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Loberamisal for Acute Ischemic Stroke
The LAIS Randomized Clinical Trial

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IMPORTANCE Effective neuroprotective and neuroreparative therapies for acute ischemic stroke remain limited. Loberamisal is a small-molecule compound that dually targets the postsynaptic density 95 (PSD-95) pathway and α2 γ-aminobutyric acid type α ($α2\text{-}GABA_A$) receptor.

OBJECTIVE To evaluate the efficacy and safety of intravenous loberamisal for improving functional outcomes in patients with acute ischemic stroke.

DESIGN, SETTING, AND PARTICIPANTS The Loberamisal for Acute Ischemic Stroke (LAIS) trial was a multicenter, double-blind, randomized, placebo-controlled phase 3 clinical trial conducted at 32 hospitals in China. Adults aged 18 to 80 years with acute ischemic stroke, a baseline National Institutes of Health Stroke Scale score of 7 to 20, and no prestroke disability (modified Rankin Scale score, ≤1) who presented within 48 hours of symptom onset were enrolled between July 24, 2024, and December 7, 2024, with final follow-up on April 8, 2025.

INTERVENTIONS Participants were randomly assigned (1:1) to receive intravenous loberamisal (40 mg) or matching placebo once daily for 10 consecutive days, in addition to standard stroke care.

MAIN OUTCOMES AND MEASURES The primary outcome was achieving a full functional outcome at 90 days, defined as a modified Rankin Scale (mRS) score of 0 to 1. Safety outcomes included adverse events, serious adverse events, and mortality.

RESULTS Among 998 randomized participants, 997 received at least 1 dose of the study drug and were included in the primary analysis (502 in the loberamisal group and 495 in the placebo group). The median age was 64 years (IQR, 57-71), 336 participants (33.7%) were women, and the median baseline NIHSS score was 8 (IQR, 7-9). At 90 days, 350 participants (69.7%) in the loberamisal group achieved an mRS score of 0 to 1 compared with 279 (56.3%) in the placebo group (relative risk, 1.24; 95% CI, 1.12-1.36; risk difference, 13.28%; 95% CI, 7.24%-19.32%). Adverse events occurred in 441 participants (87.8%) in the loberamisal group and 439 (88.7%) in the placebo group. Serious adverse events occurred in 43 participants (8.6%) in the loberamisal group and 53 (10.7%) in the placebo group. All-cause mortality occurred in 6 participants (1.2%) in the loberamisal group and 10 (2.0%) in the placebo group.

CONCLUSIONS AND RELEVANCE Among patients with acute ischemic stroke treated within 48 hours of symptom onset, intravenous loberamisal, compared with placebo, resulted in a higher proportion of patients achieving full functional outcomes at 90 days. Further studies are needed to validate these findings and establish whether the benefits could extend to a broader patient population.

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Visual Abstract
Research Summary
Editorial
Supplemental content

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Despite major advances in reperfusion therapies for acute ischemic stroke, including intravenous thrombolysis and endovascular thrombectomy,[1] a substantial proportion of patients remain ineligible for these interventions or experience persistent disability despite timely treatment. This unmet need highlights the potential role of neuroprotection or neurorecovery in complementing reperfusion strategies.[2-4]

Neuroprotection is intended to alleviate ischemic neuronal damage and save salvageable brain tissue, yet most candidate neuroprotective agents failed to show clinical efficacy in large randomized trials,[5,6] underscoring the challenges of translating promising preclinical findings into effective stroke therapies. Recent advances targeting synaptic signaling pathways have renewed interest in neuroprotection, particularly in carefully selected patient populations and treatment windows.[7-11]

Ischemic stroke triggers pathological *N*-methyl-D-aspartate (NMDA) receptor overactivation that enhances postsynaptic density protein 95-neuronal nitric oxide synthase (PSD-95-nNOS) assembly[12] and nitric oxide–mediated excitotoxic injury. Ischemia-induced impairment of γ-aminobutyric acid type A ($GABA_A$) receptor–mediated inhibitory transmission further exacerbates excitotoxicity[13] and neuroinflammation.[14-16] Sustained PSD-95-nNOS dissociation in acute and subacute stroke facilitates neurogenesis, synaptogenesis, and dendritic maturation while suppressing reactive astrogliosis, promoting poststroke functional recovery.[17-19] Loberamisal combines the disruption of PSD-95-nNOS interaction with positive allosteric modulation of the α2-$GABA_A$ receptor, representing a synergistic neuroprotective strategy.[20-22] It also inhibits stroke-associated neuroinflammation via myeloperoxidase suppression,[23] fostering a microenvironment conducive to synaptic remodeling and neuroplasticity. A phase 2 randomized trial demonstrated favorable tolerability of intravenous loberamisal, with the patients in the 40-mg group achieving maximal improvements in functional outcomes relative to placebo,[24] justifying further clinical evaluation.

The Loberamisal for Acute Ischemic Stroke (LAIS) randomized clinical trial was conducted to evaluate whether intravenous loberamisal improves functional outcomes and maintains an acceptable safety profile in patients with acute ischemic stroke treated within 48 hours of symptom onset.

Key Points

Question Does intravenous loberamisal administration achieve full functional outcomes in patients with acute ischemic stroke?

Findings In this randomized clinical trial involving 998 patients treated within 48 hours of ischemic stroke onset, 69.7% with loberamisal vs 56.3% with placebo achieved full functional (modified Rankin Scale score, 0-1) outcome at 90 days, resulting in a statistically significant difference.

