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Safety and Tolerability of NXY-059 for Acute Intracerebral Hemorrhage

The CHANT Trial

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Background and Purpose—NXY-059 is a free radical–trapping neuroprotectant developed for use in acute ischemic stroke. To facilitate prompt administration of treatment, potentially before neuroimaging, we investigated the safety of NXY-059 in patients with intracerebral hemorrhage (ICH).

Methods—We randomized 607 patients within 6 hours of acute ICH to receive 2270 mg intravenous NXY-059 over 1 hour and then up to 960 mg/h over 71 hours, or matching placebo, in addition to standard care. The primary outcome was safety: the mortality and the frequency of adverse events, and the change from baseline for a variety of serum, imaging, and electrophysiological measurements. We also studied the overall distribution of disability scores on the modified Rankin Scale (mRS) and the Barthel index.

Results—We treated 300 patients with NXY-059 and 303 with placebo. Treatment groups were well matched for prognostic variables including Glasgow Coma Scale, risk factors, and age. The mean National Institute of Health Stroke Scale score on admission was 14 in both groups. The baseline hemorrhage volume was 22.4±20.1 mL in the NXY-059 group and 23.3±22.8 mL in the placebo group (mean±SD). Most hemorrhages were related to hypertension or anticoagulant use. Mortality was similar in both groups: 20.3% for NXY-059 and 19.8% for placebo-treated patients. The proportion of patients who experienced an adverse event was the same for both groups, whereas for serious adverse events the proportion was slightly higher in the NXY-059 group. However, no pattern emerged to indicate a safety concern. Serum potassium fell transiently in both groups, lower in the NXY-059 group. There were no differences in 3-month function, disability, or neurological deficit scores. The odds ratio for an improved outcome in 3-month mRS scores in the NXY-059 group was 1.01 (95% CI 0.75, 1.35).

Conclusions—NXY-059 given within 6 hours of acute ICH has a good safety and tolerability profile, with no adverse effect on important clinical outcomes. **(*Stroke*. 2007;38:2262-2269.)**

Key Words: acute care ■ clinical trials ■ free radical scavengers ■ neuroprotectants ■ neuroprotection ■ neuroprotective agents ■ stroke management

Intracerebral hemorrhage (ICH) accounts for 15% of all strokes globally, and is associated with substantially greater mortality and worse functional outcomes than ischemic stroke.[1,2] Although ICH confers higher mortality and morbidity than acute ischemic stroke, the 2 types of strokes present similarly; thrombolytic treatment for ischemic stroke must therefore be delayed for cerebral imaging to exclude ICH.[3] Such delays in diagnosis and specialized care are associated with worse outcome.[4–7] Treatment delay could be avoided if a therapy were safe enough in all stroke patients, ischemic or hemorrhagic, to be used before baseline brain imaging.[8] To use an agent without first imaging the brain would require a demonstration of safety and tolerability in ICH patients. Ideally, such a drug would have efficacy not only in ischemic stroke but also in ICH. However, it remains unclear whether efficacy in both clinical entities would be

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The results of the CHANT trial were presented in part at the European Stroke Conference, Brussels, May 17, 2006.

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TABLE 1. Selection Criteria Used in CHANT

Inclusion	Exclusion
1. Written informed consent from the patient or legally acceptable representative.	1. Acute ischemic stroke, an epidural, subdural or subarachnoid hemorrhage, a tumor (including those associated with a hemorrhage), encephalitis, or any diagnosis other than acute ICH. Note: Small areas of epidural, subdural, or subarachnoid hemorrhage associated with large primary ICH were allowed.
2. Males and females ≥18 years old.	2. ICH attributable to trauma. Patients who suffered minimal head trauma following the onset of a primary ICH were allowed.
3. Clinical diagnosis of acute stroke with limb weakness and a neuroimaging scan (CT or MRI) showing an ICH.	3. Unconsciousness (i.e., score of 3 on item 1a. of the NIHSS). 4. Severe concurrent illness with life expectancy less than 6 months. 5. Planned surgical removal of the ICH. Minor surgical procedures such as ventriculostomy or intracranial pressure (ICP) monitor placement were allowed.
4. The sum of scores on items 5 and 6 on the NIHSS were ≥2 at baseline and the total score (items 1–11) was ≥6.	6. Patients unlikely to complete the 72-hour infusion of investigational product because of a severe clinical condition at baseline.
5. Onset of symptoms within 6 hours of the planned start of investigational product infusion. Onset time for patients who awoke with symptoms was the last time the patient was awake without symptoms of stroke.	7. Known severe renal disorder from the patient's history. Patients with a known calculated creatinine clearance of <30 mL/min using the Jaffe method or <35 mL/min using the modified Jaffe or enzymatic method to determine SCreatinine were excluded. 8. Current known alcohol or illicit drug abuse or dependence. 9. Pregnancy or breast-feeding. Women of childbearing potential were excluded unless a negative test for pregnancy has been obtained before randomization. 10. Treatment since onset of stroke symptoms with experimental (ie, drugs in clinical studies) or empirical treatments for stroke with the exception of mannitol, glycerol, and steroids for the treatment of ICP. 11. Treatment with acetazolamide and methotrexate during the 72-hour infusion.
6. Premorbid mRS score of 0 or 1.	12. Previous inclusion in CHANT or concurrent inclusion in another clinical study with an investigational drug or device, or participation in any previous clinical study within 30 days of admission assessment and start of NXY-059.

possible because some cell injury mechanisms may differ between the 2 forms of stroke.[9]

