

## ORIGINAL ARTICLE

# NXY-059 for the Treatment of Acute Ischemic Stroke

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## ABSTRACT

**BACKGROUND**

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\*The investigators participating in the Stroke–Acute Ischemic NXY Treatment II (SAINT II) trial are listed in the Appendix.

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The free-radical–trapping agent NXY-059 showed promise as a neuroprotectant in the Stroke–Acute Ischemic NXY Treatment I (SAINT I) trial, reducing disability when given to patients who had acute ischemic stroke. We sought confirmation of efficacy in a second, larger trial.

**METHODS**

We enrolled 3306 patients with acute ischemic stroke in a randomized, double-blind trial to receive a 72-hour infusion of intravenous NXY-059 or placebo within 6 hours after the onset of stroke symptoms. Our primary end point was the distribution of disability scores on the modified Rankin scale at 90 days. We examined scores on neurologic and activities-of-daily-living scales as secondary end points. We also tested the hypothesis that NXY-059 would reduce alteplase-related intracranial hemorrhages.

**RESULTS**

The efficacy analysis was based on 3195 patients. Prognostic factors were well balanced between the treatment groups. Mortality was equal in the two groups, and adverse-event rates were similar. The distribution of scores on the modified Rankin scale did not differ between the group treated with NXY-059 (1588 patients) and the placebo group (1607 patients;  $P=0.33$  by the Cochran–Mantel–Haenszel test; odds ratio for limiting disability, 0.94; 95% confidence interval [CI], 0.83 to 1.06). Analysis of categorized scores on the modified Rankin scale confirmed the lack of benefit: the odds ratio for trichotomization into modified Rankin scale scores of 0 to 1 versus 2 to 3 versus 4 to 6 was 0.92 (95% CI, 0.80 to 1.06). There was no evidence of efficacy for any of the secondary end points. Among patients treated with alteplase, there was no difference between the NXY-059 group and the placebo group in the frequency of symptomatic or asymptomatic hemorrhage.

**CONCLUSIONS**

NXY-059 is ineffective for the treatment of acute ischemic stroke within 6 hours after the onset of symptoms. (ClinicalTrials.gov number, NCT00061022.)

**C**URRENTLY, THROMBOLYSIS WITH ALTEPLASE (tissue plasminogen activator [rt-PA]) is the only widely approved treatment for acute stroke, and it is underused. There is an urgent need for new therapies that are safer and can be offered to a higher percentage of patients.

Cerebral tissue can be protected in animal models by a variety of agents that attenuate neuronal injury after ischemia,<sup>1</sup> but none of these putative neuroprotectants have been confirmed as an effective therapy in clinical trials. NXY-059, a free-radical-trapping agent, has been extensively tested in animal models of focal ischemic stroke and has been shown to improve functional recovery and reduce the size of the cerebral infarction.<sup>2</sup> A large study reported recently showed that NXY-059 was significantly better than placebo in improving the outcome in patients with ischemic stroke treated within 6 hours after the onset of symptoms.<sup>3</sup> Further support for the suggestion that NXY-059 is a true biologic signal came from post hoc analysis of the data, which also revealed that treatment with NXY-059 significantly reduced the incidence of intracranial hemorrhage among patients in whom alteplase was also used.<sup>3</sup> We sought to confirm the results of the Stroke–Acute Ischemic NXY Treatment I (SAINT I) trial with a larger trial, SAINT II.

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## METHODS

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### STUDY DESIGN

This randomized, double-blind, placebo-controlled study enrolled 3306 patients from May 2003 through June 2006. The study involved 362 centers from 31 countries and was approved by local or national institutional review boards as appropriate. Patients were assigned to treatment only after they had given informed consent or, for patients who were unable to do so, after consent had been obtained from an acceptable surrogate.

The study was part of the SAINT program, which consists of two large, independent, double-blind studies. Its design and conduct were developed by a steering committee of stroke experts from Europe, North America, and Australia. The steering committee had complete access to all data and was responsible for writing the manuscript. An independent data and safety monitoring committee was responsible for safety reviews and futility analysis. The sponsor, AstraZeneca, was responsible for operational aspects of the trial,

including collecting and storing the data, and performing analyses according to the approved plan. The academic authors vouch for the completeness and veracity of the data and analyses.

