Evolving Treatment Goals to Achieve Freedom From Attacks and Long-Term Prophylaxis Following a One-Time Treatment With Lonvoguran Ziclumeran (Lonvo-z; NTLA-2002)

Aleena Banerji,[1] Markus Magerl,[2,3] Padmalal Gurugama,[4] Constance H. Katelaris,[5] Catherine Miller,[6] Adele Golden,[6] David Maag,[6] Danny M. Cohn[7]

[1]Massachusetts General Hospital, Boston, MA; [2]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [3]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP Immunology and Allergology, Berlin, Germany; [4]Cambridge University Hospitals, NHS Foundation Trust, Cambridge, UK; [5]Campbelltown Hospital and Western Sydney University, Sydney, NSW, Australia; [6]Intellia Therapeutics, Cambridge, MA; [7]Amsterdam University Medical Center, Cardiovascular Sciences, Department of Vascular Medicine, University of Amsterdam, Amsterdam, The Netherlands

Poster 005

Introduction

Current Treatment Goals in Hereditary Angioedema (HAE)

- Current HAE treatment goals focus on the ability to reduce attacks and ultimately normalize patients' lives[1,2]
  - Evaluating if a patient has reached normalization requires individualized assessment and may not be easily defined by an objective endpoint[3]
- To further describe treatment goals, **experts agreed that the ultimate goal for treatment of HAE is to achieve attack-free status**[4]
  - It was agreed that 2 goals of HAE treatment should be to achieve total control of the disease (95% consensus) and to normalize the patient's life (100% consensus)
- Importantly, **patients also prioritize being attack-free**[5]
  - The most important efficacy endpoints reported by patients living with HAE in the United States included having zero attacks and having an increase in attack-free days[5]
  - In a separate study among patients living with HAE in the United States, most respondents (61%) felt staying attack-free for a minimum of 6-12 months would be meaningful (**Table 1**)[6]
- Despite current long-term prophylactic therapies, patients still report attacks (**Table 2**)[7-9]
- The **burden of chronic treatments** to manage HAE may prevent some patients from reaching normalization
  - Experts felt that minimizing treatment burden was important to achieve normalization (90% consensus)[4]
  - Patients reported that lifetime use of long-term prophylaxis (LTP; 55%) and efficacy (52%) were the 2 most important improvements needed to achieve normalization[6]
- Multiple aspects related to chronic treatment use identified by patients living with HAE that prevent normalization may not be fully appreciated by HAE experts as being meaningful when considering HAE disease control (**Figure 1**)[9]

Table 1. Minimum meaningful attack-free period (N=100)[6]

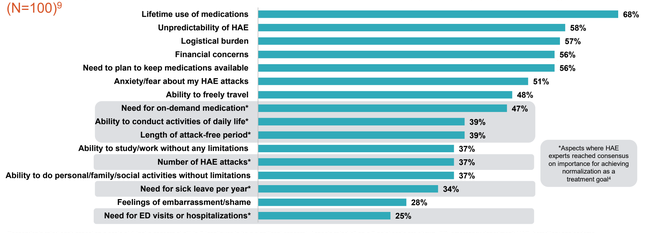
<1 week	1-3 months	6 months to 1 year
10%	29%	**61%**

Table 2. Real-world, patient-reported attack rates

Study design	Sample size	Proportion of patients with attacks	Recall period
Survey of US patients with HAE (2017)[7]	N=445	96.6% reported ≥1 attack	Prior 6 months
Survey of US patients with HAE (2023)[8]	N=94	91% reported ≥1 attack	Prior 30 days
Survey of US patients with HAE (2025)[9]	N=100	80% reported ≥1 attack	Prior 12 months

HAE, hereditary angioedema; US, United States.

Figure 1. Aspects of normalization that continue to be a concern reported by patients living with HAE (N=100)[9]



Respondents rated each aspect on a scale of 1 (not a concern at all) to 7 (continues to be a significant concern). Aspects rated ≥5 on a 7-point scale are shown. ED, emergency department; HAE, hereditary angioedema.