Meaning Among patients with acute ischemic stroke within 48 hours of symptom onset, loberamisal, compared with placebo, resulted in a greater likelihood of full functional outcome at 90 days.

Methods

Study Design and Oversight

The LAIS trial was a multicenter, randomized, double-blind, placebo-controlled phase 3 clinical trial conducted at 32 hospitals in China. Details of the rationale, design, and methods of the trial have been reported.[25] The trial was approved by the institutional review board of the Beijing Tiantan Hospital (No. YW2024-006-02) and by the ethics committees of all participating centers. The trial was conducted in accordance with the principles of the Declaration of Helsinki[26] and Good Clinical Practice guidelines. Written informed consent was obtained from all participants or their legally authorized representatives. The full protocol and statistical analysis plan are available in Supplement 1 and Supplement 2, respectively. Statistical analyses were performed independently by 2 groups. An academic statistical team from the China National Clinical Research Center for Neurological Diseases developed the statistical analysis plan and conducted analyses using the locked database accordingly (eMethods 1 in Supplement 3). An external statistical consulting group (Nanjing Yike PowerData Medical Technology Co, Ltd, funded by NeuroDawn Pharmaceutical Co, Ltd) performed analyses in compliance with the requirements of local regulatory authorities. These analyses of primary outcomes are presented in this manuscript as sensitivity analyses. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[27]

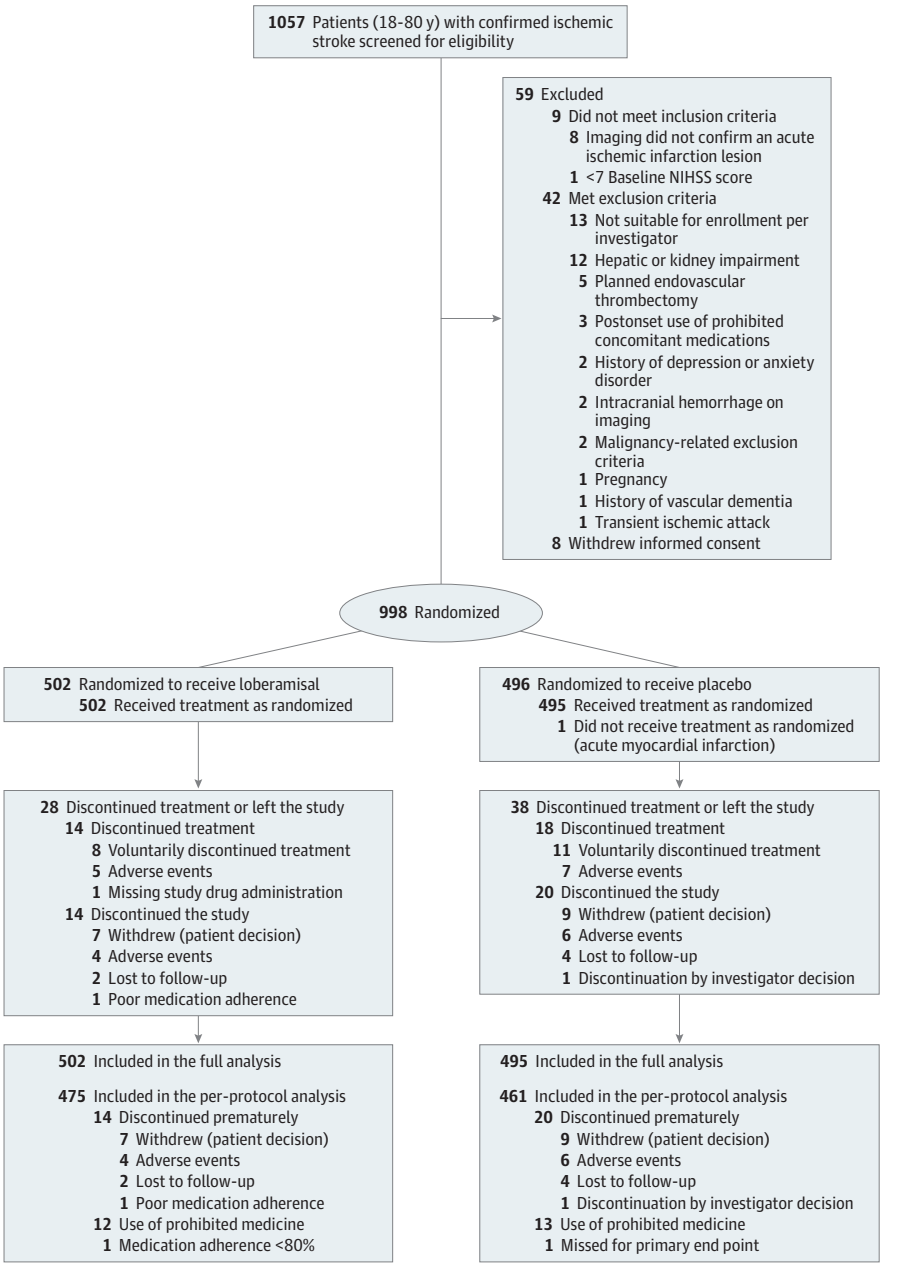
Participants

Eligible participants were adults aged 18 to 80 years with confirmed acute ischemic stroke who presented within 48 hours of symptom onset. Key inclusion criteria were a baseline National Institutes of Health Stroke Scale (NIHSS) score of 7 to 20 and a prestroke modified Rankin Scale (mRS) score of 0 or 1. Patients without prior pharmacological reperfusion therapy or those receiving only intravenous thrombolysis were eligible for enrollment, whereas participants treated with endovascular thrombectomy were excluded from the trial. Patients with a history of severe psychiatric disorders, dementia, depression, or anxiety or those receiving antidepressant or anxiolytic medications were excluded. Additional inclusion and exclusion criteria are provided in eMethods 2 in Supplement 1.

