Stroke

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Nelonemdaz for Patients With Acute Ischemic Stroke Undergoing Endovascular Reperfusion Therapy: A Randomized Phase II Trial

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BACKGROUND: Nelonemdaz is a multitarget neuroprotectant that selectively blocks N-methyl-D-aspartate receptors and scavenges free radicals, as proven in preclinical ischemia-reperfusion studies. We aimed to evaluate the safety and efficacy of nelonemdaz in patients with acute ischemic stroke receiving endovascular reperfusion therapy.

METHODS: This phase II randomized trial involved participants with large-artery occlusion in the anterior circulation at baseline who received endovascular reperfusion therapy <8 hours from symptom onset at 7 referral stroke centers in South Korea between October 29, 2016, and June 1, 2020. Two hundred thirteen patients were screened and 209 patients were randomly assigned at a 1:1:1 ratio using a computer-generated randomization system. Patients were divided into 3 groups based on the medication received—placebo, low-dose (2750 mg) nelonemdaz, and high-dose (5250 mg) nelonemdaz. The primary outcome was the proportion of patients with modified Rankin Scale scores of 0–2 at 12 weeks.

RESULTS: Two hundred eight patients were assigned to the placebo (n=70), low-dose (n=71), and high-dose (n=67) groups. The groups had similar baseline characteristics. The primary outcome was achieved in 183 patients, and it did not differ among the groups (33/61 [54.1%], 40/65 [61.5%], and 36/57 [63.2%] patients; *P*=0.5578). The common odds ratio (90% CI) indicating a favorable shift in the modified Rankin Scale scores at 12 weeks was 1.55 (0.92–2.60) between the placebo and low-dose groups and 1.61 (0.94–2.76) between the placebo and high-dose groups. No serious adverse events were reported.

CONCLUSIONS: The study arms showed no significant difference in the proportion of patients achieving modified Rankin Scale scores of 0–2 at 12 weeks. Nevertheless, nelonemdaz-treated patients showed a favorable tendency toward achieving these scores at 12 weeks, without serious adverse effects. Thus, a large-scale phase III trial is warranted.

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GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cerebral infarction ■ ischemic stroke ■ neuroprotective agent ■ odds ratio ■ reperfusion

Nelonemdaz, previously known as Neu2000, is a derivative of aspirin and sulfasalazine and is a multitarget neuroprotective agent with potent inhibitory effects against Ca^{2+} permeability of the NMDA (N-methyl-D-aspartate) receptor.[1] Moreover, the drug with high selectivity inhibits the NR2B subunit of the NMDA receptor,

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Nonstandard Abbreviations and Acronyms

ASPECTS	Alberta Stroke Program Early CT Score
ERT	endovascular reperfusion therapy
mRS	modified Rankin Scale
NMDA	N-methyl-D-aspartate
r-tPA	recombinant tissue-type plasminogen activator
SONIC	Safety and Optimal Neuroprotection of Neu2000 in Acute Ischemic Stroke With Recanalization

strongly scavenges reactive oxygen species, and prevents blood-brain barrier disruption.[1–3] Studies have demonstrated the therapeutic potential of nelonemdaz in preclinical animal stroke models subjected to ischemia and reperfusion; they have shown the excellent efficacy and wide therapeutic time window of the drug.[1–3]

Recent clinical trials have shown that endovascular reperfusion therapy (ERT) has remarkable benefits in terms of the outcome of patients presenting with acute ischemic stroke in the proximal anterior circulation.[4] However, numerous patients with stroke remain disabled despite the high reperfusion rate and striking improvements in clinical outcomes resulting from mechanical thrombectomy.[5] The potential of neuroprotective agents as a promising treatment in patients with acute ischemic stroke is being revisited in the ERT era, owing to the optimization of preclinical efficacy in ischemia and reperfusion models.[6] The above preclinical results and good patient tolerance to and lack of serious adverse effects of nelonemdaz in phase I trials performed in the United States and China have warranted a phase II randomized clinical trial.

The current SONIC trial (Safety and Optimal Neuroprotection of Neu2000 in Acute Ischemic Stroke With Recanalization) was designed as a phase II trial aiming to evaluate the safety and efficacy of nelonemdaz. This trial was a proof-of-concept study on adjuvant neuroprotection beyond state-of-the-art treatments such as ERT. The aim of this study was to test whether the potential therapeutic benefits of nelonemdaz observed in preclinical studies can be translated to clinical practice.

METHODS

Data Availability

Anonymized data are available to qualified investigators at reasonable request by the corresponding author. This trial study was completed in accordance with the CONSORT guidelines[7]; the CONSORT guideline checklists is available in the Supplemental Material.

Study Design and Population

The SONIC trial was a multicenter, randomized, double-blinded, placebo-controlled, 3-arm, phase II clinical study with blinded-end point evaluation. Seven hospitals in various regions of the Republic of Korea participated in this trial. All participating centers obtained institutional review board approval before trial initiation. Written informed consent for the trial was obtained from the legal guardians of patients before study enrollment. The current trial has been registered at ClinicalTrials.gov (eDocument 1).

