# Lonvoguran Ziclumeran: Pharmacodynamics and Mechanism of Action Using Cleaved High-Molecular-Weight Kininogen

David Maag,[1] Yuanxin Xu,[1] Danny M. Cohn,[2] Carri Boiselle,[1] Adam Amaral,[1] Jing Pan,[1] Catherine R. Miller,[1] James Butler[1]

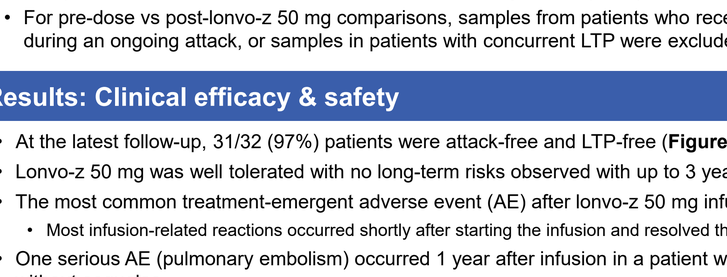
[1]Intellia Therapeutics, Cambridge, MA, USA; [2]Amsterdam Cardiovascular Sciences, Amsterdam University Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

## Introduction

- In most patients with hereditary angioedema (HAE), C1 inhibitor (C1INH) deficiency imbalances the kallikrein-kinin system (KKS), leading to excess bradykinin production and debilitating swelling attacks (**Figure 1**)[1,2]
- Lonvoguran ziclumeran (lonvo-z) is an investigational, *in vivo* CRISPR-based one-time treatment designed to permanently inactivate the *KLKB1* gene to reset the balance of the KKS in patients with HAE-C1INH (**Figure 1**)[3,4]

**Figure 1.** Lonvo-z is thought to exert clinical effect by permanently inactivating the *KLKB1* gene, thereby reducing bradykinin production and HAE attacks[3,4]

**The KKS is imbalanced in HAE, causing excessive production of BK that leads to swelling attacks[1-4]**




**There are multiple places along the pathway to evaluate the MOA of lonvo-z:**

1. Measurement of kallikrein levels, as well as kallikrein activity as biomarkers[3,4]
2. Measurement of cHK as a biomarker of BK production
3. Estimating effect on kallikrein and resultant BK levels in a QSP model (Phillips, et al. BK Symposium 2026)[5]

BK, bradykinin; C1INH, C1 inhibitor; cHK, cleaved HK; HAE, hereditary angioedema; HK, high-molecular-weight kininogen; KKS, kallikrein-kinin system; MOA, mechanism of action; QSP, quantitative systems pharmacology.

## Objective

- Explore the clinical efficacy and safety of permanently inactivating *KLKB1* following a one-time treatment with lonvo-z
- Develop and apply a plasma high-molecular-weight kininogen (HK) cleavage assay to characterize the mechanism of action of lonvo-z and to evaluate patient-level responses among patients who were not attack-free and/or long-term prophylaxis (LTP)-free 12 months following lonvo-z infusion

## Methods

*Phase 1/2 study*

- Lonvo-z was evaluated in a Phase 1/2 study[2,3]
  - Phase 1: an open-label, dose-escalation, multicentre study in adults with HAE[2]
  - 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[3]
  - 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 (NCT06262399)

