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Nelonemdaz and Patients With Acute Ischemic Stroke and Mechanical Reperfusion
The RODIN Randomized Clinical Trial

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Abstract

IMPORTANCE Nelonemdaz selectively antagonizes the 2B subunit of the *N*-methyl-D-aspartate glutamate receptor and scavenges free radical species.

OBJECTIVE To evaluate whether nelonemdaz enhances the clinical outcomes of patients with acute ischemic stroke undergoing emergent reperfusion therapy.

DESIGN, SETTING, AND PARTICIPANTS This multicenter double-blind placebo-controlled randomized phase 3 trial (December 25, 2021, to June 30, 2023, in South Korea) recruited patients with acute ischemic stroke who met the following criteria: National Institutes of Health Stroke Scale score greater than or equal to 8, Alberta Stroke Program Early Computed Tomography score greater than or equal to 4, and endovascular thrombectomy within 12 hours after stroke onset.

INTERVENTION Patients were assigned in a 1:1 ratio to receive intravenous infusions of nelonemdaz twice a day for 5 days or a matching placebo.

MAIN OUTCOMES AND MEASURES The primary end point was a favorable shift in the modified Rankin scale (mRS) 12 weeks after stroke onset. The secondary end points included various composites of the mRS at 5 and 12 weeks, symptomatic intracranial hemorrhage, and infarct volume. Both intention-to-treat and per-protocol analyses were conducted.

RESULTS A total of 496 patients were enrolled across 24 Korean stroke centers, of whom 39 dropped out (254 men [55.6%]; mean [SD] age, 72.9 [12.1] years). Baseline characteristics of study participants did not significantly differ. For the primary end point, the distribution of the mRS scores at 12 weeks did not significantly differ between the nelonemdaz and placebo groups (common odds ratio, 0.95; 95% CI, 0.69-1.31). For the secondary end points, a median of mRS at 5 weeks (3 vs 3) and mRS 0 at 12 weeks (18.1% vs 18.2%) did not differ substantially between groups. The occurrence of symptomatic intracranial hemorrhage (2.7% vs 0.9%) and infarct volume within 24 hours of the last trial drug infusion (42 vs 38 mL) did not differ significantly between groups. No serious adverse events were reported regarding the trial drug and placebo.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, nelonemdaz did not meet the primary efficacy end point compared with placebo.

(continued)

Key Points

Question Does emergent infusion of nelonemdaz, a selective *N*-methyl-D-aspartate receptor antagonist and free radical scavenger, improve clinical outcomes in patients who had acute ischemic stroke and received endovascular thrombectomy?

Findings In a phase 3 randomized clinical trial among 496 patients, the results by shift analysis did not meet the prespecified primary end point in terms of the distribution of the modified Rankin scale scores 3 months after treatment. The occurrence of symptomatic intracranial hemorrhage and infarct volume within 24 hours of the last infusion did not differ significantly between the treatment and control groups.

Meaning The findings of this trial suggest the novel neuroprotective agent nelonemdaz did not demonstrate efficacy in reducing acute ischemic injury following reperfusion therapy.

+ Visual Abstract

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

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Introduction

Patients with acute ischemic stroke can be effectively treated with medical thrombolysis or endovascular thrombectomy (EVT), but efforts to develop neuroprotective treatments have not been successful.[1-3] Endovascular thrombectomy for acute ischemic stroke has been approved, and its indications have been expanded in recent years.[4-10] Although EVT for large-vessel occlusion markedly improves the outcomes of individuals who experience stroke, approximately half of patients who receive EVT are unable to live independently thereafter.[11]

Glutamate excitotoxicity and free radicals mediate brain tissue damage during ischemic insults and reperfusion.[12-17] Nelonemdaz (2-hydroxy-5-[2,3,5,6-tetrafluoro-4-trifluoromethyl-benzylamino] benzoic acid) reduces excitotoxicity by selectively blocking the 2B subtype of *N*-methyl-D-aspartate (NMDA) receptors and additionally scavenges free radicals.[18-21] Therefore, it could potentially further reduce brain infarction and improve functional outcomes in patients with acute ischemic stroke who receive EVT.

Preclinical studies of nelonemdaz have reported substantial neuroprotective outcomes in in vitro experiments and in vivo rodent models with cerebral ischemia/reperfusion.[18,22,23] A phase 2 clinical trial on nelonemdaz suggested the potential for clinical improvement in patients with acute ischemic stroke undergoing EVT for large-vessel reperfusion.[24] We therefore conducted a phase 3 trial to examine the use of nelonemdaz in patients with acute ischemic stroke undergoing EVT.