Patients with acute ischemic stroke caused by large-vessel occlusion in the anterior circulation were eligible for the study if they were aged ≥19 years, were previously functionally independent, had a National Institutes of Health Stroke Scale score of ≥8 on admission, had baseline angiography results showing large-vessel occlusion, including the intracranial internal carotid artery and middle cerebral artery M1 or its equivalent M2, had a baseline noncontrast Alberta Stroke Program Early CT Score (ASPECTS) of ≥6, were eligible for ERT, and had an estimated time from stroke onset to groin puncture of <8 hours. In contrast, patients were excluded if their baseline noninvasive angiography results showed simultaneous occlusion in either both middle cerebral and anterior cerebral arteries, middle cerebral and posterior cerebral arteries, and left and right large vessels or both large vessels of the anterior and posterior circulations, indicating a high malignant potential.

Randomization

The participants were randomly divided at a 1:1:1 ratio to one of the following 3 arms: placebo, low-dose nelonemdaz, and high-dose nelonemdaz groups. Randomization was stratified according to the centers of the participants and was based on computer-generated cards before study initiation. All study investigators and participants were blinded to the treatment allocations except for personnel who were assigned to prepare the investigational products and were not involved in any other part of the study. The study and placebo drugs were identically packaged.

Management

As the current trial was based on ERT for acute ischemic stroke caused by large-vessel occlusion in the anterior circulation, intravenous r-tPA (recombinant tissue-type plasminogen activator) administration and mechanical thrombectomy were performed in eligible patients. Stent retrieval or contact aspiration methods were selected according to the discretion of the neurointerventionists. Other methods, including balloon and stent angioplasty, and the use of glycoprotein IIb/IIIa inhibitors were also permitted. After the randomization of patients, they were immediately prepared for endovascular treatment and trial drug infusion. The first infusion of the trial drug was initiated before thrombus retrieval. Subsequent injection was continued twice per day with a 12-hour interval for 5 consecutive days. In the high-dose group, the initial infusion dose was 750 mg mixed with 250 mL of saline, and the subsequent 9 doses were 500 mg each (total, 5250 mg). In the low-dose group, the initial infusion dose was 500 mg, and the subsequent 9 doses were 250 mg each (total, 2750 mg). The placebo group received 250 mL of saline 10 times. All patients received care in the stroke unit or neurointensive care unit after ERT.

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Outcome Measurements

The primary outcome was the proportion of patients with a modified Rankin Scale (mRS) score of 0–2 at 12 weeks among the groups. The secondary outcomes included the distributional change in the mRS score, the proportion of patients with an National Institutes of Health Stroke Scale score of 0–2, and the proportion of patients with a Barthel index of >90 at 1, 4, and 12 weeks among the groups. For safety, all symptoms, signs, and blood test abnormalities were recorded during the 12-week observation period. Any symptomatic intracranial hemorrhage with neurological deterioration on cerebral computed tomography within 24 to 48 hours was reported. This information was documented in an open form when the images were sent or uploaded.

Overall, the clinical outcomes were evaluated at 1, 4, and 12 weeks after randomization. The evaluations at 1 week were performed during admission, whereas the evaluations at 4 and 12 weeks were performed in the outpatient clinic. Patients who were bedridden and could not attend the clinical evaluations in the participating centers were excluded from the evaluation, although information of those who died was collected. However, the protocol (version 4.3) was amended on April 16, 2019, allowing the evaluation of mRS scores via telephone in patients who could not visit the hospital.

Statistical Analysis

The primary hypothesis of this study was that treatment with nelonemdaz before ERT will increase the proportion of patients achieving functional independence (mRS score, 0–2) at 3 months, compared with treatment with placebo. The expected proportions of patients achieving functional independence were 20% and 45% in the placebo and nelonemdaz groups, respectively. According to a 2-sided superiority test, 177 patients (59 in each group) who could be assessed for the primary end point would provide 90% power with a 2-sided type I error of 10%. Assuming a 15% dropout rate, we planned to enroll 210 patients. We performed the primary end point analysis using the χ^2 test. Secondary end point analyses were performed using the χ^2 test, Cochran-Mantel-Haenszel shift test, and Kruskal-Wallis test, as appropriate. The primary and secondary end points were evaluated in the full analysis set, which included all randomized patients with an available primary end point. The results were presented as the odds ratio for estimating the relative risk with a 90% CI. Safety was evaluated in the intention-to-treat population.

An independent statistician performed the statistical analyses. All reported *P* values are 2-sided, and statistical analyses were performed using SAS (version 9.4; SAS Institute Inc, Cary, NC). Statistical significance was set at $P<0.1$.

RESULTS

General Demographics

From October 29, 2016, to June 1, 2020, 213 patients were screened and 208 patients were randomly assigned to the 3 groups. Finally, 61 patients were included in the placebo group, 65 patients in the low-dose nelonemdaz group, and 57 patients in the high-dose nelonemdaz group for the full analysis set (ie, patients with available mRS scores at 12 weeks). Protocol violations was recorded in 12 of 61, 10 of 65, and 9 of 57 patients in the placebo, low-dose, and high-dose groups, respectively. The flowchart of this study is shown in Figure 1.