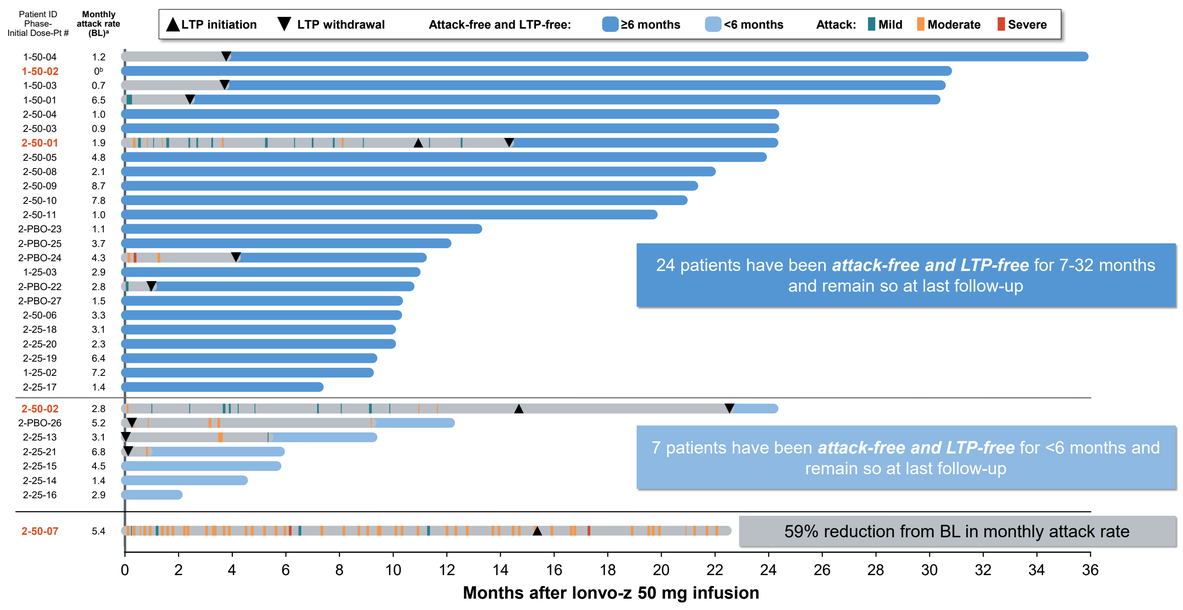
*cHK assay*

- A Western blot assay was developed for semiquantitative analysis of intact HK and cleaved (cHK)
- A cHK reference range was established from healthy donors (n=10)
- Activated factor XII (FXIIa) was used to stimulate the system
- Samples were collected from the lonvo-z Phase 1/2 study before (n=26) and after treatment with lonvo-z 50 mg (n=27)
- For pre-dose vs post-lonvo-z 50 mg comparisons, samples from patients who received lonvo-z 25 mg or 75 mg, samples during an ongoing attack, or samples in patients with concurrent LTP were excluded

## Results: Clinical efficacy & safety

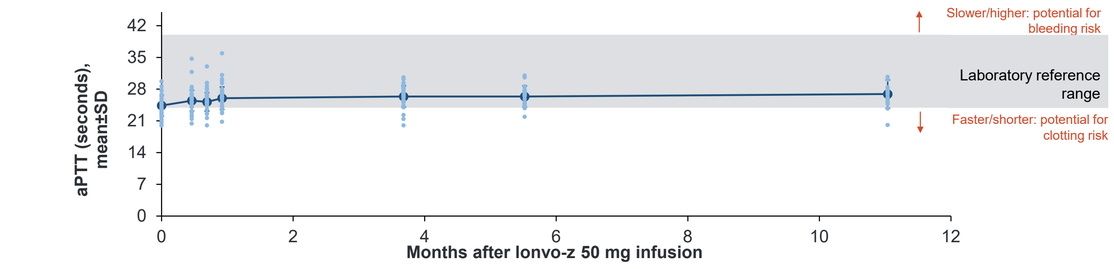
- At the latest follow-up, 31/32 (97%) patients were attack-free and LTP-free (**Figure 2**)
- Lonvo-z 50 mg was well tolerated with no long-term risks observed with up to 3 years of follow-up
- The most common treatment-emergent adverse event (AE) after lonvo-z 50 mg infusion was infusion-related reaction (53%)
  - Most infusion-related reactions occurred shortly after starting the infusion and resolved the same day; all were Grade 1 or 2
- One serious AE (pulmonary embolism) occurred 1 year after infusion in a patient with multiple risk factors; the event resolved without sequelae
- In the long-term follow-up study (n=17), there were no serious AEs or treatment-related AEs reported with lonvo-z 50 mg
- The hallmark of Fletcher deficiency (prolonged aPTT) was not observed after lonvo-z 50 mg infusion (**Figure 3**)

**Figure 2.** After becoming attack-free and LTP-free for ≥6 months, all patients maintained their response




Data cutoff date: 29 August 2025. Phase 1 eligibility was determined by historical attack period. [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.