Methods

Trial Design and Patients

Rescue on Reperfusion Damage in Cerebral Infarction by Nelonemdaz (RODIN) was a multicenter double-blind placebo-ctonrolled randomized phase 3 clinical trial conducted by 24 hospitals in South Korea. Patient enrollment began December 25, 2021, and concluded June 30, 2023. The protocol was approved by the institutional review board at each participating hospital and the Asan Medical Center Institutional Review Board and was published elsewhere.[25] Patients or authorized family members provided written informed consent. The study adhered to the Declaration of Helsinki[26] principles and the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The protocol is available in Supplement 1 and the statistical analysis plan is available in Supplement 2.

Patients were enrolled if they presented to a participating hospital emergency department (ED) with acute ischemic stroke caused by large-vessel occlusion (intracranial internal carotid artery, or M1 or M2 segments of the middle cerebral artery as confirmed by baseline angiography) and if EVT was expected to be initiated within 12 hours from the last known time before symptoms appeared. Additional inclusion criteria included age 19 years or older, baseline National Institutes of Health Stroke Scale (NIHSS) score greater than or equal to 8, prestroke modified Rankin Scale (mRS) score of 0 or 1, and baseline Alberta Stroke Program Early Computed Tomography Scores (ASPECTS) greater than or equal to 4 on computed tomography (CT) or diffusion-weighted imaging.

Using an interactive web-response system, participants were randomly assigned to either the nelonemdaz group or a corresponding placebo group in a 1:1 ratio. Before the allocation process, the participating centers were divided using a centralized stratified block randomization method.

End Points

The primary end point was a favorable shift in mRS scores 12 weeks after treatment. The secondary end points included the proportion of patients with mRS scores 0 to 2 at 5 and 12 weeks, the proportion of patients with mRS scores 0 at 5 and 12 weeks, the distribution of mRS scores at 5 weeks, NIHSS scores 0 to 4 within 24 hours and at 5 and 12 weeks, and Barthel Index scores greater than or equal to 95 at 5 and 12 weeks. Infarct volume was compared using brain magnetic resonance imaging (MRI) at 7 and 12 weeks. Symptomatic intracranial hemorrhage within 7 days, defined as intracranial hemorrhage accompanied by neurologic deterioration (NIHSS score increase ≥4), was documented. Analyses for primary and secondary end points were conducted using the full analysis set.

Safety end points included the frequency of adverse and serious adverse events, such as major bleeding and mortality, at 12 weeks. Any major bleeding, as defined by the International Society of Thrombosis and Haemostasis,[27] was recorded (fatal bleeding or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, peritoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or bleeding causing a decrease in hemoglobin levels of 2 g/dL or more [to convert to grams per liter, multiply by 10] or leading to transfusion of 2 or more units of packed red blood cells or whole blood).

Assessments

Clinical evaluations of functional status were conducted in person at the outpatient clinic by personnel who were blinded to the study. However, telephone interviews with patients or their caregivers were permitted according to a standardized protocol if the patient was unable to visit due to severe disability or death. Infarct volume was measured by an independent imaging analysis company (Nunaps Inc). In addition to self-reports of ASPECTS (CT or MRI) and post-EVT modified thrombolysis in cerebral infarction (mTICI) grade, the imaging core laboratory of the RODIN trial analyzed ASPECTS on noncontrast CT (J.H.S., J.Y.C., S.I.S.) and post-EVT extended TICI (eTICI) grade (J.S.L., J.Y.C, M.P.) simultaneously for subgroup analyses.

Statistical Analysis

The target total sample size of 496 patients (248 patients in each group) was calculated to achieve 80% statistical power, based on phase 2 trial data,[24] in demonstrating the superiority of nelonemdaz over placebo in reducing stroke-related disability in patients with acute ischemic stroke who have undergone EVT. As a result of the previous phase 2 trial,[24] nelonemdaz increased the odds for improvement across all cutoff points of the scale compared with placebo (common odds ratio [cOR], 1.71; 95% CI, 0.90-3.25). Thus, we assumed a 20% dropout rate, a favorable treatment effect with a cOR of 1.65 and a 2-sided statistical significance threshold of $P < .05$.