We originally planned to enroll 1700 patients in SAINT II, but on the basis of the results of SAINT I,<sup>3</sup> we planned to increase the power of the trial by enlarging the study population to 3200 patients without unblinding of any SAINT II data.<sup>4</sup>

### PATIENTS

Patients were eligible for enrollment if they were 18 years of age or older and had a clinical diagnosis of an acute ischemic stroke with an onset within the previous 6 hours. They had to score at least six points on the National Institutes of Health Stroke Scale (NIHSS),<sup>5</sup> with at least two points for limb weakness. All patients received appropriate routine stroke care according to local treatment practice, including alteplase for eligible patients presenting within 3 hours after the onset of the stroke. For patients receiving alteplase, treatment with the study drug had to be started within 30 minutes after completion of the alteplase infusion.

### STUDY INTERVENTION

Patients were randomly assigned by a computer-generated coding system to receive an intravenous infusion of either NXY-059 or placebo. The treating centers were required to maintain an average time of no more than 4 hours to the start of infusion of the study drug. Randomization was stratified according to country, NIHSS score at baseline, side of the infarction, and intention to treat with alteplase. AstraZeneca supplied the study drug as a concentrate to be diluted to 15 mg per milliliter in 500 ml of 0.9% saline solution. The initial infusion rate was 2270 mg per hour, and the rate was reduced after an hour to 480 to 960 mg (32 to 64 ml) per hour for a further 71 hours, with the aim of maintaining a target serum concentration of 260  $\mu$ mol of unbound study drug per liter. The infusion rate was guided by the estimated rate of creatinine clearance, based on the serum creatinine concentration.<sup>6</sup> The infusion rate was adjusted to 32 ml per hour for clearance rates of 30 to 50 ml per minute, 44 ml per hour for clearance rates of 51 to 80 ml per minute, and 64 ml per hour for clearance rates greater than 80 ml per minute. For patients with clearance rates of less than 30 ml per minute, treatment was withdrawn.

**CLINICAL ASSESSMENT**

Patients were assessed at various times throughout the study, including at the time of enrollment, 24 and 72 hours after the start of infusion of the study drug, and on days 7, 30, and 90. Initial assessments included a physical examination, neuroimaging, and an NIHSS assessment to determine the severity of the stroke. The examiners were trained and certified in the use of the NIHSS examination (scores range from 0 to 42, with a higher score indicating greater stroke severity).<sup>5</sup>

Assessments after completion of infusion of the study drug were primarily functional or neurologic, including the score on the modified Rankin scale<sup>7</sup> (assessed on days 7, 30, and 90), the NIHSS (days 7 and 90), and the Barthel index<sup>8</sup> (days 7, 30, and 90). The modified Rankin scale is a global disability scale with a range from 0, indicating no residual symptoms, to 5, for patients who are bedridden and require constant care. In this study, patients who died were assigned a score of 5 on the modified Rankin scale. The investigators were trained, tested, and certified in the use of the modified Rankin scale according to a method involving the use of a DVD developed specifically for this trial.<sup>9</sup> The NIHSS quantifies the level of neurologic deficit, with higher scores at day 90 predictive of dependence. The Barthel index measures activities of daily living; scores range from 0 to 100, with 0 indicating complete dependence and 100 indicating independence.

**SAFETY ASSESSMENTS**

Vital signs were recorded at enrollment and at specified times throughout the infusion and during the follow-up period. Routine laboratory data were obtained at the time of enrollment and at 24 hours, 72 hours, and 7 days. Electrocardiograms were obtained at enrollment and at 24 hours, 72 hours, and (if the findings at 72 hours were abnormal) 7 days. Laboratory and electrocardiographic results were analyzed centrally. To determine whether NXY-059 had any effect on hemorrhagic transformation (intracerebral hemorrhage) after treatment with alteplase, brain imaging was repeated after 72 hours in patients receiving concomitant alteplase. On the basis of the results of SAINT I, we defined symptomatic intracerebral hemorrhage as a worsening in the NIHSS score by four or more points within 36 hours plus the presence of any blood on imaging after alteplase treatment; asymptomatic intracerebral hemor-