The baseline characteristics were similar among the 3 groups (Table 1); however, patients were younger (P=0.0426) and the use of intravenous alteplase (P=0.0331) was more frequent in the low-dose group than in the placebo and high-dose groups. Overall, the median age was 69 (interquartile range, 60–77) years, and 36.6% of the patients were women. The median National Institutes of Health Stroke Scale score was 15 (interquartile range, 12–18), whereas the median ASPECTS was 8 (interquartile range, 6–9). The median time from stroke onset to groin puncture was 185 (interquartile range, 153–270) minutes. The rates of successful reperfusion (modified Treatment in Cerebral Ischemia score 2b–3) were 83.5%, 89.0%, and 85.7% in the placebo, low-dose, and high-dose groups, respectively (P=0.9230).

Outcome Analyses

In the full analysis set (Table 2), an mRS score of 0–2 at 12 weeks was achieved in 33 (54.1%), 40 (61.5%), and 36 (63.2%) patients in the placebo, low-dose, and high-dose groups, respectively (P=0.5578; Figure 2). The common odds ratio (90% CI) indicating a favorable shift in mRS scores at 12 weeks was 1.55 (0.92–2.60) between the placebo and low-dose groups and 1.61 (0.94–2.76) between the placebo and high-dose groups. A Barthel index of >90 at 12 weeks was observed in 24 (43.6%), 34 (54.8%), and 34 (63.0%) patients in the placebo, low-dose, and high-dose groups, respectively (P=0.1264), and the difference between the placebo and high-dose groups was statistically significant (P=0.0480). The outcomes in the per-protocol set (Table S1) were similar to those in the full analysis set. Subgroup analysis for the primary outcome showed no difference among the variables (Figure 3). Patients with a medical history of diabetes in the high-dose group tended to show less favorable outcomes than the patients in the placebo group; however, the difference was not significant.

Adverse Events

No serious adverse events were reported. The adverse events that occurred in ≥5% of patients in the safety set included pyrexia, a decreased hemoglobin level, an increased C-reactive protein level, headache, urinary retention, hematuria, constipation, diarrhea, aspiration pneumonia, and cough; however, their frequencies did not differ among the groups (Table 3). Symptomatic intracerebral hemorrhage occurring 24 to 48 hours after randomization was not reported in any of the groups.

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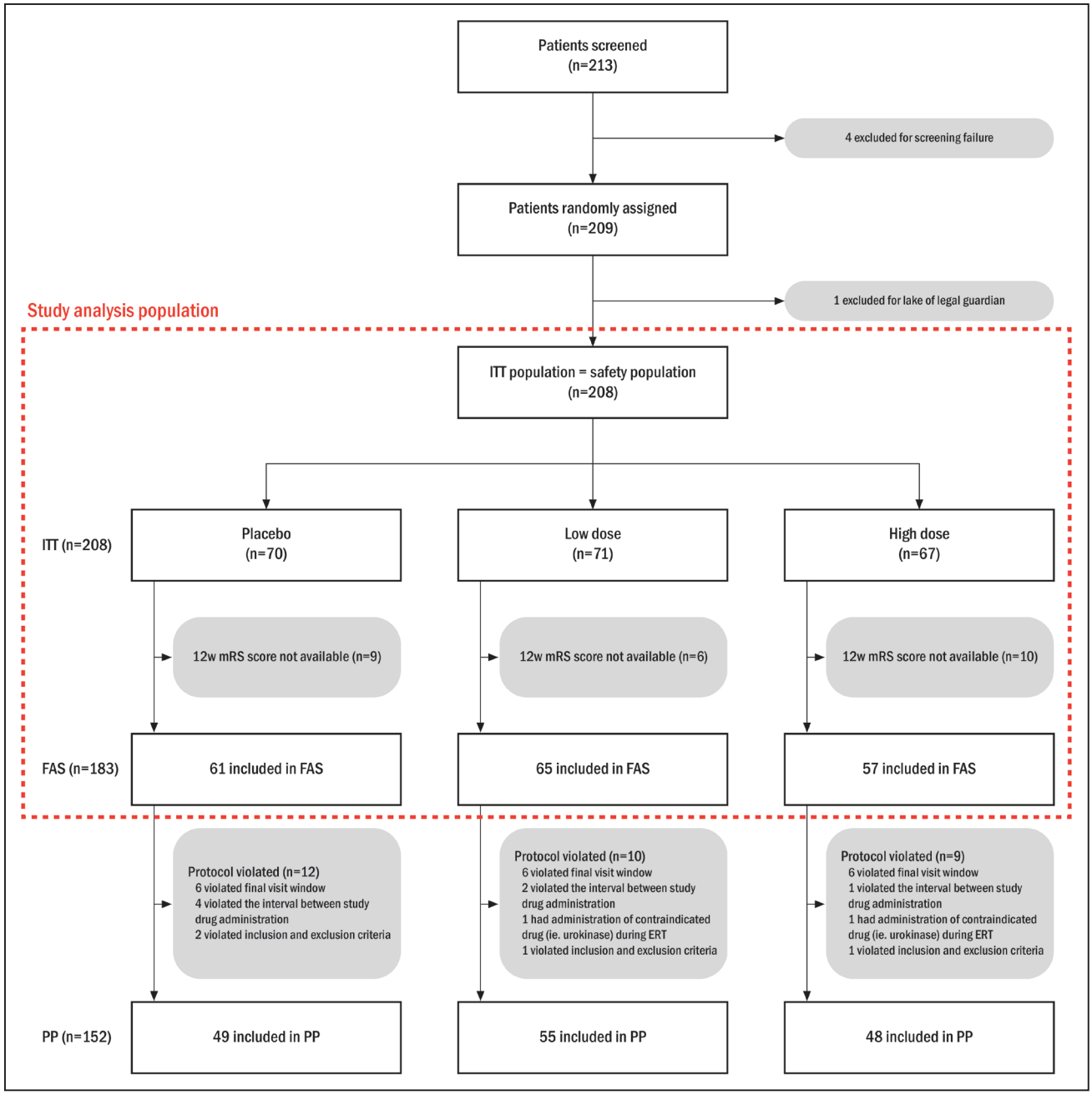