**Figure 3.** Abnormal prolongation of aPTT was not observed after lonvo-z 50 mg

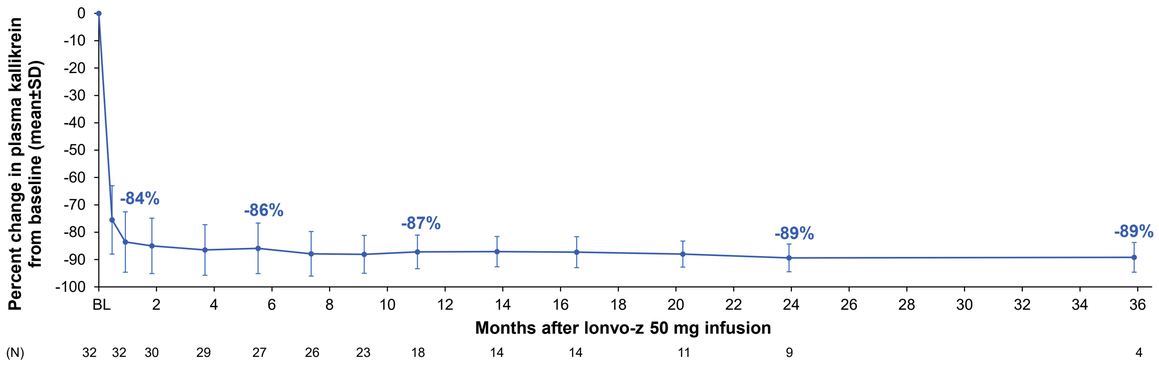



Data cutoff date: 29 August 2025. The gray shading represents aPTT laboratory reference range (23.9-40). aPTT, activated partial thromboplastin time.

## Results: Biomarkers to understand lonvo-z mechanism - kallikrein

- In the Phase 1/2 study (NCT05120830), a mean reduction of 84% in total plasma kallikrein protein (prekallikrein and kallikrein) was observed 4 weeks after lonvo-z 50 mg, which was maintained with up to 3 years of follow-up (**Figure 4**)

**Figure 4.** Kallikrein reductions were rapid and sustained following lonvo-z 50 mg

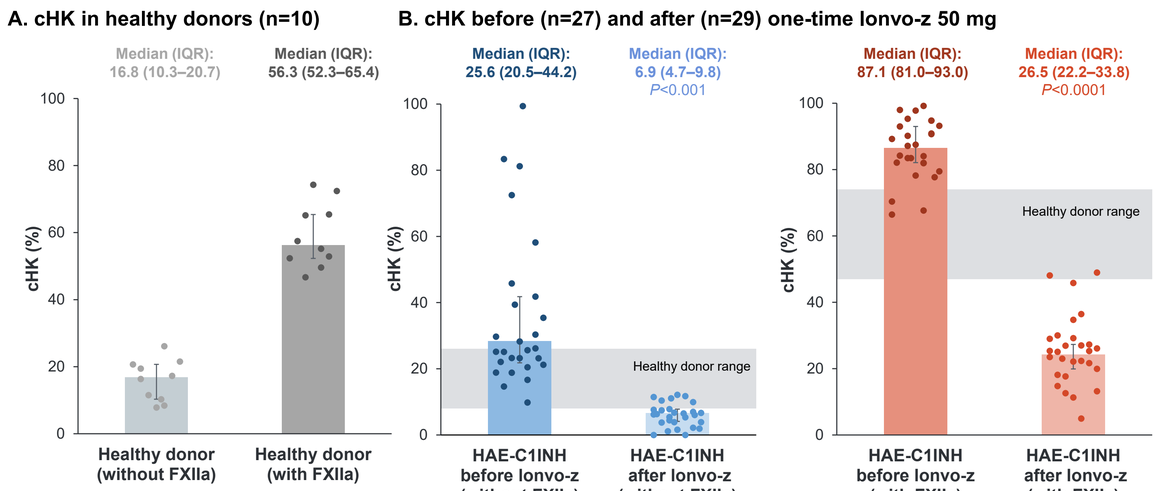



Data collected as of 26 September 2025. One month=30.4375 days. BL, baseline.

