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Letter to the Editor

Early Administration of Nelonemdaz May Improve the Stroke Outcomes in Patients With Acute Stroke

Jin Soo Lee,[1,*] Ji Sung Lee,[2,*] Seong Hwan Ahn,[3,*] Hyun Goo Kang,[4] Tae-Jin Song,[5] Dong-Ick Shin,[6] Hee-Joon Bae,[7] Chang Hun Kim,[8] Sung Hyuk Heo,[9] Jae-Kwan Cha,[10] Yeong Bae Lee,[11] Eung Gyu Kim,[12] Man Seok Park,[13] Hee-Kwon Park,[14] Jinkwon Kim,[15] Sungwook Yu,[16] Heejung Mo,[17] Sung Il Sohn,[18] Jee Hyun Kwon,[19] Jae Guk Kim,[20] Young Seo Kim,[21] Jay Chol Choi,[22] Yang-Ha Hwang,[23] Keun Hwa Jung,[24] Soo-Kyoung Kim,[8] Woo Keun Seo,[25] Jung Hwa Seo,[10] Joonsang Yoo,[15] Jun Young Chang,[26] Mooseok Park,[4] Kyu Sun Yum,[6] Chun San An,[27] Byoung Joo Gwag,[27] Dennis W. Choi,[28] Ji Man Hong,[1] Sun U. Kwon[26]; the SONIC and RODIN Investigators

[1]Department of Neurology, Ajou University School of Medicine, Ajou University Medical Center, Suwon, Korea
[2]Clinical Research Center, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[3]Department of Neurology, Chosun University Hospital, Chosun University College of Medicine, Gwangju, Korea
[4]Department of Neurology, Research Institute of Clinical Medicine of Jeonbuk National University-Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju, Korea
[5]Department of Neurology, Ewha Womans University Seoul Hospital, Ewha Womans University College of Medicine, Seoul, Korea
[6]Department of Neurology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea
[7]Department of Neurology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[8]Department of Neurology, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju, Korea
[9]Department of Neurology, Kyung Hee University Hospital, Kyung Hee University College of Medicine, Seoul, Korea
[10]Department of Neurology, Dong-A University Hospital, College of Medicine, Dong-A University, Busan, Korea
[11]Department of Neurology, Gil Medical Center, Gachon University College of Medicine, Incheon, Korea
[12]Department of Neurology, Busan Paik Hospital, College of Medicine, Inje University, Busan, Korea
[13]Department of Neurology, Chonnam National University Medical School, Chonnam National University Hospital, Gwangju, Korea
[14]Department of Neurology, Inha University Hospital, Inha University College of Medicine, Incheon, Korea
[15]Department of Neurology, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Korea
[16]Department of Neurology, Korea University Anam Hospital, Korea University Medicine, Seoul, Korea
[17]Department of Neurology, Inha University Hospital, Inha University College of Medicine, Incheon, Korea
[18]Department of Neurology, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, Korea
[19]Department of Neurology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea
[20]Department of Neurology, Daejeon Eulji Medical Center, Eulji University School of Medicine, Daejeon, Korea
[21]Department of Neurology, Wonkwang University Hospital, School of Medicine, Wonkwang University, Iksan, Korea
[22]Department of Neurology, Jeju National University Hospital, Jeju National University College of Medicine, Jeju, Korea
[23]Department of Neurology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea
[24]Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea
[25]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[26]Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[27]GNT Pharma Co., Ltd., Yongin, Korea
[28]Department of Neurology, Stony Brook University School of Medicine, Stony Brook, NY, USA

Dear Sir:

A phase III clinical trial did not demonstrate a significant impact of nelonemdaz on patients with acute ischemic stroke.[1] Although not prespecified in the original protocol, *post-hoc* analyses suggested potential interactions between treatment effects and time-related metrics, leading us to hypothesize that earlier drug administration may yield better outcomes. This study aimed to determine the treatment effect of nelonemdaz when administered early after emergency room (ER) arrival.

