Lonvoguran Ziclumeran Demonstrated Consistent Benefit in All Hereditary Angioedema Patient Subgroups in the Phase 3 HAELO Study

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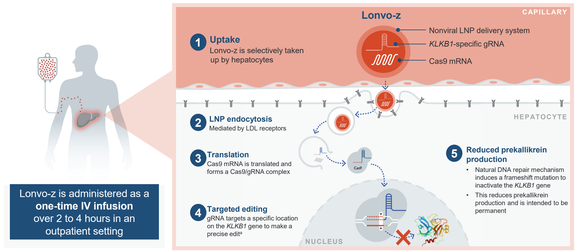
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Poster R072

Introduction

- 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 to treat hereditary angioedema due to C1 inhibitor deficiency or dysfunction (HAE-C1INH; **Figure 1**)[1,2]

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



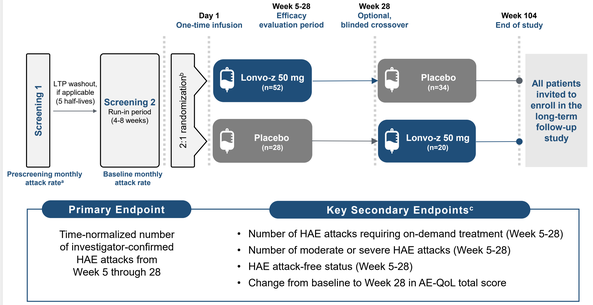
[a]The Cas9 enzyme is only activated when the gRNA is highly matched to *KLKB1*.[3]
Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; gRNA, guide RNA; IV, intravenous; LDL, low-density lipoprotein; LNP, lipid nanoparticle; mRNA, messenger RNA.

- In the Phase 1/2 study (NCT05120830), with up to 3 years of follow-up, 97% (31/32) of patients became attack-free and long-term prophylaxis (LTP)-free after a one-time treatment with lonvo-z 50 mg; lonvo-z was well tolerated[4]
- The Phase 3 HAELO study (NCT06634420), designed to evaluate the efficacy and safety of lonvo-z in patients with HAE-C1INH, achieved its primary endpoint; the least squares mean monthly attack rate from Week 5-28 was 0.26 (95% CI: 0.15, 0.45) with lonvo-z 50 mg vs 2.10 (95% CI: 1.55, 2.86) with placebo (relative difference: -87%; 95% CI: -93%, -78%; $P<0.001$)[5]
- Here, we present attack rate analyses based on patient demographics and baseline characteristics in the HAELO study

Methods

- Eligible patients were aged ≥16 years with HAE-C1INH and had ≥2 investigator-confirmed attacks during the up to 8-week run-in period (**Figure 2**)
- The primary analysis was conducted when at least 60 patients reached Week 28
- Attack rate ratios (lonvo-z vs placebo) were evaluated in all prespecified subgroups

Figure 2. HAELO study design[5]



Primary Endpoint

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

Key Secondary Endpoints[c]

- 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 total score

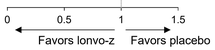
[a]The prescreening monthly attack rate was calculated based on patient-reported attacks occurring in the 90 days prior to the Screening visit. [b]Patients were stratified by baseline number of investigator-confirmed HAE attacks per month from Screening-2 visit to randomization (>3 vs ≤3). [c]Attacks were investigator confirmed; attack rate was time normalized.
AE-QoL, Angioedema Quality of Life Questionnaire; HAE, hereditary angioedema; LTP, long-term prophylaxis.

Results: Attack rate reduction favored lonvo-z over placebo in all subgroups

- As of February 10, 2026, the median (range) follow-up was 7.5 (4.9-12.8) months
- Patient demographics and baseline characteristics were balanced between arms
- All 80 patients continue to be followed in the study; no patient has discontinued
- Following lonvo-z infusion, the median (range) attack rate during Weeks 5-28 was 0 (0-3.17), compared with 2.92 (0-7.79) for placebo, representing a >99% change from baseline in median HAE attack rate
- All subgroups demonstrated a consistent benefit in attack rate reduction favoring lonvo-z over placebo (attack rate ratio <1 favors lonvo-z), regardless of demographic and physical (**Figure 3**) and baseline (**Figure 4**) characteristics
  - Attack rate ratios were not estimable for the aged ≥65 years (N=6; lonvo-z n=2) and HAE-C1INH-Type 2 (N=6; lonvo-z n=3) subgroups due to their small sample sizes; however, the 5 patients randomized to lonvo-z in these subgroups were attack-free during the efficacy evaluation period
- Results should be interpreted with caution given the limited sample sizes in certain subgroups

Figure 3. A consistent benefit favoring lonvo-z over placebo was observed across all demographic and physical characteristic subgroups[6]

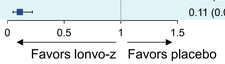
Subgroup	Lonvo-z, n	Placebo, n	Attack rate ratio (95% CI)
Age			
<50 years	39	20	0.14 (0.08, 0.25)
50 to <65 years	11	4	0.08 (0.02, 0.31)
≥65 years	2	4	NE
Sex			
Female	35	20	0.16 (0.08, 0.30)
Male	17	8	0.07 (0.02, 0.25)
BMI categories			
<25 kg/m²	16	6	0.12 (0.04, 0.32)
25 to <30 kg/m²	19	11	0.11 (0.03, 0.36)
≥30 kg/m²	17	11	0.16 (0.07, 0.36)



BMI, body mass index; NE, not evaluable.