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 Therapeutics, Intellia Therapeutics, and Ionis, and served as a consultant and on advisory boards for ADARx Pharmaceuticals, Astria Therapeutics, BioCryst, BioMarin Pharmaceutical, CSL Behring, Intellia Therapeutics, KalVista Pharmaceuticals, Pharvaris, and Shire/Takeda. **MM** has received speaking fees from BioCryst, CSL Behring, and Takeda; participated in advisory boards for BioCryst, CSL Behring, Intellia Therapeutics, and Takeda; acted as an investigator for BioCryst, CSL Behring, Intellia Therapeutics, Ionis Pharmaceuticals, and Takeda; and served on safety monitoring committees for Octapharma USA, Inc. **PG** has received fees for consultation and speaking from BioCryst, KalVista, and Takeda and travel grants from CSL Behring, Pharming, and Shire. **CHK** has acted as a consultant or participated in advisory boards for Eli Lilly, Pharvaris, Seqirus, and Takeda; and received honorarium from GlaxoSmithKline. **CM**, **AG**, and **DM** are employees of and hold equity in Intellia Therapeutics. **DMC** has received speaking fees from CSL Behring, Ionis Pharmaceuticals, Pharvaris, and Takeda; consultancy fees from Astria, BioCryst, CSL Behring, Ionis Pharmaceuticals, KalVista, Pharming, Pharvaris, and Takeda; and research support from Ionis Pharmaceuticals, KalVista, Pharvaris, and Takeda.

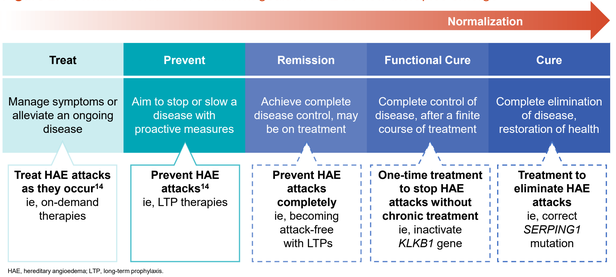
Acknowledgments: This study is funded by Intellia Therapeutics. Medical writing and editorial support were provided by Ellen Woon, PhD, and Melissa Austin of Helios Global Group, and funded by Intellia Therapeutics.

References: 1. Busse PJ, et al. *J Allergy Clin Immunol Pract.* 2021;9(1):132-150.e3. 2. Mauer M, et al. *Allergy.* 2022;77(7):1961-1990. 3. Bork K, et al. *Allergy Asthma Clin Immunol.* 2021;17(1):40. 4. Mauer M, et al. *J Allergy Clin Immunol.* 2021;148(6):1526-1532. 5. Friedhoff S, et al. Presented at US HAEA National Summit; Jul 20-23, 2023; Orlando, FL. 6. Busse PJ, et al. Presented at AAAAI 2026; Feb 27-Mar 2, 2026; Philadelphia, PA. 7. Banerji A, et al. *Ann Allergy Asthma Immunol.* 2020;124(6):600-607. 8. O'Connor M, et al. *World Allergy Organ J.* 2025;18(8):101083. 9. Busse PJ, et al. Presented at ACAAI 2025; Nov 6-10, 2025; Orlando, FL. 10. Zuraw BL, et al. *J Allergy Clin Immunol Pract.* 2013;1(5):458-467. 11. Menzies-Gow A, et al. *J Allergy Clin Immunol.* 2020;145(3):757-765. 12. Ghany MG, et al. *Hepatology.* 2023;79(5):1254-1269. 13. Jacobson IM, et al. *J Viral Hepat.* 2012;19(4):236-243. 14. Bork K, et al. *Allergy Asthma Clin Immunol.* 2021;17(1):40. 15. Longhurst HJ, et al. *N Engl J Med.* 2024;390(5):432-441. 16. Cohn DM, et al. *N Engl J Med.* 2025;392(5):458-467.