We conducted a *post-hoc* analysis using pooled data from two clinical trials investigating nelonemdaz in acute ischemic stroke: the phase II SONIC trial (Safety and Optimal Neuroprotection of Neu2000 in Acute Ischemic Stroke With Recanalization) and the phase III RODIN trial (Rescue on Reperfusion Damage in Cerebral Infarction by Nelonemdaz) (Supplementary Table 1).[1,2] Both trials and the current study adhered to the Declaration of Helsinki principles. We combined the study populations after excluding the low-dose group from the SONIC trial. Our exploratory analysis revealed a significant interaction between treatment effect and the time from ER arrival to initial trial drug administration (Supplementary Figure 1). Based on subsequent subgroup analyses of time metrics, we established a 70-minute threshold from ER arrival to first trial drug infusion and included only patients who received treatment within this timeframe.

The efficacy of nelonemdaz was primarily assessed using the modified Rankin Scale (mRS) at 12 weeks post-treatment. Using ordinal logistic regression, the primary analysis evaluated a favorable shift in the distribution of mRS scores across the entire ordinal scale (0 [normal] to 6 [death]) at 12 weeks. As a secondary outcome measure, we analyzed the proportion of patients achieving functional independence, defined as mRS 0–2 at 12 weeks, using modified Poisson regression. Both regression models were adjusted for the following well-known major confounders: age, female sex, time from symptom onset to ER arrival (hours), baseline stroke severity (National Institutes of Health Stroke Scale [NIHSS] score), Alberta Stroke Program Early CT Score (ASPECTS), administration of intravenous alteplase, and achievement of successful reperfusion (modified Thrombolysis in Cerebral Infarction 2b-3).

The treatment effect was expressed as a common odds ratio (cOR) with the corresponding 95% confidence interval (CI) for mRS at 12 weeks and as a relative risk (RR) with 95% CI for mRS 0–2 at 12 weeks. Statistical significance was set at P<0.05 (two-sided) for all analyses. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Baseline characteristics, treatment, and outcomes are summarized in Table 1. Regarding baseline characteristics, age was younger in the nelonemdaz group than in the placebo group (74.8±10.1 vs. 70.2±11.7, P=0.040). The baseline NIHSS score and ASPECTS did not differ between groups. Past stroke history tended to be more frequent in the nelonemdaz group than in the placebo group (12.5% vs. 27.5%, P=0.064). Variables regarding time metrics did not differ between groups. Regarding revascularization treatment, the frequency of intravenous alteplase infusion, endovascular thrombectomy (EVT) techniques, and successful post-EVT reperfusion did not differ between groups.

The regression analysis is presented in Table 2. The median score on the mRS at 12 weeks was 1 (interquartile range, 0 to 4) in the nelonemdaz group and 3 (interquartile range, 1 to 4) in the placebo group (adjusted cOR for a shift in the direction of a better outcome on the mRS, 2.22; 95% CI, 1.03 to 4.80; P=0.043). A favorable outcome (mRS 0–2) at 12 weeks occurred in 35 of 51 patients (68.6%) in the nelonemdaz group and in 24 of 48 patients (50.0%) in the placebo group (adjusted RR, 1.26; 95% CI, 0.95 to 1.69; P=0.112). Figure 1 shows the distribution of mRS scores in unadjusted and adjusted analyses, respectively.

Our *post-hoc* analysis demonstrated that early time from door to the 1st trial drug administration was associated with better treatment outcomes of nelonemdaz, aligning with the pathophysiological time window concept for neuroprotective therapy. This finding fits with current understandings of the underlying pathophysiological cascade in focal cerebral ischemia and the mechanism of action of neuroprotective agents, which is based on the concept of ischemic penumbra and infarct core.

The importance of hyperacute treatment in acute ischemic stroke cannot be overstated. When intracranial large vessel occlusion occurs, an ischemic penumbra forms throughout the affected region, leading to loss of neuronal function.[3] During cerebral ischemia, glutamate is released and accumulated, resulting in Ca^{2+} overload through excess activation of postsynaptic N-methyl-D-aspartate (NMDA) receptors and fulminant neuronal death.[4] Following recanalization, toxic free radicals produced in mitochondria contribute to additional neuronal death.[3] These progressive pathological processes result in irreversible neuronal death, and the affected brain region becomes the infarct core.

