HAELO, a Phase 3, Global, Randomised, Double-Blind, Placebo-Controlled Study of Lonvoguran Ziclumeran, a CRISPR-Based Gene Editing Therapy, in Patients with Hereditary Angioedema

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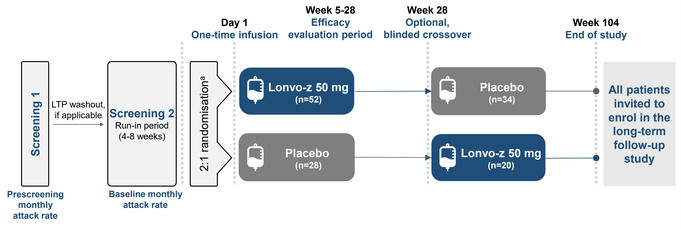
Introduction and Methods: HAELO is a Phase 3 study evaluating lonvo-z in patients with HAE-C1INH

- Lonvoguran ziclumeran (lonvo-z; NTLA-2002) is an investigational *in vivo* CRISPR-based one-time treatment[1,2]
- Lonvo-z is designed to permanently inactivate the *KLKB1* gene to reduce kallikrein production with the goal of treating hereditary angioedema due to C1 inhibitor deficiency (HAE-C1INH)
- HAELO is a Phase 3 study designed to evaluate the efficacy and safety of lonvo-z in patients with HAE-C1INH[3]

Figure 1: HAELO study design



Primary Endpoint

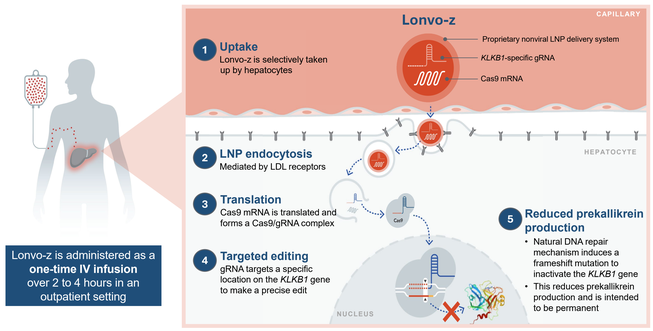
Time-normalised number of investigator-confirmed HAE attacks from Week 5 through 28

Key Secondary Endpoints[b]

- Number of HAE attacks requiring on-demand treatment (Week 5-28)
- Number of moderate or severe HAE attacks (Week 5-28)
- HAE attack-free status (Week 5-28)
- Change from baseline to Week 28 in AE-QoL Questionnaire total score

[a]Patients were stratified by baseline number of investigator-confirmed HAE attacks per month from Screening 2 to Randomisation (>3 vs ≤3).
[b]Attacks were investigator confirmed; attack rate was time normalised.
AE-QoL, Angioedema Quality of Life; HAE, hereditary angioedema; LTP, long-term prophylaxis.

Figure 2. Lonvo-z mechanism of action[1,2]



Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; gRNA, guide RNA; IV, intravenous; LDL, low-density lipoprotein; LNP, lipid nanoparticle; mRNA, messenger RNA.