Randomization and Intervention Procedures

Participants were randomly assigned in a 1:1 ratio to receive intravenous loberamisal or placebo using a centralized, web-based randomization system (Clinflash IRT, V2.8.3; **Figure 1**). Loberamisal was formulated as a lyophilized powder with a corresponding solvent, whereas the placebo consisted of lyophilized powder only. Randomization was stratified by study center and time from symptom onset to randomization (≤12 hours vs >12 hours). The study drug and

Figure 1. Flow of Patients Through the Loberamisal for Acute Ischemic Stroke Trial



Participants were randomly assigned in a 1:1 ratio to receive intravenous loberamisal or placebo. Randomization was stratified by study center and time from symptom onset to randomization (≤12 hours vs >12 hours). The primary analysis population included all participants who received at least 1 dose of study drug after randomization. The per-protocol population included patients in the primary analysis population who, based on the prespecified criteria and the conclusions of the blinded data review meeting, had no protocol deviations considered likely to affect efficacy evaluation. Therefore, the number of deviations reported does not correspond directly to the number of participants excluded from the per-protocol population. A total of 25 participants with protocol deviations related to use of prohibited medicine were excluded from the per-protocol population. NIHSS indicates National Institutes of Health Stroke Scale.

placebo were identical in appearance, packaging, and labeling. Participants, investigators, care providers, outcome assessors, and statisticians were blinded to treatment allocation throughout the trial.

Participants received intravenous loberamisal at a dose of 40 mg or matching placebo once daily for 10 consecutive days. Each infusion was administered over 60 (±10) minutes through a dedicated intravenous line. Study drug administration was initiated as soon as feasible after randomization, and all infusions were administered during hospitalization. All participants received standard-of-care treatment for acute ischemic stroke in accordance with contemporary clinical guidelines. Administration of edavarone-dexborneal and edavarone was not permitted in accordance with the study protocol.

Outcomes

The primary efficacy outcome was the proportion of participants achieving a fully functional outcome at 90 days, defined as an mRS score of 0 to 1 (range, 0 [no neurologic deficit, no symptoms, or completely recovered] to 6 [death]). Prespecified secondary efficacy outcomes included sliding dichotomy mRS score at 90 days based on baseline stroke severity, ordinal shift across the mRS at 90 days, substantial neurological improvement at 10 and 30 days, defined as an NIHSS score change of at least 4 points from baseline, and

a Barthel Index score of at least 95 at 90 days. NIHSS scores range from 0 to 42, with higher scores indicating more severe stroke, and scores on the Barthel Index range from 0 to 100, with higher scores indicating better independent function. The sliding dichotomy mRS score was defined as an mRS score of 0 in patients with a baseline NIHSS score of 4 to 7; 0 to 1 in those with a score of 8 to 14; and 0 to 2 in those with a score of 15 to 25.

Exploratory outcomes included poststroke depression assessed using the Montgomery-Åsberg Depression Rating Scale (range, 0-60, with higher scores indicating more severe depressive symptoms) and poststroke anxiety assessed using the Hamilton Anxiety Scale (range, 0-56, with higher scores indicating more severe anxiety symptoms). Prespecified analyses evaluated Montgomery-Åsberg Depression Rating Scale scores of 12 or higher and 22 or higher, and Hamilton Anxiety Scale scores of 14 or higher and 21 or higher.

Safety outcomes included adverse events, serious adverse events, treatment-emergent adverse events, suspected unexpected serious adverse reactions, and mortality.

Clinical follow-up assessments for efficacy and safety were conducted at each participating site by trained, certified, and blinded investigators at 10 days, 30 days, and 90 days after randomization. The mRS score with a simplified questionnaire at 90 days was evaluated either through in-person visits or telephone interviews. Serious adverse events and adverse events were classified in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Sample Size Calculation

The sample size was calculated assuming that 71.5% of patients in the loberamisal group and 60.7% of patients in the placebo group would achieve an mRS score of 0 to 1 at 90 days based on the previous clinical trial.[24] A total of 399 participants per group would be needed to provide 90% power to detect this difference at a 2-sided significance level of .05. Allowing for up to 20% loss to follow-up, the target enrollment was 998 participants.

Statistical Analysis

Efficacy analyses were performed in the primary analysis population, defined as all patients with at least 1 dose of the study drug after randomization. They were also performed, as supplementary analyses of the estimands, in the per-protocol population, defined as treated participants without major protocol deviations that could materially affect the efficacy assessment. Analyses followed the ICH-E9(R1) framework, with intercurrent events addressed through different strategies in evaluation of estimands (eTable 1 and eMethods 2 in Supplement 3). Remaining missing data (14 [2.8%] for the loberamisal group and 20 [4.0%] for the placebo group) were handled using multiple imputation. Under a missing-at-random assumption, 100 datasets were imputed separately by treatment group using fully conditional specification. Logistic regression with an augmented likelihood approach was used for mRS score outcomes at days 10, 30, and 90 and the Barthel Index outcome at day 90, whereas predictive mean matching with 5 nearest neighbors was used for NIHSS outcomes at days 10 and 30. The imputation model included relevant baseline characteristics, follow-up outcomes, comorbidities, death, and prespecified intercurrent-event indicators. Patients who died were assigned the worst possible outcomes.