The full analysis included all randomly assigned patients who received at least one dose of the trial drug and underwent measurement of the mRS score at 12 weeks. Per-protocol analysis was also conducted on patients who did not have any major protocol violations regarding the inclusion and exclusion criteria and had a nelonemdaz or placebo adherence rate of 80% or higher.

The primary end point analysis used a Cochran-Mantel-Haenszel shift test for superiority to assess the distribution of the mRS scores at 12 weeks. Shift analysis examines changes across all levels of the mRS to assess the overall impact of an intervention or treatment. Instead of focusing on a single dichotomized outcome (eg, favorable vs unfavorable), shift analysis evaluates shifts in the distribution of scores across the entire scale. This method provides a more comprehensive picture of the effect of a treatment. The shift of mRS scores toward a better functional outcome was estimated using an ordinal logistic model. A cOR with 95% CIs was derived after verifying the proportional odds assumption ($P = .52$).

Analysis of secondary end points and safety end points was conducted using the χ^2 test, Fisher exact test, Cochran-Mantel-Haenszel shift test, and Wilcoxon rank-sum test based on the type of

variables. All treatment effects for binary secondary end points were estimated as relative risks with 95% CIs.

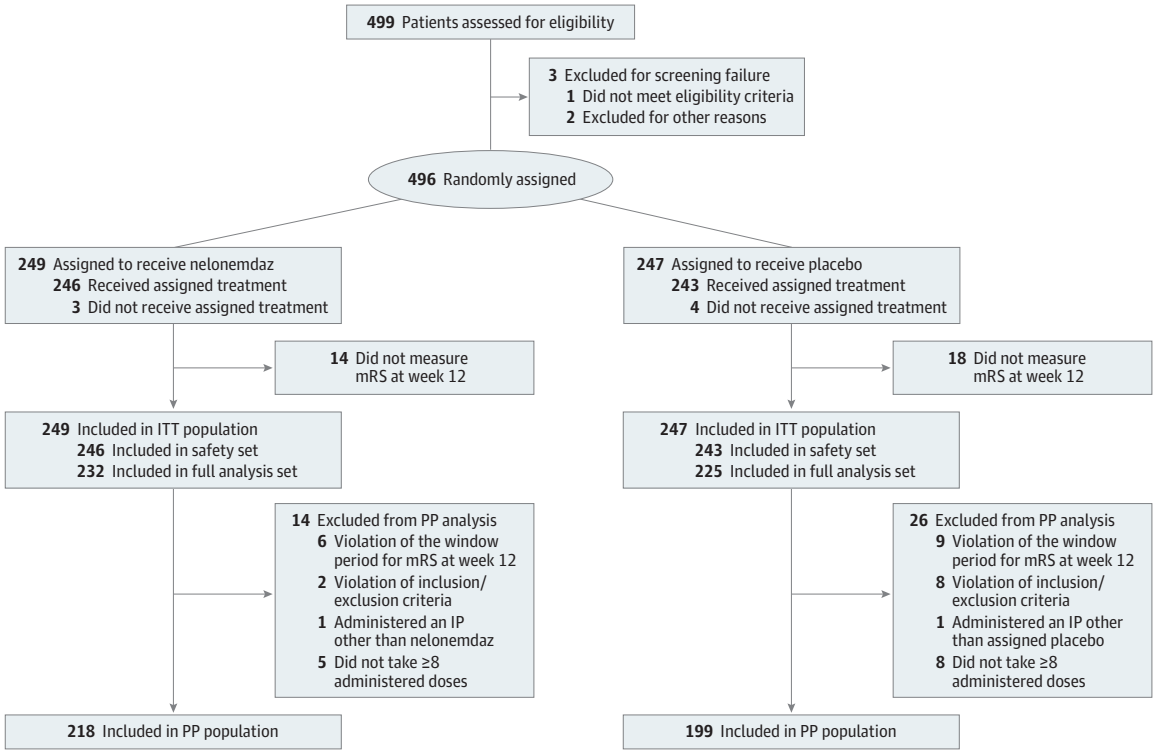
We conducted subgroup analyses of the primary end point based on age, sex, baseline NIHSS, diabetes, ASPECTS, baseline imaging protocol, administration of alteplase, eTICI grade, and cause of the stroke. No multiplicity correction was applied for subgroup analyses. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc).

