Two-Year Durability/Safety of One-Time Lonvoguran Ziclumeran (Lonvo-z, NTLA-2002) 50 mg in Patients With Hereditary Angioedema

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Data cutoff date of 29 August 2025 with up to 3 years follow-up after lonvo-z 50 mg infusion

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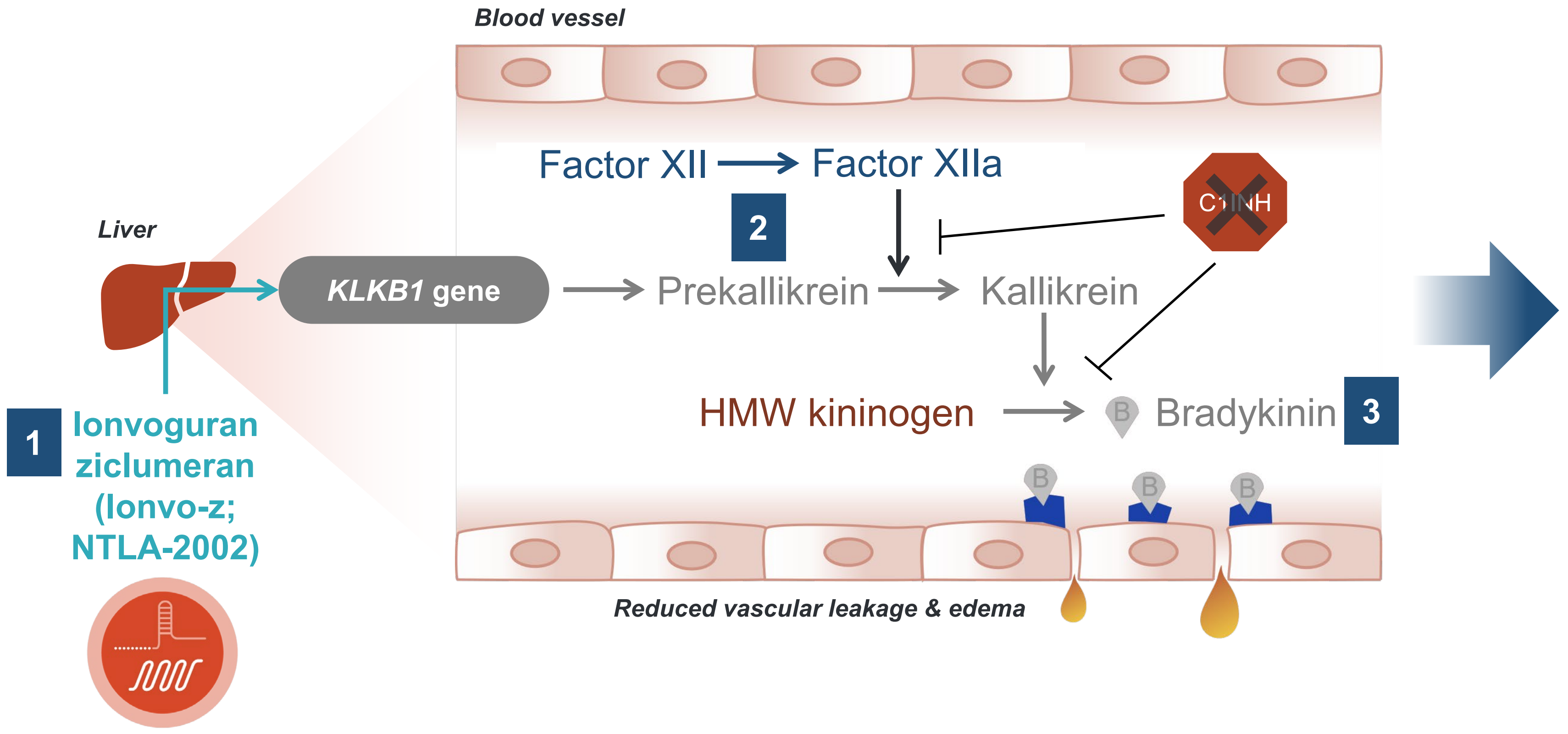
Disclosure