For the primary efficacy outcome, the proportion of patients achieving an mRS score of 0 to 1 at 90 days was summarized for each group. Relative risks (RRs) and 95% CIs for loberamisal vs placebo were estimated using a generalized linear model with a binomial distribution and log link, adjusted for randomization stratification factor (time from onset to randomization: ≤12 hours vs >12 hours). Risk differences (RDs) and 95% CIs were estimated using generalized linear models with a binomial distribution and identity link, with the same adjustment. Sensitivity analyses assessed robustness to alternative imputation methods, statistical models, and covariate sets. Subgroup analyses were prespecified according to age (<65 vs ≥65 years), sex (males vs females), time from symptom onset to study drug (≤12 vs >12 to ≤24 vs >24 hours), prestroke mRS score (0 vs 1), baseline NIHSS score (4-7 vs 8-14 vs ≥15), stroke history (yes vs no), and thrombolysis therapy (yes vs no). Binary secondary efficacy outcomes were analyzed using statistical methods consistent with those applied to the primary outcome. For the ordinal mRS score shift analysis at day 90, the proportional odds assumption was assessed using the score test. If the proportional odds assumption was met, an ordinal logistic regression model adjusted for randomization stratification factor was prespecified to estimate the common odds ratio and 95% CI.[28] For continuous efficacy outcome, an analysis of covariance was used, adjusting for treatment group, randomization stratification factor, and baseline NIHSS. Across multiple imputations, patient counts were averaged, whereas proportions and effect sizes with 95% CIs were pooled using the Rubin rules.

Safety analyses were performed in the safety set, which includes all participants who received at least 1 dose of the study drug and had at least 1 safety evaluation. Missing data were not imputed. Similar to the binary efficacy outcome analyses, safety outcomes were summarized by group, and RRs, RDs, and their respective 95% CIs were calculated using a generalized linear model.

This study had only 1 primary estimand and no adjustment for multiple comparisons was required for the primary outcome. Secondary outcomes were not adjusted for multiple comparisons and should be considered exploratory. No interim analysis was planned. All data analyses were conducted using SAS software version 9.4 (SAS Institute Inc). All tests were 2-sided, and $P < .05$ was considered statistically significant.

Results

Participants

Between July 24, 2024, and April 8, 2025, a total of 1057 patients with acute ischemic stroke were screened, of whom 998 were randomized at 32 participating centers (eMethods 3 in

Table 1. Characteristics of Patients in the Primary Analysis Population[a]

Characteristic	No. (%) of patients	
	Loberamisal group (n = 502)	Placebo group (n = 495)
Age, median (IQR), y	64.0 (57.0-71.0)	64.0 (56.0-71.0)
Age group, y		
<65	253 (50.4)	253 (51.1)
≥65	249 (49.6)	242 (48.9)
Sex		
Female	181 (36.1)	155 (31.3)
Male	321 (63.9)	340 (68.7)
History of stroke	166 (33.1)	157 (31.7)
Comorbidities		
Hypertension	418 (83.3)	403 (81.4)
Hyperlipidemia	262 (52.2)	259 (52.3)
Diabetes	177 (35.3)	168 (33.9)
Coronary heart disease	98 (19.5)	87 (17.6)
Atrial fibrillation	15 (3.0)	13 (2.6)
BMI, median (IQR)	24.2 (22.3-26.7)	24.2 (22.5-26.7)
Prestroke mRS, score[b]		
0	459 (91.4)	454 (91.7)
1	43 (8.6)	41 (8.3)
Baseline NIHSS score, median (IQR)[c]	8.0 (7.0-8.0)	8.0 (7.0-9.0)
Time from symptom onset to study drug, median (IQR), h	25.2 (17.0-33.3)	25.5 (17.0-32.7)
Time from symptom onset to study drug		
≤12 h	75 (14.9)	64 (12.9)
>12 to ≤24 h	159 (31.7)	158 (31.9)
>24 h	268 (53.4)	273 (55.2)
Thrombolytic therapy	82 (16.3)	89 (18.0)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

[a] Analyses were performed on actual collected data.

[b] The mRS score ranges from 0 (no neurological deficit, no symptoms, or completely recovered) to 6 (death), with higher scores indicating more severe stroke.

[c] Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe stroke.

Supplement 3). One participant assigned to the placebo group did not receive the study drug, resulting in 997 participants included in the primary analysis and safety populations (502 in the loberamisal group and 495 in the placebo group). A total of 936 participants were included in the per-protocol population. Reasons for exclusion from the per-protocol population and protocol deviations are shown in Figure 1 and detailed in (eTable 2 in Supplement 3).

Baseline Characteristics

Baseline demographic and clinical characteristics were well balanced between groups (**Table 1**). The median age was 64.0 years (IQR, 57.0-71.0) in the loberamisal group and 64.0 (IQR, 56.0-71.0) years in the placebo group, and approximately two-thirds of participants were men (n = 661). The median baseline NIHSS score was 8 (IQR, 7-8) in the loberamisal group and 8 (IQR, 7-9) in the placebo group. The median time from symptom onset to study drug administration was 25.2 hours (IQR, 17.0-33.3) in the loberamisal group and 25.5 hours (IQR, 17.0-32.7) in the placebo group. Baseline characteristics were similar in the per-protocol population (eTable 3 in Supplement 3).

Primary Outcome

At 90 days, 350 of 502 patients (69.7%) in the loberamisal group achieved an full functional outcome (mRS score, 0-1) compared with 279 of 495 (56.3%) in the placebo group (RR, 1.24; 95% CI, 1.12-1.36; **Table 2** and **Figure 2**). Results were consistent in the observed data, per-protocol population, and across sensitivity analyses using prespecified statistical principles (eTables 4 and 5 and eFigures 1-3 in Supplement 3.

