RESCUE: A Phase 2 Trial of RNS60 Shows Safety, Reduces Infarct Growth and Demonstrates Signs of Efficacy in Subjects with Ischemic Stroke Receiving Mechanical Thrombectomy

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INTRODUCTION AND PURPOSE

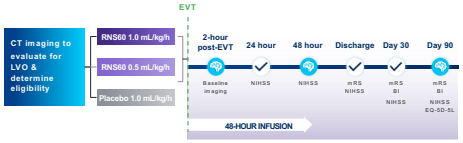
Although reperfusion therapies have improved stroke prognosis profoundly, there remains a need for adjunct cytoprotective therapies to enhance the brain's resilience to and recovery from a stroke. RNS60 is an experimental cytoprotective therapy that promotes survival of neurons and oligodendrocytes under stress and reduces gliosis. It has been shown to provide bioenergetic support via increased mitochondrial biogenesis and oxidative metabolism in cultured neurons and oligodendrocytes under stress.

RNS60 showed significant efficacy in rodent and non-human primate (NHP) models of acute ischemic stroke. In a mouse model of transient middle cerebral artery occlusion (tMCAO), RNS60 treatment reduced brain infarction, amyloid pathology, neuronal death, microglial activation and white matter damage, and improved microvascular perfusion and cognitive function[1]. In an NHP tMCAO model, IV infusion of RNS60 for 48 hours reduced infarct size and edema, reduced gliosis, and improved neurobehavioral functions (unpublished data). RNS60 has also demonstrated similar neuroprotective effects in preclinical models of traumatic brain injury and multiple chronic neurodegenerative diseases including ALS[1-3]. RNS60 has not elicited any significant findings in preclinical toxicological studies.

Clinically, RNS60 has been generally safe and well tolerated in Phase 1 and 2 studies (400+ humans dosed to date) after IV infusion, nebulization (inhalation), or a combination of the two routes of administration. The promising preclinical efficacy and the favorable safety profile in the clinic make RNS60 an ideal candidate to be tested in stroke trials for cerebroprotection.

RESCUE was the first study to test RNS60 as an adjunctive therapy in ischemic stroke patients with large vessel occlusion (LVO) undergoing endovascular thrombectomy (EVT). The primary objective of the study was to evaluate safety and first signs of efficacy to inform future trials.

RESCUE DESIGN



EVT = Endovascular Thrombectomy, NIHSS = National Institutes of Health Stroke Scale, mRS = Modified Rankin Scale, BI = Barthel Index

INCLUSION/EXCLUSION CRITERIA

INCLUSION:

- ✓ Age ≥ 18 years
- ✓ NIHSS >5 for ICA, M1-MCA
  NIHSS >10 for M2-MCA
- ✓ mRS ≤2
- ✓ Stroke onset <24 hours
- ✓ Selected for EVT
- ✓ Confirmed qualifying occlusion

EXCLUSION:

- X ASPECTS 0-4
- X Absence of collateral flow
- X MI within 6 months
- X History of CHF
- X Seizure at stroke onset
- X Ischemic stroke within 30 days
- X EVT procedure complete

STUDY ENDPOINTS

PRIMARY:

- Frequency & severity of SAEs
- 90-day mortality

SECONDARY:

- Non-disability based on mRS score 0-2 at Day 90
- Infarct volume (progression/regression) at 48 hours
- Disability and recovery (NIHSS) 24 hours
- Proportion of subjects with worsening of stroke at 48 hours/duration of admission
- Functional independence (proportion of subjects with Barthel Index >95) at Day 90
- Health related quality of life (EQ-5D-5L) at Day 90

RESULTS

Table 1. Baseline Demographics

Characteristic	Placebo 1.0 mL/kg/h N=28	RNS60 0.5 mL/kg/h N=30	RNS60 1.0 mL/kg/h N=24
Age			
Mean (SD)	66.0 (12.50)	68.0 (12.51)	67.8 (10.65)
Male (%)	60.7	56.7	70.8
Female (%)	39.3	43.3	29.2
IV Thrombolysis (%)	28.6	53.3	37.5
NIHSS at Baseline			
Mean (SD)	16.5 (6.32)	15.7 (6.09)	14.1 (4.93)
6-10 (%)	21.4	23.3	16.7
>10 (%)	78.6	76.7	83.3
Infarct Volume at Baseline			
Mean (SD)			
Geometric Mean	49.0 (55.93)	37.9 (41.82)	43.6 (40.26)
Median	26.4	20.2	23.5
	29.0	22.6	28.8
ASPECTS			
Mean (SD)	8.3 (1.50)	8.4 (1.41)	8.3 (1.33)
Time Since Last Known Well			
Mean (SD)	9.1 (5.27)	6.8 (4.67)	8.6 (5.32)

Table 2. Safety Overview

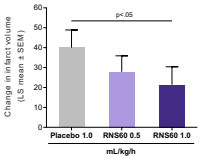
Treatment Emergent AEs (TEAEs)	Placebo 1.0 mL/kg/h N=28 n (%)	RNS60 0.5 mL/kg/h N=30 n (%)	RNS60 1.0 mL/kg/h N=24 n (%)
Any TEAE	27 (96)	30 (100)	23 (96)
Any Severe TEAE[1]	6 (21)	7 (23)	4 (17)
Any Related TEAE	4 (14)	6 (20)	2 (8)
Serious AEs[2]	8 (29)	10 (33)	7 (29)
TEAEs Leading to D/C of study drug infusion	0	0	0
TEAEs Leading to Death	4 (14)	2 (7)	2 (8)