Neuroprotective agents represent substances that reduce ischemic brain damage by interrupting harmful molecular events rather than by improving cerebral blood flow. Their therapeutic potential primarily lies in the ischemic penumbra, the salvageable tissue, where molecular interventions can still effectively prevent cell death.[3] In this context, we investigated nelonemdaz (previously, Neu2000), which exhibits dual mechanisms of action: moderate NR2B-selective NMDA receptor antagonist and potent antioxidant.[5-7] These therapeutic mechanisms specifically target the critical pathways in the neuronal death cascade described above, supporting its potential efficacy as a neuroprotective agent when administered before the ischemic penumbra progresses to infarct core. In the phase III clinical trial, nelonemdaz failed to demonstrate efficacy in the main results when tested on patients who received EVT for acute ischemic stroke. However, in the current study using pooled data of phase II and III trials, beneficial effect of nelonemdaz was observed in cases where the time from ER to 1st trial drug infusion was early.

As time is brain, neuroprotective therapy may also be time-dependent. While a short door-to-needle time favorably modi-

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Table 1. Baseline characteristics, treatments, and outcomes of the current study population

	Placebo (n=48)	Nelonemdaz (n=51)	*P**
Numbers from phase II	9	11	
Numbers from phase III	39	40	
Age (yr)	74.8±10.1	70.2±11.7	0.040
Female sex	19 (39.6)	19 (37.3)	0.812
NIHSS score	15 (12–18)	15 (11–19)	0.737
ASPECTS	8 (7–10)	8 (7–9)	0.382
Occlusion locations (multiple choice)			
Proximal ICA (tandem occlusion)	5 (10.4)	7 (13.7)	0.614
Intracranial ICA	12 (25.0)	14 (27.5)	0.782
MCA M1	37 (77.1)	32 (62.7)	0.121
MCA M2	2 (4.2)	11 (21.6)	0.010
Hypertension	34 (70.8)	35 (70.0)	0.928
Diabetes mellitus	21 (43.8)	16 (32.0)	0.230
Hyperlipidemia	17 (35.4)	16 (32.0)	0.721
Coronary artery disease	4 (8.3)	6 (12.0)	0.741
Atrial fibrillation	29 (60.4)	29 (58.0)	0.808
Smoking	12 (25.0)	19 (38.0)	0.167
Past stroke history	6 (12.5)	14 (27.5)	0.064
Time from onset to ER (min)	121 (61–295)	96 (61–233)	0.333
Time from onset to 1st trial drug infusion (min)	183 (123–342)	155 (120–297)	0.295
Time from onset to EVT (min)	204 (140–348)	166 (130–300)	0.548
Time from ER to 1st trial drug infusion (min)	59 (50–65)	59 (52–64)	0.961
Time from ER to EVT (min)	61 (52–73)	65 (53–81)	0.201
Intravenous alteplase	24 (50.0)	27 (52.9)	0.770
EVT techniques (multiple choice)			
Stent retrieval	22 (45.8)	29 (56.9)	0.272
Catheter aspiration	22 (45.8)	30 (58.8)	0.196
Others	18 (37.5)	13 (25.5)	0.198
Post-EVT mTICI 2b–3	41 (89.1)	43 (84.3)	0.487
mRS at 12 weeks	3 (1–4)	1 (0–4)	0.031
mRS 0–2 at 12 weeks	24 (50.0)	35 (68.6)	0.059

Values are presented as n (%) or median (interquartile range).
NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; MCA M1, M1 segment of the middle cerebral artery; MCA M2, M2 segment of the middle cerebral artery; ER, emergency room; EVT, endovascular thrombectomy; mTICI, modified Thrombolysis in Cerebral Infarction; mRS, modified Rankin Scale.
**P*-values were calculated using chi-square test, Fisher's exact test, Cochran-Mantel-Haenszel shift test, Student's t-test, or Wilcoxon rank sum test, as appropriate.