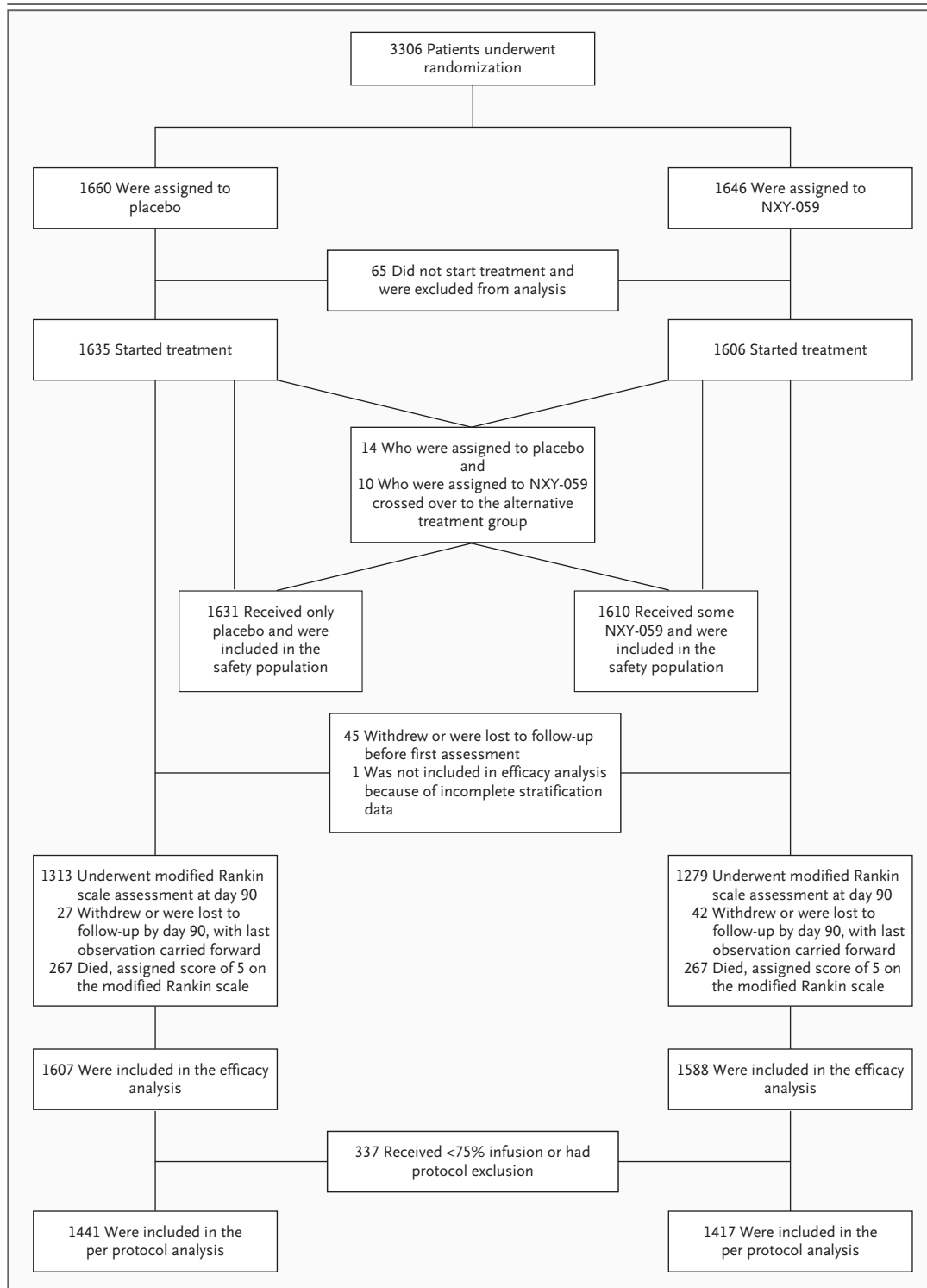
**Figure 1 (facing page). Enrollment, Group Assignment, and Follow-up.**

After randomization, 24 patients received the wrong treatment kit. Fourteen patients assigned to placebo received at least some NXY-059; these patients were considered in the efficacy analysis to have been treated with placebo and were considered in the safety analysis to have been treated with NXY-059. Ten patients assigned to NXY-059 were treated only with placebo; these patients were considered in the efficacy analysis to have been treated with NXY-059 and were considered in the safety analysis to have been treated with placebo. The efficacy analysis included all patients who underwent randomization and received any investigational treatment and for whom stratification data and any post-treatment assessment data were available. The last observation was carried forward for survivors who were unable to undergo assessment with the modified Rankin scale at 90 days. Patients who died were assigned a score of 5 on the scale (worst outcome) and were considered to have a valid assessment; 3126 patients (97.8%) had a valid 90-day assessment, and 69 (2.2%) had an earlier observation carried forward. The per protocol population (2858 patients, 88.2% of all treated patients) consisted of patients for whom there were no major protocol violations and who received at least 75% of the target dose for their rate of creatinine clearance. Patients in whom the study drug was stopped because of progressive stroke or death were retained in the per protocol population.

