and ibuprofen (20% [10/51])

Figure 6. Lonvo-z infusion management for IRRs[a]

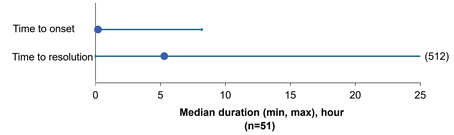


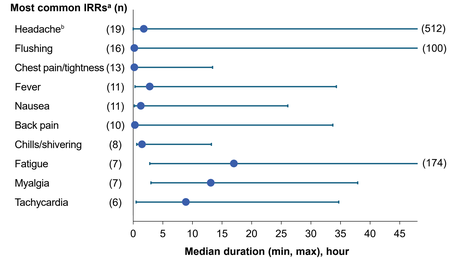
[a]Percentages may not sum to 100% due to rounding; percentages are calculated from the number of patients who experienced an IRR. [b]For 9 patients, the IRR event began after infusion was completed.
IRR, infusion-related reaction.

Most IRRs occurred shortly after the start of infusion and were resolved the same day

- Median (range) time to onset of IRRs was 12 minutes (immediately to 8.2 hours)
- The median (range) time to resolution for IRRs was 5.3 hours (immediately to 21.3 days)
  - 59% (30/51) of patients with an IRR experienced onset during infusion only
  - 24% (12/51) of patients with an IRR experienced onset during infusion and after infusion completion
  - 18% (9/51) of patients with an IRR experienced onset after infusion completion only
    - Of those with IRR onset after infusion, symptoms presented at a median (range) 2.0 (0.3-5.3) hours after infusion completion

Figure 7. IRRs generally resolved within 24 hours





[a]IRR symptoms reported in >5% of patients. IRR symptoms were assessed independently from TEAEs; reporting an event as an IRR symptom did not preclude it from also being recorded as a TEAE. Any observed IRR symptoms that did not fall into the predefined categories were classified as "Other" (18% [17/93] of patients; median [min, max] duration: 1.6 [0-150] hours). [b]One patient experienced a Grade 1 headache from Day 1 to Day 22 following lonvo-z 50 mg infusion. IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.

Conclusions

- In this integrated analysis, a one-time treatment with lonvo-z 50 mg durably reduced monthly attack rates, which were sustained through up to 4 years of follow-up
  - All patients (93/93) were without LTP as of last follow-up
- Lonvo-z 50 mg demonstrated a favorable long-term safety profile across the Phase 1/2, Phase 3 HAELO, and LTFU studies
  - IRRs were managed in outpatient settings and generally resolved within 24 hours
- These results support the potential use of lonvo-z 50 mg as a one-time treatment for patients with HAE-C1INH

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

DISCLOSURES

AB has received grant/research/clinical trial support from Astria, Intellia, and Ionis, and served as a consultant and on advisory boards for ADARx, Astria, BioCryst, BioMarin, CSL Behring, Intellia, KalVista, Pharvaris, and Shire/Takeda.

ACKNOWLEDGMENTS

These studies are funded by Intellia Therapeutics. We wish to extend our gratitude to the patients, their caregivers, and their families; study site coordinators and staff; and the staff of Simbec-Orion and Medpace for assistance with study management and operations support. Medical writing and editorial support were provided by Aya Jishi, PhD, and Melissa Austin of Helios Global Group, and funded by Intellia Therapeutics.

REFERENCES

1. Zuraw B. *N Engl J Med*. 2008;359(10):1027-1036. 2. Zuraw B, et al. *J Allergy Clin Immunol*. 2021;148(1):164-172.e9. 3. Banerji A, et al. *JAMA*. 2018;320(20):2108-2121. 4. Longhurst HJ, et al. *N Engl J Med*. 2024;390(5):432-441. 5. Cohn DM, et al. *N Engl J Med*. 2025;392(5):458-467. 6. NIH. Accessed Jul 30, 2026. https://clinicaltrials.gov/study/NCT05120830. 7. Cohn DM, et al. *N Engl J Med*. 2026;395(15):1471-1482.

Please scan this QR code to obtain a copy of this presentation for personal use only.
Copies may not be reproduced without permission from the authors.

Presented at the American College of Allergy, Asthma & Immunology (ACAAI) Annual Meeting | November 12-16, 2026 | Phoenix, AZ