Prespecified subgroup analyses demonstrated no significant heterogeneity of treatment effect across subgroups defined by age, sex, time from symptom onset to treatment, prestroke functional status, baseline stroke severity, prior stroke, or receipt of intravenous thrombolysis (eFigure 4 in Supplement 3).

Secondary and Exploratory Outcomes

A favorable result for the sliding dichotomy mRS score at 90 days was observed in 246 participants (49.0%) in the loberamisal group and 197 participants (39.8%) in the placebo group (RR, 1.23; 95% CI, 1.07-1.42; Table 2). Components of the sliding dichotomy mRS at 90 days, stratified by baseline NIHSS score, are presented in eTable 6 in Supplement 3. For the ordinal mRS shift analysis at 90 days, the common odds ratio for loberamisal vs placebo was not estimated, because the proportional odds assumption was not met (score test $P < .001$). No statistically significant between-group differences were observed for other prespecified and post hoc secondary outcomes (Table 2; Figure 2; eTables 4 and 7; and eFigures 1 and 2 in Supplement 3).

Table 2. Primary and Secondary Efficacy Outcomes in the Primary Analysis Population[a]

	No. (%) of patients			
	Loberamisal group (n = 502)	Placebo group (n = 495)	Risk difference, % (95% CI)	Relative risk (95% CI)
Primary efficacy outcomes				
mRS 0-1 90 d[b]	350 (69.7)	279 (56.3)	13.28 (7.24 to 19.32)	1.24 (1.12 to 1.36)
Secondary efficacy outcomes				
Sliding dichotomy mRS score at 90 d[c]	246 (49.0)	197 (39.8)	9.30 (3.08 to 15.52)	1.23 (1.07 to 1.42)
mRS score at 90 d, median (IQR)	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)		
Ordinal mRS score at 90 d[d]				
0	123 (24.5)	112 (22.7)		
1	232 (46.1)	174 (35.1)		
2	39 (7.8)	104 (21.1)		
3	71 (14.1)	62 (12.6)		
4	29 (5.7)	28 (5.7)		
5	2 (0.4)	2 (0.4)		
6	6 (1.3)	12 (2.5)		
NIHSS score change ≥4 from baseline at 10 d[e]	225 (44.7)	243 (49.0)	−4.36 (−10.62 to 1.90)	0.91 (0.80 to 1.04)
NIHSS score change ≥4 from baseline at 30 d	369 (73.5)	360 (72.7)	0.86 (−4.76 to 6.48)	1.01 (0.94 to 1.09)
Barthel Index ≥95 at 90 d[f]	355 (70.7)	348 (70.4)	0.31 (−5.50 to 6.12)	1.00 (0.92 to 1.09)

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

[a] Analyses were performed in the primary analysis population. Missing data were imputed by multiple imputations with 100 replicates. This study had only 1 primary estimand and did not involve multiple testing issues. The number and proportion of patients, and the differences were averaged from the multiple imputations. Effect sizes and 95% CIs are derived using the Rubin rules to pool results across multiple imputations. Percentages may not total 100 because of rounding.

[b] Scores on the mRS range from 0 (no neurological deficit, no symptoms, or completely recovered) to 6 (death).

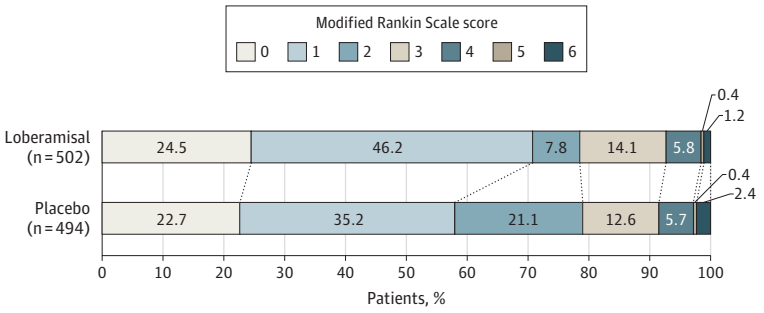
[c] Defined as a mRS score of 0 in patients with a baseline NIHSS score of 4 to 7; an mRS score of 0 to 1 in patients with a baseline NIHSS score of 8 to 14; and a modified Rankin Scale score of 0 to 2 in patients with a baseline NIHSS score of 15 to 25.

[d] For the ordinal mRS shift analysis at 90 days, the proportional odds assumption was not met according to the score test ($P < .001$); therefore, a common odds ratio was not estimated.

[e] Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe stroke.

[f] Scores on the Barthel Index range from 0 to 100, with higher scores indicating better independent function.

Figure 2. Stacked Bar Chart Showing Distribution of Modified Rankin Scale (mRS) Scores on Day 90



Analyses were performed in the primary analysis population, with missing data handled by multiple imputation. The 90-day mRS score was imputed for 14 patients in the loberamisal group and 20 patients in the placebo group. Percentages were averaged across imputations and may not total 100% due to rounding.

Among exploratory outcomes, no significant difference between participants treated with loberamisal were observed compared with placebo for the Montgomery-Åsberg Depression Rating Scale score of 22 or greater at 90 days (24 [4.9%] vs 39 [7.8%]; RR, 0.63; 95% CI, 0.38-1.04) and for the Hamilton Anxiety Scale score of 21 or greater (24 [4.7%] vs 36 [7.2%]; RR, 0.66; 95% CI, 0.39-1.11; eTables 8 and 9 in Supplement 3).