rhage was defined as the presence of any blood on imaging after alteplase treatment in the absence of such worsening of the NIHSS score.<sup>3</sup> Patients meeting the criterion for progressive stroke (an increase of at least four points on the NIHSS score) or new stroke in the first week also underwent repeated imaging studies. Follow-up scans were read centrally by readers who were unaware of treatment assignments.

**STATISTICAL ANALYSIS**

The analyses were prespecified. For the efficacy analysis, we included all patients with baseline data who had commenced any treatment and had undergone any post-treatment assessment. The patients were analyzed according to the treatment assignment for efficacy outcomes and according to the treatment actually received for safety outcomes. The primary outcome measure was the score on the modified Rankin scale at 90 days or the last rating, analyzed across the whole distribution of scores with the use of the Cochran-Mantel-Haenszel test, with adjustment for stratification variables (NIHSS score, side of the infarct, and use or nonuse of alteplase) and with the use



of modified ridit scores<sup>10</sup> (i.e., the midrank score  $\div$  [the number of observations + 1]), to account for ordered categories. The generalized Cochran–Mantel–Haenszel test is a nonparametric method

linked to the van Elteren test that allowed us to analyze the modified Rankin scale as an ordinal rather than a binary outcome, without assuming proportional odds.<sup>11</sup> Dichotomized and trichoto-

mized scores on the modified Rankin scale were also analyzed.

The sample size of 3200 patients was chosen to provide at least 80% power to detect a common odds ratio of 1.2 (across all cutoff points of the modified Rankin scale), the result that was seen in the SAINT I study.<sup>3</sup> Additional measurements of the modified Rankin scale were completed at 7 and 30 days. Neurologic function was assessed on the basis of the total NIHSS score, the first secondary end point, at 90 days or at the time of the last rating, and it was also analyzed by means of the Cochran–Mantel–Haenszel test with a modified ridit score and adjustment for the baseline NIHSS score, side of the infarct, and use or non-use of alteplase.<sup>10,11</sup>

We ordered the analysis of efficacy outcomes hierarchically, avoiding the need for further adjustment for multiplicity, because formal statistical testing was performed only if the preceding

end point was significant. The primary end point, the score on the modified Rankin scale, was the first outcome, and a positive trial would have been declared if this end point had been significant, irrespective of end points lower in the hierarchy.

Safety end points included death, serious and nonserious adverse events, laboratory measurements, vital signs, and neuroimaging data. The incidence of intracranial hemorrhage in patients who were treated concomitantly with alteplase was prospectively analyzed with the chi-square test. Descriptive statistics (number and frequency) were used to summarize all types of intracranial hemorrhage for each treatment group.

## RESULTS

### BASELINE CHARACTERISTICS

Of the 3306 patients randomly assigned to treatment, 3241 were treated with NXY-059 or placebo (Fig. 1). In 65 patients, the infusion was not started, most commonly because of delayed recognition that the patient did not meet the eligibility criteria (20 patients assigned to NXY-059 and 19 assigned to placebo). The investigators became aware of the study-drug assignment in five cases. End-of-study assessment of drug infusion was completed in 3074 patients (1542 [95.8%] of those receiving NXY-059 and 1532 [93.9%] of those receiving placebo), and 2593 patients (80.0%) completed the 90-day follow-up assessment. Among the 3241 patients treated, modified-Rankin-scale outcome data were unavailable for 46 (23 assigned to NXY-059 and 23 assigned to placebo).

The baseline characteristics of the patients are shown in Table 1. The mean time from the onset of symptoms to the start of infusion of the study drug was 3 hours 48 minutes. A total of 1426 patients (44.0%) received treatment with alteplase. According to extrapolation from measured concentrations, in 96.6% of NXY-059–treated patients, a target plasma unbound concentration of 150  $\mu\text{mol}$  per liter was reached, which is well above the levels that have been shown to be neuroprotective in animal models of stroke.