Figure 1. Flowchart of the SONIC trial (Safety and Optimal Neuroprotection of Neu2000 in Acute Ischemic Stroke With Recanalization).
FAS indicates full analysis set; ITT, intention-to-treat; mRS, modified Rankin Scale; and PP, per protocol.

DISCUSSION

In the current phase II SONIC trial, we did not statistically prove the efficacy of nelonemdaz in patients with acute ischemic stroke and large-vessel occlusion who received ERT. Nevertheless, no relevant adverse effects of the drug were observed, and the low-dose and high-dose groups showed a favorable tendency toward the primary end point. However, the low-dose group had more favorable baseline prognostic factors, such as younger age and higher rates of intravenous alteplase infusion, than the placebo and high-dose groups. The distribution of the 12-week mRS scores showed a favorable shift toward the high-dose group over the placebo group. Such tendencies toward favorable clinical outcomes and the lack of relevant adverse effects warrant further phase III clinical trials, appropriate number of patients and methodology of which should be determined based on the results of this study.

This clinical trial supported the concept from preclinical studies on the potential therapeutic benefits of nelonemdaz. A trend of a favorable shift toward excellent outcomes, such as an mRS score of 0 and a Barthel index of >90

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Table 1. Baseline Characteristics of Patients in the Full Analysis Set (n=183)

	Placebo (n=61)	Low dose (n=65)	High dose (n=57)	*P* value
Age, mean±SD	70.0±10.1	64.9±13.3	68.6±11.0	0.0426
Female, n (%)	24 (39.3)	23 (35.4)	20 (35.1)	0.8627
Past stroke history, n (%)	6 (9.8)	12 (18.5)	11 (19.3)	0.2872
Hypertension, n (%)	34 (55.7)	35 (53.8)	34 (59.6)	0.8079
Diabetes, n (%)	12 (19.7)	14 (21.5)	7 (12.3)	0.3815
Dyslipidemia, n (%)	12 (19.7)	8 (12.3)	4 (7.0)	0.1225
Coronary disease, n (%)	2 (3.3)	7 (10.8)	3 (5.3)	0.2303
Smoking, n (%)	27 (44.3)	29 (44.6)	20 (35.1)	0.4925
Atrial fibrillation, n (%)	29 (47.5)	30 (46.2)	22 (38.6)	0.5764
NIHSS, median (IQR)	15 (12–19)	16 (13–18)	15 (10–18)	0.5116
ASPECTS, median (IQR)	7 (6–9)	8 (7–9)	8 (6–9)	0.1767
Occlusion location–ICA, n (%)	7 (11.5)	8 (12.3)	6 (10.5)	0.9537
Intravenous alteplase (tPA), n (%)	35 (57.4)	50 (76.9)	33 (57.9)	0.0331
Door to tPA, min, median (IQR)	44 (35–56)	42 (31–55)	46 (39–51)	0.7024
Door to groin puncture, min, median (IQR)	103 (90–129)	102 (89–127)	102 (91–123)	0.9477
Onset to groin puncture, min, median (IQR)	202 (165–295)	180 (137–240)	184 (152–255)	0.0527
Door to IP administration, min, median (IQR)	101 (83–113)	98 (75–122)	98 (77–116)	0.9845
ERT primary method, n (%)				
Stent retrieval	52 (85.2)	48 (73.8)	43 (76.8)	0.2750
Catheter aspiration	14 (23.0)	16 (24.6)	17 (30.4)	0.6334
Other (balloon or stent angioplasty)	3 (4.9)	5 (7.7)	9 (16.1)	0.0996
mTICI score, n (%)				0.9230
0	3 (4.9)	2 (3.1)	2 (3.6)	
1	0 (0.0)	1 (1.6)	1 (1.8)	
2a	7 (11.5)	4 (6.3)	5 (8.9)	
2b	19 (31.1)	23 (35.9)	15 (26.8)	
3	32 (52.5)	34 (53.1)	33 (58.9)	