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DISCLOSURES:
DMC: 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. **PG:** received fees for consultation and speaking from BioCryst, KalVista, and Takeda and travel grants from CSL Behring, Pharming, and Shire. **HJL:** acted as a consultant or speaker, received educational sponsorship or participated in research with Astria Therapeutics, CSL Behring, Intellia Therapeutics, KalVista, Pharvaris, and Takeda. **EA-P:** consultancy for Astria, BioCryst Pharmaceuticals, Inc., CSL Behring, KalVista, Pharvaris, and Takeda Pharmaceuticals; speaking engagements for BioCryst Pharmaceuticals, Inc., CSL Behring, and Takeda Pharmaceuticals; advisory boards for Astria, BioCryst Pharmaceuticals, Inc, CSL Behring, and Intellia Therapeutics; institutional grants from CSL Behring for studies related to hereditary angioedema. **TJC:** speaker for CSL Behring, Grifols, Ionis, KalVista Pharmaceuticals, and Takeda; has received research and consultancy grants from ADARx, ARGO, Astria, BioCryst, BioMarin, CSL Behring, Grifols, Ionis, KalVista Pharmaceuticals, Pharvaris, and Takeda; and is on the Medical Advisory Board for the US Hereditary Angioedema Association, Director of ACARE Angioedema Center at Penn State University, Hershey, PA, USA. **HF:** grants/fees from or consultancy for Astria, BioCryst, BioCryst Ionis, CSL Behring, Intellia, KalVista, ONO Pharmaceutical, Pharming, Pharvaris, and Shire/Takeda. **JSJ:** received fees for sponsored research, consultancy, and speaking from AstraZeneca, Genentech, GSK, Regeneron Pharmaceuticals, and Teva Pharmaceuticals. **WRL:** grants, consulting fees, and/or honoraria from Astria, AstraZeneca, BioCryst, BioMarin, CSL Behring, Express Scripts/CVS, Fresenius Kabi, GlaxoSmithKline, Grifols, Intellia Therapeutics, Ionis, KalVista, Magellan, OptiNose, Optum, Pharming, Pharvaris, Sanofi/Regeneron, Takeda/Shire, and Teva; and serves on the board of the US HAEA and the Dallas/Fort Worth Metroplex Allergy Society. **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, Ionis Pharmaceuticals, and Takeda; and served on safety monitoring committees for Octapharma USA, Inc. **JP:** received educational/research grant support and/or speaker's fees and/or advisory board honorarium from Astria, BioCryst, Celldex, CSL Behring, Intellia, Novartis, Pharvaris, Sanofi, and Takeda. **MAR:** received research grants from Astria, BioCryst, BioMarin Pharmaceutical, CSL Behring, Intellia, Ionis, KalVista, Pharvaris, and Takeda; consulted for Astria, BioCryst, BioMarin Pharmaceutical, Celldex, CSL Behring, Cycle Pharma, Grifols, Intellia Therapeutics, Ionis, KalVista, Novartis, Pharming, Pharvaris, Sanofi-Regeneron, and Takeda; and provided speaker presentations for BioCryst, CSL Behring, Grifols, Pharming, and Takeda. **DM, AG, MYS, JSB,** and **DL:** employees of and hold equity in Intellia Therapeutics. **AB:** 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.

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Results: Patient demographics and baseline characteristics were balanced between arms

- As of 10 February 2026, the median follow-up was 7.5 months (range, 4.9-12.8 months)
- Prior to study entry, 67% and 79% of patients in the lonvo-z and placebo arms, respectively, were receiving long-term prophylaxis (LTP)

Table 1. HAELO demographics and baseline characteristics

Demographic characteristics	Lonvo-z (n=52)	Placebo (n=28)
Age, median, years (range)	42 (23–71)	40 (19–76)
Female, n (%)	35 (67)	20 (71)
Hereditary angioedema type, n (%)		
Type 1	49 (94)	25 (89)
Type 2	3 (6)	3 (11)
Hereditary angioedema treatment prior to study enrolment, n (%)[a]		
Long-term prophylaxis	35 (67)	22 (79)
On-demand therapy only	17 (33)	6 (21)
Long-term prophylaxis prior to study enrolment, n (%)[a]		
Lanadelumab	25 (48)	12 (43)
C1 inhibitor	5 (10)	3 (11)
Berotralstat	4 (8)	1 (4)
Garadacimab	1 (2)	3 (11)
Other	2 (4)	3 (11)
Historic typical attack severity, n (%)		
Mild	7 (14)	5 (18)
Moderate	30 (58)	20 (71)
Severe	15 (29)	3 (11)
Mean monthly attack rate in the 3 months prior to screening (SD)	1.8 (2.1)	1.5 (1.7)
Mean monthly attack rate during run-in (baseline), mean (SD)[b]	3.5 (1.8)	3.5 (1.9)

[a]Long-term prophylaxis prior to study enrolment was defined as the last dose of long-term prophylaxis being discontinued within 100 days of the Screening-1 visit.
[b]Run-in period is from Screening-2 visit to randomisation.