fied nelonemdaz effect in exploratory analysis, no modification effect was seen with time from stroke onset to first trial drug infusion. This finding parallels previous EVT trials, where shorter times from ER arrival to EVT or shorter EVT procedural times were independently associated with good clinical outcomes, while time from stroke onset to ER arrival showed weaker statistical associations.[8] This phenomenon can be explained by two key factors. First, individual variations in collateral status significantly influence the rate of tissue damage, making the absolute time from symptom onset less predictive of salvageable tissue.[9] Some patients with good collaterals may maintain viable penumbra for extended periods, while others with poor collaterals might experience rapid infarct progression. Second, systematic patient selection occurs immediately after ER arrival: patients with established infarcts are excluded from EVT consideration, regardless of their onset-to-door time. This tissue-based selection process effectively creates a population with preserved tissue viability, making post-ER time metrics more directly relevant to outcomes

Table 2. Ordinal and modified Poisson regression models for favorable outcomes

	Favorable shift of mRS at 12 weeks		mRS 0–2 at 12 weeks	
	Adjusted cOR (95% CI)	*P*	Adjusted RR (95% CI)	*P*
Age	0.97 (0.94–1.00)	0.076	0.99 (0.97–1.00)	0.137
Female	1.44 (0.66–3.13)	0.363	1.10 (0.85–1.42)	0.450
Time from onset to ER (h)	0.88 (0.76–1.01)	0.072	0.91 (0.84–0.99)	0.032
NIHSS score	0.82 (0.75–0.90)	<0.001	0.95 (0.92–0.98)	0.002
ASPECTS	1.33 (1.07–1.67)	0.011	1.13 (1.02–1.25)	0.023
Intravenous alteplase	1.38 (0.58–3.29)	0.473	1.02 (0.76–1.36)	0.902
mTICI 2b–3	19.41 (5.64–66.76)	<0.001	4.35 (1.25–15.14)	0.021
Nelonemdaz	2.22 (1.03–4.80)	0.043	1.26 (0.95–1.69)	0.112

mRS, modified Rankin Scale; cOR, common odds ratio; RR, relative risk; CI, confidence interval, ER, emergency room; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score; mTICI, modified Thrombolysis in Cerebral Infarction.

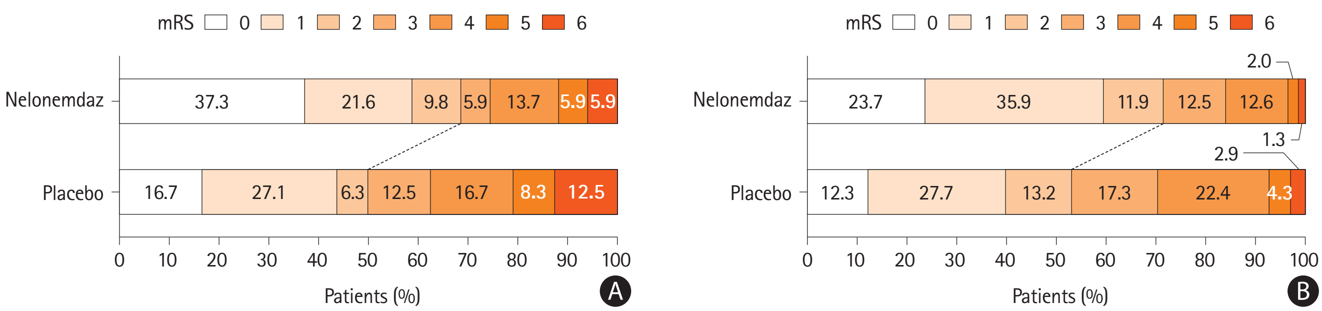

Figure 1. Distribution of the modified Rankin Scale (mRS) scores at 12 weeks in (A) unadjusted and (B) adjusted populations, respectively.

than onset-to-door time alone. This clinical trial approach is particularly significant because the neuroprotective drug was tested under conditions that closely mirror those used for selecting EVT candidates, where tissue viability and collateral status, rather than absolute time from onset, guide patient selection.

Our time from ER arrival to the 1st trial drug infusion showed remarkable similarity to the ESCAPE trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times),[10] a landmark study in EVT. The ESCAPE trial intended to initiate treatment within 60 minutes of computed tomography (CT) completion. Considering that the entire process from ER arrival to CT image acquisition and processing typically takes 10 minutes, reducing treatment initiation to within 70 minutes of ER arrival might enable neuroprotective treatments to demonstrate efficacy similar to EVT. Therefore, future clinical trials of neuroprotective therapy with nelonemdaz should consider adopting similar in-hospital time-based protocols as the ESCAPE trial.