The *P* values were calculated using the χ^2 test, Fisher exact test, ANOVA, and Kruskal-Wallis test, as appropriate. ASPECTS indicates Alberta Stroke Program Early CT Score; ERT, endovascular reperfusion therapy; ICA, internal carotid artery; IP, investigational product; IQR, interquartile range; mTICI, modified Treatment in Cerebral Ischemia; NIHSS, National Institutes of Health Stroke Scale; and tPA, tissue-type plasminogen activator.

and reduced mortality (mRS score, 6) at 12 weeks, was observed in the nelonemdaz treatment groups. Although the small number of patients (208 patients) limited the demonstration of a statistically significant benefit of nelonemdaz compared with the placebo, the shift toward favorable clinical outcomes observed in this study may be more promising than that previously reported in similar studies, including the SAINT I (Stanford Accelerated Interlligent Neuromodulation Therapy; 1699 patients), SAINT II (3195 patients), and ESCAPE NA1 (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke Nerinetide; 1105 patients) trials, in which the differences in the mRS score distribution at 3 months seemed to be unremarkable.[8–10] Nevertheless, in this study, the low-dose nelonemdaz group showed a tendency of higher rate of r-tPA administration and a shorter starting time for groin puncture. This favorable trend should be interpreted cautiously, as it may reflect a favorable outcome bias for low-dose group.

Nelonemdaz is a salicylic acid compound that has multiple neuroprotective actions through its strong NMDA antagonism and antioxidant mechanism, as revealed in various rodent and in vitro models.[1,3,11–14] Glutamate toxicity via the NMDA receptor and free radical toxicity have pivotal roles in the pathophysiology of acute cerebral infarction and reperfusion. NXY-059, which has free radical-trapping properties and has demonstrated a neuroprotective effect in an animal model of cerebral ischemia,[15] was expected to show a neuroprotective effect in the clinical setting; however, the SAINT I and SAINT II trials failed to prove a treatment benefit in patients with acute ischemic stroke.[9,10] In animal studies, large-artery occlusion with transient (≈2 hours) ischemia and reperfusion is normally induced in rodents, causing severe cerebral infarction in the middle cerebral artery territory within 24 hours. In contrast, patients in the clinical setting present various subtypes of acute ischemic stroke. The severity can be mild, moderate, or severe, and

Table 2. Primary, Secondary, and Mortality Outcomes in the Full Analysis Set (n=183)

	Placebo (n=61)	Low dose (n=65)	High dose (n=57)	*P* value*	Low dose vs placebo		High dose vs placebo	
					RR or common OR (2-sided 90% CI)	*P* value	RR or common OR (2-sided 90% CI)	*P* value
Primary outcome								
mRS score 0–2 at 12 wk	33 (54.1%)	40 (61.5%)	36 (63.2%)	0.5578	1.14(0.88–1.46)	0.4008	1.17 (0.90–1.51)	0.3190
Secondary outcome								
mRS at 1 wk				0.1856	1.67 (0.99–2.82)	0.1043	1.64 (0.96–2.81)	0.1290
0	2 (3.3%)	7 (10.9%)	9 (15.8%)					
1	12 (19.7%)	11 (17.2%)	8 (14.0%)					
2	6 (9.8%)	12 (18.8%)	10 (17.5%)					
3	9 (14.8%)	10 (15.6%)	7 (12.3%)					
4	15 (24.6%)	12 (18.8%)	9 (15.8%)					
5	16 (26.2%)	11 (17.2%)	14 (24.6%)					
6	1 (1.6%)	1 (1.6%)	0 (0.0%)					
mRS at 4 wk				0.1954	1.55 (0.92–2.61)	0.1651	1.77 (1.02–3.06)	0.0857
0	8 (13.1%)	12 (18.5%)	14 (245.9%)					
1	14 (23.0%)	17 (26.2%)	10 (18.5%)					
2	6 (9.8%)	9 (13.8%)	7 (13.0%)					
3	6 (9.8%)	9 (13.8%)	7 (13.0%)					
4	18 (29.5%)	16 (24.6%)	10 (18.5%)					
5	4 (6.6%)	4 (6.2%)	6 (11.1%)					
6	5 (8.2%)	2 (3.1%)	0 (0.0%)					
mRS at 12 wk				0.2621	1.55 (0.92–2.60)	0.1638	1.61 (0.94–2.76)	0.1419
0	8 (13.1%)	14 (21.5%)	17 (29.8%)					
1	19 (31.1%)	17 (26.2%)	9 (15.8%)					
2	6 (9.8%)	9 (13.8%)	10 (17.5%)					
3	5 (8.2%)	10 (15.4%)	4 (7.0%)					
4	10 (16.4%)	9 (13.8%)	10 (17.5)					
5	8 (13.1%)	3 (4.6%)	4 (7.0%)					
6	5 (8.2%)	3 (4.6%)	3 (5.3%)					
NIHSS score 0–2 at 1 wk	18 (30.0%)	22 (34.9%)	20 (35.1%)	0.7984	1.16 (0.76–1.79)	0.5616	1.17 (0.75–1.81)	0.5575
NIHSS score 0–2 at 4 wk	24 (43.6%)	31 (49.2%)	28 (52.8%)	0.6278	1.13 (0.81–1.57)	0.5474	1.21 (0.87–1.68)	0.3411
NIHSS score 0–2 at 12 wk	31 (62.0%)	32 (55.2%)	31 (62.0%)	0.7011	0.89 (0.68–1.16)	0.4716	1.00 (0.77–1.29)	1.0000
Barthel index >90 at 1 wk	14 (23.7%)	23 (36.5%)	20 (35.7%)	0.2469	1.54 (0.96–2.46)	0.1326	1.51 (0.93–2.44)	0.1648
Barthel index >90 at 4 wk	22 (40.0%)	30 (47.6%)	27 (50.9%)	0.5012	1.19 (0.84–1.69)	0.4097	1.27 (0.90–1.81)	0.2566
Barthel index >90 at 12 wk	24 (43.6%)	34 (54.8%)	34 (63.0%)	0.1264	1.26 (0.92–1.72)	0.2334	1.44 (1.06–1.96)	0.0480

mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and RR, relative risk.
*Placebo vs low dose vs high dose.

the occlusion can involve a small artery, a branch vessel, or a large vessel. In the early 21st century, the reperfusion rates were low, even in cases of large-vessel occlusion. Conversely, the reperfusion rates have been reported to reach ≈85% since the introduction of novel intervention methods, such as mechanical thrombectomy.[4,16,17] These procedures have provided a high level of evidence that recommends the treatment of acute ischemic stroke caused by large-vessel occlusion. It may now be timely for physicians specialized in stroke to revisit neuroprotective agents because the discrepancy between animal studies and clinical practice has substantially diminished.

The role of biological mediators in cellular death after a cerebral ischemic insult has been well elucidated.[18] In this context, a multitarget neuroprotection strategy, such as therapeutic hypothermia, would be more effective than a single-target strategy in the clinical setting.[19,20] Several preclinical studies have shown the positive effects of a multitarget strategy on neuronal protection, especially in temporary cerebral ischemia and reperfusion models compared with that in permanent occlusion models.[21] A postreperfusion strategy has been attempted in experimental studies and clinical trials, which have proven that therapeutic hypothermia is particularly effective in resuscitated patients with cardiac arrest.[22,23]

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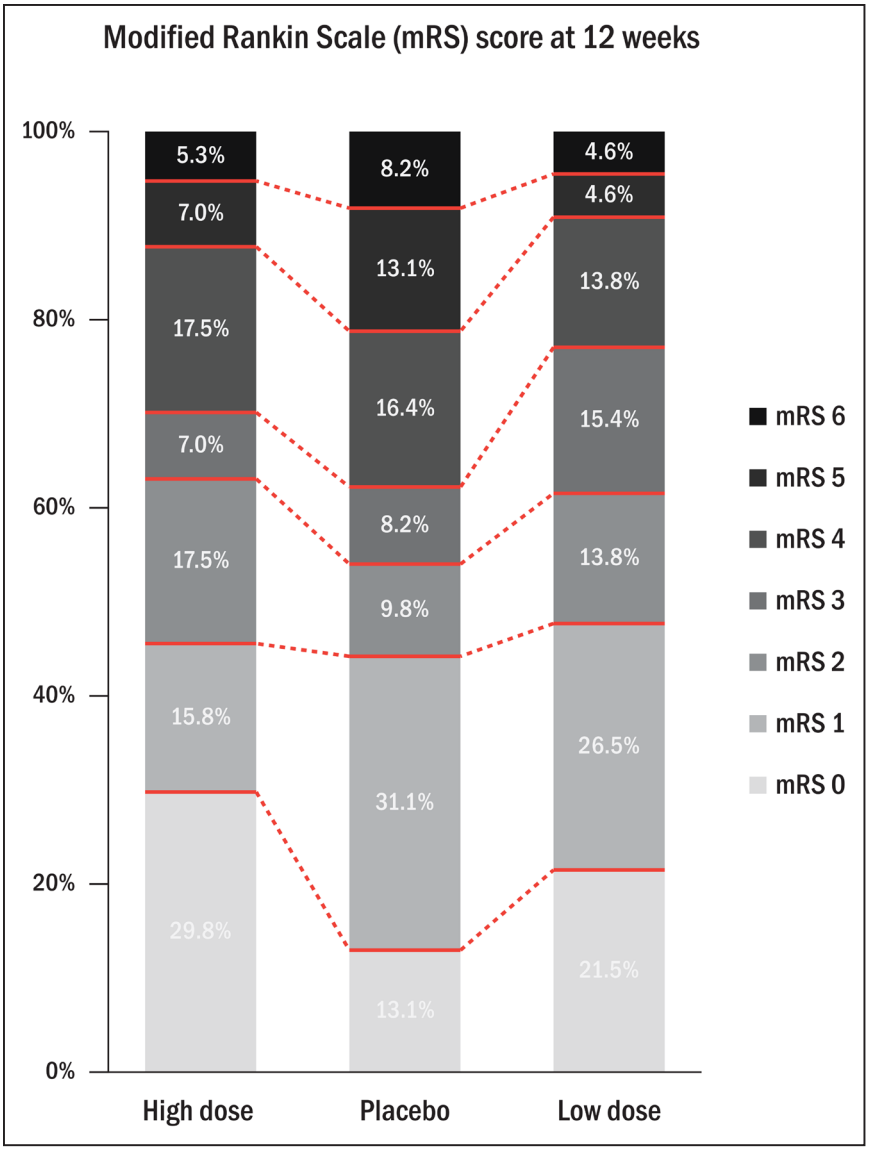

Figure 2. Distribution of the primary outcome at 12 wk according to group (n=183).
mRS indicates modified Rankin Scale.