Results

Baseline Characteristics

A total of 496 patients were enrolled of 499 screened patients in 24 Korean stroke centers, and 39 (7.9%) dropped out (**Figure 1**). Patients were randomly assigned to receive nelonemdaz (249 patients) or placebo (247 patients). Baseline and demographic characteristics are described in **Table 1**. A total of 203 women (44.4%) and 254 men (55.6%) were included; mean (SD) age was 72.9 (12.1) years. The median of the time from the onset of stroke symptoms to ED arrival was 100 (IQR, 50-218) minutes, and the median of the time from ED arrival to EVT was 102 (IQR, 77-131) minutes. Baseline characteristics of the study participants, including mean age, the proportion of male sex, and major cardiovascular risk factors, did not differ significantly between the groups. There was a higher prevalence of atrial fibrillation and cardioembolic stroke and a history of ischemic stroke in the nelonemdaz group compared with the placebo group. The frequency of intravenous alteplase administration and the final reperfusion grade defined by mTICI did not significantly differ as well. Likewise, the 2 groups did not show significant differences in the time from stroke onset to arrival at the ED, as well as the time from ED arrival to intravenous alteplase, EVT, and the first trial drug infusion.

Figure 1. Trial Flowchart



IP, investigational product; ITT, intention-to-treat; mRS, modified Rankin scale; PP, per protocol.

Primary and Secondary End Points

In the full analysis set, the nelonemdaz and placebo groups did not show significant differences in the primary and secondary end points (**Table 2**). In particular, there was no significant difference in the mRS score at 12 weeks between the groups as assessed by shift analysis (**Figure 2**). The cOR for a favorable shift of mRS scores at 12 weeks was not statistically significant (0.95; 95% CI, 0.69-1.31). The median mRS score at 12 weeks was 2 (IQR, 1-4) in both groups, with no statistically significant difference in treatment effect. For the secondary end points, there was no significant difference in the median mRS score at 5 weeks (3 vs 3; odds ratio, 1.00; 95% CI, 0.73-1.38), as well as the

Table 1. Characteristics of Patients at Baseline in the Full Analysis Set

Characteristic	No. (%)	
	Nelonemdaz (n = 232)	Placebo (n = 225)
Age, mean (SD), y	72.3 (12.4)	73.4 (11.9)
Sex		
Female	102 (44.0)	101 (44.9)
Male	130 (56.0)	124 (55.1)
Hypertension	158 (69.0)	159 (71.3)
Diabetes	75 (32.8)	73 (32.7)
Hyperlipidemia	82 (35.8)	82 (36.8)
Coronary artery disease	38 (16.6)	33 (14.8)
Atrial fibrillation	133 (58.1)	105 (47.1)
Current smoking	38 (16.6)	29 (13.0)
Current alcohol consumption	54 (23.6)	52 (23.3)
Family history of ischemic stroke	40 (17.5)	25 (11.2)
History of ischemic stroke	64 (27.6)	42 (18.7)
Premorbid mRS score		
0	181 (78.0)	182 (80.9)
1	51 (22.0)	43 (19.1)
NIHSS score, median (IQR)	14 (10-18)	13 (10-17)
ASPECTS (self-report), median (IQR)	8 (7-9)	8 (7-9)
Occlusion location (multiple choice)		
Intracranial ICA	62 (26.7)	59 (26.2)
MCA M1	135 (58.2)	139 (61.8)
M1-equivalent M2	59 (25.4)	46 (20.4)
Major imaging protocol for patient selection		
CT	205 (88.4)	197 (87.6)
MRI	27 (11.6)	28 (12.4)
TOAST		
Cardioembolic	154 (66.4)	125 (55.6)
Noncardioembolic	78 (33.6)	100 (44.4)
Intravenous alteplase	115 (49.6)	116 (51.6)
mTICI on endovascular thrombectomy (self-report)		
0	12 (5.3)	11 (5.0)
1	8 (3.5)	3 (1.4)
2a	11 (4.8)	10 (4.6)
2b	69 (30.4)	80 (36.5)
3	127 (55.9)	115 (52.5)
Time from onset of stroke symptoms to ED arrival, median (IQR), min	101 (47-218)	100 (50-223)
Time from ED arrival to intravenous alteplase if applied, median (IQR), min [No. of patients]	41 (32-56) [104]	36 (29-57) [107]
Time from ED arrival to endovascular thrombectomy, median (IQR), min	101 (78-131)	103 (77-132)
Time from ED arrival to the trial drug infusion, median (IQR), min	103 (80-134)	107 (82-137)

