

ORIGINAL ARTICLE

NXY-059 for Acute Ischemic Stroke

Kennedy R. Lees, M.D., Justin A. Zivin, M.D., Tim Ashwood, Ph.D., Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D., James Grotta, M.D., Patrick Lyden, M.D., Ashfaq Shuaib, M.D., Hans-Göran Hårdemark, M.D., and Warren W. Wasiewski, M.D., for the Stroke–Acute Ischemic NXY Treatment (SAINT I) Trial Investigators*

ABSTRACT

BACKGROUND

From the Acute Stroke Unit and Cerebrovascular Clinic, University Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, Glasgow (K.R.L.); the Department of Neurosciences, University of California, San Diego, La Jolla (J.A.Z.); AstraZeneca Research and Development Södertälje, Medical Neuroscience, Södertälje, Sweden (T.A., H.-G.H.); the Department of Neurosciences, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain (A.D.); the Department of Neurology, Royal Melbourne Hospital, University of Melbourne, Parkville, Melbourne, Victoria, Australia (S.M.D.); the Department of Neurology, University Duisburg-Essen, Essen, Germany (H.-C.D.); the Department of Neurology, University of Texas–Houston Medical School, Houston (J.G.); University of California, San Diego, Stroke Center, La Jolla (P.L.); the Department of Neurology, University of Alberta, Edmonton, Alta., Canada (A.S.); and AstraZeneca, Clinical Research, Emerging Products, Wilmington, Del. (W.W.W.). Address reprint requests to Dr. Lees at the Acute Stroke Unit and Cerebrovascular Clinic, University Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, 44 Church St., Glasgow G11 6NT, United Kingdom, or at k.r.lees@clinmed.gla.ac.uk.

*The investigators and institutions participating in the SAINT I trial are listed in the Appendix.

N Engl J Med 2006;354:588-600.
Copyright © 2006 Massachusetts Medical Society.

NXY-059 is a free-radical-trapping agent that is neuroprotective in animal models of stroke. We tested whether it would reduce disability in humans after acute ischemic stroke.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial involving 1722 patients with acute ischemic stroke who were randomly assigned to receive a 72-hour infusion of placebo or intravenous NXY-059 within 6 hours after the onset of the stroke. The primary outcome was disability at 90 days, as measured according to scores on the modified Rankin scale for disability (range, 0 to 5, with 0 indicating no residual symptoms and 5 indicating bedbound, requiring constant care).

RESULTS

Among the 1699 subjects included in the efficacy analysis, NXY-059 significantly improved the overall distribution of scores on the modified Rankin scale, as compared with placebo ($P=0.038$ by the Cochran–Mantel–Haenszel test). The common odds ratio for improvement across all categories of the scale was 1.20 (95 percent confidence interval, 1.01 to 1.42). Mortality and rates of serious and nonserious adverse events were each similar in the two groups. NXY-059 did not improve neurologic functioning as measured according to the National Institutes of Health Stroke Scale (NIHSS): the difference between the two groups in the change from baseline scores was 0.1 point (95 percent confidence interval, -1.4 to 1.1 ; $P=0.86$). Likewise, no improvement was observed according to the Barthel index ($P=0.14$). In a post hoc analysis of patients who also received alteplase, NXY-059 was associated with a lower incidence of any hemorrhagic transformation ($P=0.001$) and symptomatic intracranial hemorrhage ($P=0.036$).

CONCLUSIONS

The administration of NXY-059 within six hours after the onset of acute ischemic stroke significantly improved the primary outcome (reduced disability at 90 days), but it did not significantly improve other outcome measures, including neurologic functioning as measured by the NIHSS score. Additional research is needed to confirm whether NXY-059 is beneficial in ischemic stroke. (ClinicalTrials.gov number, NCT00119626.)

ACUTE STROKE IS THE SECOND LEADING cause of death in industrialized countries¹ and the leading medical cause of acquired adult disability. Rapid intervention after the onset of a stroke can limit neurologic damage and improve patients' recovery of functioning.² In most countries, only thrombolysis with the use of alteplase is currently approved for treatment, and it must be initiated within the first three hours after the onset of an acute ischemic stroke. The brief window of time and a perceived risk of bleeding, along with an absolute necessity for neuroimaging before the treatment can be initiated and the required training in the use of alteplase, have limited its application to less than 5 percent of patients with stroke, even in the United States.³ There is a pressing need for a more widely applicable therapy.

So far, neuroprotection in patients with stroke has been unsuccessful.^{4,5} To help in the identification of potential treatments, the Stroke Therapy Academic Industry Roundtable (STAIR) group has recommended criteria that should be met before a putative neuroprotectant is evaluated in advanced clinical trials.⁶ A major contributor to brain injury after stroke is tissue oxidation as a result of processes initiated by free radicals. Studies in genetically modified mice that overexpress or are deficient in antioxidant proteins indicate that the capacity for an antioxidant defense critically influences the extent of permanent brain damage after ischemia.⁷ NXY-059 is a free-radical-trapping agent⁸ that reduces the size of the infarct and preserves brain functioning in animal models of acute ischemic stroke and is a neuroprotectant that meets the STAIR criteria.^{6,9-16}

We report the results of the Stroke-Acute Ischemic NXY Treatment (SAINT I) study, the first of two efficacy trials involving patients with acute ischemic stroke, in which clinically attainable plasma concentrations of the study drug were used that have an acceptable adverse-event profile.^{17,18}

METHODS

STUDY DESIGN

We conducted a randomized, double-blind, placebo-controlled trial in which patients were enrolled from May 2003 through November 2004 at 158 hospitals in 24 countries. The trial was approved by local and national institutional review

boards, and informed consent was obtained from the patients or from legally acceptable surrogates. The steering committee developed the trial protocol, approved the statistical plan, had full access to the data, wrote the manuscript, and was responsible for decisions with regard to publication. The academic authors vouch for the veracity and completeness of the data and the data analyses. An independent data safety monitoring board conducted safety reviews and a futility analysis.

PATIENTS

Patients were eligible if they were conscious, were 18 or more years of age, had a clinical diagnosis of acute stroke that had commenced within the six hours before entry into the study, had limb weakness, and had a score of at least 6 on the National Institutes of Health Stroke Scale (NIHSS).

STUDY INTERVENTION

Patients were randomly assigned to receive an intravenous infusion of either NXY-059 or placebo within six hours after the onset of the stroke, but each site was required to maintain an average time from onset of the stroke to treatment of no more than four hours. Randomization was performed by telephone with the use of a central interactive voice-response system that was accessed by the investigators. Patients undergoing randomization were stratified according to country, NIHSS score at baseline, side of cerebral infarct, and intention to treat with alteplase; we used a dynamic algorithm to maintain a balance of prognostic factors between the two study groups.¹⁹ The study drug was supplied as a concentrate to be diluted to 15 mg per milliliter in 500 ml of a solution of 0.9 percent saline. The vials containing the study drug and the placebo were visually identical. Apart from 11 documented cases, investigators and assessors were unaware of the treatment assignments throughout the trial until after the database was locked; no laboratory test or adverse event was known to distinguish the active drug from the placebo. The initial infusion rate was 2270 mg (5940 μmol) per hour, reduced after 1 hour to 480 to 960 mg (1260 to 2520 μmol) (32 to 64 ml) per hour for a further 71 hours, with the aim of maintaining a target concentration of 260 μmol per liter. An estimated rate of creatinine clearance based on the serum creatinine concentration²⁰ guided the rate adjustment (to 44 ml per hour for an estimated rate of creatinine clearance of 51 to 80 ml per minute, and

32 ml per hour for an estimated rate of creatinine clearance of 30 to 50 ml per minute) within the first four hours; patients with an estimated rate of creatinine clearance below 30 ml per minute were withdrawn from the study treatment. In all other respects, patients received the standard of care for acute stroke.