In neuroprotection studies beyond ERT for a large-vessel occlusion stroke, a shift analysis would be more suitable than a dichotomized analysis. A dichotomized analysis is used to evaluate whether a treatment can increase the number of patients with a good outcome (defined by functional independence) compared with the conventional treatment, whereas a shift analysis is used to evaluate whether a treatment can produce a better outcome (favorable shift in mRS score distribution) compared with conventional methods.[24] In addition, a shift analysis allows a smaller number of patients than a dichotomized analysis.[24]

The shift analysis has already been applied in major clinical trials of ERT, including the MR CLEAN (A Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), ESCAPE, and SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment) trials.[25–27] These trials showed a favorable shift in the mRS score distribution along with a high odds ratio for a good outcome (mRS score, 0–2).[4] However, the results of the current trial and another recent neuroprotection trial (ESCAPE NA1) based on large-vessel occlusion and ERT have shown that there may be a ceiling effect in the increase in the frequency of good outcomes. The rates of good outcomes in the placebo group (59%) of the ESCAPE NA1 trial were slightly higher than those in the ERT group (53%) of the ESCAPE trial.[8,26] The populations of the 2 groups were very similar and had the same treatment, although the criterion for baseline infarct core volume estimated using noncontrast computed tomography ASPECTS was rather wider in the NA1 placebo group (ASPECTS, 5–10) than in the ESCAPE endovascular group (ASPECTS, 6–10). In the current trial, a favorable tendency was observed in terms of both having an mRS score of 0–2 and mRS score distribution but without statistical significance. Nevertheless, the favorable shift in the mRS score distribution seemed to

