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Lonvoguran Ziclumeran — In Vivo CRISPR Gene Editing in Hereditary Angioedema

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ABSTRACT

BACKGROUND

Hereditary angioedema is a rare and potentially life-threatening genetic condition characterized by recurrent and debilitating swelling attacks. Lonvoguran ziclumeran (lonvo-z) — an investigational, in vivo gene-editing treatment based on clustered regularly interspaced short palindromic repeats (CRISPR) — is being developed as a single-dose treatment for hereditary angioedema.

METHODS

In a phase 3, double-blind trial, we randomly assigned, in a 2:1 ratio, patients who were 16 years of age or older and had hereditary angioedema with C1 inhibitor deficiency to receive a single intravenous infusion of lonvo-z (at a dose of 50 mg) or placebo. The primary end point was the number of investigator-confirmed hereditary angioedema attacks per month (the monthly attack rate) from week 5 through week 28 after infusion.

RESULTS

A total of 80 patients underwent randomization; 52 were assigned to receive lonvo-z and 28 to receive placebo. As of February 10, 2026, the median duration of follow-up was 7.5 months (range, 4.9 to 12.8). The least-squares mean monthly attack rate from weeks 5 through 28 was 0.26 (95% confidence interval [CI], 0.15 to 0.45) in the lonvo-z group and 2.10 (95% CI, 1.55 to 2.86) in the placebo group (relative difference, −87%; 95% CI, −93 to −78; P<0.001). Adverse events that occurred during or after infusion of lonvo-z or placebo were reported in 92% and 86% of the patients in the lonvo-z and placebo groups, respectively, from day 1 through week 28. Among the adverse events that occurred during or after infusion and more often in the lonvo-z group than in the placebo group, the most common (occurring in >10% of the patients in the lonvo-z group) included infusion-related reaction, headache, fatigue, back pain, and upper respiratory tract infection. No serious or grade 3 or higher adverse events were reported in the lonvo-z group.

CONCLUSIONS

Among patients with hereditary angioedema, a single intravenous infusion of lonvo-z resulted in a significantly lower rate of hereditary angioedema attacks than placebo. (Funded by Intellia Therapeutics; HAELO ClinicalTrials.gov number, NCT06634420.)

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*A complete list of the HAELO investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Hereditary angioedema is a rare, autosomal-dominant disorder characterized by unpredictable, recurrent, and potentially fatal attacks of swelling in the gastrointestinal tract, upper airway, and skin, which can result in substantial physical and psychosocial challenges.[1,2] Hereditary angioedema due to C1 inhibitor deficiency results from pathogenic variants in the gene that encodes C1 inhibitor (*SERPING1*), which causes either low C1 inhibitor levels or impaired C1 inhibitor function.[2] This deficiency results in dysregulated plasma kallikrein activity and excessive bradykinin production, which lead to episodes of increased vascular permeability and swelling.[2]

Hereditary angioedema remains a challenge for patients despite the availability of on-demand therapy for the treatment of attacks and long-term prophylactic medications. Although the availability of on-demand therapy and long-term prophylaxis has improved the management of hereditary angioedema, incomplete disease control, lack of access to treatments, and the need for lifelong use still impose a burden on patients. Results of phase 3 trials of long-term prophylaxis suggest that approximately 40 to 60% of patients can become attack-free.[3-5] However, in a 2025 survey of patients with hereditary angioedema who were not participating in clinical trials, 80% of the patients reported having attacks, even though 89% of the patients reported using long-term prophylaxis.[6] Fear and anxiety about the next attack profoundly affect patients, and this psychosocial burden is influenced by the degree of attack control.[7]

Reducing plasma kallikrein production or activity is a clinically validated treatment strategy to reduce bradykinin production, although currently approved treatment options require chronic or on-demand dosing to show efficacy.[2-5,8,9] Plasma kallikrein is derived from prekallikrein, and since the liver is the primary source of prekallikrein,[10] the use of a nonviral, liver-directed lipid nanoparticle to deliver clustered regularly interspaced short palindromic repeats (CRISPR) gene editing in vivo is being investigated as a therapeutic strategy. Lonvoguran ziclumeran (also known as lonvo-z or NTLA-2002) contains CRISPR components — a guide RNA that targets the prekallikrein gene *KLKB1* and a codon-optimized human mRNA sequence of *Streptococcus pyogenes* Cas9 protein. Lonvo-z was designed to reduce the level of plasma prekallikrein by inactivating *KLKB1*, with the intent of resetting the balance of the kallikrein–kinin system and normalizing bradykinin levels.[10]

In a phase 1–2 trial (ClinicalTrials.gov number, NCT05120830), all 37 of the patients who received treatment with lonvo-z had rapid and deep reductions in total plasma kallikrein levels that were sustained through the last follow-up visit; 20 of the 21 patients treated with 50 mg of lonvo-z became attack-free without the use of long-term prophylaxis.[11] The optimal biologic dose of lonvo-z was identified as 50 mg. Here we report the primary results from HAELO (A Phase 3 Study to Evaluate NTLA-2002 in Participants with Hereditary Angioedema), which evaluated the efficacy and safety of a single intravenous infusion of 50 mg of lonvo-z in patients with hereditary angioedema due to C1 inhibitor deficiency (Fig. S1).