### CLINICAL OUTCOMES

The distribution of scores on the modified Rankin scale at 90 days was similar in the two groups ( $P=0.33$  by the Cochran–Mantel–Haenszel test; number of patients, 3195; odds ratio for a favor-

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Placebo (N=1631)	NXY-059 (N=1610)
Mean age — yr	69.0	68.8
Male sex — no. (%)	870 (53.3)	898 (55.8)
Mean time from onset of stroke to treatment — hr:min	3:49	3:46
Mean NIHSS score	13.0	13.0
Treatment or intention to treat with alteplase — no. (%)	716 (43.9)	710 (44.1)
Mean time from onset of stroke to administration of alteplase — hr:min	2:24	2:22
Mean age — yr	68.6	67.7
Mean NIHSS score at trial entry	13.8	14.1
History — no. (%)		
Hypertension	1246 (76.4)	1243 (77.2)
Stroke	356 (21.8)	357 (22.2)
Transient ischemic attack	161 (9.9)	135 (8.4)
Ischemic heart disease	536 (32.9)	531 (33.0)
Atrial fibrillation	499 (30.6)	438 (27.2)
Diabetes mellitus	406 (24.9)	386 (24.0)
Use of antiplatelet drugs	566 (34.7)	590 (36.6)
Cardioembolic stroke†	775 (47.6)	738 (46.1)

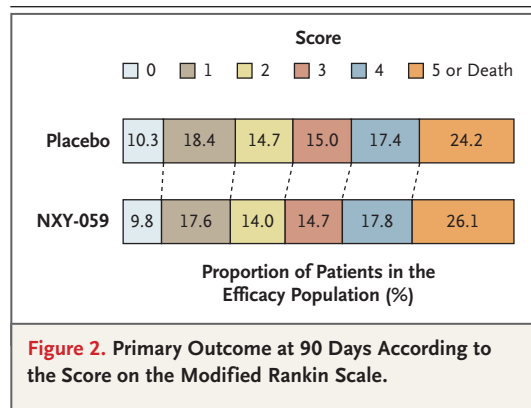
\* Scores on the NIHSS (National Institutes of Health Stroke Scale) range from 0, indicating normal functioning, to 42, indicating most severe impairment.

† Percentages are based on 1627 patients in the placebo group and 1600 in the NXY-059 group.

able outcome, 0.94; 95% confidence interval [CI], 0.83 to 1.06) (Fig. 2). We evaluated all possible dichotomizations of the scale as well as the trichotomization into categories 0 to 1, 2 to 3, and 4 to 5, as has been tested elsewhere.<sup>3</sup> There were no significant differences between the two groups in any of the cutoff points: the P value for the trichotomization was 0.23 (odds ratio, 0.92; 95% CI, 0.80 to 1.06). Analysis of the group of patients who received at least 75% of the infusion and who were in full compliance with the protocol also did not show a significant difference between the two groups (P=0.25 by the Cochran-Mantel-Haenszel test; odds ratio, 0.93; 95% CI, 0.81 to 1.06). There was no improvement in disability among survivors in the NXY-059 group at 7, 30, or 90 days, as measured by the Cochran-Mantel-Haenszel test (day 90, P=0.53; odds ratio, 0.96; 95% CI, 0.83 to 1.10).

NXY-059 had no effect on any of the pre-specified secondary end points. The total NIHSS score at the last rating in the NXY-059 group was not significantly different from that in the placebo group (P=0.73 by the Cochran-Mantel-Haenszel test; Mann-Whitney U statistic, 0.50; 95% CI, 0.48 to 0.52).