CLINICAL ASSESSMENT

Patients were formally assessed at enrollment, at 24 and 72 hours after enrollment, and at 7, 30, and 90 days. The initial assessments were focused on the severity of the stroke according to scores on the NIHSS (scores range from 0 to 42, with higher scores indicating increasing severity) and were performed by observers trained and certified in the use of this scale.²¹ Assessments during follow-up included functional measures, primarily the score on the modified Rankin scale (with a range from 0, indicating no residual symptoms, to 5, indicating bedbound, requiring constant care) and the Barthel index (with a range from 0 to 100, with 100 indicating no deficit and 0 indicating complete dependence).^{22,23} Investigators were trained, tested, and certified in the use of the modified Rankin scale, according to a method involving a DVD developed specifically for this trial.

Lower in our hierarchy of tests were two additional outcome measures, the Stroke Impact Scale (SIS) and the European Quality of Life-5 Dimensions (EuroQoL EQ-5D) instrument for assessing health status and the health-related quality of life. Scores on the SIS and EuroQoL EQ-5D visual-analogue scale range from 0 to 100, with lower numbers indicating a worse quality of life. Scores on the EuroQoL EQ-5D weighted index range from -0.59 to 1.0, with negative scores associated with a quality of life that is considered worse than death.

SAFETY ASSESSMENTS

While patients were receiving infusions, vital signs and adverse events were recorded regularly. Samples for routine laboratory tests obtained at enrollment, at 24 hours after the onset of the stroke, at a further 72 hours, and at day 7 were analyzed centrally. To assess any effect of NXY-059 on hemorrhagic transformation after the administration of alteplase, neuroimaging was repeated after 72 hours in patients receiving treatment with alteplase. Patients meeting the criteria for progressive stroke (an increase in the NIHSS score of 4 points) or a new stroke during the first

week also underwent follow-up imaging. Follow-up scans were read centrally by a radiologist who was unaware of the treatment allocation.

STATISTICAL ANALYSIS

The statistical analyses were prespecified and followed the intention-to-treat principle. The primary end point 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 of alteplase), and with the use of modified ridit scores (i.e., midrank score divided by [the number of observations + 1]), to account for ordered categories.²⁴ Odds ratios were calculated with the use of proportional-odds logistic regression, assuming a common odds ratio across all cut points of the modified Rankin scale, and are provided only as an estimate of the treatment effect. The odds ratios were adjusted in the same way as for the primary end point. The sample size was chosen to provide 90 percent power to detect a common odds ratio for reduction of disability at 90 days of 1.3. Deaths were included in the category of worst outcome (a modified Rankin scale score of 5).

The change from the baseline NIHSS score (termed coprimary in the study protocol) was estimated by analysis of covariance with adjustment for baseline variables (baseline scores on the NIHSS, the side of infarct, and the use of alteplase); deaths from any cause were scored as 42 (worst) on the NIHSS.

Analysis of efficacy outcomes was ordered hierarchically, and formal statistical testing was performed only if the preceding end point in the hierarchy of end points was significant, with nominal P values reported beyond that point. The primary end point (modified Rankin scale) was the first in the hierarchy of end points, and the trial was considered positive if this end point was found to be significant, irrespective of end points lower in the hierarchy.²⁵ Neurologic functioning was deemed to be an important supporting outcome measure of stroke recovery. However, the classification of the NIHSS as the coprimary end point in the study protocol was not intended to imply joint testing with the modified Rankin scale; instead, the intention was for the NIHSS to serve as the principal end point among the secondary end points, and thus as second in the overall hierarchy of end points.

For the safety analysis, patients were considered as treated, whereas for the efficacy analyses, they were considered as randomized. The safety end points included death, serious and nonserious adverse events, laboratory values, vital signs, and neuroimaging data — neuroimaging especially for patients receiving thrombolysis. Analyses conducted post hoc included the comparison of the rates of hemorrhagic transformation after receipt of alteplase and nonparametric approaches to the examination of the NIHSS data.

The academic authors assume full responsibility

for the completeness, integrity, and interpretation of the data. The sponsor, AstraZeneca, was responsible for operational aspects of the trial, including the data collection, the data storage, and the analysis, according to the approved study plan.

RESULTS

BASELINE CHARACTERISTICS

Of 1722 patients who underwent randomization, 1705 received a study infusion; 287 died, and 1387

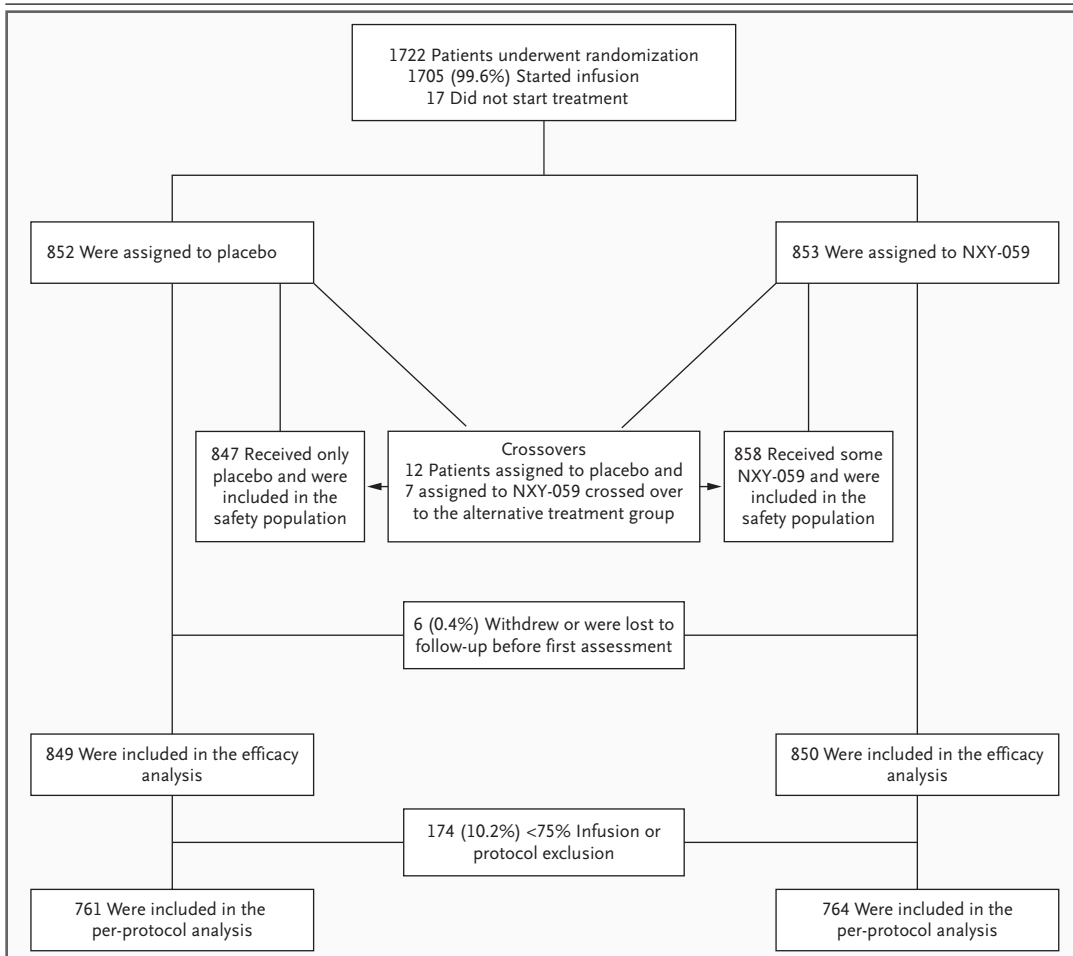


Figure 1. Disposition of Patients in the Study.