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; CT, computed tomography; ED, emergency department; ICA, internal carotid artery; MCA, middle cerebral artery; MRI, magnetic resonance imaging; mRS, modified Rankin scale; mTICI, modified thrombolysis in cerebral infarction; NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

proportion of patients with mRS scores of 0 to 2 at 5 (OR, 0.99; 95% CI, 0.82-1.19) and 12 (OR, 0.98; 95% CI, 0.82-1.16) weeks or those with an mRS score of 0 at 5 (OR, 1.12; 95% CI, 0.73-1.71) and 12 (OR, 0.99; 95% CI, 0.67-1.47) weeks. The proportion of patients with NIHSS scores of 0 to 4 within 24 hours of the last trial drug infusion (OR, 1.02; 95% CI, 0.82-1.27) and at 5 (OR, 1.00; 95% CI, 0.82-1.22) and 12 (OR, 1.04; 95% CI, 0.89-1.21) weeks did not significantly differ between the 2 groups. In addition, infarct volumes measured within 24 hours of the last dose of treatment (42 vs 38 mL) and at 12 weeks (12 vs 11 mL) were not significantly different. The frequency of symptomatic intracranial hemorrhage within 24 hours of the last trial drug infusion also did not significantly differ between the 2 groups (hazard ratio, 2.91; 95% CI, 0.59-14.25).

Table 2. Trial End Points[a]

End point	Analysis set							
	Full analysis				Per protocol			
	Nelonemdaz (n = 232)	Placebo (n = 225)	Treatment effect (95% CI)	*P* value[b]	Nelonemdaz (n = 218)	Placebo (n = 199)	Treatment effect (95% CI)	*P* value[b]
Primary end point								
mRS score at 12 wk, median (IQR)	2 (1-4)	2 (1-4)	0.95 (0.69-1.31)	.76	2 (1-4)	2 (1-4)	0.90 (0.65-1.27)	.56
Secondary end point								
mRS score at 5 wk, median (IQR)	3 (1-4)	3 (1-4)	1.00 (0.73-1.38)	>.99	3 (1-4)	2 (1-4)	0.99 (0.70-1.38)	.93
mRS score 0-2 at 5 wk, No. (%)	114 (49.1)	112 (49.8)	0.99 (0.82-1.19)	.89	108 (49.5)	102 (51.3)	0.97 (0.80-1.17)	.73
mRS score 0-2 at 12 wk, No. (%)	122 (52.6)	121 (53.8)	0.98 (0.82-1.16)	.80	116 (53.2)	110 (55.3)	0.96 (0.81-1.15)	.67
mRS score 0 at 5 wk, No. (%)	38 (16.4)	33 (14.7)	1.12 (0.73-1.71)	.61	38 (17.4)	26 (13.1)	1.33 (0.84-2.11)	.22
mRS score 0 at 12 wk, No. (%)	42 (18.1)	41 (18.2)	0.99 (0.67-1.47)	.97	40 (18.3)	35 (17.6)	1.04 (0.69-1.57)	.84
NIHSS 0-4 scores evaluated within 24 h of the last dose of treatment onset, No. (%)	94 (41.4)	89 (40.6)	1.02 (0.82-1.27)	.87	89 (41.2)	79 (39.9)	1.03 (0.82-1.30)	.79
NIHSS 0-4 scores evaluated at 5 wk, No. (%)	86 (55.1)	84 (55.3)	1.00 (0.82-1.22)	.98	81 (56.3)	75 (57.3)	0.98 (0.80-1.21)	.87
NIHSS 0-4 scores evaluated at 12 wk, No. (%)	114 (64.8)	113 (62.4)	1.04 (0.89-1.21)	.65	107 (64.8)	103 (64.4)	1.01 (0.86-1.18)	.93
Barthel index ≥95 evaluated at 5 wk, No. (%)	90 (39.3)	91 (40.6)	0.97 (0.77-1.21)	.77	86 (40.0)	82 (41.4)	0.97 (0.77-1.22)	.77
Barthel index ≥95 evaluated at 12 wk, No. (%)	99 (43.0)	101 (45.3)	0.95 (0.77-1.17)	.63	94 (43.5)	90 (45.7)	0.95 (0.77-1.18)	.66
Infarct volume based on brain MRI (alternatively, brain CT) within 24 h of the last dose of treatment onset, median (IQR), mL	42 (12-131)	38 (14-111)	4[c]	.84	43 (13-140)	38 (15-121)	5[c]	.80
Infarct volume based on brain MRI (alternatively, brain CT) at 12 wk, median (IQR), mL	12 (3-55)	11 (3-42)	1[c]	.81	12 (3-55)	12 (3-42)	0[c]	.73
Symptomatic intracranial hemorrhage within 24 h of the last dose of treatment onset, No. (%)	6 (2.7)	2 (0.9)	2.91 (0.59-14.25)	.29	6 (2.8)	2 (1.0)	2.78 (0.57-13.59)	.29