## Results: Biomarkers to understand lonvo-z mechanism - cHK

- The median (interquartile range) percent cHK reference range established from healthy donors (n=10) was 16.8% (10.3%-20.7%) in uninduced (without FXIIa) and 56.3% (52.3%-65.4%) in induced (with FXIIa) conditions (**Figure 5A**)
- Prior to a one-time treatment with lonvo-z 50 mg, patients with HAE-C1INH demonstrated higher median cHK than healthy donors in both uninduced and induced conditions
- Following treatment with lonvo-z 50 mg, patients with HAE-C1INH demonstrated lower median cHK than healthy donors without complete elimination in both uninduced and induced conditions (**Figure 5B**)

**Figure 5.** cHK assay is sensitive and reliable, showing differences between healthy donors, and treated and untreated HAE-C1INH



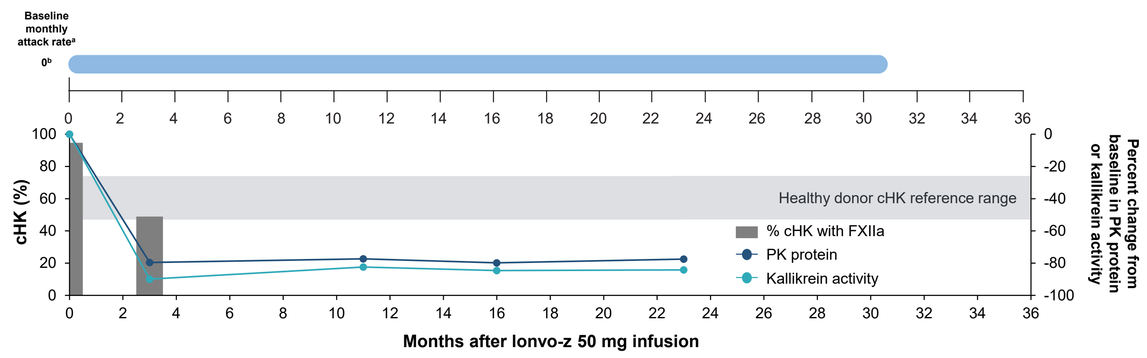

Healthy donor cHK (%) reference range: 8–26 (-FXIIa) and 47–74 (+FXIIa). Dots represent one individual sample. IQR represents the 25th and 75th percentile. Median difference assessed using Hodges-Lehmann estimate; *P* value is based on exact Wilcoxon two-sample test; nominal *P* values are presented for exploratory purposes; results should be interpreted as hypothesis generating.
C1INH, C1 inhibitor; cHK, cleaved high-molecular-weight kininogen; FXIIa, activated factor XII; HAE, hereditary angioedema; IQR, interquartile range; LTP, long-term prophylaxis.

## Results: Understanding mechanism of attacks after lonvo-z

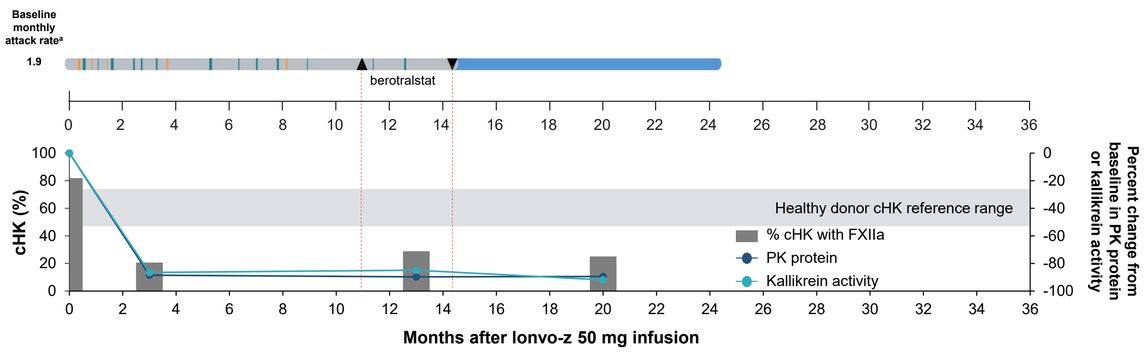
- Among patients who were not attack-free and/or LTP-free 12 months following lonvo-z infusion (**Figure 6**):
  - Prekallikrein protein and kallikrein activity levels were consistent with attack-free patients
  - cHK levels decreased to at or below the healthy donor reference range