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this multinational, double-blind, randomized, placebo-controlled trial at 31 sites in Australia, Canada, France, Germany, the Netherlands, New Zealand, South Africa, the United Kingdom, and the United States. The trial was approved by the institutional review board or ethics committee at each participating trial site. All the patients provided written informed consent. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. An independent data monitoring committee assessed trial conduct and interim safety summaries during the trial. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. The first draft of the manuscript was written by medical writers funded by Intellia Therapeutics. The authors reviewed and edited the manuscript and made the decision to submit it for publication. The contributions of individual authors are provided in the Supplementary Appendix (available at NEJM.org).

PATIENTS

Eligible patients were at least 16 years of age, had received a diagnosis of hereditary angioedema due

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to C1 inhibitor deficiency, and had at least two investigator-confirmed hereditary angioedema attacks during the 4- to 8-week run-in period. Patients were not permitted to use long-term prophylaxis within five half-lives before the start of the run-in period through the end of week 28. Full eligibility criteria are listed in the protocol. Screening was stopped when it was estimated that a sufficient number of patients would be enrolled.

RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 2:1 ratio to receive a single infusion of lonvo-z at a dose of 50 mg or placebo. The baseline number of attacks per month (≤3 or >3) was used as a stratification factor for randomization. On day 1, the infusion was administered intravenously over the course of approximately 4 hours. The efficacy evaluation period was defined as week 5 (day 29) through week 28 (day 197) after infusion. During this time, no use of long-term prophylaxis was permitted. At week 28, patients in both trial groups could elect to cross over to receive a single blinded infusion of placebo (for patients in the lonvo-z group) or lonvo-z (for patients in the placebo group). All patients will undergo additional observation for 76 weeks after the end of the efficacy evaluation period, for a total trial duration of 104 weeks.

To mitigate the risk of infusion-related reactions, patients received an oral glucocorticoid (dexamethasone at a dose of 8 mg or equivalent therapy) at home 8 to 24 hours before infusion. In addition, 1 to 2 hours before infusion, patients received either an oral or intravenous glucocorticoid (dexamethasone [10 mg] or equivalent therapy) and H_1 and H_2-antihistamines: intravenous diphenhydramine (50 mg or equivalent) or oral cetirizine (10 mg or equivalent) and intravenous or oral famotidine (20 mg or equivalent). To mitigate the risk of a hereditary angioedema attack during the infusion (given the washout of long-term prophylaxis), C1 inhibitor short-term prophylaxis was required immediately before infusion. Access to therapy to treat attacks was required throughout the trial.

CLINICAL ASSESSMENT

Each patient recorded angioedema symptoms, attacks, and treatments in an electronic diary that was reviewed by an investigator to confirm whether an event represented a hereditary angioedema attack. Blood samples for pharmacodynamic and pharmacokinetic analyses were obtained. Additional evaluations are described in the protocol.

TRIAL END POINTS

The primary end point was the time-normalized number of investigator-confirmed hereditary angioedema attacks per month (the attack rate) from week 5 through week 28, with a month defined as 28 days. Key secondary end points from week 5 through week 28 were the time-normalized number of investigator-confirmed hereditary angioedema attacks per month requiring on-demand therapy, the time-normalized number of moderate or severe investigator-confirmed attacks per month, and investigator-confirmed attack-free status. The change from baseline (last assessment before randomization) to week 28 in the total score on the Angioedema Quality of Life (AE-QoL) questionnaire was also a key secondary end point. The AE-QoL questionnaire is a validated, angioedema-specific patient-reported outcome measure; total scores range from 0 to 100, with lower scores indicating less impairment.

Other secondary end points were response status (a reduction from baseline of at least 50%, 70%, or 90% in the time-normalized number of investigator-confirmed hereditary angioedema attacks per month from week 5 through week 28) and the time-normalized number of investigator-confirmed attacks per month from week 1 through week 28. Additional secondary end points from week 1 through week 28 included the number of attacks per month requiring on-demand therapy, the number of moderate or severe attacks, attack-free status, and response status. End points related to long-term efficacy at week 104 are described in the protocol. Additional end points included safety (as assessed on the basis of adverse events), pharmacodynamics (the change from baseline in total plasma kallikrein protein level), pharmacokinetics, and immunogenicity.

STATISTICAL ANALYSIS

We planned to enroll a total of 60 patients (40 patients in the lonvo-z group and 20 patients in the placebo group), which would provide the trial with 99% power to detect a monthly attack rate ratio of 0.25 for the difference between the lonvo-z group and the placebo group, with a two-sided alpha level of 0.05.