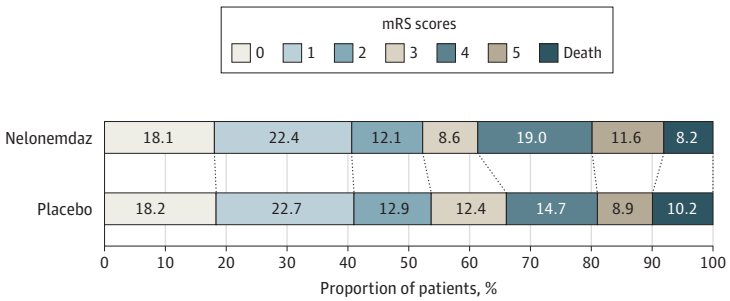
Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

[a] Treatment effects are reported as relative risks with 95% CIs for all end points, except for the ordinal shift across the range of mRS scores toward a better end point, for which the treatment effect is reported as a common odds ratio with the 95% CI. The widths of CIs for secondary end points were not adjusted for multiple comparisons, and no definite conclusions can be drawn from these data.

[b] *P* values were calculated by Cochran-Mantel-Haenszel shift test, χ^2 test, Fisher exact test, or Wilcoxon rank-sum test, as appropriate.

[c] Absolute volume difference of medians.

Figure 2. Distribution of Modified Rankin Scale (mRS) at 12 Weeks



Safety Outcomes

The 2 groups did not show significant differences in the frequencies of any serious adverse events or any adverse events leading to permanent interruption of nelonemdaz or placebo (eTable in Supplement 3). The following adverse effects are listed in order of frequency, and the frequencies did not differ significantly between the 2 groups: pyrexia, constipation, pneumonia, urinary tract infection, headache, hematuria, atrial fibrillation, aspiration pneumonia, anemia, and brain edema. The rate of mortality at 12 weeks did not significantly differ between the 2 groups (7.7% vs 9.5%; *P* = .49).

Subgroup Analysis

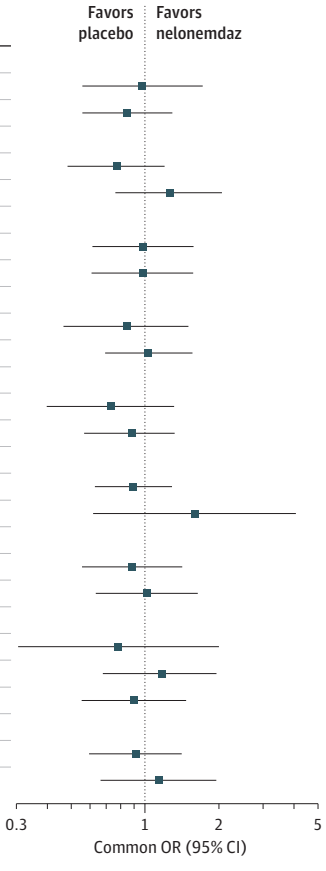
Among the prespecified variables, no interaction was found regarding the treatment effects based on age, sex, NIHSS score, diabetes, ASPECTS determined by core laboratory evaluation, MRI- vs CT-based randomization, intravenous alteplase administration, eTICI grade determined by core laboratory evaluation, and Trial of Org 10172 in Acute Stroke Treatment classification (cardioembolic vs noncardioembolic) (**Figure 3**).

Discussion

In this phase 3 randomized clinical trial, nelonemdaz did not show significant efficacy in patients with acute ischemic stroke due to large-vessel occlusion who were treated with mechanical reperfusion.