- Dr. Cohn 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

Lonvo-z is an investigational one-time treatment intended to inactivate the *KLKB1* gene to reduce HAE attacks

In HAE, C1 inhibitor deficiency imbalances the kallikrein-kinin system, leading to excess bradykinin production and debilitating swelling attacks



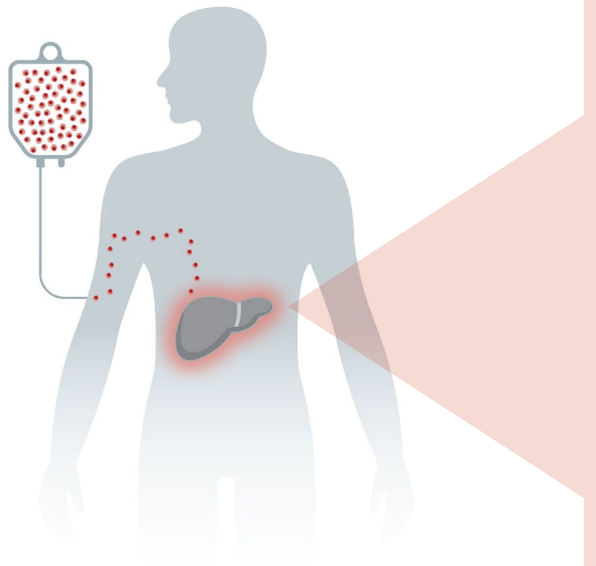
1 Lonvo-z is designed to inactivate the *KLKB1* gene to prevent production of kallikrein

2 Decreasing kallikrein rebalances the pathway by reducing bradykinin production

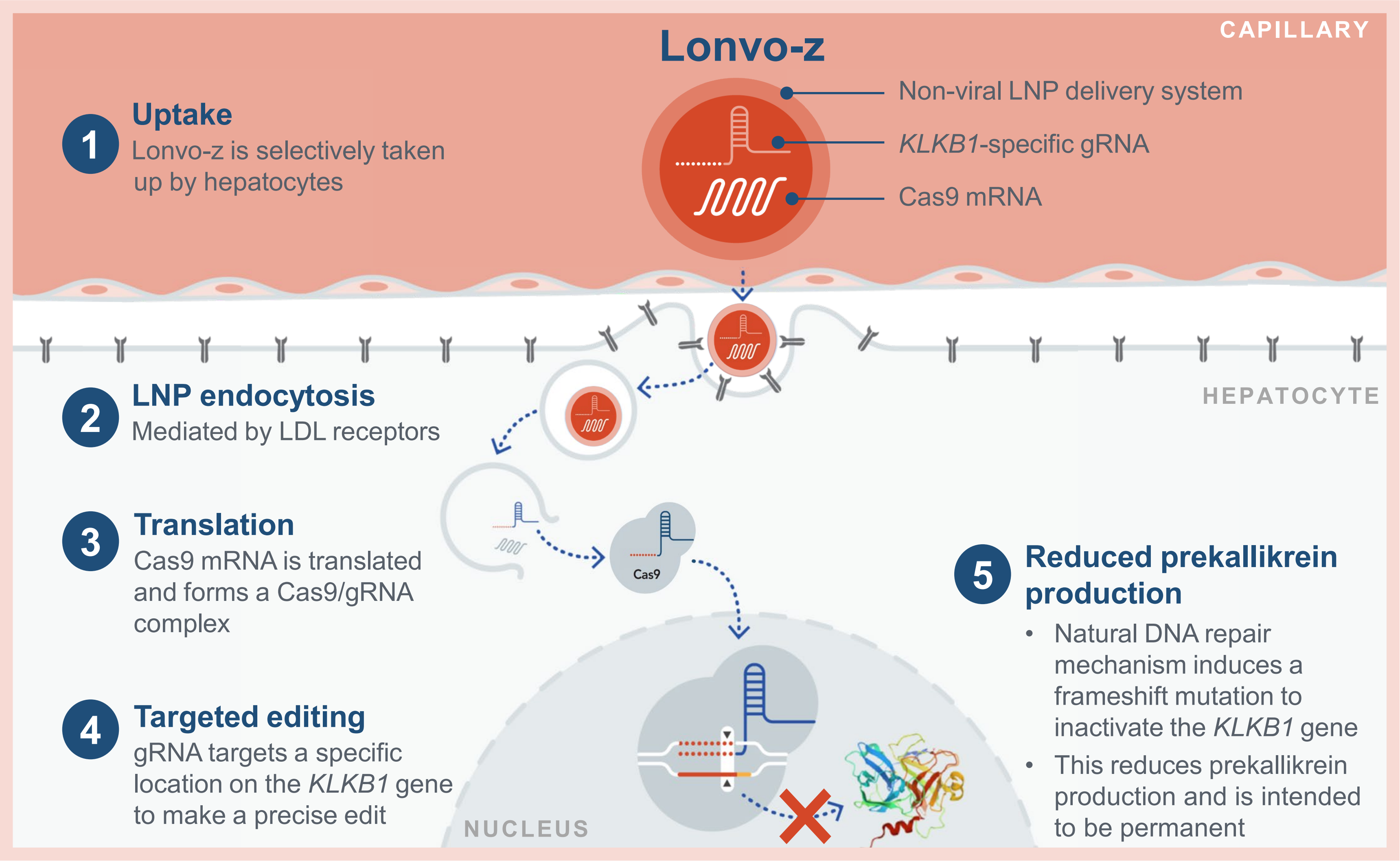
3 Reducing bradykinin reduces HAE attacks