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Formal statistical hypothesis testing was performed for the primary end point and four key secondary end points with a hierarchical gatekeeping testing procedure. If a significant difference was observed for the primary end point, the key secondary end points were to be evaluated in the following hierarchical order: the time-normalized number of investigator-confirmed hereditary angioedema attacks requiring on-demand therapy from week 5 through week 28, the time-normalized number of moderate or severe investigator-confirmed attacks from week 5 through week 28, investigator-confirmed attack-free status from week 5 through week 28, and the change from baseline to week 28 in the AE-QoL questionnaire total score. The secondary end points were tested in the order described only if the primary end point and each preceding secondary end point in the hierarchy were statistically significant. The family-wise type I error rate was controlled at a two-sided alpha level of 0.05. The primary analysis was based on a prespecified completion date after at least 60 patients had completed the week 28 visit or had discontinued the trial.

From week 5 through week 28, the number of attacks, attacks requiring on-demand therapy, and moderate or severe attacks were analyzed with a Poisson regression model with Pearson chi-square scaling of standard errors to account for potential overdispersion. The model included trial group and baseline attack rate (≤3 or >3 attacks per month) as covariates, and the logarithm of follow-up duration for each patient from week 5 through week 28 as the offset variable. Attack-free status from week 5 through week 28 was assessed with the Cochran–Mantel–Haenszel test, with stratification according to the baseline attack rate. The change from baseline to week 28 in AE-QoL questionnaire total score was assessed with a mixed model for repeated measures that included trial group, AE-QoL questionnaire total score at baseline, visit, and trial-group-by-visit interaction as independent variables.

For patients who started long-term prophylaxis before the week 28 assessment, only attacks that started before initiation of long-term prophylaxis were included in the analysis. For patients who had not yet completed the week 28 visit at the time of the data-cutoff date (February 10, 2026), all data through their latest attack assessment were included in the analysis. Missing data were assumed to be missing at random since the unobserved data were administratively censored and no imputation was performed in the analysis. In a sensitivity analysis, multiple imputation was performed under missing-at-random and jump-to-reference assumptions for the primary and key secondary end points. Additional statistical methods are provided in the Supplementary Appendix. The 95% confidence intervals have not been not adjusted for multiplicity and should not be used in place of hypothesis testing.

The full analysis population, which was used for efficacy analyses, included all the patients who had undergone randomization. The safety analysis population included all the patients who had undergone randomization and received at least a partial dose of lonvo-z or placebo. Safety data were summarized with the use of descriptive statistics according to trial group.

RESULTS

PATIENTS

Owing to an unexpectedly low incidence of screening failure, 80 of the 92 screened patients underwent randomization; 52 patients were assigned to receive lonvo-z and 28 were assigned to receive placebo (Fig. S2). As of February 10, 2026 (the data-cutoff date), the median follow-up was 7.5 months (range, 4.9 to 12.8). The data from the primary analysis are reported here, and longer-term follow-up of the trial is ongoing. A total of 64 patients (43 in the lonvo-z group and 21 in the placebo group) reached at least the week 28 evaluation; the remaining 16 patients reached at least week 20. As of the data-cutoff date, all 80 patients continued to be followed and were included in the primary analysis.

Forty-nine patients received the full dose of lonvo-z. Two patients received a nearly full dose (97% and 98% of the planned dose), with nominal volume loss related to the management of occlusions during infusion. One patient received a partial dose (17% of the planned dose) due to an infusion pump error that resulted in the infusion duration exceeding the permitted time frame.

The demographic and clinical characteristics of the patients at baseline were balanced in the two groups (Table 1 and Table S1) and were generally representative of the population of patients with hereditary angioedema (Table S2). The median

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Lonvo-z (N=52)	Placebo (N=28)	All Patients (N=80)
Median age at screening (range) — yr	42.0 (23.0–71.0)	40.0 (19.0–76.0)	41.5 (19.0–76.0)
Sex — no. (%)			
Female	35 (67)	20 (71)	55 (69)
Male	17 (33)	8 (29)	25 (31)
Type of hereditary angioedema — no. (%)†			
C1INH type 1	49 (94)	25 (89)	74 (92)
C1INH type 2	3 (6)	3 (11)	6 (8)
Previous treatment for hereditary angioedema before trial enrollment — no. (%)			
Long-term prophylaxis‡	35 (67)	22 (79)	57 (71)
On-demand treatment only	17 (33)	6 (21)	23 (29)
Typical severity of angioedema attacks — no. (%)			
Mild	7 (13)	5 (18)	12 (15)
Moderate	30 (58)	20 (71)	50 (62)
Severe	15 (29)	3 (11)	18 (22)
No. of hereditary angioedema attacks per month during the run-in period	3.5±1.79	3.5±1.91	3.5±1.82
AE-QoL total score§	58.4±18.05	58.0±12.54	58.3±16.25