Evolving Treatment Goals in HAE

- Guideline recommendations for treating HAE have evolved as new therapies and approaches have emerged[1,10]
- In other disease states, advances in treatments have made the terms "remission," "functional cure," and "cure" new therapeutic goals, although definitions differ. Examples include:
  - Remission: asthma (clinical or complete, on-treatment or off-treatment)[11]
  - Functional cure: hepatitis B (complete disease suppression and lower transmission risk in combination with a finite treatment period)[12]
  - Cure: hepatitis C (sustained virological response in the absence of treatment)[13]
- A functional cure, which can be defined as no symptoms (attack-free) without chronic therapy (no LTP), may be possible for patients living with HAE as new therapies become available (**Figure 2**)

Figure 2. Potential evolution of treatment goals in HAE as new therapies emerge



HAE, hereditary angioedema; LTP, long-term prophylaxis.

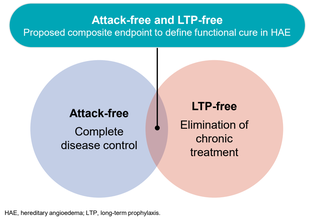
Objective

- To better understand if a functional cure is an achievable goal in HAE, we explored the potential for patients to become attack-free and LTP-free after receiving a one-time treatment with lonvoguran ziclumeran (lonvo-z)

Methods

- Lonvo-z is an *in vivo* CRISPR-based therapy currently under investigation for its ability to reduce HAE attacks
- Lonvo-z is intended to permanently inactivate the *KLKB1* gene and is administered as a one-time infusion over 2 to 4 hours in an outpatient setting
- Lonvo-z was evaluated in an ongoing Phase 1/2 study (NCT05120830) and an ongoing long-term follow-up (LTFU) study (NCT06262399); details have been reported previously[15,16]
  - Phase 1 was unblinded and dose escalating[15]; Phase 2 was blinded and placebo controlled through at least Week 16[16]
- Patients who received lonvo-z 50 mg at any point in the Phase 1/2 study were included in this current analysis. Data were analyzed from the time of 50 mg infusion; the study is ongoing
- A novel composite endpoint was assessed, defined as attack-free and LTP-free from Week 5 (**Figure 3**)

Figure 3. Proposed HAE functional cure endpoint



HAE, hereditary angioedema; LTP, long-term prophylaxis.

Results

- As of August 29, 2025, 32 patients have been treated with lonvo-z 50 mg with a median duration of follow-up of 12.2 months (range, 2.4 months to 3.0 years) (**Table 3**)

Table 3. Phase 1/2 demographics and baseline characteristics

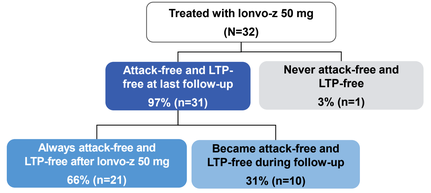
	Lonvo-z 50 mg (N=32)
Age, median (range), years	48.5 (18-76)
Female, n (%)	16 (50)
HAE type, n (%)	
Type 1	26 (81)
Type 2	6 (19)
LTP immediately prior to Phase 1/2 study entry, n (%)	18 (56)
Lanadelumab	5 (16)
Attenuated androgens	5 (16)
Berotralstat	5 (16)
C1 esterase inhibitor	2 (6)
Tranexamic acid	1 (3)
Historic typical HAE attack severity, n (%)	
Mild	4 (13)
Moderate	21 (66)
Severe	7 (22)
Baseline monthly attack rate, mean (SD)[a]	3.4 (2.3)

[a]Baseline is defined as the screening period (50 mg initial dose or 25 mg to 50 mg) 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 Phase 1, patients may have been on LTP.
HAE, hereditary angioedema; LTP, long-term prophylaxis.