The HAELO study achieved all primary and key secondary endpoints

Figure 3. HAELO primary and key secondary endpoints

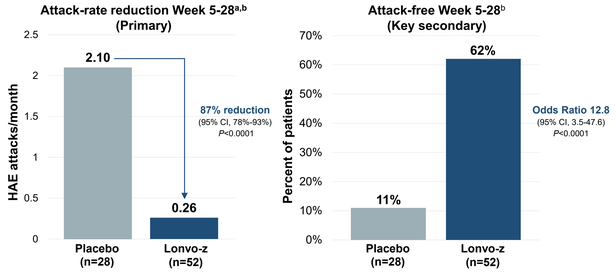


Table 2. Additional key secondary endpoints

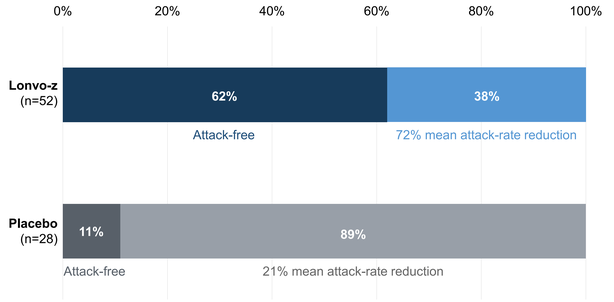
	Lonvo-z (n=52)	Placebo (n=28)
Number of attacks requiring on-demand treatment from Week 5-28, LS mean (95% CI)[a,b]	0.19 (0.10, 0.36)	1.79 (1.27, 2.54)
Reduction vs placebo (95% CI)	**89% (79%, 94%), *P*<0.0001**	
Number of moderate/severe attacks from Week 5-28, LS mean (95% CI)[a,b]	0.11 (0.06, 0.23)	1.23 (0.84, 1.81)
Reduction vs placebo (95% CI)	**91% (81%, 96%), *P*<0.0001**	
Change in AE-QoL total score from baseline to Week 28, LS mean (95% CI)[c,d]	-23.51 (-27.64, -19.38)	-6.47 (-12.26, -0.68)
LS mean difference vs placebo (95% CI)	**-17.04 (-24.15, -9.93), *P*<0.0001**	

[a]The mean number of HAE attacks per month is estimated using a Poisson regression model with Pearson chi-square scaling of standard error with treatment arm and baseline attack rate (>3 vs ≤3 attacks per month) as covariates. Baseline is defined as the time from date of Screening-2 visit to randomisation. A month is defined as 28 days.
[b]For patients who initiated any long-term prophylaxis before the Week 28 assessment, only attacks that started prior to prophylaxis initiation were included in the analysis. For patients who did not reach Week 28 assessment, all data through their latest attack assessment were included.
[c]The total score change from baseline at Week 28 is estimated using mixed model repeated measures analysis with baseline total score, treatment arm, visit, and treatment by visit interaction as fixed effects, with participant as a random effect. For patients who initiated any long-term prophylaxis before the Week 28 assessment, only AE-QoL data collected prior to prophylaxis initiation were included in the analysis.
[d]At Week 28, n=44 in the lonvo-z arm and n=20 in the placebo arm.
AE-QoL, Angioedema Quality of Life questionnaire; HAE, hereditary angioedema; LS, least-squares.