After randomization, 30 patients received the wrong treatment kit and 7 received treatment from more than one kit. Of these 37 patients, 21 had been assigned to receive placebo and 16 to receive NXY-059. Of the 21 patients in the placebo group, 12 received some NXY-059 and 7 of the 16 patients in the NXY-059 group received only placebo. For the efficacy analyses, data on patients were analyzed according to treatment assignment. Among the patients included in the safety analysis, there was a net shift of five patients to the NXY-059 group. For three patients in each group there was no follow-up information after the patients received the infusion, and these patients were excluded from the efficacy analyses, leaving 99.6 percent of the patients in the analyses. The per-protocol population (1525 patients; 89.4 percent of all treated patients) comprised patients who did not have major violations of the study protocol. The main reason for exclusion was that the infusion was stopped for technical or other reasons not primarily related to the stroke before at least 75 percent of the target dose was administered.

completed the 90 days of follow-up. Of the 1705 patients treated, outcome data were not available for 6; thus, 1699 patients were included in the efficacy analysis. Of these 1699 patients, 850 received NXY-059 and 849 received placebo (Fig. 1). In the trial population, the mean age was 68.4 years, and 947 of the 1705 patients (55.5 percent) were men. The two study groups were well balanced with respect to baseline prognostic variables (Table 1). The mean time from the onset of stroke to treatment was 3 hours 46 minutes, and 28.7 percent of the patients received treatment with alteplase. Approximately 96 percent of the patients assigned to NXY-059 achieved an unbound, steady-state plasma concentration of NXY-059 greater than 150 μmol per liter.

CLINICAL OUTCOMES

Among patients who received NXY-059, the distribution of scores on the modified Rankin scale for the primary end point of disability at 90 days was improved, as compared with the placebo group ($P=0.038$ by the Cochran–Mantel–Haenszel test) (Fig. 2). The odds for improvement integrat-

ed across all cut points of the scale were increased by NXY-059, as compared with placebo (odds ratio, 1.20; 95 percent confidence interval, 1.01 to 1.42). The primary analysis considered the full distribution of scores on the modified Rankin scale, but the difference when we categorized the scores into 0 to 1 versus 2 to 3 versus 4 to 5, as used elsewhere,⁴ was significant ($P=0.03$) and two of the five possible separate dichotomizations were also significant: a further 3.7 percent of patients recovered the ability to walk (modified Rankin scale score, ≤ 3 ; $P=0.02$) and a further 4.4 percent of patients were completely cured (modified Rankin scale score, 0; $P=0.003$). In an analysis of the distribution of the scores in the per-protocol population, the benefit remained (Cochran–Mantel–Haenszel test, $P=0.028$) (Fig. 2). Consistent with findings at 90 days, NXY-059 improved outcomes at 7 and 30 days (odds ratio, 1.31; 95 percent confidence interval, 1.09 to 1.57; and odds ratio, 1.27; 95 percent confidence interval, 1.07 to 1.52, respectively). Among survivors, functional outcome, as measured on the modified Rankin scale and analyzed by the Cochran–Mantel–Haenszel test, was improved ($P=0.007$).

NXY-059 had no effect on the prespecified analysis of the coprimary neurologic end point: the difference between the two groups in the change from baseline was only 0.1 point in the average NIHSS score (95 percent confidence interval, -1.4 to 1.1 ; $P=0.86$). NIHSS scores showed a skewed bimodal distribution, which may have compromised the planned parametric analysis; however, a post hoc nonparametric analysis of the scores (by the Cochran–Mantel–Haenszel test, as used for the analysis of scores according to the modified Rankin scale) was also not statistically significant ($P=0.10$). In additional post hoc analyses, complete neurologic recovery (NIHSS score, 0) was more common after treatment with NXY-059 (21.9 percent of those in the NXY-059 group and 17.3 percent of those in the placebo group; odds ratio, 1.39; 95 percent confidence interval, 1.08 to 1.79; $P=0.01$), but the difference between the two groups in the frequency of excellent neurologic outcomes (NIHSS score, 0 or 1) was not statistically significant (33.1 percent in the NXY-059 group vs. 30.9 percent in the placebo group; odds ratio, 1.13; 95 percent confidence interval, 0.90 to 1.41; $P=0.28$). We did not intend to test scores according to the Barthel index or other secondary end points formally unless end

Table 1. Baseline Characteristics of Patients Included in the Safety Analysis *

Characteristic	Placebo Group (N=847)	NXY-059 Group (N=858)
Mean age — yr	68.5	68.4
Male sex — no. (%)	472 (55.7)	475 (55.4)
Mean time from onset of stroke to treatment (hr:min)	3:47	3:45
Mean NIHSS score	12.5	12.6
Treated with alteplase — no. (%)	249 (29.4)	240 (28.0)
Mean time to administration of alteplase — hr:min	2:26	2:27
Mean age — yr	66.3	65.8
Mean NIHSS score at trial entry	14.5	14.1
History — no. (%)		
Hypertension	585 (69.1)	591 (68.9)
Previous stroke	141 (16.6)	125 (14.6)
Previous TIA	84 (9.9)	95 (11.1)
Ischemic heart disease	284 (33.5)	275 (32.1)
Atrial fibrillation	269 (31.8)	240 (28.0)
Diabetes mellitus	182 (21.5)	161 (18.8)
Use of antiplatelet drugs	273 (32.2)	240 (28.0)
Cardioembolic stroke	378 (44.9)	360 (42.1)

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

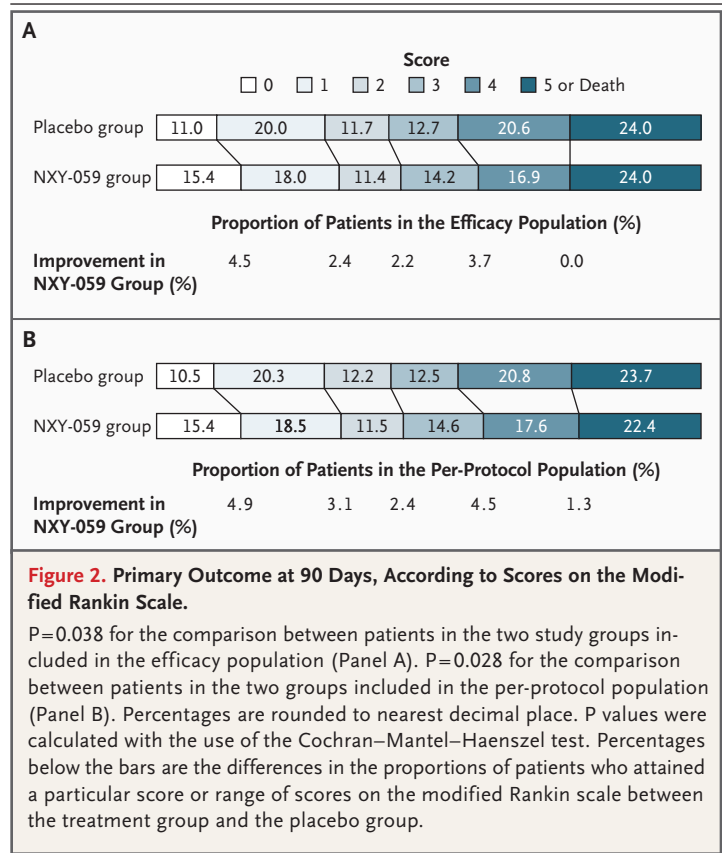
points with higher priority were significant, but most nominal P values were greater than 0.05 (Table 2).

There was no significant interaction between the treatment effect of the investigational drug and stroke severity, treatment with alteplase, or time from the onset of stroke to treatment, indicating that the treatment benefit is present irrespective of these factors (P=0.72, P=0.93, and P=0.92, respectively, for interaction). Such analyses inevitably have low power, however, especially because the distribution of times from the onset of stroke to treatment is narrow and the proportion of patients receiving alteplase was small. We explored analyses of numerous other subgroups to assess the effect of baseline prognostic factors or coexisting conditions on the treatment effect but found no evidence of nominal significance for any biologically likely factor.