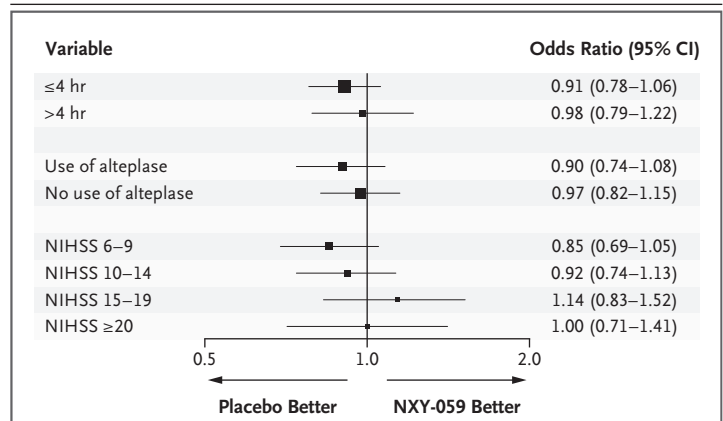
In addition, there was no significant difference between the groups in the percentage of patients who had a complete recovery, as measured by an NIHSS score of 0 versus 1 to 42 (16.3% in the NXY-059 group and 16.6% in the placebo group), or a nearly complete recovery, as measured by an NIHSS score of 0 to 1 versus 2 to 42 (27.6% in both groups). Finally, there was no significant difference between the groups in the percentage of patients with a Barthel index score of 95 or more (40.9% in the NXY-059 group and 42.3% in the placebo group).



There were no significant interactions between the treatment effect of NXY-059 and the time from the onset of symptoms to treatment (4 hours or less vs. more than 4 hours), presence of diabetes or hypertension, severity of stroke, or use of alteplase (Fig. 3).

**SAFETY ANALYSIS**

There were 534 deaths, 267 in each treatment group (16.5% of patients). The mean (±SE) time from randomization to death was 24.3±1.4 days in the NXY-059 group and 21.9±1.4 days in the placebo group (P=0.98 by the log-rank test). Few deaths were reported during the drug infusion: 18 in the NXY-059 group (1.1%) and 18 in the placebo group (1.1%). The most common causes of death were neurologic damage from the initial stroke (in 83 patients in the NXY-059 group [31.1%] and 107 in the placebo group [40.1%]) and bronchopneumonia (41 in the NXY-059 group [15.4%] and 34 in the placebo group [12.7%]). Adverse events were reported in 84.2% of patients in the NXY-059 group and 84.5% of patients in



**Figure 3. Treatment Interactions with Important Covariates.**

There was no significant interaction with any stratification variable or pre-specified covariate. The primary outcome measure was the score on the modified Rankin scale at 90 days or the last rating, as analyzed with the Cochran-Mantel-Haenszel test with a modified ridit score, adjusted for baseline stratification variables. The Cochran-Mantel-Haenszel test considers the full range of the modified Rankin scale, with deaths assigned a modified Rankin score of 5. Odds ratios were estimated by logistic regression, adjusted for baseline stratification variables, and are shown with their estimated 95% confidence intervals. Interactions between covariates and treatment effect were analyzed with the Cochran-Mantel-Haenszel test: P=0.82 for time to treatment, P=0.61 for use of alteplase, and P=0.70 for severity of stroke according to the National Institutes of Health Stroke Scale (NIHSS) category. Since none of these were significant, the individual odds ratios and their 95% confidence intervals are provided only for illustration. The size of the squares corresponds to the size of each subgroup.

the placebo group. Serious adverse events were reported in 39.6% of patients in the NXY-059 group and 40.2% of patients in the placebo group (Table 2). The percentage of patients who discontinued medication was 4.5% in the NXY-059 group and 6.3% in the placebo group. The only adverse event that occurred significantly more frequently in the NXY-059 group than in the placebo group was hypokalemia. Hypokalemia occurred in 12.1% of NXY-059–treated and 9.2% of placebo-treated patients at any stage and in 9.1% and 6.3% of patients, respectively, during the infusion but was not associated with any cardiac or

other complications. Hypokalemia resolved within 7 days.

In our prespecified analysis of patients treated with alteplase, there were no significant differences between the NXY-059 group and the placebo group in the percentage of patients with symptomatic cerebral hemorrhage (4.6% and 5.3%, respectively;  $P=0.57$ ), asymptomatic cerebral hemorrhage (17.9% and 16.1%, post hoc analysis), or overall cerebral hemorrhage (22.5% vs. 21.4%,  $P=0.60$ ).

## DISCUSSION

This second trial of NXY-059 included a generous sample of patients with acute ischemic stroke. Although the trial was adequately powered to detect a clinically useful difference in the primary end point, the modified Rankin score, we failed to confirm the efficacy of NXY-059.