[1] None were treatment related
[2] Only one subject in the RNS60 low dose group had a related SAE

RESULTS

Figure 1. Progression of Infarct After 48 Hours of Dosing

A

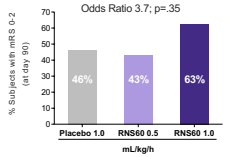


B

Change from baseline (ml)	Placebo 1.0 mL/kg/h N=28	RNS60 0.5 mL/kg/h N=30	RNS60 1.0 mL/kg/h N=24
LS mean (SE)	40.05 (9.08)	27.88 (8.01)	21.43 (8.99)
Mean infarct volume	40.6	27.1	21.4
Geometric mean infarct volume	22.4	13.4	10.6
Median infarct volume	26.3	13.4	12.9

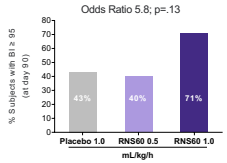
Infarct progression/regression was assessed by MRI brain imaging after 48-h infusion treatment. The change in infarct volume was measured by comparing 48-hour images to baseline images (as assessed by MRI 2 hours post EVT) on a log scale between the three treatment arms using generalized linear mixed modeling (GLM). Covariates included the log of baseline infarct volume along with age, baseline NIHSS, ASPECTS binary factors used for block urn randomization, baseline perfusion status, baseline occlusion location, and study site. A significant reduction in infarct growth compared to placebo was noted in the RNS60 1.0 mL/kg/h group (LS mean difference of 18.62; nominal p<.05).

Figure 2. Global Disability Assessment with the Modified Rankin Scale (mRS) on Day 90



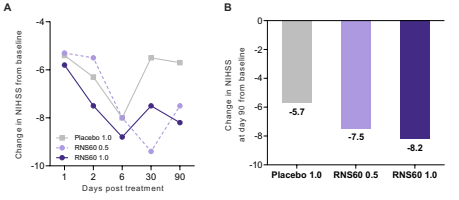
The effect of treatment on global disability at Day 90 was examined by comparing the proportion of subjects who had good outcome (mRS 0-2) between the three treatment arms using GLM. Covariates included age, baseline NIHSS, and ASPECTS binary factors used for block urn randomization and baseline (pre-morbid) mRS, baseline occlusion location, study site, baseline perfusion status, and log of baseline infarct volume. 63% of the subjects in the RNS60 1.0 mL/kg/h group had no disability (mRS 0-2) compared to 46% in the dose matched placebo group and 43% in RNS60 0.5 mL/kg/h with an odds ratio of 3.7 (p=.35) in favor of RNS60 1.0 mL/kg/h when compared to placebo.

Figure 3. Functional Independence Assessment with the Barthel Index (BI) on Day 90



The proportion of subjects who achieved functional independence (BI score ≥ 95) on Day 90 was compared between the three treatment arms using GLM. Covariates included age, baseline NIHSS, and ASPECTS binary factors used for block urn randomization and baseline BI total, log of baseline infarct volume, baseline perfusion status, baseline occlusion location, and study site. Treatment, visit day, and interaction of treatment and visit day are included as categorical fixed effects. 71% of subjects on RNS60 1.0 mL/kg/h compared to only 43% on placebo had a BI ≥ 95; (OR 5.8, p=.12).

Figure 4. Neurological Recovery as Measured with the National Institutes of Health Stroke Scale (NIHSS)



A. The NIHSS was assessed at multiple time points and at each time point, the RNS60 1.0 mL/kg/h group had numerically greater (improved) change from baseline compared to the placebo group, although the difference did not reach statistical significance. **B**. At Day 90, the highest favorable change from baseline was observed in the RNS60 high dose group.

The absolute NIHSS score also showed greater numerical benefit for the RNS60 high dose group. At 24 hour there was an LS mean (SE) difference of -1.57 (1.54) favoring RNS60 high dose (p=.31), at Day 30 an LS mean (SE) difference of -4.45 (3.32) favoring RNS60 high dose (p=.18) and at Day 90 an LS mean (SE) difference of -2.97 (3.26) favoring RNS60 high dose (p=.37) compared to placebo.

SUMMARY

PRIMARY ENDPOINT:

- RNS60 demonstrated similar rates of SAEs and lower mortality compared to placebo

SECONDARY EFFICACY ENDPOINTS:

- High dose RNS60 was numerically better compared to placebo in all prespecified endpoints:
  - ✓ Infarct volume change from ~2 hours post EVT to 48 hours (p<.05)
  - ✓ mRS dichotomized and ordinal analysis (data not shown for the ordinal analysis)
  - ✓ Barthel Index at 90 days (p=.056)
  - ✓ NIHSS at each specified timepoint

CONCLUSION

RNS60 was generally safe and well tolerated. Moreover, RNS60 treatment significantly reduced infarct growth post EVT and showed promising effects on multiple endpoints at day-90, which warrants future testing in a larger study powered for efficacy.

REFERENCES

[1]Baena-Caldas et al., *PLoS One* 2024 Jan 2;19(1)
[2]Rangasamy et al. *Exp Neurol.* 2020 Jun:328:113279
[3]Vallarola et al., *J Neuroinflammation.* 2018 Mar 1;15(1):65