**Figure 6.** Prekallikrein, kallikrein, and cHK clinical vignettes

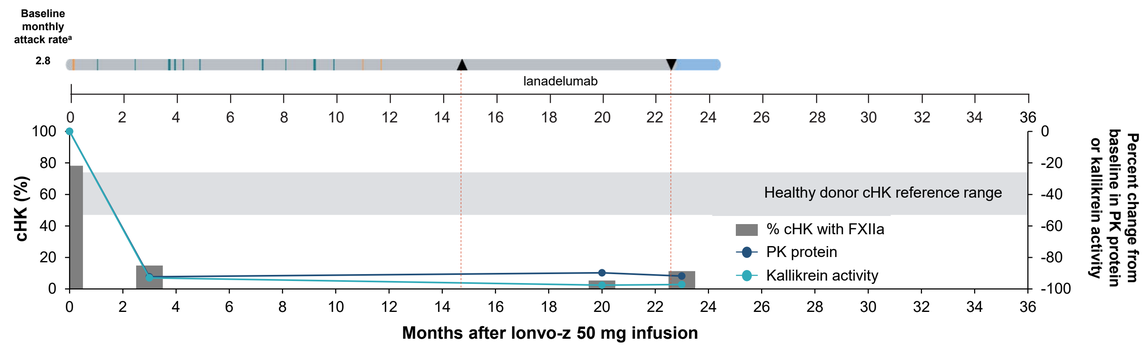
**Patient 1-50-02: Patient always attack-free and LTP-free** (kallikrein reduction ≈90%)



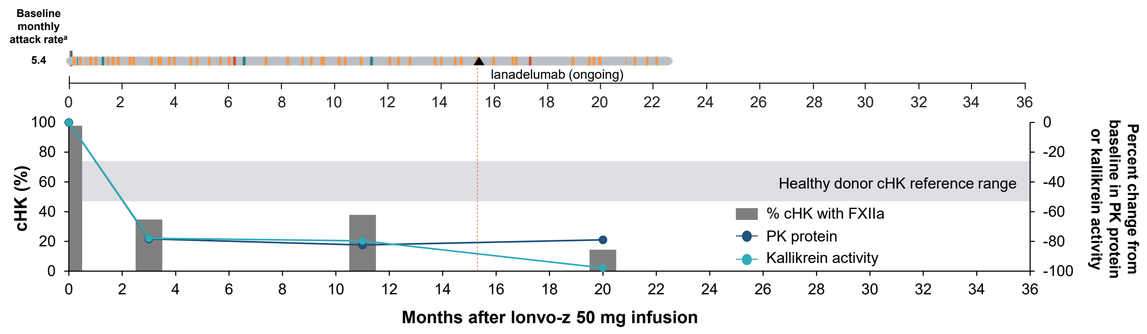

**Patient 2-50-01: Patient with a prolonged time to become attack-free** (kallikrein reduction ≈90%)




**Patient 2-50-02: Patients with a prolonged time to become attack-free** (kallikrein reduction ≈90%)




**Patient 2-50-07: Patient who continued to experience attacks** (kallikrein reduction ≈82%)




Healthy donor cHK (%) reference range: 47–74 (+FXIIa).
[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. cHK, cleaved high-molecular-weight kininogen; FXIIa, activated factor XII; LTP, long-term prophylaxis; PBO, placebo; PK, prekallikrein.

## Conclusions

- The majority of patients treated with lonvo-z were attack-free and LTP-free at last follow-up
- Lonvo-z did not induce the Fletcher deficiency phenotype (prolonged aPTT) in patients with HAE-C1INH, suggesting that the KKS pathway is not fully suppressed—this may be due, in part, to the underlying C1INH deficiency, which is not present in healthy individuals
- Prior to a one-time treatment with lonvo-z 50 mg, patients with HAE-C1INH demonstrated higher median cHK than healthy donors; following treatment, patients demonstrated lower median cHK than healthy donors
- Kallikrein-directed therapies have the potential to further inhibit the KKS after lonvo-z administration
- Together, with the reductions in plasma kallikrein, these results support the mechanism of lonvo-z to permanently reset the KKS in patients with HAE-C1INH without fully eliminating the KKS pathway
- For patients who continue to experience attacks following lonvo-z 50 mg, alternative aetiologies for ongoing symptoms should be evaluated

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**References:** 1. Zuraw B. *N Engl J Med*. 2008;359(10):1027-1036. 2. De Maat S, et al. *J Thromb Haemost*. 2018;16(9):1674-1685. 3. Longhurst HJ, et al. *N Engl J Med*. 2024;390(5):432-441. 4. Cohn DM, et al. *N Engl J Med*. 2025;392(5):458-467. 5. Kaplan AP, et al. Presented at: AAAAI Annual Meeting; 27 February-2 March 2026; Philadelphia, PA. Poster 003.

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