* Complete data on demographic and clinical characteristics are provided in the Supplementary Appendix. Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Hereditary angioedema C1 inhibitor (C1INH) type 1 includes patients with low C1 inhibitor levels; C1INH type 2 includes those with impaired C1 inhibitor function.
‡ Long-term prophylaxis before trial enrollment was defined as the last dose of long-term prophylaxis being discontinued within 100 days before the first screening visit.
§ The Angioedema-Quality of Life (AE-QoL) questionnaire is a validated, angioedema-specific patient-reported outcome measure; total scores range from 0 to 100, with lower scores indicating less impairment.

age of the patients was 41.5 years (range, 19.0 to 76.0), and 71% of the patients were receiving long-term prophylaxis before enrollment. The mean (±SD) baseline monthly attack rate during the run-in period was 3.5±1.8 in the lonvo-z group and 3.5±1.9 in the placebo group.

EFFICACY

Primary End Point

The least-squares mean monthly rate of investigator-confirmed hereditary angioedema attacks from week 5 through week 28 was 0.26 (95% confidence interval [CI], 0.15 to 0.45) in the lonvo-z group and 2.10 (95% CI, 1.55 to 2.86) in the placebo group (relative difference, –87%; 95% CI, –93 to –78; P<0.001) (Table 2). The difference in the mean number of attacks per month between the two trial groups appeared within 4 weeks after infusion, and the response to lonvo-z remained stable through follow-up, albeit in diminishing numbers of patients at later time points (Fig. 1). The responses of individual patients are depicted in Figure S3. The results appeared to be generally consistent in prespecified subgroup analyses (Fig. S4).

Key Secondary End Points

The least-squares mean monthly rate of investigator-confirmed hereditary angioedema attacks requiring on-demand therapy from week 5 through week 28 was 0.19 (95% CI, 0.10 to 0.36) in the lonvo-z group and 1.79 (95% CI, 1.27 to 2.54) in the placebo group (relative difference, –89%; 95% CI, –94 to –79; P<0.001). The least-squares mean monthly rate of moderate or severe attacks from week 5 through week 28 was 0.11 (95% CI, 0.06 to 0.23) in the lonvo-z group and 1.23 (95% CI, 0.84 to 1.81) in the placebo group (relative difference, –91%; 95% CI, –96 to –81; P<0.001). From week 5 through week 28, the patients who

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Table 2. Primary and Key Secondary End Points.

End Point	Lonvo-z (N = 52)	Placebo (N = 28)
Primary end point		
LS mean no. of investigator-confirmed hereditary angioedema attacks per month, wk 5 through wk 28 (95% CI)*†‡	0.26 (0.15 to 0.45)	2.10 (1.55 to 2.86)
Percent difference vs. placebo (95% CI)	−87 (−93 to −78)	
P value	<0.001	
Key secondary end points		
LS mean no. of investigator-confirmed hereditary angioedema attacks requiring on-demand therapy, wk 5 through wk 28 (95% CI)*†‡	0.19 (0.10 to 0.36)	1.79 (1.27 to 2.54)
Percent difference vs. placebo (95% CI)	−89 (−94 to −79)	
P value	<0.001	
LS mean no. of moderate or severe hereditary angioedema attacks, wk 5 through wk 28 (95% CI)*†‡	0.11 (0.06 to 0.23)	1.23 (0.84 to 1.81)
Percent difference vs. placebo (95% CI)	−91 (−96 to −81)	
P value	<0.001	
Attack-free status, wk 5 through wk 28 — no. (%)†‡	32 (62)	3 (11)
95% CI§	47.0 to 74.7	2.3 to 28.2
Odds ratio vs. placebo (95% CI)	12.81 (3.45 to 47.55)	
P value	<0.001	
LS mean change from baseline to wk 28 in AE-QoL questionnaire total score — (95% CI)‡¶	−23.51 (−27.64 to −19.38)	−6.47 (−12.26 to −0.68)
LS mean difference vs. placebo (95% CI)	−17.04 (−24.15 to −9.93)	
P value	<0.001	

* The mean number of hereditary angioedema attacks per month was estimated with the use of a Poisson regression model with Pearson chi-square scaling of standard error with treatment group and baseline attack rate (≤3 or >3 attacks per month) as covariates. Baseline was defined as the time from the date of the second screening visit to randomization. A month was defined as 28 days.

† For patients who initiated any long-term prophylaxis before the week 28 assessment, only attacks that started before prophylaxis initiation were included in the analysis. For patients who did not reach week 28 assessment, all data through their latest attack assessment were included.