SAFETY ANALYSIS

Mortality was unaltered by treatment with NXY-059 (146 patients [17.0 percent] died in the NXY-059 group and 141 patients [16.6 percent] in the placebo group; P=0.89 by the log-rank test) (Fig. 3). Slightly fewer patients in the NXY-059 group had adverse events than in the placebo group (662 vs. 670, respectively; 295 vs. 313 patients, respectively, had serious adverse events). Fewer patients in the NXY-059 group discontinued treatment because of adverse events than in the placebo group (45 vs. 60, respectively). With few exceptions (such as hypokalemia during infusion, which occurred in 6.4 percent of patients receiving NXY-059, as compared with 4.4 percent receiving placebo), there was no imbalance between the two groups in any adverse event and no significant change in routine laboratory values (Table 3).

In the post hoc analysis of patients treated with alteplase, hemorrhagic transformation was less common among those receiving alteplase and NXY-059 than among those receiving alteplase and placebo (P=0.001). Symptomatic hemorrhagic transformation (an increase in the NIHSS score of at least 4 points within 36 hours plus any blood on neuroimaging after receipt of alteplase) occurred in 6 of 240 patients who received NXY-059 (2.5 percent) and 16 of 249 patients assigned to placebo (6.4 percent) (P=0.036); asymptomatic hemorrhage occurred in 31 of 240 patients who received alteplase and NXY-059 (12.9 percent) and 52 of 249 patients who received al-



teplase and placebo (20.9 percent). Among those not receiving thrombolysis, computed tomographic scanning prompted by neurologic deterioration or other clinical indications occurred equally commonly in the two groups (69 of 618 patients in the NXY-059 group [11.2 percent] vs. 65 of 598 patients in the placebo group [10.9 percent]). Of those who received NXY-059, 20 patients of the 69 (29 percent) had any form of intracranial hemorrhage, as compared with 20 patients of the 65 (31 percent) in the placebo group.

DISCUSSION

This trial of NXY-059 for acute ischemic stroke showed a benefit in terms of the prespecified primary end point, a reduction in disability as measured by the modified Rankin score at 90 days. This benefit was seen at both ends of the scale: 4.4 percent more patients who received the study drug became asymptomatic (modified Rankin score, 0), and 3.7 percent more were able to walk without help (score, 0 to 3), as compared with those in the placebo group.

Table 2. Efficacy of the Study Drug at Day 90 or at the Last Rating.*

Outcome Variable	Placebo Group	NXY-059 Group	Difference between NXY-059 and Placebo† % or score (95% CI)	P Value
Modified Rankin scale score (primary end point)				
No. of patients	849	850		
Score — no. (%)				
0	93 (11.0)	131 (15.4)	4.4	
1	170 (20.0)	153 (18.0)	-2.0	
2	99 (11.7)	97 (11.4)	-0.3	
3	108 (12.7)	121 (14.2)	1.5	
4	175 (20.6)	144 (16.9)	-3.7	
5 (or death)	204 (24.0)	204 (24.0)	0	0.038
Change from baseline in total NIHSS score (coprimary outcome)				
No. of patients	851	851		
Score — LSM ±SE	-1.7±0.5	-1.8±0.5	-0.1 (-1.4 to 1.1)	0.86
Barthel index (dichotomized analysis)				
No. of patients	848	850		
Score, ≥95 — no. (%)	346 (40.8)	368 (43.3)	2.5	0.14
Stroke Impact Scale				
No. of patients	676	669		
Score — LSM ±SE	63.4±1.1	66.2±1.1	2.8 (-0.3 to 5.9)	0.08
EuroQoL EQ-5D (weighted index)				
No. of patients	816	819		
Score — LSM ±SE	0.43±0.013	0.47±0.013	0.04 (-0 to 0.07)	0.06
EuroQoL EQ-5D (VAS)				
No. of patients	671	670		
Score — LSM ±SE	62.0±0.9	64.5±0.9	2.5 (-0.1 to 5.0)	0.05

The planned coprimary analysis with the use of a scoring system for neurologic functioning (NIHSS) did not show a significant benefit of NXY-059, however. There was no statistically significant interaction between the investigational drug and stroke severity, treatment with alteplase, or time from the onset of stroke to treatment, indicating that the treatment benefit is present irrespective of these factors. Two important considerations are safety and the adverse-event profile. Both survival and the incidence of serious and nonserious adverse events were similar in the two groups, as was the case in previous trials.^{17,18}

The modified Rankin scale is robust and simple, easily understood by patients and laypersons, and has reasonable properties for statistical analysis.²⁶ This scale reflects aspects of recov-

ery from stroke that are directly important to patients' daily activities, and the categories of the scale distinguish clinically important states. Analysis with the use of the entire distribution is both more powerful and more relevant to a neuroprotectant than is the use of dichotomization.²⁷ Our use of the modified Rankin scale was rigorous, requiring all those who performed the rating to be certified as competent after undergoing training with the use of a specially developed DVD program, written guidelines, and a formal, standardized rating test involving five cases.

The NIHSS was designed to score the severity of stroke at entry into stroke-treatment trials, and not as an outcome measure. Its inclusion as the principal supporting coprimary end point was

Table 2. (Continued.)

Outcome Variable	Placebo Group	NXY-059 Group	Difference between NXY-059 and Placebo† % or score (95% CI)	P Value
Stroke Impact Scale				
Social participation				
No. of patients	672	668		
Score — LSM ±SE	55.8±1.2	57.5±1.2	1.7 (–1.7 to 5.0)	0.33
Communication				
No. of patients	674	669		
Score — LSM ±SE	79.1±0.9	80.1±0.9	1.0 (–1.6 to 3.7)	0.43
Memory and thinking				
No. of patients	674	669		
Score — LSM ±SE	75.1±1.0	76.6±1.0	1.4 (–1.4 to 4.2)	0.31
Emotion				
No. of patients	671	666		
Score — LSM ±SE	69.7±0.7	69.9±0.7	0.1 (–1.8 to 2.1)	0.88
VAS recovery				
No. of patients	672	667		
Score — LSM ±SE	61.7±1.0	64.7±1.0	3.1 (0.4 to 5.7)	0.02

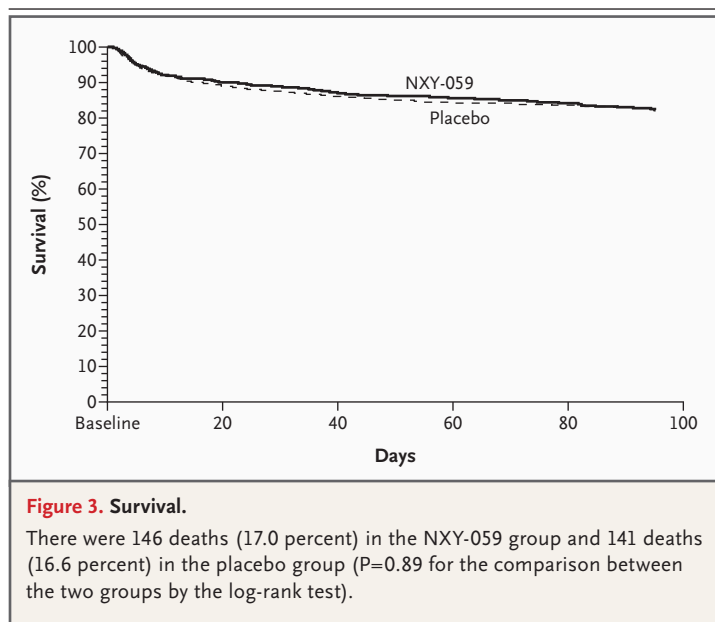
* The results are shown according to the prespecified, hierarchical, sequential testing of outcomes at day 90 or the last rating. Each end point was tested independently. Outcomes are listed in the order of testing. Lower-ordered end points were to be subjected to formal statistical testing only if all higher-ordered end points had a P value of less than 0.05. Only higher-ordered end points were subjected to formal testing; other P values are descriptive. Scores on the modified Rankin scale, in six categories, range from 0, indicating no residual symptoms, to 5, indicating bedbound, requiring constant nursing care. Scores on the NIHSS range from 0, indicating normal functioning, to 42, indicating most severe impairment. Scores on the Barthel index, in increments of 5 points, range from 100, indicating no help required for activities of daily living, to 0, indicating total dependence. All Stroke Impact Scale measures and scores on the EuroQoL EQ-5D VAS range from 0, indicating worst, to 100, indicating best. Scores on the EuroQoL EQ-5D weighted index range from –0.59, indicating worst, to 1.0, indicating best. CI denotes confidence interval, NIHSS National Institutes of Health Stroke Scale, LSM least-squares mean, EuroQoL EQ-5D European Quality of Life–5 Dimensions, and VAS visual analogue scale.