Figure 4. A consistent benefit favoring lonvo-z over placebo was observed across all baseline characteristic subgroups[6]

Subgroup	Lonvo-z, n	Placebo, n	Attack rate ratio (95% CI)
HAE-C1INH			
Type 1	49	25	0.13 (0.07, 0.23)
Type 2	3	3	NE
Historical attack severity			
Mild	7	5	0.12 (0.02, 0.58)
Moderate	30	20	0.13 (0.06, 0.26)
Severe	15	3	0.10 (0.03, 0.30)
Historical attack frequency			
≤3 attacks/month	38	19	0.10 (0.04, 0.21)
>3 attacks/month	14	9	0.20 (0.09, 0.44)
Prior LTP use at study entry[a]			
Yes	35	22	0.08 (0.04, 0.18)
No	17	6	0.23 (0.09, 0.55)
Prior use of lanadelumab as LTP			
Yes	25	12	0.08 (0.03, 0.20)
No	27	16	0.18 (0.09, 0.34)
Baseline attack rate			
≤3 attacks/month	24	12	0.21 (0.08, 0.54)
>3 attacks/month	28	16	0.11 (0.05, 0.22)

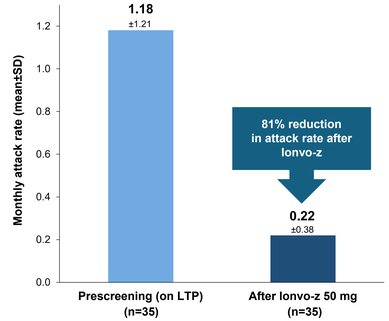


[a]Prior use of LTP at study entry was defined as the last dose of LTP being discontinued within 100 days of Screening-1 visit.
C1INH, C1 inhibitor; HAE, hereditary angioedema; LTP, long-term prophylaxis; NE, not evaluable.

Patients treated with lonvo-z 50 mg had improved HAE outcomes compared with prior LTP use

- In patients with LTP use at study entry (n=35), lonvo-z 50 mg led to an 81% reduction in attack rates compared with patient-reported prescreening attack rates (**Figure 5**)

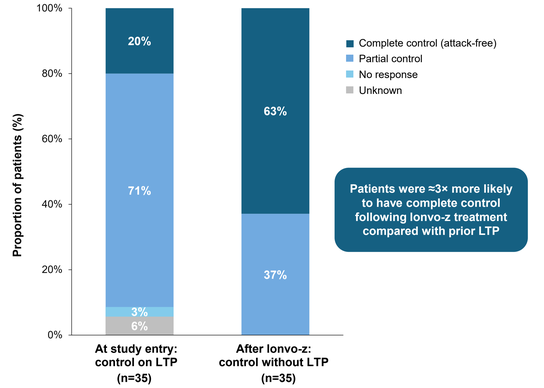
Figure 5. Attack rates following lonvo-z infusion (Week 5-28) compared with prior LTP[a]



[a]Prior use of LTP at study entry was defined as the last dose of LTP being discontinued within 100 days of Screening-1 visit. Monthly attack rate at Screening was based on patient-reported attacks occurring in the 90 days prior to the Screening visit.
LTP, long-term prophylaxis.

- All patients treated with lonvo-z 50 mg experienced a reduction from baseline in attack rate or were attack-free, including those on prior LTP and those with no prior LTP use at study entry
- Among patients with LTP use at study entry (n=35), 97% (34/35) experienced stable or improved control of their HAE following treatment with lonvo-z compared with their prior LTP (**Figure 6**)

Figure 6. HAE attack control before and after lonvo-z[a] (Week 5-28) in patients with prior LTP[b]



[a]Attack response was defined based on the reduction in monthly attack rate from baseline: 100% reduction was considered complete control; >0% to <100% reduction was considered partial control; 0% reduction was considered no response. [b]Prior use of LTP at study entry was defined as the last dose of LTP being discontinued within 100 days of Screening-1 visit. Best response to prior LTP was reported categorically by patients.
HAE, hereditary angioedema; LTP, long-term prophylaxis.

Lonvo-z had a favorable safety and tolerability profile

- No serious or Grade ≥3 treatment-emergent adverse events were reported with lonvo-z (**Table 1**)
- All infusion-related reactions were mild or moderate and transient
- 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 (median [range] follow-up time: 1.4 months [0.3-4.5 months])

Table 1. HAELO TEAEs through Week 28[5]

	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 (13)	3 (11)
Nasopharyngitis	7 (13)	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.

Conclusions

- In the Phase 3 HAELO study, one-time treatment with lonvo-z 50 mg substantially reduced attack rates compared with placebo without the need for LTP
  - Benefits in attack rate reduction of lonvo-z compared with placebo were consistent across all subgroups, with no significant differences corresponding to demographics or baseline characteristics
- One-time treatment with lonvo-z 50 mg reduced monthly attack rates and improved or maintained attack response compared with LTP use at study entry
  - Attack control on prior LTP did not impact patient response to lonvo-z, and reductions in attack rate following lonvo-z 50 mg were observed regardless of prior LTP efficacy
- The safety profile of lonvo-z 50 mg was favorable and paralleled the profiles observed in the Phase 1/2 studies[7]
- Results of the HAELO study support the use of lonvo-z as a one-time treatment for HAE-C1INH

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

DISCLOSURES

MAR has 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.

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