Safety

A total of 97.2% of participants received more than 80% of the prescribed dose. Drug exposure and medication adherence were similar between groups (eTable 10 in Supplement 3). In the safety population, adverse events occurred in 441 of 502 participants (87.8%) in the loberamisal group and 439 of 495 participants (88.7%) in the placebo group. Serious adverse events occurred in 43 participants (8.6%) and 53 participants (10.7%), and deaths in 6 participants (1.2%) and 10 participants (2.0%) in the loberamisal and placebo groups, respectively. No suspected unexpected serious adverse reactions were reported. Discontinuation of the study drug due to adverse events was uncommon and did not differ between groups. (**Table 3** and eTables 11- 14 in Supplement 3).

Discussion

In this multicenter randomized clinical trial involving patients with acute ischemic stroke treated within 48 hours of symptom onset, intravenous loberamisal was associated with a significantly higher proportion of patients achieving full functionality outcomes at 90 days than with placebo, without an increase in serious adverse events or mortality.

Previous randomized trials of neuroprotective agents targeting single molecular pathways have largely failed to demonstrate benefit.[5,6] Recent advances have rekindled optimism. Nerinetide (NA-1), a PSD-95 inhibitor, has completed 3 randomized clinical trials for acute ischemic stroke. The Efficacy and Safety of Nerinetide in Participants With Acute Ischemic Stroke Undergoing Endovascular Thrombectomy Excluding Thrombolysis (ESCAPE-NEXT) trial,[11] designed to avoid the nerinetide-alteplase interaction identified in the ESCAPE-NA1 trial,[8] failed to show benefit for patients undergoing endovascular thrombectomy without intravenous thrombolysis. This outcome highlights the need to define nerinetide's optimal treatment window and responsive subpopulation. The FRONTIER trial[9] and an individual patient data meta-analysis[10] suggested potential benefits for reperfusion candidates presenting within 3 hours. Collectively, these clinical data suggest that PSD-95 represents a promising therapeutic target, yet additional confirmatory evidence is still required for validation.

Loberamisal's disrupting the interaction between nNOS and PSD-95 not only reduces NMDAR-mediated excitotoxicity[12] but also enhances neuroplasticity, including neurogenesis, synaptogenesis, spine growth, and dendrite development after stroke[17,19] and enhances brain-derived neurotrophic factor -tropomyosin receptor kinase B signaling.[18] Moreover, loberamisal inhibited enzymatic activity of myeloperoxidase in vitro and in vivo, and inhibited myeloperoxidase expression in ischemia or reperfusion brain injury, thereby inhibiting neuroinflammation and reactive oxygen species generation.[23] Global brain neuroinflammation might continuously shape the evolving pathology after a stroke and affect the patients' long-term neurological outcome.[29] Moreover, levels of proinflammatory cytokines in the serum were associated with poor mRS score outcomes 3 months or 1 year after stroke.[30-32] This pathway may serve as a key potential mechanistic basis underlying the therapeutic benefits of a much longer treatment time. The subgroup analysis of the phase 2 trial[24] (allowing treatment within 48 hours of onset) found no reduction in efficacy when loberamisal was given more than 24 hours after symptom onset compared with less than 24 hours of symptom onset. This 48-hour window is clinically valuable because it includes patients who arrive too late for reperfusion therapy but remain at risk of ongoing neuronal loss. Despite multiple plausible mechanisms having been validated in preclinical models, the primary pathway mediating these clinical improvements remains unidentified.

Loberamisal was designed to modulate complementary synaptic mechanisms involving PSD-95 signaling and α2-$GABA_A$ receptor function.[20-23] The RESTORE BRAIN trial[33] reported no efficacy of S44819, a selective α5-$GABA_A$ receptor antagonist, when administered beyond 48 hours after stroke onset. The effects of α5-$GABA_A$ receptor antagonists may be time dependent, although they may improve recovery in the subacute phase, it could exacerbate acute injury by disrupting GABA-mediated protection against excitotoxicity.[34] Unlike S44819, loberamisal is a positive allosteric modulator of α2-$GABA_A$ receptor. The combined disruption of PSD-95-nNOS coupling and enhancement of α2-$GABA_A$ receptor signaling may therefore more effectively attenuate poststroke excitotoxic injury. Although α2-$GABA_A$ receptor subunits mediate anxiolytic and antidepressant effects,[35] our trial found no between-group differences in severe anxiety or depression at day 90.

Neuroprotective therapy is encouraged to be administered in combination with thrombolytic therapy. Although the LAIS study permitted enrollment of patients who received intravenous thrombolysis within the standard time window, the vast majority of screened patients had symptom onset exceeding 4.5 hours, resulting in patients who received intravenous thrombolysis accounting for less than one-fifth of the total population. Subgroup analyses showed that loberamisal may provide clinical benefit among patients both with and without intravenous thrombolysis. Further research is needed to explore whether patients who underwent endovascular thrombectomy also benefit from loberamisal.

Safety findings were reassuring, with no excess in serious adverse events or mortality. The incidence and spectrum of adverse events were similar to those receiving placebo. Among participants who received intravenous thrombolysis, no increased risk of hemorrhagic transformation was observed, supporting the safety of loberamisal when combined with standard reperfusion therapies.