C1INH, C1 esterase inhibitor; HAE, hereditary angioedema; HMW, high-molecular weight.
Adapted from Zuraw BL. *N Engl J Med*. 2008;359(10):1027-1036.
This presentation includes data for an investigational product not yet approved by regulatory authorities.

As an *in vivo* CRISPR-based therapy, lonvo-z was designed to make a precise and permanent edit to the *KLKB1* gene



Lonvo-z is administered as a **one-time IV infusion** over 2 to 4 hours in an outpatient setting



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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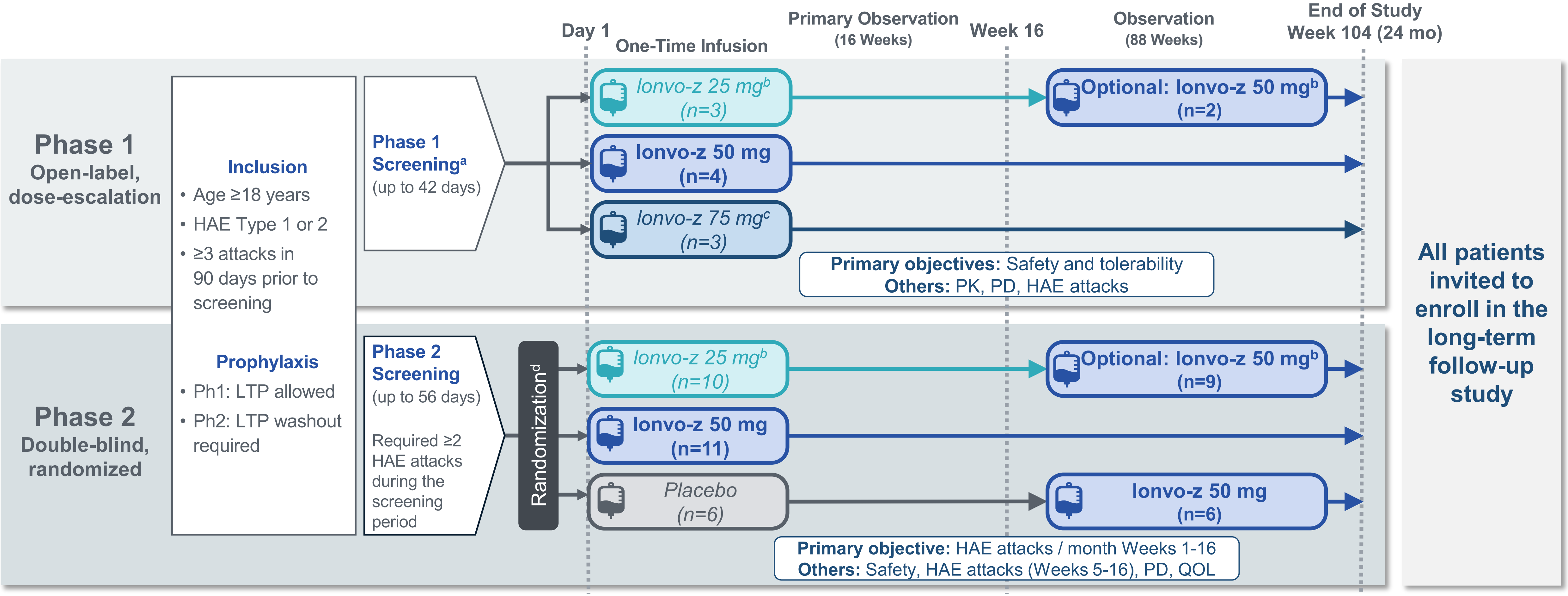
Pooled analysis of patients treated with lonvo-z 50 mg in the Phase 1/2 study