† The value is the percentage in the NXY-059 group minus the percentage in the placebo group for each category.

influenced by European regulatory advice.²⁸ The change in the NIHSS score from baseline to the last rating was not improved by treatment with NXY-059; however, the planned parametric analysis was compromised by the bimodal distribution of changes in scores, partly because of the arbitrary score of 42 (worst) assigned to patients who died. In a post hoc analysis with use of an accepted alternative test,^{29,30} NXY-059 was not associated with a significant increase in the number of patients who achieved an NIHSS score of no more than 1, but the odds ratio and confidence limits were consistent with the results according to the modified Rankin scale. A considerably larger study is needed to assess secondary outcome measures reliably.

Several features attest to the validity of the

results. Patients and investigators remained strictly unaware of the treatment assignments, and the blinding was not compromised by the occurrence or nature of adverse events. Data were missing only rarely, and missing data were handled conservatively. Prognostic factors that influence stroke outcome were well matched and showed no interaction with the treatment effect. The per-protocol analysis confirmed the result of the intention-to-treat analysis. We examined the effect of treatment at 7 and 30 days, when any dilutional effect of unrelated conditions and age would be less: a greater benefit with NXY-059 was seen at both times. There was also evidence of a biologic signal in patients treated with alteplase: the reduction in the occurrence of intracerebral hemorrhage is consistent with protec-



tion by NXY-059 of endothelial cells against oxidative stress.^{11,31,32}

If the result according to scores on the modified Rankin scale is confirmed, the extent of the treatment benefit would be clinically important in light of the disabling nature of stroke. According to the dichotomized approach to outcome, which is commonly used, the number needed to treat would be 22 to produce cure or 27 to restore ambulation after stroke. However, dichotomization underestimates treatment benefits in stroke, since individual cut points are relevant only to a fraction of patients.³³ We designed the trial to test for improvements in outcome across a range of potential disabilities, rather than to provide evidence of movement across an arbitrary threshold. This design enhances the power of the trial, since it uses statistical information that would otherwise be disregarded. It also reflects the theoretical effects

Table 3. Safety Outcomes Recorded over 90 Days of Follow-up.*

Event	Placebo Group (N=847)	NXY-059 Group (N=858)	Difference between Groups† %
Serious adverse event — no. (%)			
Stroke in evolution	63 (7.4)	55 (6.4)	-1.0
Ischemic stroke	22 (2.6)	33 (3.8)	1.2
Pneumonia	18 (2.1)	17 (2.0)	-0.1
Cardiac failure	7 (0.8)	16 (1.9)	1.1
Bronchopneumonia	12 (1.4)	14 (1.6)	0.2
Pulmonary embolism	16 (1.9)	14 (1.6)	-0.3
Atrial fibrillation	12 (1.4)	10 (1.2)	-0.2
Brain edema	25 (3.0)	9 (1.0)	-2.0
Carotid artery stenosis	4 (0.5)	9 (1.0)	0.5
Cerebral hemorrhage‡	10 (1.2)	9 (1.0)	-0.2
Other adverse events — no. (%)			
Pyrexia	163 (19.2)	163 (19.0)	-0.2
Constipation	99 (11.7)	84 (9.8)	-1.9
Headache	82 (9.7)	82 (9.6)	-0.1
Urinary tract infection	58 (6.8)	76 (8.9)	2.1
Stroke in evolution	69 (8.1)	56 (6.5)	-1.6
Hypokalemia	37 (4.4)	55 (6.4)	2.0
Atrial fibrillation	56 (6.6)	46 (5.4)	-1.2
Hypertension	44 (5.2)	44 (5.1)	-0.1
Pneumonia	37 (4.4)	40 (4.7)	0.3
Vomiting	40 (4.7)	39 (4.5)	-0.2

of neuroprotection and clinical relevance,²⁷ and it is in line with regulatory advice.²⁸ The benefit amounts to an average improvement of 0.13 point on the modified Rankin scale per patient, which suggests that about eight patients would need to be treated to achieve improvement equal to 1 point on the scale for one patient. On the basis of evidence from experiments in animals with regard to the effect of NXY-059, a moderate benefit delivered to many patients is a more intuitive concept than a dramatic benefit delivered to a minority.

In summary, our findings provide support for a future clinical application of neuroprotection through disruption of the ischemic cascade, as has been shown in animal models. Our results were statistically significant for the primary outcome measure, but not for other outcome measures. A confirmatory study is needed to determine whether NXY-059 has a benefit in stroke. The sample size for the companion study, SAINT II, was increased in July 2005 from 1700 to 3200 to provide 80 percent power to replicate the present findings according to the modified Rankin

Table 3. (Continued.)

Event	Placebo Group (N=847)	NXY-059 Group (N=858)	Difference between Groups† %
Laboratory values‡			
Increase in serum alanine aminotransferase — no. (%)	84 (10.0)	113 (13.3)	3.3
Mean increase — U/liter	0.9±18	-0.4±26	
Increase in serum bilirubin — no. (%)	97 (11.5)	69 (8.1)	-3.4
Mean increase — μmol/liter	2.0±6.0	1.6±5.6	
Increase in serum urea — no. (%)	110 (13.1)	94 (11.1)	-2.0
Mean increase — mmol/liter	-1.0±2.5	-1.2±2.5	
Decrease in serum potassium — no. (%)	62 (7.4)	117 (13.8)	6.4
Mean decrease — mmol/liter	-0.1±0.6	-0.3±0.6	
Decrease in serum calcium — no. (%)	207 (24.6)	239 (28.1)	3.5
Mean decrease — mmol/liter	-0.1±0.2	-0.1±0.2	
Increase in plasma glucose — no. (%)	173 (20.6)	143 (16.8)	-3.8
Mean increase — mmol/liter	0.1±4.2	-0.3±2.8	
Increase in INR — no. (%)	229 (27.3)	192 (22.6)	-4.7
Mean increase	0.1±1.6	0.0±1.6	
Increase in neutrophil count — no. (%)	136 (16.2)	115 (13.5)	-2.7
Mean increase — ×10 ⁻⁹ /liter	-0.5±3.0	-0.8±2.9	
Increase in platelet count — no. (%)	66 (7.9)	40 (4.7)	-3.2
Mean increase — ×10 ⁻¹² /liter	-10±38	-16±39	

* The events included are the 10 most common serious and the 10 most common nonserious events in the NXY-059 group. Plus-minus values are means ±SD. INR denotes international normalized ratio.

† A negative number indicates fewer outcomes in the NXY-059 group. Laboratory findings are included if there was a difference of no less than 2 percentage points in incidence between the two groups in either the increase or decrease of a value by the end of infusion — a difference between groups that will occur with a probability of approximately 0.05 before adjustment for multiplicity.

‡ Only cerebral hemorrhages that involved prolonged hospitalization or were considered immediately life-threatening were included; those attributed by investigators to other causes (such as cerebral edema) were excluded, even if bleeding was present on neuroimaging. Events defined as symptomatic hemorrhages (an increase in the NIHSS score of 4 points within 36 hours plus any blood on post-treatment neuroimaging) are described in the text (and in the Figure in the Supplementary Appendix, available with the full text of this article at www.nejm.org).