Table 3. Safety Outcomes in the Safety Population[a]

	No. (%) of patients	
	Loberamisal group (n = 502)	Placebo group (n = 495)
Adverse events	441 (87.8)	439 (88.7)
Treatment-emergent adverse events[b]	441 (87.8)	439 (88.7)
Serious adverse events[c]	43 (8.6)	53 (10.7)
Discontinuation of treatment due to adverse events	6 (1.2)	6 (1.2)
Significant adverse events[d]	4 (0.8)	4 (0.8)
All-cause mortality	6 (1.2)	10 (2.0)

[a] Patients who experienced at least 1 event, rather than the total number of events. Analyses were performed on actual collected data. See eTables 11 and 12 in Supplement 3 for adverse events and serious adverse events reported in 10 or more participants, and eTables 13 and 14 in Supplement 3 for complete listings.

[b] Defined as an adverse event occurring after initiation of the study treatment.

[c] Defined as an adverse event that resulted in death, was life-threatening, required or prolonged hospitalization; resulted in persistent or substantial disability or incapacity; or caused a congenital anomaly or birth defect.

[d] Any adverse event (other than a serious adverse event) that led to a temporary drug interruption and/or permanent drug discontinuation.

Limitations

This study has several limitations. First, the trial population consisted exclusively of patients enrolled in China, which may limit generalizability to other populations. Second, patients with very mild or very severe strokes were underrepresented, and patients undergoing endovascular thrombectomy were excluded. Third, no significant between-group differences were observed for several secondary efficacy outcomes, such as the early change from baseline in NIHSS and the proportion of participants achieving a Barthel Index score at least 95 at day 90, which weaken the primary outcome finding of mRS 0 to 1. Fourth, biomarker and imaging correlates of treatment response were not assessed, limiting mechanistic interpretation.

Conclusions

Among patients with acute ischemic stroke treated within 48 hours of symptom onset, intravenous loberamisal improved full functional outcomes at 90 days compared with placebo and demonstrated an acceptable safety profile. These findings support further evaluation of loberamisal as a neuroprotective and neuroreparative therapy in acute ischemic stroke.

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REFERENCES

1. Prabhakaran S, Gonzalez NR, Zachrison KS, et al; Peer Review Committee. Guideline for the early management of patients with acute ischemic stroke: a guideline from the American Heart Association/American Stroke Association. *Stroke*. 2026;57(8):e316-e436. doi:10.1161/STR.0000000000000513

2. Chamorro Á, Dirnagl U, Urra X, Planas AM. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. *Lancet Neurol*. 2016;15(8):869-881. doi:10.1016/S1474-4422(16)00114-9

3. Savitz SI, Baron JC, Fisher M, Stair X; STAIR X Consortium. Stroke treatment academic industry roundtable X: brain cytoprotection therapies in the reperfusion era. *Stroke*. 2019;50(4):1026-1031. doi:10.1161/STROKEAHA.118.023927

4. Fisher M, Savitz SI. Pharmacological brain cytoprotection in acute ischaemic stroke—renewed hope in the reperfusion era. *Nat Rev Neurol*. 2022;18(4):193-202. doi:10.1038/s41582-021-00605-6

5. O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1026 Experimental treatments in acute stroke. *Ann Neurol*. 2006;59(3):467-477. doi:10.1002/ana.20741

6. Chamorro Á, Lo EH, Renú A, van Leyen K, Lyden PD. The future of neuroprotection in stroke. *J Neurol Neurosurg Psychiatry*. 2021;92(2):129-135. doi:10.1136/jnnp-2020-324283

7. Cook DJ, Teves L, Tymianski M. Treatment of stroke with a PSD-95 inhibitor in the gyrencephalic primate brain. *Nature*. 2012;483(7388):213-217. doi:10.1038/nature10841

8. Hill MD, Goyal M, Menon BK, et al; ESCAPE-NA1 Investigators. Efficacy and safety of nerinetide for the treatment of acute ischaemic stroke (ESCAPE-NA1): a multicentre, double-blind, randomised controlled trial. *Lancet*. 2020;395(10227):878-887. doi:10.1016/S0140-6736(20)30258-0

9. Christenson J, Hill MD, Swartz RH, et al. Efficacy and safety of intravenous nerinetide initiated by paramedics in the field for acute cerebral ischaemia within 3 h of symptom onset (FRONTIER): a phase 2, multicentre, randomised, double-blind, placebo-controlled study. *Lancet*. 2025;405(10478):571-582. doi:10.1016/S0140-6736(25)00193-X

10. Tymianski M, Hill MD, Goyal M, et al; ESCAPE-NA1, ESCAPE-NEXT, and FRONTIER Investigators. Safety and efficacy of nerinetide in patients with acute ischaemic stroke enrolled in the early window: a post-hoc meta-analysis of individual patient data from three randomised trials. *Lancet Neurol*. 2025;24(3):208-217. doi:10.1016/S1474-4422(24)00515-5

11. Hill MD, Goyal M, Demchuk AM, et al; ESCAPE-NEXT Investigators. Efficacy and safety of nerinetide in acute ischaemic stroke in patients undergoing endovascular thrombectomy without previous thrombolysis (ESCAPE-NEXT): a multicentre, double-blind, randomised controlled trial. *Lancet*. 2025;405(10478):560-570. doi:10.1016/S0140-6736(25)00194-1

12. Zhou L, Li F, Xu HB, et al. Treatment of cerebral ischemia by disrupting ischemia-induced interaction of nNOS with PSD-95. *Nat Med*. 2010;16(12):1439-1443. doi:10.1038/nm.2245

13. Garcia JD, Gookin SE, Crosby KC, et al. Stepwise disassembly of GABAergic synapses during pathogenic excitotoxicity. *Cell Rep*. 2021;37(12):110142. doi:10.1016/j.celrep.2021.110142