50 mg was selected as the optimal dose for Phase 3



Data cutoff: 29 Aug 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]). Both patients remain attack-free as of the current data cutoff date. [c]The three patients who received lonvo-z 75 mg remain attack-free as of the current data cutoff date. [d]Randomization was 2:2:1.
HAE, hereditary angioedema; LTP, long-term prophylaxis; PD, pharmacodynamics; Ph, phase; PK, pharmacokinetics; QOL, quality of life.
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Phase 1/2 demographics and baseline characteristics

Pooled Phase 1/2 Analysis

Parameter	Lonvo-z 50 mg (N=32)
Age, median (range), years	48.5 (18, 76)
Female, n (%)	16 (50)
Hereditary angioedema type, n (%)	
Type 1	26 (81)
Type 2	6 (19)
Long-term prophylaxis 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 attack severity, n (%)	
Mild	4 (13)
Moderate	21 (66)
Severe	7 (22)
Mean baseline monthly attack rate, mean (SD)[a]	3.4 (2.3)

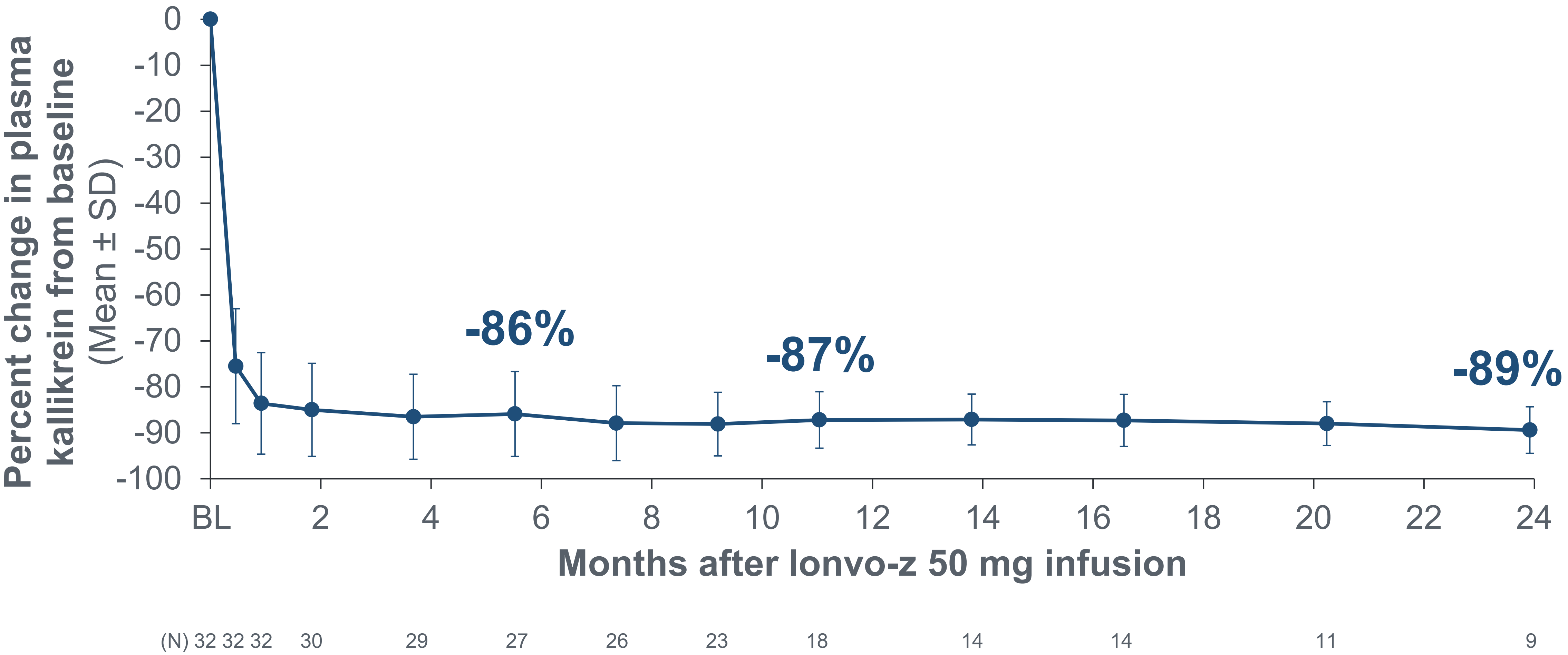
Median follow-up after receiving lonvo-z 50 mg: 12.2 months (range: 2.4 months to 3.0 years)
in the Phase 1/2 and long-term follow-up studies

