Safety/Tolerability of a One-Time Infusion of Lonvoguran Ziclumeran (lonvo-z; NTLA-2002) for Hereditary Angioedema

Poster #R111

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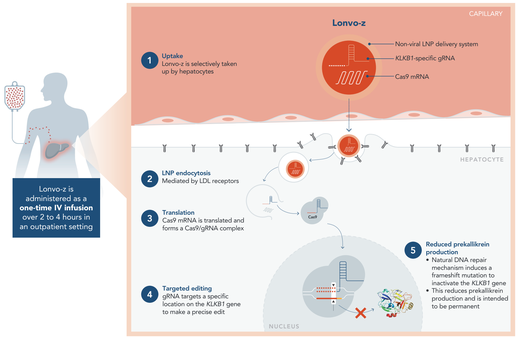
INTRODUCTION

- In hereditary angioedema (HAE), C1 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 to prevent HAE attacks[4,5] (**Figure 1**)

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

- To report updated safety and tolerability of all patients treated with lonvo-z 50 mg in the Phase 1/2 study (NCT05120830), focusing on adverse events (AEs) occurring within the first 24 hours after the start of infusion

DISCLOSURES:

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. **DMC** has received speaking fees from CSL Behring, Ionis Pharmaceuticals, Pharvaris, and Takeda; consultancy fees from Astria, BioCryst, CSL Behring, Ionic Pharmaceuticals, KalVista, Pharming, Pharvaris, and Takeda; and research support from Ionic Pharmaceuticals, KalVista, Pharvaris, and Takeda. **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, Phavaris, Seqirus, and Takeda; and received honorarium from GlaxoSmithKline. **AG**, **MYS**, and **AS** are employees of and hold equity in Intellia Therapeutics. **HJL** has acted as a consultant or speaker, received educational sponsorship or participated in research with Astria Therapeutics, CSL Behring, Intellia Therapeutics, KalVista, Pharvaris, and Takeda.

ACKNOWLEDGMENTS:

We thank the volunteers who are participating in this study, the investigators, researchers, and coordinators who are contributing to this study, as well as the staff of Simbec-Orion for assistance with study management and operations support. This study is sponsored by Intellia Therapeutics. Medical writing and editorial support were provided by Ellen Woon, PhD, and Melissa Austin of Apollo Medical Communications, part of Helios Global Group, and funded by Intellia Therapeutics.

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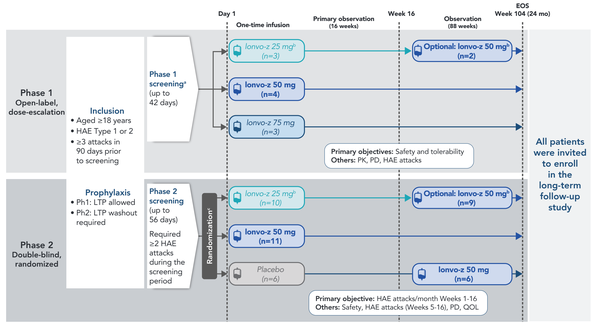
Presented at the American College of Allergy, Asthma & Immunology (ACAAI) Congress, November 6-10, Orlando, FL

METHODS

- Lonvo-z was evaluated in a Phase 1/2 study (**Figure 2**); details have been reported previously[4,5]
  - The Phase 1 portion was an open-label, dose-escalation, multicenter study in adults with HAE[4]
  - The Phase 2 portion was a double-blind study in which adults with HAE 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

FIGURE 2. LONVO-Z PHASE 1/2 STUDY[4,5]

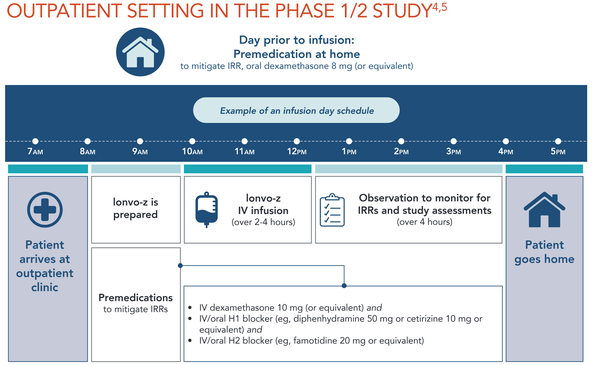
50 mg was selected as the optimal dose for Phase 3



Data cutoff: Aug 29, 2025. ClinicalTrials.gov ID: Phase 1/2: NCT05120830; Long-term follow-up study: NCT06262399.
[a]No prespecified number of attacks required. [b]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 (one due to patient choice, one due to ineligibility (transient alanine aminotransferase elevation)). [c]Randomization was 2:2:1.
EOS, end of study; HAE, hereditary angioedema; LTP, long-term prophylaxis; PD, pharmacodynamics; Ph, phase; PK, pharmacokinetics; QOL, quality of life.

- A descriptive analysis was conducted of the infusion-related reactions (IRRs) reported after a one-time infusion of lonvo-z, including time to onset, duration, and outcome (**Figure 3**)
  - IRRs are a known side effect of intravenously administered proteins and lipid nanoparticles[6]
  - If an IRR occurred during the study, all associated symptoms were additionally captured via a drop-down list, with the option to report "other" and use free text to provide additional detail

FIGURE 3. LONVO-Z WAS INFUSED OVER 2-4 HOURS IN AN OUTPATIENT SETTING IN THE PHASE 1/2 STUDY[4,5]



H1, histamine receptor 1; H2, histamine receptor 2; IRR, infusion-related reaction; IV, intravenous.

