Long-Term Durability and Safety of Lonvoguran Ziclumeran (Lonvo-z; NTLA-2002) 50 mg in Patients With Hereditary Angioedema

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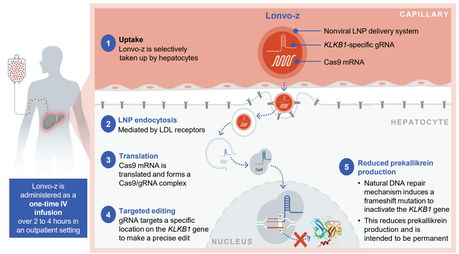
Introduction

- In hereditary angioedema (HAE), C1 esterase inhibitor deficiency imbalances the kallikrein-kinin system, leading to excess bradykinin production and debilitating swelling attacks[1]
- Kallikrein, a facilitator of bradykinin production, is a clinically validated target for preventing HAE attacks[2,3]
- Lonvoguran ziclumeran (lonvo-z; NTLA-2002) is an investigational *in vivo* CRISPR-based one-time treatment[4,5]
- Lonvo-z is designed to permanently inactivate the *KLKB1* gene to reduce kallikrein production with the goal of treating HAE (**Figure 1**)[4,5]

Figure 1. Lonvo-z mechanism of action[4,5]



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.

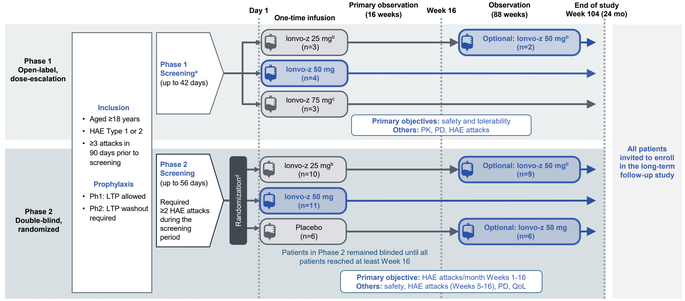
Objective

- Describe longer-term durability and safety among all patients who were treated with lonvo-z 50 mg in the Phase 1/2 study (NCT05120830)

Methods

- Lonvo-z was evaluated in a Phase 1/2 study (**Figure 2**); details have been reported previously[4,5]
  - Phase 1: an open-label, dose-escalation, multicenter study in adults with HAE[4]
  - Phase 2: a double-blind study in adults with HAE who were randomly assigned in a 2:2:1 ratio to receive lonvo-z as a single dose of 25 mg or 50 mg, or placebo[5]
  - Following identification of the optimal biological dose (50 mg), patients who received placebo or a suboptimal dose (25 mg) were allowed to receive a single dose of lonvo-z 50 mg, provided they met eligibility criteria
- Once patients completed Phase 1/2, they entered the long-term follow-up study; those data are included as part of the follow-up time
- A pooled analysis was conducted following treatment with lonvo-z 50 mg in the Phase 1/2 study

Figure 2. Lonvo-z Phase 1/2 study design



Data cutoff: Aug 29, 2025. ClinicalTrials.gov ID: Phase 1/2: NCT05120830; Long-term follow-up study: NCT06262399.
*No prespecified number of attacks required. [a]Patients receiving lonvo-z 25 mg could remain on the study beyond 104 weeks to receive the optimal biological dose of 50 mg. Two patients did not receive a follow-on dose of lonvo-z 50 mg (1 due to patient choice, 1 due to ineligibility [transient alanine aminotransferase elevation]). Both patients remain attack-free as of the current data cutoff date. [b]The 3 patients who received lonvo-z 75 mg remain attack-free as of the current data cutoff date. [c]Randomization was 2:2:1.
HAE, hereditary angioedema; LTP, long-term prophylaxis; PD, pharmacodynamics; Ph, phase; PK, pharmacokinetics; QoL, quality of life.