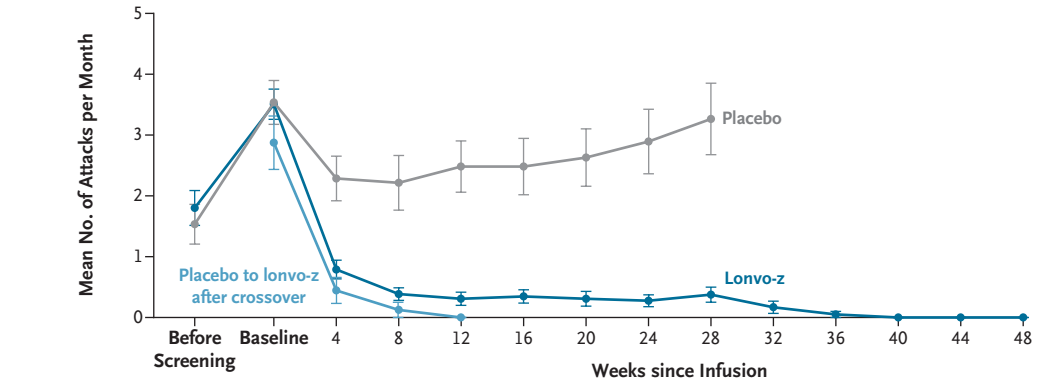
‡ All 16 patients who had not yet reached week 28 at the time of the data-cutoff date owing to later enrollment remained in follow-up, and all available data through their latest assessment were included in the analysis for the primary and key secondary end points. No imputation was performed in the analyses.

§ The exact confidence intervals were calculated with the Clopper–Pearson method.

¶ The AE-QoL questionnaire total score ranges from 0 to 100, with lower scores indicating better quality of life. The minimal clinically important difference is defined as a change of 6 points.[12] The total score change from baseline at week 28 was estimated with the use of a mixed model for repeated measures, with baseline total score, trial group, visit, and trial-group-by-visit interaction as fixed effects, and with patient as a random effect. For patients who initiated any long-term prophylaxis before the week 28 assessment, only AE-QoL data that were obtained before initiation of prophylaxis were included in the analysis. At week 28, data were available for 44 patients in the lonvo-z group and 20 patients in the placebo group.

remained attack-free included 32 of 52 patients (62%; 95% CI, 47 to 75) in the lonvo-z group and 3 of 28 patients (11%; 95% CI, 2 to 28) in the placebo group (odds ratio, 12.81; 3.45 to 47.55; P<0.001). Patients in the lonvo-z group had a greater improvement in the AE-QoL total score from baseline to week 28 than those in the placebo group, with a least-squares mean change from baseline of −23.51 points (95% CI, −27.64 to −19.38) in the lonvo-z group and −6.47 points (95% CI, −12.26 to −0.68) in the placebo group (mean difference, −17.04 points; 95% CI, −24.15 to −9.93; P<0.001), a finding that exceeded the minimal clinically important differ-

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No. at Risk														
Lonvo-z	52	52	52	52	52	52	52	50	44	43	20	8	6	3
Placebo	28	28	28	28	27	27	27	25	21	0	0	0	0	0
Placebo to lonvo-z	0	20	20	8	3	0	0	0	0	0	0	0	0	0

Figure 1. Monthly Hereditary Angioedema Attack Rate over Time.

The mean number of hereditary angioedema (HAE) attacks per month before screening was calculated on the basis of the number of patient-reported attacks occurring in the 90 days before the screening visit. The baseline monthly attack rate was defined as the number of HAE attacks per month from the date of the second screening visit to randomization. For patients in the placebo-to-lonvo-z crossover group, the baseline period was defined as the time from the date of the second screening visit to the day before lonvo-z crossover administration or the day before the start of long-term prophylaxis, whichever was earlier. The baseline attack rate and attack rates after infusion were confirmed by the investigator. During the efficacy evaluation period, two patients in the placebo group restarted long-term prophylaxis owing to a high number of attacks. For these patients, data were censored at the time of long-term prophylaxis initiation and only attacks occurring before long-term prophylaxis initiation were included in the analysis. Both patients discontinued long-term prophylaxis before receiving the lonvo-z crossover infusion. I bars indicate the standard error.

ence of a change of 6 points in the AE-QoL total score.[12]

Other End Points

From week 5 through week 28, a reduction from baseline of 90% or more in the monthly attack rate was observed in 39 of the 52 patients (75%) in the lonvo-z group and in 5 of the 28 patients (18%) in the placebo group (Fig. S5A). Similar results were observed from week 1 through week 28 (Fig. S5B). From week 1 through week 28, the least-squares mean monthly attack rate was 0.32 (95% CI, 0.20 to 0.51) in the lonvo-z group and 2.07 (95% CI, 1.55 to 2.75) in the placebo group (relative difference, −84%; 95% CI, −91 to −75) (Table S3). From week 5 through the last follow-up assessment, among patients treated with lonvo-z, the mean reduction from baseline in the monthly attack rate was 89±20.1% (Table S4), and 60% (31 of 52) of the patients were attack-free without the use of long-term prophylaxis. No patients in the lonvo-z group and 2 patients in the placebo group restarted long-term prophylactic therapy.