All patients in the lonvo-z arm experienced attack-rate reductions from baseline during Week 5-28

- The overall mean (SD) attack-rate reduction from Week 5-28 compared with baseline for patients treated with lonvo-z was 89% (20.3) compared with 29% (45.4) for placebo
  - All patients treated with lonvo-z improved
- All patients treated with lonvo-z remained LTP-free through the latest follow-up
  - Two patients in the placebo arm resumed LTP during the primary observation period and discontinued just prior to crossover

Figure 4. Change in attack-rate from Week 5-28 compared with baseline[a]

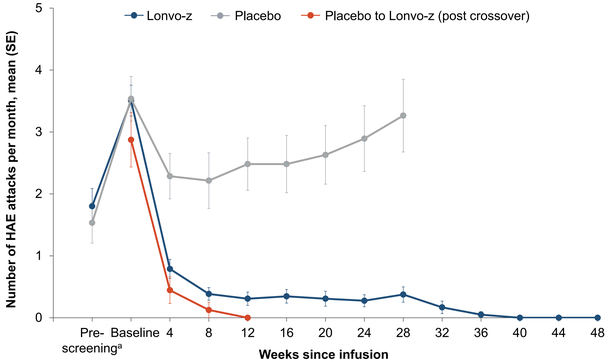


[a]Baseline attack rate is from Screening-2 visit to randomisation.

Rapid attack-rate reductions were observed after lonvo-z infusion

- All patients treated with lonvo-z had a rapid reduction in HAE attacks, reaching levels lower than attack rates observed prescreening while patients were receiving standard of care therapy

Figure 5. Monthly hereditary angioedema attack rate over time



Lonvo-z (n)	52	52	52	52	52	52	52	50	44	43	20	8	6	3	
Placebo (n)	28	28	28	28	27	27	27	25	21	0	0	0	0	0	
Placebo to Lonvo-z (n)	0	20	20	8	3	0	0	0	0	0	0	0	0	0	

[a]Prescreening monthly attack rate was patient reported and calculated based on attacks occurring in the 90 days prior to the Screening visit.
During the efficacy evaluation period, 2 patients in the placebo arm restarted LTP due to a high number of attacks. For these patients, data were censored at the time of LTP initiation and only attacks occurring prior to LTP initiation were included in the analysis. Both patients discontinued LTP before receiving the lonvo-z crossover infusion.
HAE, hereditary angioedema; LTP, long-term prophylaxis.

Lonvo-z had a favourable safety and tolerability profile

Table 3. HAELO treatment-emergent adverse events through Week 28

	Lonvo-z (n=52) n (%)	Placebo (n=28) n (%)
TEAEs in ≥10% of patients in the lonvo-z arm		
Infusion-related reaction	32 (62)	5 (18)
Headache	10 (19)	3 (11)
Fatigue	7 (14)	3 (11)
Nasopharyngitis	7 (14)	9 (32)
Back pain	6 (12)	3 (11)
Upper respiratory tract infection	6 (12)	2 (7)
Serious TEAEs	0	1 (4)[a]
Grade ≥3 TEAEs	0	0

[a]One patient in the placebo arm experienced a serious TEAE (Grade 2 supraventricular tachycardia on Day 39, which resolved in 2 days).
TEAE, treatment-emergent adverse event.

- No serious TEAEs or Grade ≥3 TEAEs were reported in the lonvo-z arm
- All infusion-related reactions were mild or moderate and were transient
- There were no meaningful differences between treatment arms in clinical chemistries
  - A single Grade 2 alanine aminotransferase elevation was observed in the lonvo-z arm; it resolved without treatment in 1 week
- As of the data cutoff, a consistent safety profile was observed in patients who crossed over to lonvo-z after Week 28, although follow-up was limited[a]

[a]In the placebo to lonvo-z crossover arm, median follow-up was 1.4 months (range: 0.3-4.5 months).
TEAE, treatment-emergent adverse event.

Conclusions

- A one-time treatment with lonvo-z 50 mg resulted in a significantly lower attack rate and improved quality of life compared with placebo
- Lonvo-z enabled the majority of patients to become attack-free without LTP
- The safety profile of lonvo-z was favourable and consistent with the Phase 1/2 study
- Results of this Phase 3 study support the use of lonvo-z as a one-time treatment for HAE-C1INH
- The safety and efficacy of lonvo-z will be further evaluated in the long-term follow-up study

HAE-C1INH, hereditary angioedema due to C1 inhibitor deficiency.

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ORIGINAL ARTICLE

Lonvoguran Ziclumeran — in vivo CRISPR Gene Editing in Hereditary Angioedema

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