Data cutoff: 29 Aug 2025.

[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 long-term prophylaxis, whichever occurred first. In Phase 1, patients may have been on long-term prophylaxis. SD, standard deviation. This presentation includes data for an investigational product not yet approved by regulatory authorities.

Deep kallikrein reduction remained stable after a one-time treatment with lonvo-z 50 mg

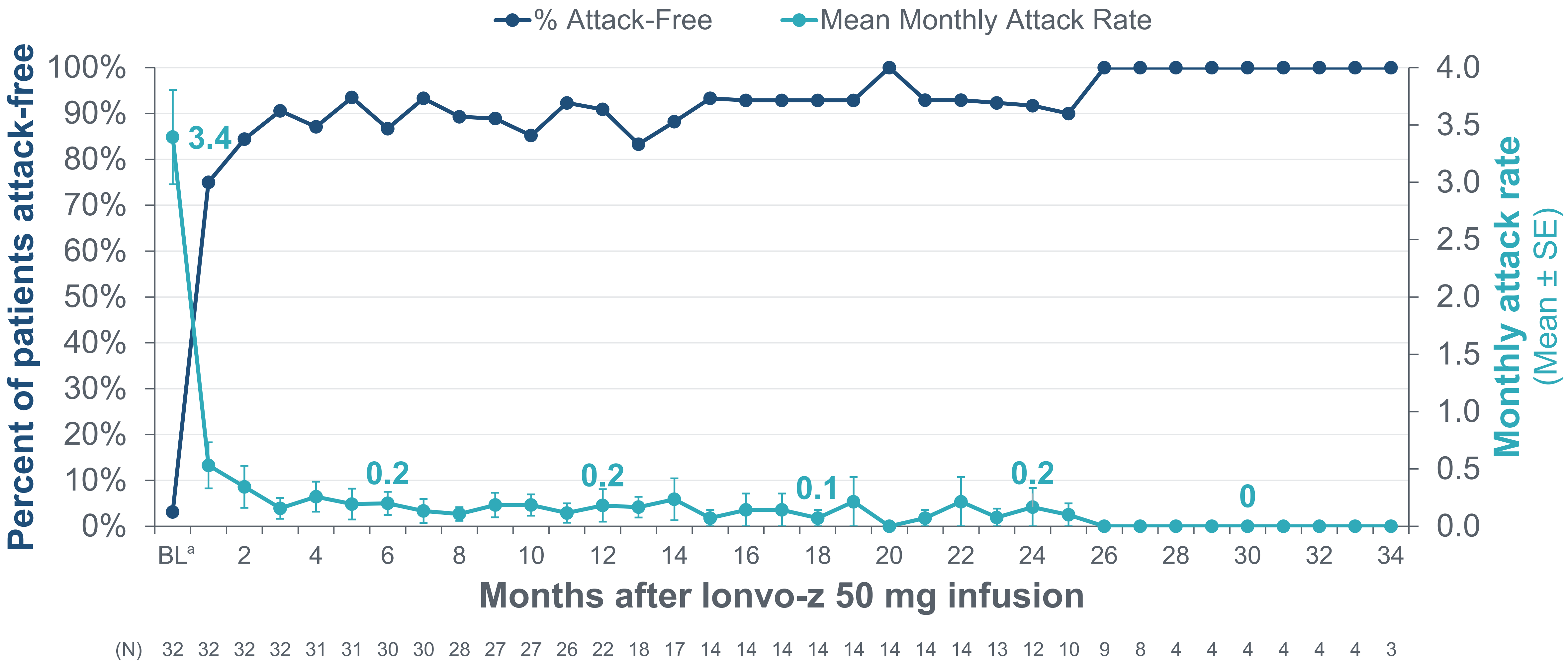
Pooled Phase 1/2 Analysis



Data cutoff: 29 Aug 2025.
BL, baseline; SD, standard deviation. One month = 30.4375 days
This presentation includes data for an investigational product not yet approved by regulatory authorities.