SAFETY

Adverse events that occurred during or after infusion of lonvo-z or placebo from day 1 through week 28 were reported in 48 of the 52 patients (92%) in the lonvo-z group and in 24 of the 28 patients (86%) in the placebo group (Table 3 and Table S5). The most common adverse event reported in the lonvo-z group was infusion-related reaction, which occurred in 32 patients (62%) in the lonvo-z group and in 5 patients (18%) in the placebo group. All adverse events were grade 1 or 2, no adverse events of grade 3 or higher were reported in either group, and no serious adverse events were reported in the lonvo-z group for the duration of follow-up.

All infusion-related reactions were grade 1 or 2 and were considered by the investigator to be related to lonvo-z or placebo (Table S6); most were transient, occurred shortly after initiation

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Table 3. Adverse Events during or after Infusion of Lonvo-z or Placebo through Week 28.*

Event	Lonvo-z (N=52)	Placebo (N=28)
Any adverse event — no. (%)	48 (92)	24 (86)
Related to trial regimen	37 (71)	6 (21)
Any serious adverse event — no. (%)	0	1 (4)†
Adverse events occurring in >5% of patients in the lonvo-z group — no. (%)		
Infusion-related reaction	32 (62)	5 (18)
Headache	10 (19)	3 (11)
Fatigue	7 (14)	3 (11)
Nasopharyngitis	7 (14)	9 (32)
Back pain	6 (12)	3 (11)
Upper respiratory tract infection	6 (12)	2 (7)
Upper abdominal pain	5 (10)	0
Abdominal pain	4 (8)	0
Influenza	3 (6)	1 (4)
Pain in extremity	3 (6)	0

* All adverse events were graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5. No serious adverse events were reported in the lonvo-z group. One event of grade 2, serious supraventricular tachycardia, was reported in the placebo group. Related events refer to those that were deemed by the investigators to be probably or possibly related to lonvo-z or placebo or those for which data regarding the relationship to the trial regimen were missing.

† This patient had serious supraventricular tachycardia, which started on day 39, resolved in 2 days, and was considered by the investigator to be unrelated to the investigational product.

of the infusion, and resolved the same day (Table S7). The most common symptoms associated with infusion-related reactions were headache, flushing, and chest pain or tightness. A total of seven patients in the lonvo-z group had infusion-related reactions that resulted in a decrease in the infusion rate or temporary infusion interruptions. The median time for lonvo-z infusion on day 1 was 3.9 hours (range, 2.5 to 5.3).

Shifts in the levels of liver enzymes, most of which occurred within 6 weeks after infusion, were transient, asymptomatic, and resolved without intervention (Fig. S6). In the lonvo-z group, elevated levels of aspartate aminotransferase, alanine aminotransferase, or both were observed in eight patients (15%). The levels were all less than 3 times the upper limit of the normal range, with the exception of the levels in one patient (2%), who had an elevated alanine aminotransferase level that fell between 3 times and less than 5 times the upper limit of the normal range with a concurrent upper respiratory tract infection. This patient also had an elevated level of alanine aminotransferase during the screening period. In the placebo group, three patients (11%) had elevations of aspartate aminotransferase or alanine aminotransferase (or both) of less than 3 times the upper limit of the normal range, and no patients had a level that was 3 or more times the upper limit of the normal range. The mean activated partial-thromboplastin time remained similar to baseline levels throughout follow-up (Fig. S7).

PHARMACODYNAMICS, PHARMACOKINETICS, AND IMMUNOGENICITY

Total plasma kallikrein protein levels decreased by the first measurement at week 2 (day 15) in the lonvo-z group, with a mean reduction from baseline of 65±15.7%; in the placebo group, levels increased by 18±19.8% (Fig. 2). Absolute reductions in the total plasma kallikrein protein levels are shown in Figure S8. Steady-state reductions in total plasma kallikrein protein levels were reached by week 5 and were maintained through the last follow-up assessment. The levels of the component analytes of lonvo-z (exogenous lipids [LP000001 and DMG-PEG2k], Cas9 messenger RNA, and a single guide RNA) rapidly declined after infusion, with levels falling below the limit of quantification within 2 to 4 weeks (Fig. S9). After infusion of lonvo-z, transient anti-drug antibodies were detected in 8 patients and anti-Cas9 antibodies were detected in 50 patients (Table S8). No discernible effects of these antibodies on pharmacokinetics, pharmacodynamics, or safety were seen.