SAINT I showed promising results, with reduction of global disability.<sup>3</sup> The effect on disability was moderate but was thought to be consistent with a neuroprotective action. Although there were no significant effects on the prespecified secondary end points, post hoc analyses showed supportive trends for other end points.<sup>4</sup> Moreover, patients treated with alteplase and NXY-059 had fewer cerebral hemorrhages.<sup>3</sup> We had refined the SAINT II protocol after the successful SAINT I trial; changes included an increase in the sample size from 1700 to 3200 patients, a revised approach to analysis of the NIHSS score, and a prospective analysis of intracerebral hemorrhage. However, none of the benefits demonstrated in SAINT I were confirmed in the SAINT II study. With the exception of mild, asymptomatic hypokalemia, the numbers and types of adverse events and serious adverse events, including neurologic events, were similar in the two groups.

Faced with conflicting results from the two pivotal trials of NXY-059, we must examine possible explanations. These trials followed nearly identical protocols, with minimal differences in statistical analysis. With the exception of a higher frequency of alteplase use in SAINT II (44% vs. 29%), the baseline characteristics and demographic features of the study populations were similar. In both trials, the average time to treatment was less than 4 hours and target plasma drug concentrations were achieved and maintained in more than 95% of patients.

**Table 2. Safety Outcomes Recorded during 90 Days of Follow-up.\***

Variable	Placebo (N=1631)	NXY-059 (N=1610)
	no. (%)	
<b>Serious adverse events</b>		
Stroke in evolution	157 (9.6)	150 (9.3)
Ischemic stroke	62 (3.8)	55 (3.4)
Pneumonia	37 (2.3)	39 (2.4)
Hemorrhagic transformation stroke	28 (1.7)	30 (1.9)
Aspiration pneumonia	20 (1.2)	26 (1.6)
Brain edema	28 (1.7)	24 (1.5)
Cerebral hemorrhage	25 (1.5)	23 (1.4)
Sepsis	9 (0.6)	22 (1.4)
Myocardial infarction	25 (1.5)	18 (1.1)
Atrial fibrillation	7 (0.4)	16 (1.0)
<b>Adverse events</b>		
Pyrexia	268 (16.4)	289 (17.9)
Headache	227 (13.9)	256 (15.9)
Hypokalemia	150 (9.2)	195 (12.1)
Constipation	151 (9.3)	170 (10.6)
Urinary tract infection	161 (9.9)	164 (10.2)
Stroke in evolution	164 (10.1)	152 (9.4)
Atrial fibrillation	103 (6.3)	111 (6.9)
Nausea	113 (6.9)	111 (6.9)
Pneumonia	90 (5.5)	103 (6.4)
Insomnia	79 (4.8)	101 (6.3)

\* The events included are the 10 most common serious adverse events and the 10 most common adverse events in the NXY-059 group (adverse events include those that were also coded as serious). In the analysis of safety, patients were considered as treated and not as randomly assigned to treatment. Because of the large number of potential adverse events that could be examined (>100), formal statistical testing was not conducted; as a guide, a difference of 1.5% or more between groups will occur with a probability of approximately 0.05 before adjustment for multiplicity.

We first considered whether the conflicting results of the two trials might be related to the higher rate of alteplase use in SAINT II. However, we found no evidence of an interaction between alteplase use and the effect of NXY-059 in either trial. Although we cannot completely rule out a ceiling effect in SAINT II resulting from an already maximal improvement due to alteplase use, monotherapy with NXY-059 was also ineffective. From these data, we cannot draw any conclusion about the arguments for or against including patients treated with alteplase in future trials of putative neuroprotectants.

We did not use perfusion imaging as a selection criterion for this trial. It is conceivable that any treatment effect might have been diluted by the inclusion of patients with established infarction or without a perfusion deficit at the time of randomization. However, because of the large sample size and the expectedly high proportion of patients in whom penumbra would still have been present within 4 hours after the onset of stroke, we do not think that the use of imaging would have transformed the outcome of this trial. In addition, we did not collect data on the subtype of stroke, but we find no evidence from our data on the severity of stroke that the treatment effect was likely to have been influenced by the subtype of stroke.

We do not consider that our statistical approach was responsible for the false positive result in SAINT I. In both trials, the same method was used to analyze the results for the primary end point — namely, comparison of the distribution of disability scores rather than simple dichotomy. Our analysis takes into account any potential harm by requiring that any deleterious effect at one end of the scale be more than balanced by a benefit at other levels if significance is to be achieved. We consider that the disparity between the two studies occurred by chance, possibly because of the inclusion of patients with a latent poorer prognosis in the placebo group in SAINT I. However, there was no notable imbalance between the treatment groups with respect to any single measured variable or combination of variables. The likelihood that our prior trial was positive simply because of the play of chance underscores the need for replication by a second pivotal trial.