§ To convert values for bilirubin to milligrams per deciliter, divide by 17.1. To convert values for potassium to milligrams per deciliter, divide by 0.258. To convert values for calcium to milligrams per deciliter, divide by 0.250. To convert values for glucose to milligrams per deciliter, divide by 0.05551.

scale. Stroke is a disabling condition that has a substantial social cost, and treatments that have even a moderate overall benefit may prove to be important.

Presented in part at the European Stroke Conference, Bologna, Italy, May 28, 2005.

Drs. Lees, Zivin, Grotta, and Davis report having received fees and reimbursement for expenses for work on the steering committee and lecture fees from AstraZeneca, but having no financial or related interest in AstraZeneca, Renovis, or NXY-059. Dr. Davalos reports having received consulting fees or speaker's fees from AstraZeneca, Boehringer Ingelheim, Pfizer, Merck Sharp and Dohme, Sanofi-Synthelabo, Bristol-Myers Squibb, Bayer, Paion, Forest, Daiichi Asubio, Lilly, Fujisawa, Novo Nordisk, and Ferrer International; Dr. Diener, consulting fees or speaker's fees from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, BASF, Abbott, Novartis, Parke-Davis, Merck Sharp and Dohme, Servier, Sanofi-Synthelabo, Bayer, Fresenius, and Janssen Cilag; Dr. Lyden,

consulting fees or speaker's fees from AstraZeneca, Bayer, Mitsubishi, Pfizer, Lilly, and Merck and holding research contracts with AstraZeneca and Bayer; Dr. Grotta, research support from AstraZeneca, Novo Nordisk, and Boehringer Ingelheim; and Dr. Shuaib, consulting fees or speaker's fees from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Pfizer, Roche, Merck, and Sanofi-Synthelabo. Drs. Ashwood, Hårdemark, and Wasiewski are employees of AstraZeneca and hold stock in the company. The SAINT I and II trials are sponsored by AstraZeneca. NXY-059 is subject to a partnership agreement between AstraZeneca and Renovis. Renovis had no influence on the conduct of the study or the analysis or interpretation of the data. No other potential conflict of interest relevant to this article was reported.

We are indebted to the patients who participated in this trial and their relatives; to the clinical and research teams of the stroke units; to the coordinating and monitoring staff at AstraZeneca; to Dr. Tomas Odergren, who led the development of NXY-059 at AstraZeneca; to Dr. Algirdas Kakarieka, the lead clinician; and to the scientific, data management, and statistical teams.

APPENDIX

The following investigators and institutions participated in the SAINT I study: **Steering Committee** — K.R. Lees, Glasgow, United Kingdom (*chair*); J.A. Zivin, San Diego, Calif. (*joint chair, planning and conduct stage*), 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, Calif.; A. Kakarieka (*sponsor representative, planning and conduct stage*); S. Sheth, Wilmington, Del. (*sponsor representative, analysis and reporting stage*); A. Shuaib, Edmonton, Alta., Canada; W. Wasiewski, Wilmington, Del. (*sponsor representative*); **Data and safety monitoring board** — S. Pockock, London (*chair*); H. Adams, Iowa City; P. Bath, Nottingham, United Kingdom; D. Oakes, Rochester, N.Y.; N.G. Wahlgren, Stockholm. **Study team leader** — Karin Söderberg, Södertälje, Sweden; **Study team physician** — H.G. Hårdemark; **Study team statisticians** — V. Alderfer, Wilmington, Del.; A. Grönlund, Södertälje, Sweden; U. Emeribe, Wilmington, Del. **Contract research organizations** — Covance Central Laboratory Services, Perceptive Informatics, eResearch Technology, Fisher Clinical Services.

Clinical Centers — **Australia**: C. Staples, Redcliffe and Caboolture Hospitals, Peninsula Clinical Research Centre, Kippa Ring, Queensland; C. Bladin, Box Hill Hospital, Melbourne, Vic.; C. Levi, John Hunter and Newcastle Misericordiae Hospitals, Newcastle, N.S.W.; S. Davis, Royal Melbourne Hospital, Melbourne, Vic.; D. Dunbabin, Royal Hobart Hospital, Hobart, Tasmania; D. Schultz, Flinders Medical Centre, Adelaide, S.A.; D. Crimmins, Central Coast Neuroscience Research, Gosford Hospital, Gosford, N.S.W.; G. Donnan, National Stroke Research Institute Austin and Repatriation Medical Centre, Melbourne, Vic.; R. Gerraty, St. Vincent's Hospital, Melbourne, Vic.; **Belgium**: V. Thijs, U.Z. Gasthuisberg, Leuven; C. Willems, Virga Jesse Ziekenhuis, Hasselt; P. De Deyn, A.Z. Middelheim Hospital, Antwerp; G. Vanhooren, A.Z. St-Jan Hospital, Bruges; P. Desfontaines, Clinique de l'Espérance Montegnée; J. Caekebeke, O.L. Vrouwziekenhuis Aalst, Aalst; U. Etienne, C.H. Notre-Dame and Reine Fabiola, Montignies-Sur-Sambre; **Bulgaria**: P. Stamenova, Multispecialized Hospital for Active Treatment "Queen Joanna," Clinic of Neurology, Sofia; V. Platikanov, Multispecialized Hospital for Active Treatment, Pleven; D. Baldaranov, 5th Multispecialized Hospital for Active Treatment, Department of Neurology, Sofia; D. Minchev, Multispecialized Hospital for Active Treatment "St. Marina"—Varna, 2nd Clinic of Neurology, Varna; A. Tunev, Multispecialized Hospital for Active Treatment—Plovdiv, Department of Neurology, Plovdiv; T. Nocheva, Multispecialized Hospital for Active Treatment Russe, 2nd Neurology Department, Russe; **Czech Republic**: M. Bar, Fakultni nemocnice Ostrava, Ostrava-Poruba; D. Vaclavik, Vitkovická nemocnice Blahoslavené Marie Antoniny, Vitkovice; H. Lachmann, Fakultni nemocnice Motol, Praha; E. Ehler, Krajské Nemocnice Pardubice Neurologické oddelení, Pardubice; J. Bauer, Všeobecná fakultni nemocnice, Praha; O. Skoda, Nemocnice Pelhřimov, Pelhřimov; G. Waberzinek, Fakultni Nemocnice, Hradec Králové; O. Keller, Fakultni Thomayerova Nemocnice, Praha; K. Urbanek, Fakultni Nemocnice Olomouc, Olomouc; I. Rektor, Fakultni nemocnice u Sv. Anny, Brno; P. Kalvach, Fakultni nemocnice Kralovske Vinohrady, Praha; **Denmark**: P. Meden, Bispebjerg Hospital, Copenhagen; G. Andersen, Århus Kommunehospital, Århus; **Finland**: M. Kaste, Helsinki University Central Hospital/Meilahden Sairaala, Helsinki; K. Koivisto, Seinäjoki Keskussairaala, Seinäjoki; A. Rissanen, Keski-Suomen Keskussairaala, Jyväskylä; H. Numminen, Etelä-Karjalan Keskussairaala, Lappeenranta; A. Muuronen, Jorvin Sairaala, Espoo; **France**: P. Amareco, Hôpital Bichat-Claude Bernard, Paris; A. Bonafe, Hôpital Gui-de-Chauliac, Montpellier; F. Ziegler, Centre Hospitalier de Belfort-Montbéliard, Belfort; J. Boulliat, Centre Hospitalier Fleyriat, Bourg en Bresse; T. Moulin, Hôpital Jean Minjoz, Besançon; P. Clavelou, Hôpital Gabriel Montpied, Clermont-Ferrand; D. Sablot, Centre Hospitalier Maréchal Joffroy, Périnanal; E. Rollet, Hôpital Tenon, Paris; P. Lavage, Hôpital Crimea, Names; C. Lucas, Hôpital Roger Salinger, Lille; B. Guillon, H. Laënnec Saint Herblain; **Germany**: D. Schneider, Universitätskrankenhaus Leipzig, Leipzig; P. Vogel, Allgemeines Krankenhaus St. Georg, Hamburg; J. Glahn, Klinikum I Minden, Minden; G.F. Hamann, Klinikum Grosshadern, Munich; C. Weiller, Universitätskrankenhaus Hamburg-Eppendorf, Hamburg; A. Hetzel, Universitätsklinik Freiburg, Freiburg; C. Diener, Universitätsklinik Essen, Essen; M. Hennerici, Klinikum Mannheim GmbH, Mannheim; M. Eicke, Universitätsklinik Mainz, Mainz; G. Deuschl, Universitätsklinikum Schleswig-Holstein, Kiel; L. Lachenmayer, Allgemeines Krankenhaus Barnbek, Hamburg; D. Sander, Neurologische Klinik und Poliklinik der Technische Universität München, Munich; O.W. Witte, Klinik für Neurologie Jena, Jena; U. Sliwka, Sana-Klinikum Remscheid, Remscheid; B. Widder, Klinik für Neurologie im Bezirkskrankenhaus Günzburg, Günzburg; S. Meves, St. Josef-Hospital Bochum, Bochum; **Hong Kong**: P.W. Ng, United Christian Hospital, Kwun Tong; L. Ka Sing Wong, Prince of Wales Hospital, New Territories; R. Cheung, Queen Mary Hospital, Pokfulam; **Hungary**: Z. Nagy, Országos Pszichiátriai és Neurológiai Intézet, Budapest; C. Béla, Hajdú-Bihar Megyei Önkormányzat; K. Gyula, Kórház-Rendelőintézet, Debrecen; A. Csányi, Petz Aladár Megyei Oktató Kórház, Győr; H. Sándor, Pest Megyei Flór Ferenc Kórház Kistarcsa, Kistarcsa; C. László, Debreceni Egyetem Orvos-és Egészségtudományi Centrum, Neurológiai Klinika, Debrecen; **Italy**: G. Miceli, Fondazione Istituto Neurologico Casimiro Mondino-Pavia, Pavia; G. Agnelli, Università degli Studi di Perugia, Ospedale Monteluca, Genoa; C. Gandolfo, Università Degli Studi di Genova, Ospedale, S. Martino, Genoa; A. Carolei, Ospedale S. Salvatore, l' Aquila, l' Aquila; D. Guidetti, Arcispedale S. Maria Nuova, Reggio Emilia; D. Inzitari, Azienda Ospedaliera Care-