Several limitations warrant careful interpretation of our findings. First, this analysis was exploratory and *post-hoc* in nature, rather than a prespecified subgroup analysis. Although the original trials were randomized, our analysis focused on a selected subgroup where treatment effect was observed, potentially introducing selection bias that cannot be fully addressed through statistical adjustment. Second, while the treatment effect remained significant after regression analysis, lending support to our findings, the selective nature of our analysis (focusing only on patients receiving treatment within 70 minutes of ER arrival) may limit the external validity and generalizability of these results to the broader stroke population. Third, the relatively small sample size in this subgroup analysis necessitates careful interpretation of the observed treatment effects, despite statistical significance. Future prospective trials with prespecified time-dependent analyses are warranted to validate these preliminary findings regarding nelonemdaz efficacy. Given the operational challenges of achieving such rapid drug administration in clinical trials, identification of additional responder characteristics might help establish more feasible extended time windows while maintaining efficacy.

In conclusion, in acute ischemic stroke patients undergoing EVT, nelonemdaz administration within 70 minutes of ER arrival was associated with improved functional outcomes, suggesting its possible efficacy.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.05113.

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Conflicts of interest

Dr. Jin Soo Lee reported receiving grants and personal fees from GNT Pharma outside the submitted work. Dr. Ji Sung Lee reported receiving personal fees from GNT Pharma during the conduct of the study. Dr. D. Choi reported receiving personal fees from GNT Pharma during the conduct of the study. Dr. Byoung Joo Gwag is the Chief Executive Officer and Dr. Chun San An is the Clinical Development Officer of GNT Pharma. No other disclosures were reported related to the submitted work.

Author contribution

Conceptualization: JSL (Jin Soo Lee). Study design: JSL (Jin Soo Lee). Methodology: JSL (Jin Soo Lee), JSL (Ji Sung Lee). Data collection: HGK, SHA, TJS, DIS, HJB, CHK, SHH, JKC, YBL, MSP, HKP, JK, SY, HM, JHK, JGK, YSK, JCC, YHH, KHJ, SKK, WKS, JMH. Investigation: JSL (Jin Soo Lee), JSL (Ji Sung Lee), SHA. Statistical analysis: JSL (Jin Soo Lee), JSL (Ji Sung Lee), SHA. Writing—original draft: JSL (Jin Soo Lee), JSL (Ji Sung Lee), SHA. Writing—review & editing: JSL (Jin Soo Lee), HGK, SHA, TJS, DIS, HJB, CHK, SHH, JKC, YBL, MSP, HKP, JK, SY, HM, JHK, JGK, YSK, JCC, YHH, KHJ, SKK, WKS, JHS, JY, JYC, MP, JSL (Ji Sung Lee), BJG, JMH, SUK. Funding acquisition: HGK, SHA, TJS, DIS, HJB, CHK, SHH, JKC, YBL, MSP, HKP, JK, SY, HM, JHK, JGK, YSK, JCC, YHH, KHJ, SKK, WKS, JMH. Approval of final manuscript: all authors.

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Correspondence: Jin Soo Lee
Department of Neurology, Ajou University School of Medicine, Ajou University Medical Center, 164 Worldcup-ro, Youngtong-gu, Suwon 16499, Korea
Tel: +82-31-219-5175
E-mail: jinsoo22@gmail.com
https://orcid.org/0000-0002-7225-6166