The observed reduction in the rate of hemorrhagic transformation associated with NXY-059

after thrombolysis in SAINT I was biologically plausible, given the role of free-radical-mediated disruption of the blood-brain barrier. Vasculoprotection with NXY-059 during thrombolysis was consistent with the putative mechanism of the drug.<sup>12,13</sup> The absence of this finding in SAINT II provides further confirmation of the discrepancy between the trials and suggests that this was also a chance finding or the result of differences in the study populations.

Stroke Therapy Academic Industry Roundtable (STAIR) criteria were designed to help in the development of drug therapy for acute stroke.<sup>14-16</sup> Even though it met all these criteria, the SAINT II study showed no significant effect in patients with acute ischemic stroke. It is possible that the animal models of acute focal infarction are not relevant to the patient population; they certainly are insufficient to guarantee a positive clinical-trial result. The molecular heterogeneity and pharmacodynamics in elderly patients may differ from those in the healthy and relatively young animals used for preclinical studies. The clear failure to demonstrate a benefit of NXY-059 in the SAINT II study suggests that we need to reevaluate the strategies that have been used in the development of drugs for neuroprotection. More emphasis on phase 2 studies in patients, involving a surrogate outcome measure that is more sensitive to treatment effects even if it is not acceptable for drug-registration purposes, may be necessary to supplement the preclinical data.<sup>17</sup>

In summary, SAINT II provides clear evidence that the promise offered by the preclinical data and the positive findings of SAINT I has been a false dawn. The most reasonable interpretation is that NXY-059 is safe but ineffective for the treatment of acute ischemic stroke.

Drs. Lees, Grotta, and Davis report receiving fees and expenses from AstraZeneca for steering-committee work and lectures. Dr. Davis reports receiving consulting or speaking fees from Novo Nordisk, Pfizer, Sanofi-Aventis, Bristol-Myers Squibb, Boehringer Ingelheim, Paion, and Servier; Dr. Davalos, consulting or speaking fees AstraZeneca, Boehringer Ingelheim, Pfizer, Merck Sharpe & Dohme, Sanofi-Synthelabo, Bristol-Myers Squibb, Bayer, Paion, Forest Pharmaceuticals, Daiichi Asubio, Eli Lilly, Fujisawa, Novo Nordisk, and Ferrer International; Dr. Diener, consulting or speaking fees from AstraZeneca, Glaxo-SmithKline, Boehringer Ingelheim, BASE, Abbott, Novartis, Parke-Davis, Merck Sharpe & Dohme, Servier, Sanofi-Synthelabo, Bayer, Fresenius, and Janssen-Cilag; Dr. Lyden, consulting or speaking fees from AstraZeneca, Bayer, Mitsubishi, Pfizer, Lilly, and Merck and research contracts with AstraZeneca and Bayer; Dr. Grotta, research support from AstraZeneca, Novo-Nordisk, and Boehringer Ingelheim; and Dr. Shuaib, consulting or

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the manuscript. No other potential conflict of interest relevant to this article was reported.

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APPENDIX

The following investigators participated in the SAINT II trial: *Steering committee* — K.R. Lees, Glasgow, United Kingdom (chair); A. Shuaib (principal investigator), Edmonton, AB, Canada; T. Ashwood, Södertälje, Sweden (sponsor representative); A. Davalos, Barcelona; S. Davis, Melbourne, Australia; H.C. Diener, Essen, Germany; J. Grotta, Houston; P. Lyden, San Diego, CA; W. Wasiewski, Wilmington, DE (sponsor representative). *Data and safety monitoring board* — S. Pocock, London (chair); H. Adams, Iowa City, IA; P. Bath, Nottingham, United Kingdom; D. Oakes, Rochester, NY; N.G. Wahlgren, Stockholm. *Study team leader* — C. Baker, Wilmington, DE. *Study team physicians* — W.W. Wasiewski, Wilmington, DE; L. Rodichok, Wilmington, DE; H.G. Hardemark, Södertälje, Sweden. *Study team statisticians* — V. Alderfer, Wilmington, DE; U. 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