ggi, Florence; **Malaysia:** J.S. Merican, Hospital Kuala Lumpur, Kuala Lumpur; S. Bee Fung, Gleneagles Medical Centre, Penang; T. Kay-Sin, University Malaya Medical Centre, Kuala Lumpur; R. Azman Ali, Hospital Universiti Kebangsaan, Kuala Lumpur; **New Zealand:** C. Anderson, Middlemore Hospital, Auckland; A. Barber, Auckland Hospital, Auckland; J. Fink, Christchurch Hospital, Christchurch; J. Gommans, Hawkes Bay Hospital, Hastings; **the Netherlands:** K. Keizer, Catharina-Ziekenhuis, Eindhoven; P.M.M. van Erven, Amphia Ziekenhuis, Breda A.W.F. Rutgers, Martini Ziekenhuis, Groningen; P.J.A.M. Brouwers, Medisch Spectrum Twente, Enschede; M.M. Veering, Medisch Centrum Alkmaar, Alkmaar; D. Dippel, Erasmus Medisch Centrum, Rotterdam; V.I.H. Kwa, Slotervaart Ziekenhuis, Amsterdam; C.L. Franke, Atrium Heerlen, Heerlen; R.P. Kleyweg, Albert Schweitzer Ziekenhuis, Dordrecht; A.E. Boon, St. Annaziekenhuis, Geldrop; **Norway:** P. Bjerke, Sykehuset Innlandet HF Hamar, Hamar; L. Thomassen, Nevrologisk avdeling Helse, Bergen; J. Indredavik, St. Olavs Hospital, Trondheim; B. Hermstad, Helse Nord-Trøndelag HF Sykehuset Levanger, Levanger; R. Salvesen, Helse NSS HF Nordland Sentralsykehus, Bodø; E. Jörgensen, Sykehuset Buskerud, Drammen; **Poland:** A. Czlonkowska, Instytut Psychiatrii i Neurologii, Warsaw; A. Kuczynska, Szpital Wolski, Warsaw; W. Freyze, Szpital Wojewodzski im Mikolaja Kopernika, Gdansk; A. Wlodek, M. Wiszniewska, Szpital Specjalistyczny, Pila; A. Wlodek, Samodzielny Specjalistyczny Szpital, Wojewodzki, Siedlce; **Portugal:** A. Vasco Salgado, Hospital Amadora-Sintra, Amadora; L. Cunha, Hospitais da Universidade de Coimbra, Coimbra; G. Gonçalves, Centro Hospitalar de Coimbra, Coimbra; M. Correia, Hospital Geral de Santo António, Porto; **Singapore:** I. Ng, National Neuroscience Institute, Singapore; C. Hui Meng, Singapore General Hospital, Singapore; B. Chan, National University Hospital, Singapore; **Slovakia:** M. Dvorák, Nemocnica s Poliklinikou, Levoča; M. Brozman, Fakultná Nemocnica s Poliklinikou, Nitra; E. Kurča, Martinská Fakultná Nemocnica, Martin; R. Garay, Nemocnica s Poliklinikou svätého Cyrila a Metoda, Bratislava; J. Vyletelka, Nemocnica s Poliklinikou, Žilina; M. Nyéky, Nemocnica s Poliklinikou svätej Barbory, Rožňava; J. Herényiová, Nemocnica s Poliklinikou, Lučenec; **South Africa:** J. Thorne, Excellentis Suite 103, George; F. Maritz, Tiervlei Trial Centre, Karl Bremer Hospital, Bellville; J. Green, St. Augustine's Hospital, Durban; H. Badenhorst, Panorama Medi-Clinic, Parow; J. Gardiner, Constantiaberg Medi-Clinic, Plumstead; D. Lurie, Sunninghill Hospital, Gallo Manor; E. van Graan, Muelmed Medical Centre, Arcadia; **South Korea:** B.-C. Lee, Hallym University College of Medicine, Anyang City, KyeongKi-Do; J.-S. Kim, Asan Medical Center, Seoul; K.-H. Lee, Samsung Medical Center, Seoul; J.-K. Roh, Seoul National University Hospital, Seoul; Y.-S. Lee, Seoul Municipal Boramae Hospital, Seoul; **Spain:** J. Serena Leal, Hospital Universitari Josep Trueta, Girona; J. Alvarez Sabin, Hospital Valle D'Hebron, Barcelona; A. Gil Peralta, Hospital Virgen del Rocio, Seville; F. Rubio, Hospital de Bellvitge, Barcelona; J. Roquer, Hospital del Mar, Barcelona; R. Fernández-Bolanos, Hospital Universitario "Ntra. Sra. De Valme," Seville; A. Dávalos, Hospital German Trias i Pujol, Barcelona; J. Castillo, Hospital Clinico Universitario de Santiago, Santiago de Compostela; J.M. Guiu, Hospital General Universitario de Alicante, Alicante; E. Diez Tejedor, Hospital Universitario La Paz, Madrid; J. Vivancos, Hospital Universitario de la Princesa, Madrid; J. Lluís Martí i Vilalta, Hospital de la Santa Creu i Sant Pau, Barcelona; E. Mostacero, Hospital Lozano Blesa, Zaragoza; A. Chamorro, Hospital Clinic, Barcelona; A. Gil Nunez, Hospital Gregorio Marañón, Madrid; A. Lago, Hospital Universitario La Fé, Valencia; J.A. Egido, Hospital Clinico San Carlos, Madrid; **Sweden:** M. Callander, Universitetssjukhuset, Linköping; J. Petersson, Universitetssjukhuset MAS, Malmö; A. Terent, Akademiska sjukhuset, Uppsala; T.-B. Käll, Södersjukhuset, Stockholm; V. Kostulas, Huddinge sjukhus, Huddinge; B. Leijid, St. Görans Sjukhus, Stockholm; J.-E. Karlsson, Sahlgrenska sjukhuset, Gothenberg; S. Karlsson, Universitetssjukhuset, Örebro; **United Kingdom:** K.R. Lees (*principal investigator*), Acute Stroke Unit, Western Infirmary, Glasgow; G.A. Ford, Freeman Hospital, Newcastle-Upon-Tyne; K. Muir, Southern General Hospital, Glasgow; D. Barer, Queen Elizabeth Hospital, Gateshead; A. Sharma, University Hospital Aintree, Liverpool; D. Jenkinson, Christchurch Hospital, Christchurch; C. Gray, Sunderland Royal Hospital, Sunderland; R. MacWalter, Ninewells Hospital, Dundee; T. Robinson, University Hospitals of Leicester, Leicester.