Attack-Free and LTP-Free

- Of the 32 patients treated with lonvo-z 50 mg, 31 (97%) were attack-free and LTP-free at latest follow-up (**Figure 4**)

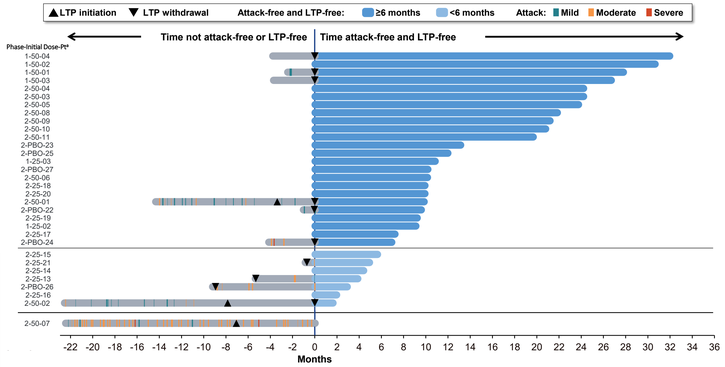
Figure 4. Proportion of patients attack-free and LTP-free during the study



LTP, long-term prophylaxis.

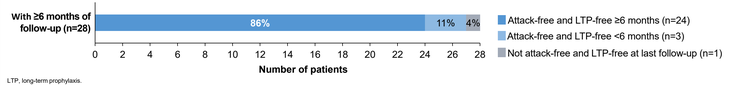
- For all 31 patients who achieved attack-free and LTP-free status, the response has been maintained through the most recent data cut (up to 3 years) and follow-up is ongoing (**Figure 5**)
  - The duration of attack-free and LTP-free status ranged from 2 months to up to 3 years, and follow-up is ongoing
  - Follow-up time after becoming attack-free and LTP-free is limited for 7 patients (<6 months)
- Among patients with ≥6 months of follow-up, the majority (86%; 24/28) have been attack-free and LTP-free for ≥6 months (**Figure 6**)

Figure 5. HAE attacks and LTP use after lonvo-z 50 mg infusion



*Patient IDs align with prior Phase 1 and Phase 2 publications.[15,16]
HAE, hereditary angioedema; LTP, long-term prophylaxis; PBO, placebo; Pt, patient.

Figure 6. Proportion of patients attack-free and LTP-free



LTP, long-term prophylaxis.

Safety

- With up to 3 years of follow-up, lonvo-z 50 mg was well tolerated with no long-term risks identified
  - Within the first 28 days following infusion, the most common treatment-emergent adverse events (TEAEs) (>10%) were infusion-related reaction (53%), fatigue (34%), and headache (19%)
  - After 28 days, the most common TEAEs (>10%) in the Phase 1/2 study were nasopharyngitis (25%), upper respiratory tract infection (19%), back pain (16%), arthralgia (13%), and COVID-19 (13%)
  - In the LTFU study, no serious adverse events (SAEs) or treatment-related AEs were reported in patients treated with lonvo-z 50 mg
  - There were no clinically significant shifts in coagulation parameters or liver enzymes reported in the Phase 1/2 or LTFU studies

Conclusions

- HAE experts and patients report that achieving attack-free status and simultaneously minimizing treatment burden is an important treatment goal in HAE[4,5]
- After a one-time treatment with lonvo-z 50 mg, 97% (31/32) of patients with HAE became both attack-free and LTP-free
- The majority of patients have been attack-free and LTP-free for >6 months, a time frame suggested by patients as clinically meaningful; long-term follow-up is ongoing[6]
- Future studies should explore the composite endpoint of attack-free and LTP-free to define functional cure in HAE and inform the impact of being attack-free and LTP-free on improving patients' ability to live normally
- In the future, a functional cure may be an achievable treatment goal for HAE with the introduction of lonvo-z, if approved

Please scan this quick response (QR) code to obtain a copy of this presentation.

- Copies of this poster obtained through this QR code are for personal use only and may not be reproduced without permission from the authors of this presentation

Presented at the American Academy of Allergy, Asthma & Immunology (AAAAI) Annual Meeting | February 27-March 2, 2026 | Philadelphia, PA