Results

- As of August 29, 2025, 32 patients have been treated with lonvo-z 50 mg in the Phase 1/2 study (**Table 1**) and 17 patients have entered the long-term follow-up study
- The median follow-up after receiving lonvo-z 50 mg was 12.2 months (range: 2.4 months to 3.0 years) in the Phase 1/2 and long-term follow-up studies
- More than half of the patients (56%) were receiving long-term prophylaxis (LTP) prior to study entry

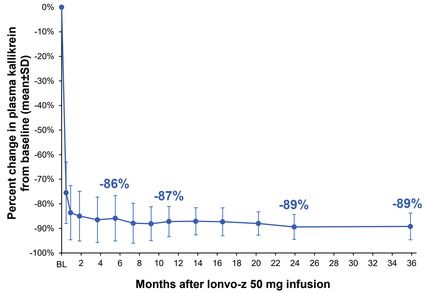
Table 1. Demographics and baseline characteristics

Parameter		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 (%)	Any	18 (56)
	Lanadelumab	5 (16)
	Attenuated androgens	5 (16)
	Berotralstat	5 (16)
	C1 esterase inhibitor	2 (6)
	Tranexamic acid	1 (3)
Historic HAE typical 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 long-term prophylaxis, whichever occurred first. In Phase 1, patients may have been on long-term prophylaxis.
HAE, hereditary angioedema; LTP, long-term prophylaxis.

- A one-time treatment with lonvo-z 50 mg led to deep, stable, and durable reductions in plasma kallikrein (**Figure 3**)

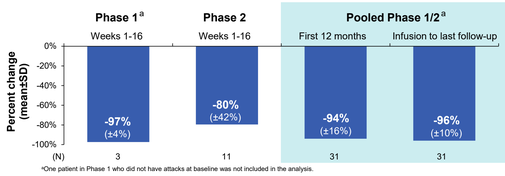
Figure 3. Change in kallikrein over time following lonvo-z 50 mg



Data collected as of Sept 26, 2025. One month=30.4375 days. BL, baseline.

- In a pooled analysis of the Phase 1/2 study, patients had a >90% mean reduction in attacks per month (**Figure 4**)
- Patients had a mean±SD of 0.2±0.5 attacks/month within the first 12 months following lonvo-z 50 mg infusion
- Patients had a mean±SD of 0.2±0.4 attacks/month following lonvo-z 50 mg infusion through last follow-up

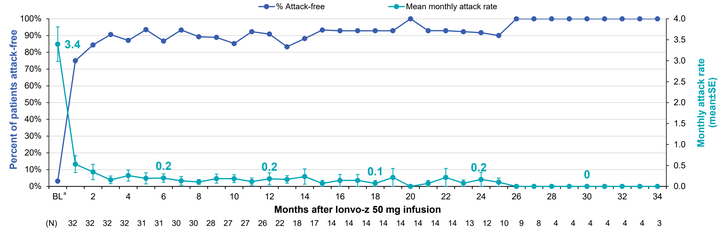
Figure 4. Percent reduction in monthly attack rate from baseline following lonvo-z 50 mg



[a]One patient in Phase 1 who did not have attacks at baseline was not included in the analysis.

- The majority of patients were attack-free after lonvo-z 50 mg; attack rate was low and stable over time with up to 3 years of follow-up (**Figure 5**)

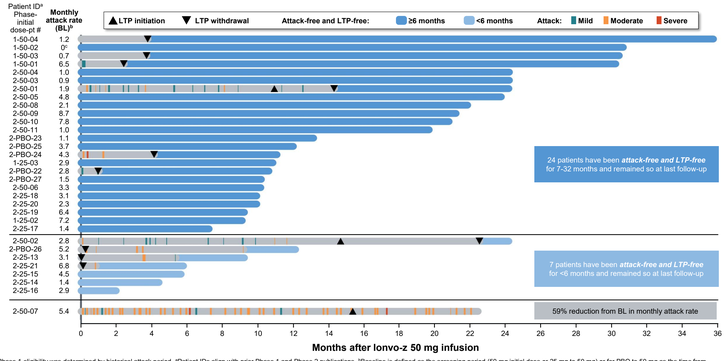
Figure 5. Attack-free status and monthly attack rate following lonvo-z 50 mg



One month=28 days. The monthly attack rate is calculated as number of attacks that occurred during each 28-day interval. Timepoints with data from ≥3 patients are presented.
[a]One patient had no attacks during the screening period. This patient was receiving long-term prophylaxis until 19 days prior to lonvo-z infusion. BL, baseline.