Figure 3. Subgroup Analysis

Variable	No. of patients	Common OR (95% CI)	*P* value	*P* value for interaction
Age, y				
<70	167	0.97 (0.56-1.67)	.91	.68
≥70	290	0.84 (0.56-1.26)	.41	
Sex				
Male	254	0.76 (0.49-1.17)	.22	.12
Female	203	1.25 (0.77-2.02)	.37	
Baseline NIHSS score				
≤13	233	0.97 (0.62-1.53)	.91	.99
>13	224	0.97 (0.61-1.54)	.90	
Diabetes				
Yes	148	0.83 (0.47-1.46)	.52	.55
No	304	1.03 (0.69-1.52)	.90	
ASPECTS (core laboratory)				
<7	140	0.72 (0.40-1.30)	.28	.63
≥7	285	0.86 (0.57-1.30)	.47	
Baseline imaging protocol				
CT based	402	0.89 (0.63-1.26)	.51	.26
MRI based	55	1.58 (0.62-4.00)	.34	
Implementation of alteplase				
Yes	231	0.88 (0.56-1.39)	.58	.68
No	226	1.01 (0.64-1.59)	.98	
eTICI grade (core laboratory)				
0-2a	56	0.77 (0.31-1.96)	.59	.69
2b	178	1.15 (0.69-1.92)	.60	
2c-3	216	0.90 (0.56-1.44)	.66	
TOAST				
Cardioembolic	279	0.91 (0.60-1.37)	.65	.52
Noncardioembolic	178	1.13 (0.67-1.90)	.65	



No multiplicity correction was applied. ASPECTS indicates Alberta Stroke Program Early Computed Tomography Scores; CT, computed tomography; eTICI, extended thrombolysis in cerebral infarction; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Glutamate neurotoxicity occurs immediately after cerebral ischemia onset, triggered by the influx of sodium and calcium through the NMDA receptors, damaging neurons and potentially leading to neuronal death.[12,13,16] Free radical cytotoxicity sourced from mitochondria, nitric oxide synthase, and arachidonic acid metabolism also occurs, especially after the reintroduction of oxygen to ischemic tissues following reperfusion.[17] Whereas glutamate neurotoxicity occurs maximally soon after ischemia onset, free radical toxicity likely participates in tissue injury cascades for hours to days later.[14,15,22,28,29] Nelonemdaz has dual effects, blocking the 2B subtype of the NMDA receptors that participate prominently in acute excitotoxcitiy as well as scavenging free radicals.[18-23,30]

While neuroprotective drug candidates for stroke have in the past mostly focused on single targets and pathophysiologic mechanisms, dual-target approaches make theoretical sense given the multiplicity of injury cascades activated by ischemia. In transient middle cerebral artery occlusion, early free radical production in the core may be substantially mediated by NMDA receptor overactivation, while late production in the penumbra may be mediated in part by iron overload.[31] Both NMDA receptor overactivation and iron overload contribute synergistically to the delayed generation of free radicals in both the core and penumbra following cerebral ischemia reperfusion. Combined treatment with MK-801, an NMDA receptor antagonist, and deferoxamine, an iron chelator, has shown better neuroprotection in experimental ischemia reperfusion compared with monotherapy.[31]

In human stroke with a wider variation in ischemic area and onset compared with experimental stroke, free radicals may be even more likely to be produced in the penumbra over hours and days. Edaravone, a free radical scavenger approved for treatment of acute ischemic stroke in Japan and China, is infused twice a day for 14 days, commencing within 72 hours of stroke onset.[32,33] Based on pharmacokinetic-pharmacodynamic data from phase 1 trials and preclinical studies, nelonemdaz was infused twice a day during 5 days in phase 2 and 3 trials with the intent of ameliorating both rapidly triggered NMDA neurotoxicity and gradually evolving free radical toxicity.

Nevertheless, considering the previous experimental results, a more rapid treatment approach may have been necessary in this clinical trial. Brain extracellular glutamate levels peak 30 to 90 minutes after ischemia onset in experimental models.[14,15] In patients who experience stroke, cerebrospinal fluid glutamate levels are higher in the first 6 hours than 6 to 24 hours after stroke onset.[34] In our study, the time from the onset of stroke symptoms to ED arrival was not significantly delayed. The median of the time from the onset of stroke symptoms to ED arrival was 100 (IQR, 50-218) minutes in both groups. In addition, the time from ED arrival to the administration of EVT was not significantly delayed, with a median time of 102 (IQR, 77-131) However, it is questionable whether the interval from ED arrival to nelonemdaz infusion was appropriate. The time of nelonemdaz infusion was only 2 to 4 minutes later than the time of EVT. It was in accordance with our planned protocol; however, numerous studies have emphasized the crucial importance of prompt in-hospital procedures for managing acute ischemic stroke.[5,35-48]