CROSSOVER ANALYSIS

At the time of the data-cutoff date, 54 patients had opted to receive a second blinded infusion (34 patients in the lonvo-z group received placebo and 20 patients in the placebo group received lonvo-z). The duration of follow-up was limited in patients who received the crossover infusion (median, 1.4 months; range, 0.3 to 4.5). The preliminary results with regard to the efficacy, safety, and pharmacodynamics of lonvo-z among the patients who crossed over from the placebo group to receive a single dose of lonvo-z after week 28 are consistent with those among the patients who had been initially assigned to the lonvo-z group (Fig. 1 and Fig. S10).

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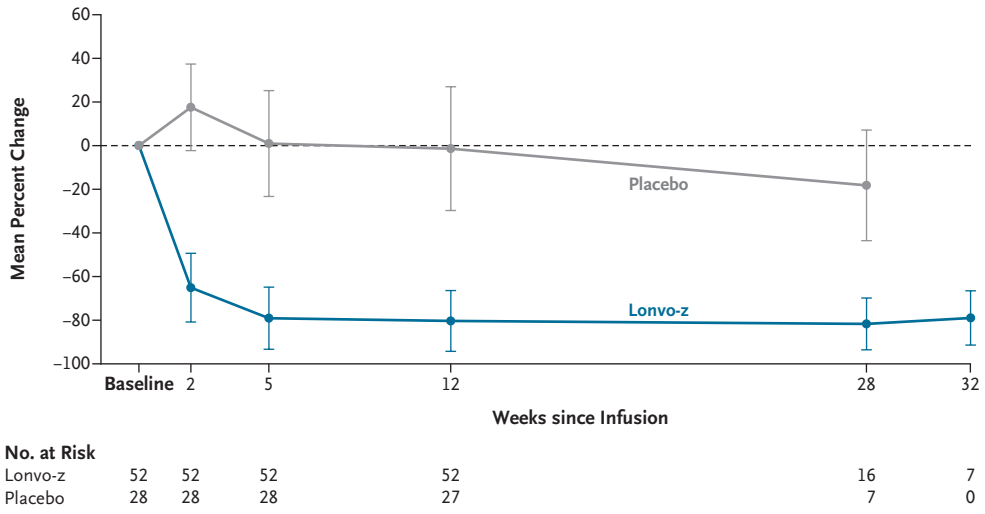


Figure 2. Change from Baseline in Total Plasma Kallikrein Protein Levels.

Shown is the mean percent change from baseline in the total plasma kallikrein protein level in patients receiving either a single infusion of 50 mg of lonvo-z or placebo. In the lonvo-z group, the mean change after infusion was −65±15.7% at week 2 (day 15) (in 52 patients), −79±14.2% at week 5 (in 52 patients), −80±13.9% at week 12 (in 52 patients), and −82±11.9% at week 28 (in 16 patients). I bars indicate standard deviations.

DISCUSSION

In this phase 3 trial, a single infusion of 50 mg of lonvo-z resulted in a significantly lower rate of hereditary angioedema attacks than placebo. Patients who received lonvo-z had an 87% lower attack rate than those who received placebo, and 62% of the patients who received lonvo-z were considered by the investigator to be attack-free from weeks 5 to 28 without the use of long-term prophylaxis. Treatment with lonvo-z was associated with a reduction in the monthly attack rate, a deep pharmacodynamic response that remained stable over time, and improvements in quality of life. The safety profile of lonvo-z was consistent with that seen in the phase 1–2 trial.[10,13] Adverse events in the lonvo-z group were mild to moderate in severity, with transient infusion-related reactions being the most common adverse event.

The efficacy results were similar to those observed in the phase 1–2 trial. Among patients who received 50 mg of lonvo-z in the open-label phase 1 and blinded phase 2 portions, 3 of 4 patients (75%) and 8 of 11 patients (73%), respectively, were attack-free without the use of long-term prophylaxis at the end of the primary observation period and had mean reductions of greater than 80% in total plasma kallikrein protein levels.[14] Over time, 20 of the 21 patients (95%) who received 50 mg of lonvo-z in the phase 1–2 trial, including 6 crossover patients, became attack-free with no use of long-term prophylaxis.[14] Although the duration of follow-up in the phase 3 trial is limited beyond week 28, with data through 40 weeks for only 8 patients who were assigned to receive lonvo-z, the low attack rate in these patients was maintained.

Hereditary angioedema attacks can be difficult to identify since some symptoms (e.g., abdominal pain) are common and can result from varied causes. This factor presents a challenge in clinical trials that rely on patient-reported symptoms to track the frequency of attacks. The lack of a validated method to definitively attribute such symptoms to the dysregulated kallikrein–kinin system may be a contributing factor as to why some patients do not initially become symptom-free in blinded, placebo-controlled clinical trials of therapies that target this pathway, despite findings of decreased levels of plasma kallikrein protein or activity.[3-5,9]

Nonclinical studies in animal models have suggested that anti-Cas9 immune responses may interfere with the safety or efficacy of gene editing therapies[15-17]; however, the clinical relevance

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of these findings has not been evaluated. In this trial, as well as in the phase 1 trial of lonvo-z,[10] we found a very low baseline prevalence of anti-Cas9 antibodies with a high incidence of transient anti-Cas9 antibody responses after treatment. Despite this finding, 11 patients who were initially treated with 25 mg of lonvo-z in the phase 1–2 trial were safely treated with a follow-on dose of 50 mg, with evidence of improved clinical responses and deeper reductions in total plasma kallikrein protein levels that were indistinguishable from those observed in patients treated with a single 50-mg dose. This preliminary evidence suggests that the occurrence of anti-Cas9 antibody responses after lonvo-z infusion does not compromise the safety or efficacy of subsequent treatment.