- Of the patients who became attack-free (31/32, 97%), all were also without LTP at the latest follow-up (**Figure 6**)
- Most patients who experienced HAE attacks after lonvo-z 50 mg experienced attacks in multiple locations, including abdominal, peripheral, and laryngeal attacks

Figure 6. After becoming attack-free and LTP-free for ≥6 months, all patients maintained their response



Phase 1 eligibility was determined by historical attack period. *Patient IDs align with prior Phase 1 and Phase 2 publications. [a]Baseline is defined as the screening period (50 mg initial dose or 25 mg to 50 mg) or for PBO to 50 mg as the time from informed consent to 50 mg infusion or start of any LTP, whichever occurred first. [b]Patient had 0.9 attacks per month in the 3 months prior to screening. BL, baseline; LTP, long-term prophylaxis; PBO, placebo; pt, patient.

- The most common treatment-emergent adverse event occurring within 28 days of lonvo-z 50 mg infusion was infusion-related reaction (IRR) (**Table 2**)
  - Most IRRs occurred shortly after starting the infusion and resolved the same day; all were Grade 1 or 2
- There were no clinically significant shifts in coagulation parameters
  - Grade 1 bleeding adverse events (AEs): epistaxis (n=2) and vaginal hemorrhage (n=1)
  - One serious AE (pulmonary embolism) occurred 1 year after infusion in a patient with multiple risk factors; the event resolved without sequelae
- There were no clinically significant shifts in liver enzymes
  - Grade 2 aspartate aminotransferase elevation occurred in 1 patient (Days 1-4)
  - As previously reported, 2 patients treated with lonvo-z 25 mg experienced transient, asymptomatic Grade 2 liver transaminase elevations with peak values at Day 22[5] and Week 156,[6] respectively; all events resolved spontaneously without intervention
- Safety of lonvo-z 50 mg after receiving the suboptimal dose (25 mg) was consistent with the overall population
- In the long-term follow-up study (n=17), there were no serious AEs or treatment-related AEs reported with lonvo-z 50 mg

Table 2. A one-time treatment of lonvo-z 50 mg was well tolerated with no long-term risks observed with up to 3 years of follow-up

	Patients treated with lonvo-z 50 mg in the Phase 1/2 study (N=32)[a]	
	Reported within 28 days of infusion, n (%)	Reported >28 days after infusion up to LTFU, n (%)
Any TEAE (≥10% of patients after lonvo-z 50 mg)	27 (84)	30 (94)
Infusion-related reaction	17 (53)	0
Fatigue	11 (34)	0
Headache	6 (19)	1 (3)
Abdominal pain	2 (6)	2 (6)
Nasopharyngitis	1 (3)	8 (25)
Upper respiratory tract infection	1 (3)	6 (19)
Arthralgia	1 (3)	4 (13)
COVID-19	1 (3)	4 (13)
Back pain	0	5 (16)
Any serious AE	0	1 (3)
Pulmonary embolism	0	1 (3)[b]

[a]AEs that occurred after each patient received lonvo-z 50 mg are reported. [b]Occurred 1 year after the infusion; the patient had multiple risk factors, which included recent COVID infection, ongoing history of smoking, and obesity; the event resolved without sequelae. AE, adverse event; LTFU, long-term follow-up; TEAE, treatment-emergent adverse event.

Conclusions

- In this pooled analysis of patients treated with lonvo-z 50 mg in the Phase 1/2 study (N=32; up to 3 years of follow-up), a one-time treatment led to:
  - Deep, stable, and durable reductions in plasma kallikrein
  - Mean monthly attack rates that were consistently low, approaching zero attacks/month
  - The majority of patients becoming attack-free and LTP-free
  - Maintenance of attack-free and LTP-free responses
- Lonvo-z 50 mg had a well-tolerated safety profile with no long-term risks identified
- The fully enrolled, ongoing Phase 3 HAELO study (NCT06634420) is evaluating lonvo-z 50 mg versus placebo in patients with HAE

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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. Longhurst HJ, et al. Presented at: EAACI Congress; June 13-16, 2025; Glasgow, Scotland.

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