The majority of patients were attack-free after a one-time treatment with lonvo-z 50 mg; attack rate was low and stable over time with up to 3 years of follow-up

Pooled Phase 1/2 Analysis



Data cutoff: 29 Aug 2025.

The monthly attack rate is calculated as number of attacks that occurred during each 28-day interval. Timepoints with data from at least 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; SE, standard error. 1 month = 28 days

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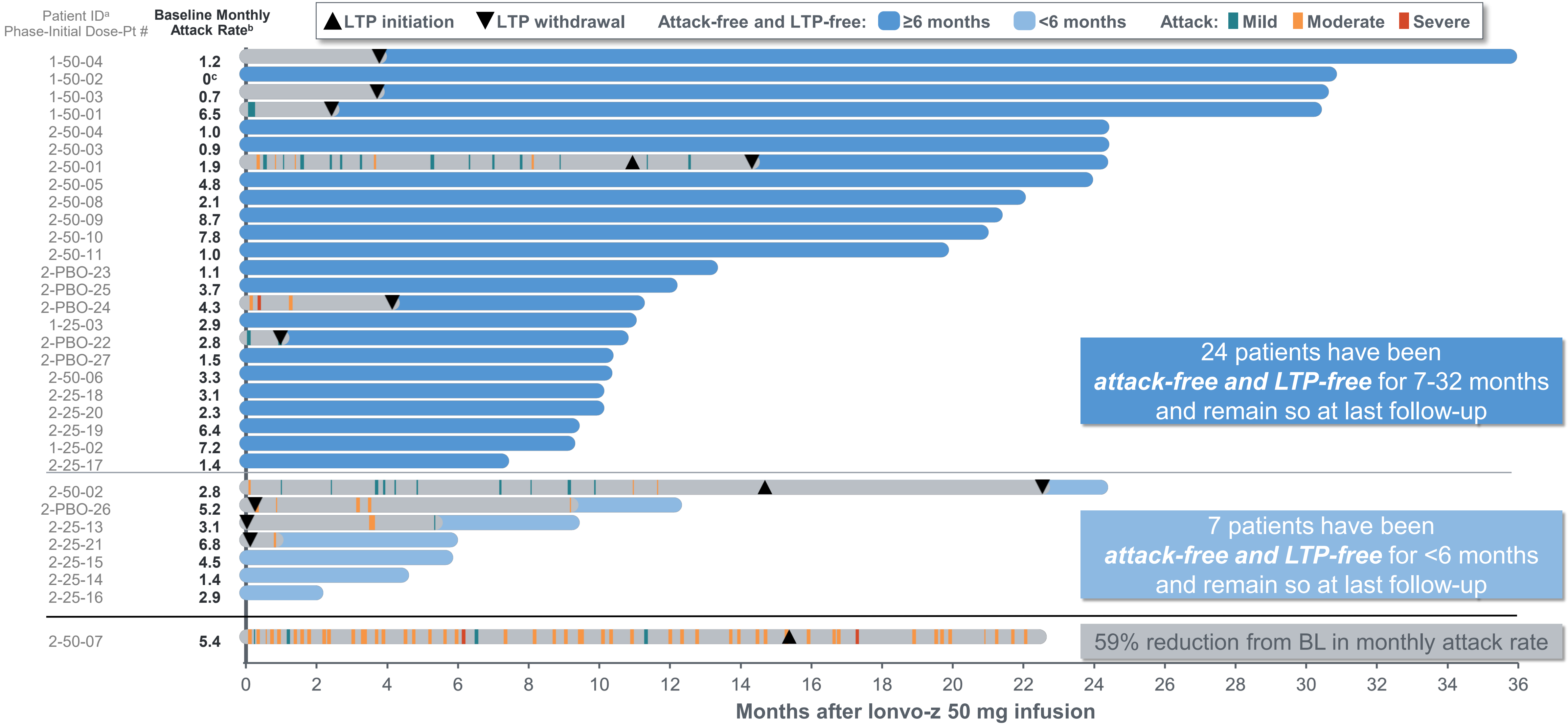
After becoming attack-free and LTP-free for ≥6 months, all patients maintained their response