The importance of rapid intervention on arrival at the ED has consistently been emphasized for both EVT and intravenous thrombolysis. In the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial,[5] which was a representative and successful clinical trial for EVT, the time from imaging just after ED arrival to treatment was intended to be less than 60 minutes. A meta-analysis examining times to EVT treatment and outcomes reported that time from ED arrival to the start of EVT, but not the time from stroke onset to ED arrival, modified the effect of EVT on clinical outcomes, such as mRS score shift, mRS scores 0 to 2, and mortality.[35] A multicenter retrospective study also showed that factors related to rapid in-hospital processing, such as reduced time from ED arrival to EVT and EVT procedural time, were independently associated with favorable clinical outcomes.[36] The time from arrival at the ED to EVT was also shown to be significant in another clinical trial testing a neuroprotective agent.[37]

Regarding intravenous thrombolysis, faster administration of alteplase (within 45 minutes vs longer than 45 minutes of hospital arrival) was associated with better patient outcomes in terms of

survival and reduced hospital readmissions in a US retrospective cohort study including 61 426 patients with acute ischemic stroke.[38] In another US study including patients aged 65 years and older receiving intravenous thrombolysis alone or in combination with EVT, expedited door-to-needle times correlated with improved long-term functional prognosis and reduced mortality rates (intravenous thrombolysis alone in 38 913 patients and combination treatment in 3946 patients).[39]

Similarly, the time from ED arrival is likely to be crucial in the administration of neuroprotective agents. To increase the likelihood of achieving positive results in clinical trials, it may be more beneficial to initiate neuroprotective therapy as soon as possible after ED admission, similar to intravenous thrombolysis, rather than focusing on reperfusion by EVT.

The failure of neuroprotective trials in patients with acute ischemic stroke undergoing EVT may be attributed to unexpectedly favorable clinical outcomes in the placebo groups. This concept might have contributed to the failure of a recent clinical trial, ESCAPE-NA1.[40,41] Despite ESCAPE-NA1 having slightly broader inclusion criteria than ESCAPE (ASPECTS 5-10 vs 6-10), the placebo (EVT only) group in ESCAPE-NA1 outperformed even the EVT group in ESCAPE (mRS score 0-2 at 3 months: 59.2% vs 53.0%). The current RODIN trial had a wider range of ASPECTS (4-10), and mRS scores of 0 to 2 in the placebo group accounted for 53.8%. Due to this ceiling effect, it is possible that nelonemdaz may not have shown efficacy in clinical trials. Recently, several clinical trials of EVT for large infarcts with ASPECTS 5 or lower have been published.[42-45] The trials found that EVT generally improved clinical outcomes compared with the control group. However, the high mortality rates and proportions of patients becoming bedridden make these results somewhat difficult to accept.[46] If we carefully apply the indications from these studies, it may be possible to design clinical trials to demonstrate the efficacy of neuroprotective drugs, including nelonemdaz.

Nelonemdaz showed no safety issues in the present trial, unlike some other NMDA antagonist drugs studied previously.[47,48] A phase 3 trial for selfotel revealed a significant reduction in survival rates in the selfotel group compared with the placebo group.[47] In addition, psychological and consciousness-related adverse effects occurred more frequently in the selfotel group than in the placebo group.[47] A phase 2/3 trial for aptiganel also showed lower survival rates in the low- and high-dose aptiganel groups than in the placebo groups.[48] Serious nonlethal adverse effects in these clinical trials also raised questions about the safety of NMDA receptor antagonists. In contrast, the mortality rate of the nelonemdaz group in the current trial was not higher than that of the placebo group, and no psychological or consciousness-related adverse effects were observed. It is believed that the lack of adverse effects is due to the specific way nelonemdaz interacts with the NMDA receptor. It selectively and reversibly binds to the 2b subunit of the receptor, which likely contributes to the favorable safety profile observed in the current study.

Limitations

This study has the following limitations. First, all participants were enrolled exclusively from South Korea. Second, atrial fibrillation, embolic stroke, and a history of ischemic stroke were more frequent in the nelonemdaz group than in the placebo group. This observed imbalance in baseline variables suggests that the sample size may have been underestimated.

Conclusions

In this randomized clinical trial, nelonemdaz did not demonstrate a therapeutic effect over placebo in patients with acute ischemic stroke due to large-vessel occlusion in those who received EVT. Further analyses to identify potential responder subgroups may inform the design of future clinical trials in this patient population.

ARTICLE INFORMATION

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SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
Statistical Analysis Plan

SUPPLEMENT 3.
eTable. Adverse Events Occurring in the Safety Analysis Set

SUPPLEMENT 4.
Data Sharing Statement