The edit to the gene *KLKB1* is intended to be permanent after treatment with lonvo-z. In a humanized mouse model, persistent editing in hepatocytes through aging and the liver-regeneration process was observed.[10] In the phase 1–2 trial, reduced plasma kallikrein protein levels remained low and stable at the latest follow-up assessment of up to 3 years after one infusion of 50 mg of lonvo-z.[11] These data suggest that the edit in *KLKB1* persists across mitoses (cell division), given the reported rates of hepatocyte turnover.[18]

Consideration must therefore be given to the long-term safety of plasma prekallikrein knockdown. Reports in the literature of a rare congenital plasma kallikrein deficiency (Fletcher factor deficiency) suggest that such persons are healthy and have prolonged activated partial-thromboplastin time without an associated bleeding risk.[19] Efforts have been made to characterize the incidence of certain clinical conditions, such as cardiovascular disorders, among persons with this deficiency.[20,21] However, the rarity of Fletcher factor deficiency, together with reporting bias, makes it difficult to draw definitive conclusions regarding its association with specific clinical outcomes. The data presented here and previously[10,13] indicate that the defining feature of congenital plasma kallikrein deficiency, prolonged activated partial-thromboplastin time, does not develop in patients with hereditary angioedema who are treated with lonvo-z. This may be due to the presence of a low level of residual plasma kallikrein in the context of a C1 inhibitor deficiency. The most prevalent cardiovascular condition reported in persons with congenital plasma kallikrein deficiency is hypertension,[20,22] which has not been reported as an adverse event in patients treated with lonvo-z to date. Consistent with this observation is that no causal association with cardiovascular risk has been reported in patients treated with approved plasma kallikrein–targeted agents.[23,24]

In other clinical trials involving in vivo gene editing, investigational therapies have been associated with acute, sometimes serious or fatal, adverse events, including increased levels of serum alanine aminotransferase and aspartate aminotransferase.[25-30] These investigational agents comprising distinct lipid components and unique active pharmaceutical ingredients are being studied in unique populations of patients, some of whom have serious underlying clinical disease and medically important coexisting conditions, a factor that makes it difficult to generalize safety findings across the therapeutic class. In this trial, no serious adverse events were observed in patients treated with lonvo-z. The most common adverse reactions were infusion-related reactions, which were generally transient and resolved without intervention. Elevated levels of serum aspartate aminotransferase and alanine aminotransferase, which occurred in approximately 10 to 15% of patients treated with lonvo-z, were transient, asymptomatic, and resolved without intervention.

Another important consideration is the potential risk of off-target editing. As gene editing technology continues to advance, each drug candidate needs to be empirically evaluated, first with a comprehensive preclinical assessment, and then by long-term clinical evaluation for the risk of off-target effects. For lonvo-z, extensive computational and laboratory assessments showed that the possibility of clinically relevant off-target editing activity was low.[10] Across all clinical trials conducted with lonvo-z to date, no evidence of adverse effects attributable to off-target editing has been observed. A long-term follow-up study is ongoing to elucidate the long-term safety and efficacy of lonvo-z (NCT06262399).

Limitations of this trial include the limited sample size and length of follow-up as of the data-cutoff date. Owing to these limitations, together with a carefully selected patient sample, it is possible that other risks, particularly in a general population with other coexisting conditions or susceptibilities that may occur outside the

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controlled setting of a clinical trial, have not yet been identified. Continued follow-up in this trial and its follow-up study will provide more data on long-term outcomes. An additional limitation is the placebo-controlled nature of the trial and the long-term prophylaxis washout requirement, which may have discouraged the participation of some patients. However, the baseline characteristics of the patients in this trial were similar to those of the broader population with hereditary angioedema.[4,5,9,31] Finally, the race and ethnic background of the patients are representative of the countries where the trial was conducted and not of the global population; however, neither race nor ethnicity are known to affect the symptoms of hereditary angioedema.[32]

In this phase 3 trial, among patients with hereditary angioedema due to C1 inhibitor deficiency, a single dose of lonvo-z resulted in a significantly lower rate of hereditary angioedema attacks than placebo from 5 through 28 weeks after infusion. All adverse events were grade 1 or 2 in severity in the lonvo-z group. These data support the use of lonvo-z as a potential treatment for hereditary angioedema.

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