14. Crowley T, Cryan JF, Downer EJ, O'Leary OF. Inhibiting neuroinflammation: the role and therapeutic potential of GABA in neuro-immune interactions. *Brain Behav Immun*. 2016;54:260-277. doi:10.1016/j.bbi.2016.02.001

15. Bhat R, Axtell R, Mitra A, et al. Inhibitory role for GABA in autoimmune inflammation. *Proc Natl Acad Sci U S A*. 2010;107(6):2580-2585. doi:10.1073/pnas.0915139107

16. Al Omran AJ, Shao AS, Watanabe S, et al. Social isolation induces neuroinflammation and microglia overactivation, while dihydromyricetin prevents and improves them. *J Neuroinflammation*. 2022;19(1):2. doi:10.1186/s12974-021-02368-9

17. Luo CX, Lin YH, Qian XD, et al. Interaction of nNOS with PSD-95 negatively controls regenerative repair after stroke. *J Neurosci*. 2014;34(40):13535-13548. doi:10.1523/JNEUROSCI.1305-14.2014

18. Cai CY, Chen C, Zhou Y, et al. PSD-95-nNOS coupling regulates contextual fear extinction in the

dorsal CA3. *Sci Rep*. 2018;8(1):12775. doi:10.1038/s41598-018-30899-4

19. Lin YH, Liang HY, Xu K, et al. Dissociation of nNOS from PSD-95 promotes functional recovery after cerebral ischaemia in mice through reducing excessive tonic GABA release from reactive astrocytes. *J Pathol*. 2018;244(2):176-188. doi:10.1002/path.4999

20. Wei W, Liu W, Du S, et al. A compound mitigates cancer pain and chemotherapy-induced neuropathic pain by dually targeting nNOS-PSD-95 interaction and $GABA_A$ receptor. *Neurotherapeutics*. 2021;18(4):2436-2448. doi:10.1007/s13311-021-01158-8

21. Wu H, Huang Z, Wang X, et al. Preclinical evaluation of ZL006-05, a new antistroke drug with fast-onset antidepressant and anxiolytic effects. *Stroke Vasc Neurol*. 2023;8(6):463-474. doi:10.1136/svn-2022-002156

22. Li J, Zhang L, Xu C, et al. A pain killer without analgesic tolerance designed by co-targeting PSD-95-nNOS interaction and α2-containning $GABA_A$Rs. *Theranostics*. 2021;11(12):5970-5985. doi:10.7150/thno.58364

23. Chen W, Wu H, Xu X, Qin YJ, Zhu L, Zhu D. ZL006-05 prevents tPA-induced haemorrhagic transformation after stroke via inhibiting neutrophil myeloperoxidase-related pathway. *Stroke Vasc Neurol*. Published online July 2, 2026;svn-2026-005289. doi:10.1136/svn-2026-005289

24. Feng B, Li H, Xu S, et al. Loberamisal injection for the treatment of acute ischaemic stroke: a multicentre, randomised, double-blind, placebo-controlled phase II clinical trial. *Stroke Vasc Neurol*. Published online November 10, 2025;svn-2025-004581. doi:10.1136/svn-2025-004581

25. Li S, Wang X, Feng B, Li H, Wang Y. Loberamisal for Acute Ischaemic Stroke (LAIS): a multicentre, randomised, double-blind, parallel, placebo-controlled phase III clinical trial. *Stroke Vasc Neurol*. Published online December 4, 2025;svn-2025-004582. doi:10.1136/svn-2025-004582

26. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human participants. *JAMA*. 2025;333(1):71-74. doi:10.1001/jama.2024.21972

27. Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomized trials. *Nat Med*. 2025;31(6):1776-1783. doi:10.1038/s41591-025-03635-5

28. McCullagh P. Regression models for ordinal data. *J R Stat Soc B (Methodol)*. 1980;42(2):109-127. doi:10.1111/j.2517-6161.1980.tb01109.x

29. Shi K, Tian DC, Li ZG, Ducruet AF, Lawton MT, Shi FD. Global brain inflammation in stroke. *Lancet Neurol*. 2019;18(11):1058-1066. doi:10.1016/S1474-4422(19)30078-X

30. Kim JW, Park MS, Kim JT, et al. The impact of tumor necrosis factor-α and interleukin-1β levels and polymorphisms on long-term stroke outcomes. *Eur Neurol*. 2018;79(1-2):38-44. doi:10.1159/000484599

31. Mengel A, Ulm L, Hotter B, et al. Biomarkers of immune capacity, infection and inflammation are associated with poor outcome and mortality after stroke—the PREDICT study. *BMC Neurol*. 2019;19(1):148. doi:10.1186/s12883-019-1375-6

32. Li X, Lin S, Chen X, et al. The prognostic value of serum cytokines in patients with acute ischemic stroke. *Aging Dis*. 2019;10(3):544-556. doi:10.14336/AD.2018.0820

33. Chabriat H, Bassetti CL, Marx U, et al; RESTORE BRAIN study investigators. Safety and efficacy of $GABA_A$ α5 antagonist S44819 in patients with ischaemic stroke: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet Neurol*. 2020;19(3):226-233. doi:10.1016/S1474-4422(20)30004-1

34. Clarkson AN, Huang BS, Macisaac SE, Mody I, Carmichael ST. Reducing excessive GABA-mediated tonic inhibition promotes functional recovery after stroke. *Nature*. 2010;468(7321):305-309. doi:10.1038/nature09511

35. Rudolph U, Knoflach F. Beyond classical benzodiazepines: novel therapeutic potential of $GABA_A$ receptor subtypes. *Nat Rev Drug Discov*. 2011;10(9):685-697. doi:10.1038/nrd3502