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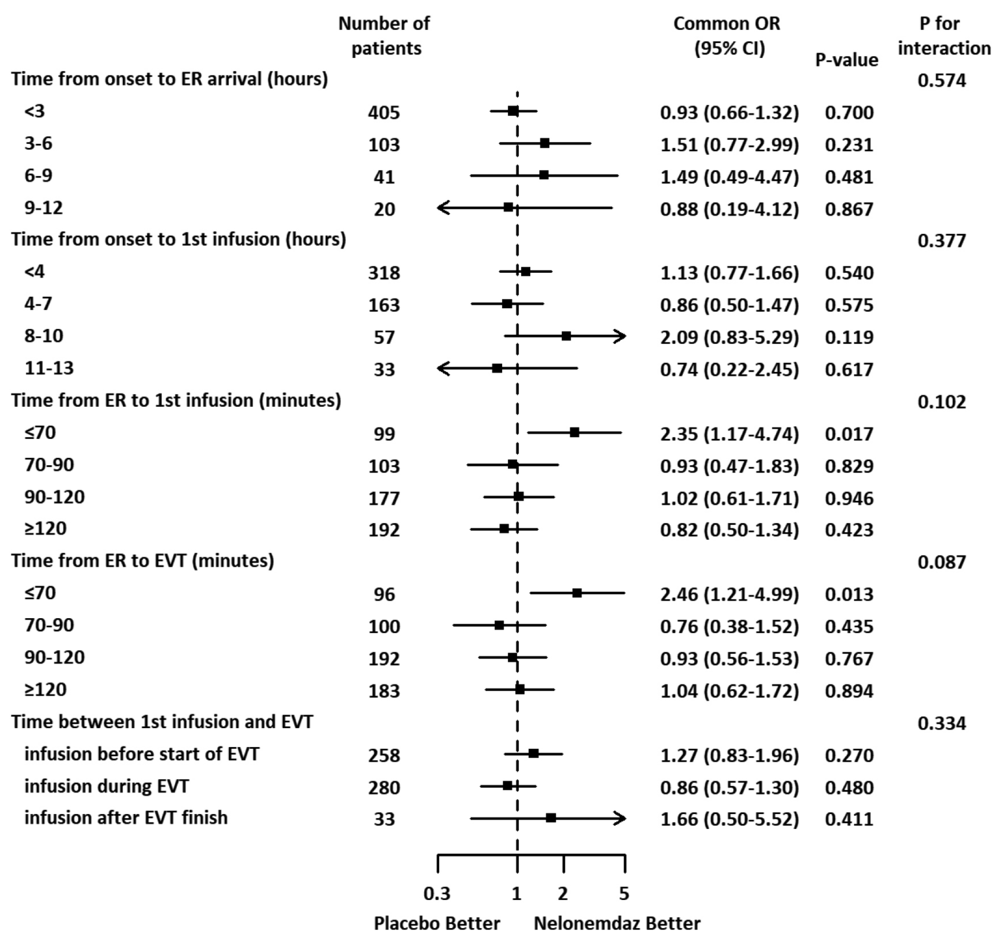
*These authors contributed equally as first author.

Supplementary Table 1. Summary of phase II and III clinical trials investigating nelonemdaz

Characteristic	SONIC trial (phase II)	RODIN trial (phase III)
Study period	October 2016 to June 2020	December 2021 to April 2023
Sample size, n	209	496
Treatment arms (full analytic set)	Placebo (n=61) Low dose (n=65) High dose (n=57)	Placebo (n=225) High dose (n=232)
Key inclusion criteria		
Age	≥19 years	≥19 years
Occlusion location	Intracranial ICA, MCA M1, M1 equivalent M2	Intracranial ICA, MCA M1, MCA M2
Onset to EVT	<8 h	<12 h
NIHSS	≥8	≥8
ASPECTS	>5	>3
Primary endpoint	Modified Rankin Scale 0–2 at 3 months	A favorable shift of modified Rankin Scale at 3 months
Outcomes	A favorable tendency	No difference

SONIC trial, Safety and Optimal Neuroprotection of Neu2000 in Acute Ischemic Stroke With Recanalization; RODIN trial, Rescue on Reperfusion Damage in Cerebral Infarction by Nelonemdaz; ICA, internal carotid artery; MCA M1, M1 segment of the middle cerebral artery; MCA M2, M2 segment of the middle cerebral artery; EVT, endovascular thrombectomy; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early CT Score.



Supplementary Figure 1. *Post-hoc* subgroup analysis regarding time metrics in total population from pooled data of nelonemdaz clinical trials. The low-dose group from phase II was excluded, and all ranges of time from ER to 1st trial drug infusion were included. OR, odds ratio; CI, confidence interval; ER, emergency room; EVT, endovascular thrombectomy.