Pooled Phase 1/2 Analysis: Of those initially treated with lonvo-z 50 mg, 4/4 Phase 1 and 10/11 Phase 2 patients were attack-free and LTP-free



Data cutoff date: 29 Aug 2025. Phase 1 eligibility was determined by historical attack period. [a]Patient IDs align with prior Phase 1 and Phase 2 publications. [b]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. [c]Patient had 0.9 attacks per month in the 3 months prior to screening. BL, baseline; LTP, long-term prophylaxis; PBO, placebo; Pt, patient.

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

Pooled Phase 1/2 Analysis

	Patients treated with lonvo-z 50 mg in the Phase 1/2 trial (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)[b]

- No clinically significant shifts in liver enzymes
  - Grade 2 AST elevation occurred in one patient (Day 1-4)[c]
- No clinically significant shifts in coagulation parameters
  - Grade 1 bleeding AEs: epistaxis (n=2) and vaginal hemorrhage (n=1)
  - One SAE (pulmonary embolism) occurred in a patient with multiple risk factors[b] one year after the infusion; the event resolved without sequelae
- Safety of lonvo-z 50 mg after receiving the suboptimal dose (25 mg) was consistent with the overall population
- In the LTFU study (n=17), there were no SAEs or treatment-related AEs reported with lonvo-z 50 mg

Data cutoff: 29 Aug 2025. [a]AEs that occurred after each patient received lonvo-z 50 mg are reported. [b]The patient had multiple risk factors which included recent COVID infection, ongoing history of smoking, and obesity. [c]Occurred following lonvo-z 50 mg infusion in a patient previously treated with lonvo-z 25 mg. As previously reported, two patients treated with lonvo-z 25 mg experienced transient, asymptomatic Grade 2 liver transaminase elevations, with peak values at Day 22 (Cohn, et al. N Engl J Med. 2024) and Week 156 (Longhurst et al. EAACI 2025), respectively. All events resolved spontaneously without intervention. AE, adverse event; AST, aspartate aminotransferase; LTFU, long-term follow-up; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

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In a 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 kallikrein
- Consistently low and stable mean monthly attack rate approaching zero attacks/month
- The majority of patients becoming attack-free and LTP-free as of the latest data cutoff date
  - All patients who were attack-free and LTP-free for ≥6 months maintained their response
  - 24 patients have been attack-free and LTP-free for 7-32 months; another 7 patients have been attack-free and LTP-free for <6 months
  - Of those initially treated with lonvo-z 50 mg, 4/4 Phase 1 and 10/11 Phase 2 patients were attack-free and LTP-free
- A well-tolerated safety profile with no long-term risks identified

HAELO Clinical Trial

Lonvo-z 50 mg is being further evaluated in patients with HAE in the ongoing Phase 3 HAELO study; fully enrolled as of September 2025

Data cutoff: 29 Aug 2025.
HAE, hereditary angioedema. LTP, long-term prophylaxis. HAELO study, NCT06634420.
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