REFERENCES

1. Mackay J, Mensah GA. The atlas of heart disease and stroke. Geneva: World Health Organization, 2004.
2. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004;363:768-74.
3. California Acute Stroke Pilot Registry (CASPR) Investigators. Prioritizing interventions to improve rates of thrombolysis for ischemic stroke. *Neurology* 2005;64:654-9.
4. Lees KR, Asplund K, Carolei A, et al. Glycine antagonist (gavestinel) in neuroprotection (GAIN International) in patients with acute stroke: a randomised controlled trial. *Lancet* 2000;355:1949-54.
5. Muir KW, Lees KR, Ford I, Davis S. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. *Lancet* 2004;363:439-45.
6. The Stroke Therapy Academic Industry Roundtable (STAIR). Recommendations for standards regarding preclinical neuroprotective and restorative drug development. *Stroke* 1999;30:2752-8.
7. Chan PH. Reactive oxygen radicals in signaling and damage in the ischemic brain. *J Cereb Blood Flow Metab* 2001;21:2-14.
8. Maples KR, Ma F, Zhang Y-K. Comparison of the radical trapping ability of PBN, S-PPBN and NXY-059. *Free Radic Res* 2001;34:417-26.
9. Stroke Therapy Academic Industry Roundtable II (STAIR-II). Recommendations for clinical trial evaluation of acute stroke therapies. *Stroke* 2001;32:1598-606.
10. Lees K, Green R, Odegren T. Comparison of neuroprotective data for NXY-059 in animal models with the STAIR criteria. *Cerebrovasc Dis* 2001;11:Suppl 4:77.
11. Kuroda S, Tsuchida R, Smith M-L, Maples KR, Siesjö BK. Neuroprotective effects of a novel nitron, NXY-059, after transient focal cerebral ischemia in the rat. *J Cereb Blood Flow Metab* 1999;19:778-87.
12. Sydserff SG, Borelli AR, Green AR, Cross AJ. Effect of NXY-059 on infarct volume after transient or permanent middle cerebral artery occlusion in the rat: studies on dose, plasma concentration and therapeutic window. *Br J Pharmacol* 2002;135:103-12.
13. Marshall JWB, Duffin KJ, Green AR, Ridley RM. NXY-059, a free radical-trapping agent, substantially lessens the functional disability resulting from cerebral ischemia in a primate species. *Stroke* 2001;32:190-8.
14. Marshall JWB, Cummings RM, Bowes LJ, Ridley RM, Green AR. Functional and histological evidence for the protective effect of NXY-059 in a primate model of stroke when given 4 hours after occlusion. *Stroke* 2003;34:2228-33.
15. Dehouck M-P, Cecchelli R, Green AR, Renftel M, Lundquist S. In vitro blood-brain barrier permeability and cerebral endothelial cell uptake of the neuroprotective nitron compound NXY-059 in normoxic, hypoxic and ischemic conditions. *Brain Res* 2002;955:229-35.
16. Green AR, Lanbeck-Vallén K, Ashwood T, et al. Brain penetration of the novel free radical trapping neuroprotectant NXY-059 in rats subjected to permanent focal ischaemia. *Brain Res* (in press).
17. Lees KR, Sharma AK, Barer D, et al. Tolerability and pharmacokinetics of the nitron NXY-059 in patients with acute stroke. *Stroke* 2001;32:675-80.

18. Lees KR, Barer D, Ford GA, et al. Tolerability of NXY-059 at higher target concentrations in patients with acute stroke. *Stroke* 2003;34:482-7.
19. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975;31:103-15.
20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
21. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989;20:864-70.
22. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1988;19:604-7.
23. Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *Md State Med J* 1965;14:61-5.
24. Stokes ME, Davis CS, Koch GG. Categorical data analysis using the SAS system. 2nd ed. Cary, N.C.: SAS Institute, 2000.
25. Chi GYH. Multiple testing: multiple comparisons and multiple endpoints. *Drug Info J* 1998;32:Suppl:1347S-1362S.
26. Weimar C, Kurth T, Kraywinkel K, et al. Assessment of functioning and disability after ischemic stroke. *Stroke* 2002;33:2053-9.
27. Saver JL. Number needed to treat estimates incorporating effects over the entire range of clinical outcomes: novel derivation method and application to thrombolytic therapy for acute stroke. *Arch Neurol* 2004;61:1066-70. [Erratum, *Arch Neurol* 2004;61:1599.]
28. Committee for Proprietary Medicinal Products (CPMP). Points to consider on clinical investigation of medicinal products for the treatment of acute stroke. London: European Agency for the Evaluation of Medicinal Products, 2001. (No. CPMP/EWP/560/98.)
29. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581-7.
30. Mayer SA, Brun NC, Begtrup K, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005;352:777-85.
31. Lapchak PA, Araujo DM, Song D, Wei J, Purdy R, Zivin JA. Effects of the spin trap agent disodium-[(tert-butylimino)methyl]benzene-1,3-disulfonate N-oxide (generic NXY-059) on intracerebral hemorrhage in a rabbit large clot embolic stroke model: combination studies with tissue plasminogen activator. *Stroke* 2002;33:1665-70.
32. Lapchak PA, Araujo DM, Song D, Wei J, Zivin JA. Neuroprotective effects of the spin trap agent disodium-[(tert-butylimino)methyl]benzene-1,3-disulfonate N-oxide (generic NXY-059) in a rabbit small clot embolic stroke model: combination studies with thrombolytic tissue plasminogen activator. *Stroke* 2002;33:1411-5.
33. Weir CJ, Kaste M, Lees KR. Targeting neuroprotection clinical trials to ischemic stroke patients with potential to benefit from therapy. *Stroke* 2004;35:2111-6.

Copyright © 2006 Massachusetts Medical Society.

FULL TEXT OF ALL JOURNAL ARTICLES ON THE WORLD WIDE WEB

Access to the complete text of the *Journal* on the Internet is free to all subscribers. To use this Web site, subscribers should go to the *Journal's* home page (www.nejm.org) and register by entering their names and subscriber numbers as they appear on their mailing labels. After this one-time registration, subscribers can use their passwords to log on for electronic access to the entire *Journal* from any computer that is connected to the Internet. Features include a library of all issues since January 1993 and abstracts since January 1975, a full-text search capacity, and a personal archive for saving articles and search results of interest. All articles can be printed in a format that is virtually identical to that of the typeset pages. Beginning six months after publication, the full text of all Original Articles and Special Articles is available free to nonsubscribers who have completed a brief registration.