RESULTS

- As of August 29, 2025, 32 patients have been treated with lonvo-z 50 mg in the Phase 1/2 study (**Table 1**)
- The median duration of 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
- Half of the patients (50%) were taking long-term prophylaxis (LTP) prior to study entry

TABLE 1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristics at Phase 1/2 study baseline		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)
Long-term prophylaxis immediately prior to Phase 1/2 study entry, n (%)	Any	18 (50)
	Lanadelumab	5 (16)
	Attenuated androgens	5 (16)
	Berotralstat	5 (16)
	C1 esterase inhibitor	2 (6)
	Tranexamic acid	1 (3)
Historic typical attack severity, n (%)	Mild	4 (13)
	Moderate	21 (66)
	Severe	7 (22)
Mean baseline monthly attack rate, n (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.

- Most treatment-emergent AEs occurring within 28 days of lonvo-z 50 mg were IRRs, which generally occurred on the same day as the infusion (**Table 2**)
- One serious AE of pulmonary embolism occurred in a patient with confounding risk factors (including recent COVID-19 infection, ongoing history of smoking, obesity) ≈1 year after the infusion; the event resolved without sequelae

TABLE 2. A ONE-TIME TREATMENT OF LONVO-Z 50 MG WAS WELL TOLERATED WITH NO LONG-TERM RISKS IDENTIFIED WITH UP TO 3 YEARS OF FOLLOW-UP

	All 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)	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 SAE	0	1 (3)
Pulmonary embolism	0	1 (3)

AEs in patients who received 25 mg or 75 mg have been previously reported; no dose-limiting toxic effects were observed.[4,5]
[a]AEs that occurred after each patient received 50 mg are reported.
AE, adverse event; LTFU, long-term follow-up; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

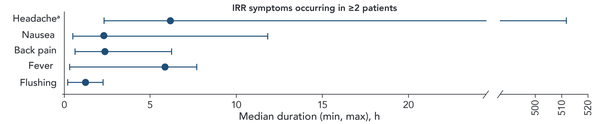
- Of all patients treated with lonvo-z 50 mg (N=32), 53% experienced an IRR (**Table 3**)
  - All IRRs were Grade 1 or 2
- IRRs had a rapid time to onset after infusion: median (range) time to onset was 18 minutes (immediately to 10 hours)
- Symptoms reported as "other" were reported in one patient each and were generally flu-like symptoms, such as body ache, chills, diarrhea; 3 were chest pain/tightness symptoms (no clinically significant findings on electrocardiogram; all resolved within minutes up to 5.1 hours)
- All IRRs resolved; the majority resolved within minutes to hours (**Figure 4**)
  - Median (range) duration of IRR was 14 hours (12 minutes to 21 days)
  - Most (59%; 10/17) IRRs resolved within 24 hours
  - IRR symptoms (maximum duration) lasting >24 hours in ≥1 patient were fever (28 hours), flushing (37 hours), abdominal bloating (3.5 days), increased thirst (7 days), and headache (22 days)

TABLE 3. IRR SUMMARY

	All patients treated with lonvo-z 50 mg (N=32)
Any TEAE of IRR, n (%)	**17 (53)**
Outcome – resolved	17 (100)
Resolved within 24 hours	10 (59)
IRR symptom reported in ≥2 patients, n (%)	
Fever	6 (19)
Headache	6 (19)
Back pain	3 (9)
Flushing	3 (9)
Nausea	3 (9)
Other	19 (59)[a]

Multiple IRR symptoms could be reported as part of a single IRR report. [a]Each "other" IRR symptom occurred in one patient.
IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.

FIGURE 4. IRR SYMPTOMS WERE TRANSIENT AND MOST RESOLVED WITHIN 24 HOURS



[a]One patient experienced a Grade 1 headache from Day 1 to Day 22 following lonvo-z 50 mg infusion. IRR, infusion-related reaction.

- Most patients (82%) with IRRs received their infusion without the need for a dose adjustment (**Table 4**)
  - All patients received the full dose of lonvo-z
  - No patients required overnight hospitalization or extended monitoring to manage IRRs
- Approximately one-third of all patients with an IRR received a concomitant medication
  - Medications commonly utilized included acetaminophen and dexamethasone

TABLE 4. MANAGEMENT OF IRR

IRR management strategy, n (%)		Patients with an IRR (n=17)
No change to infusion		14 (82)
Change to infusion	Infusion interruption	3 (18)
	Infusion rate change	0
	Permanent discontinuation	0
Use of concomitant medications		11 (65)

IRR, infusion-related reaction.

CONCLUSIONS

- To date, a one-time treatment with lonvo-z 50 mg infused over 2-4 hours in an outpatient setting was well tolerated, with IRRs being the most common AE reported
- Most IRRs occurred shortly after starting the infusion and resolved the same day
  - All patients received the full dose of lonvo-z
- Lonvo-z 50 mg enabled the majority of patients to become attack-free and LTP-free, which persisted through the most recent data cutoff date[7]
- Lonvo-z 50 mg is being further evaluated in patients with HAE in the ongoing Phase 3 HAELO study (NCT06634420), fully enrolled as of September 2025