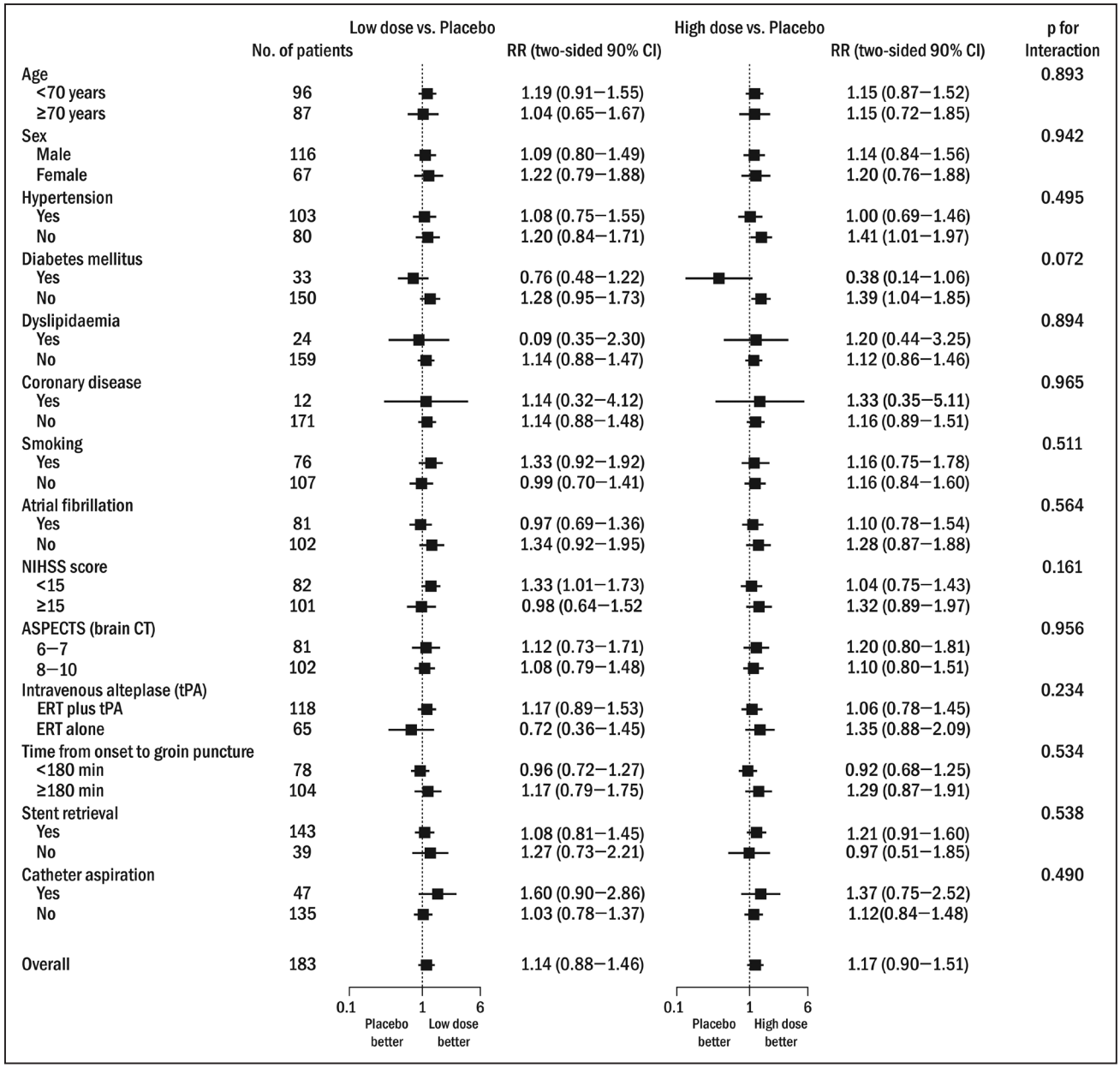

Figure 3. Subgroup analysis of the primary outcome in the full analysis set (n=183).
ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; ERT, endovascular reperfusion therapy; NIHSS, National Institutes of Health Stroke Scale; RR, relative risk; and tPA, tissue-type plasminogen activator.

be more evident than the odds ratio for having an mRS score of 0–2. In future neuroprotection trials based on an endovascular reperfusion strategy, it would be more reasonable to aim for a better outcome than for a higher number of patients achieving functional independence.

In the subgroup analysis, patients with diabetes in the high-dose group showed a tendency for worse outcomes than those with diabetes in the placebo group. However, this finding seems to be incidental to the small number of patients in the subgroup. The ratio of functional independence in the patients with diabetes in the subgroup was exceptionally high (data not shown). The clinical outcomes of patients with diabetes or admission hyperglycemia who had a large-vessel occlusion stroke and received ERT have been reported to be worse than those of patients without similar medical conditions.[28,29] Although free radicals play a role in the pathophysiology of exacerbated outcomes in patients with acute ischemic stroke and diabetes or hyperglycemia, various other mechanisms are involved.[30] Such patients show infarct growth, hemorrhagic transformation, and acute kidney injury, resulting in a relatively poor prognosis.[31] The effect of nelonemdaz in patients with diabetes should be further evaluated in a future large-scale trial.

The dropout rates in this trial were rather high. The clinical assessments initially included only patients who

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Table 3. Adverse Events in ≥5% of Patients in the Safety Set (n=208)

	Placebo (n=70)	Low dose (n=71)	High dose (n=67)	*P* value
With at least one adverse event	60 (85.7%)	56 (78.9%)	56 (83.6%)	0.5468
Pyrexia	28 (40.0%)	27 (38.0%)	29 (43.3%)	0.8179
Mild	0	0	2	
Moderate	28	27	27	
Severe	0	0	0	
Hemoglobin, decreased	22 (31.4%)	20 (28.2%)	17 (25.4%)	0.7335
C-reactive protein, increased	5 (7.1%)	7 (9.9%)	9 (13.4%)	0.4726
Headache	7 (10.0%)	4 (5.6%)	8 (11.9%)	0.4175
Urinary retention	6 (8.6%)	7 (9.9%)	5 (7.5%)	0.8819
Hematuria	6 (8.6%)	3 (4.2%)	7 (10.4%)	0.3689
Constipation	7 (10.0%)	2 (2.8%)	5 (7.5%)	0.2244
Diarrhea	4 (5.7%)	3 (4.2%)	6 (9.0%)	0.4823
Aspiration pneumonia	5 (7.1%)	5 (7.0%)	3 (4.5%)	0.8208
Cough	6 (8.6%)	2 (2.8%)	3 (4.5%)	0.3111
Pneumonia	3 (4.3%)	4 (5.6%)	4 (6.0%)	0.9293

The *P* values were calculated using the χ^2 test and Fisher exact test, as appropriate. Mild is defined as not requiring further treatment; moderate is defined as interfering with the normal function of the subject, but it recovers from antipyretic and antibiotics; severe is defined as requiring a high-level treatment is required, and the disability remains.

visited their corresponding centers. However, we observed that the number of patients who could not visit the centers because of disability was non-negligible. Therefore, our protocol was amended after approximately two-thirds of all patients had been enrolled. The mRS score assessment at 12 weeks via telephonic interview was allowed for patients who could not visit the hospital because of disability. Previous reports have shown a favorable agreement between telephonic and face-to-face assessments for mRS score evaluation.[32,33] We recommend incorporating telephone assessments into the evaluation of clinical outcomes in patients with severe disability to reduce the dropout rates in future stroke clinical trials. Since 5-day long therapy can have a paradoxical adverse effect on plasticity and recovery through NMDA receptor blocking effects, large-scale clinical studies are needed to evaluate whether multitarget neuroprotection therapy around 5 days is beneficial in the future.

In conclusion, a phase III trial comparing nelonemdaz and placebo is warranted based on the observed tendency toward favorable clinical outcomes and the lack of serious adverse effects of the trial drug in the current phase II SONIC trial.

ARTICLE INFORMATION

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Disclosures

Drs Jin Soo Lee and Choi are advisory members to GNT pharma. The other authors report no conflicts.

Supplemental Material

Table S1
CONSORT checklist

APPENDIX

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