Tissue oxidation via free radical–initiated processes mediates ischemia-related damage in the brain.[10–12] NXY-059 (disufenton sodium) is a novel free radical–trapping agent which reduces infarct size and preserves brain function in animal models of acute ischemic and hemorrhagic stroke.[13–16] Neuroprotection was shown in rat models of transient and permanent focal ischemia using measures of lesion volume when the drug was given as late as 5 hours after ischemia.[13,17] Improvements in functional outcomes, including motor deficits, spatial neglect, as well as reduction in infarction volume were demonstrated in primates after permanent ischemia.[18] A protective effect after 10 weeks was noted when therapy was delayed as late as 4 hours after ischemia.[19]

SAINT-I (Stroke-Acute Ischemic NXY Treatment) established the efficacy of NXY-059 in patients with acute ischemic stroke.[20] NXY-059 significantly reduced disability assessed on the mRS at 90 days compared with placebo and was generally well tolerated with no significant safety concerns. In patients treated with recombinant tissue plasminogen activator (rt-PA) and NXY-059, the incidence of symptomatic ICH was only 2.5% compared with 6.4% in the rt-PA–treated patients receiving placebo in place of the NXY-059.[21] None of these beneficial effects could be replicated in a second trial, SAINT 2, however (Shuaib A, et al, unpublished data, 2007).

During the SAINT 2 study, we sought to explore the safety and potential for efficacy of NXY-059 treatment in a large number of patients with ICH in the Cerebral Hematoma And NXY Treatment trial (CHANT). We studied safety by measuring mortality and the frequency of serious adverse events and adverse events; we collected functional outcome data to assure the drug did not negatively impact long-term neurological recovery after hemorrhage and to explore a potential neuroprotective effect. We tested for potential efficacy by measuring hematoma growth during the infusion period, because hematoma growth was recently shown to significantly influence outcome.[22]

Methods

Study Design

CHANT was a randomized, double-blind, placebo-controlled trial conducted at 131 SAINT 2 study sites in 20 countries (please see appendix for a list of study sites). The trial was approved by local and national institutional review boards. Informed consent was obtained from the patient or legally acceptable surrogate. The steering committee assisted in developing the trial protocol, approved the statistical plan, had full access to the data, wrote the manuscript, and was responsible for decisions regarding publication. The principal investigator assumes full responsibility for the integrity and interpretation of the data. The sponsor, AstraZeneca, was responsible for operational aspects of the trial including collecting and storing the data and performing analysis according to the approved plan. An independent data safety monitoring board formally conducted a safety review after 200 patients were enrolled.

Patients

Patients 18 years of age or older with a clinical diagnosis of acute ICH confirmed by brain imaging were included. The protocol allowed enrollment if there were small amounts of hemorrhage outside the parenchyma associated with large primary ICH, but not if the hemorrhage was deemed to arise primarily from a location outside the brain. Patients were to manifest limb weakness as part of the presenting deficit, and onset of symptoms within the previous 6 hours was required. If the onset time was unknown, the last time the patient was known to be well was assumed to be the onset time. Other key selection criteria are summarized in Table 1.

Study Intervention

Patients were randomly assigned to receive an intravenous infusion of placebo (normal saline) or NXY-059 as a loading infusion over 1 hour, which was followed by a maintenance infusion over 71 hours.

TABLE 2. Baseline Characteristics and Timing of Treatment in CHANT

Field	Total	NXY	PLAC
No. randomized	607	305	302
No. treated	603	300	303
Females/Males	214/389	111/189	103/200
Average time to onset of infusion Hours:min±SD	4:20±1:04	4:19±1:04	4:21±1:04
Infratentorial origin N (%)	14 (2.3)	5 (1.7)	9 (3)
Average age, years (range)	66.1 (29–93)	66.6 (40–93)	65.7 (29–92)
NIHSS, mean (range) median	14 (6–33) 14	14 (6–33) 13	14 (6–28) 13
GCS, average (range) median	13.8 (7–15) 15	13.7 (7–15) 15	13.9 (7–15) 15
IVH, n	168	83	85
ICH volume (ML), mean±SD (range)	22.8±21.5 (0.5–144)	22.4±20.1 (1–123)	23.3±22.8 (0.5–144)
ICH score, mean (range median)	0.9 (0–4) 1	0.9 (0–4) 1	0.9 (0–4) 1
Glucose on admission, mmol/l		7.7±3.0	7.8±2.7

Selected baseline characteristics of the treatment groups are listed. Abbreviations as defined in the text. The groups are well balanced with respect to important characteristics that might influence safety or response to therapy.

Treatment could commence up to 6 hours after stroke onset, but each site was urged to begin treatment as early as possible. Randomization was performed by a central interactive voice response system accessed by telephone. We stratified randomization for country and total ICH score (0, 1, 2, >3)[23] at admission, which is based on location and size of the hematoma, involvement of ventricles, age, and the Glasgow Coma Scale.[24] The Glasgow Coma Scale is not validated for use specifically in stroke patients, but indicates the level of consciousness in brain injured patients.

The study drug was prepared for infusion to a final concentration of 15 mg/mL in 0.9% saline, with NXY-059 and placebo (0.9% saline) in vials of identical appearance. No laboratory or adverse events were known to identify active drug from placebo. The loading rate was 151 mL/h for all patients (2270 mg/h). After 1 hour the infusion rate was reduced to 64 mL/h. Estimated creatinine clearance (ClCr) based on a serum creatinine measurement, age, sex, and weight[25] was used to determine the need for further rate adjustment within the first 4 hours (to 44 mL/h for ClCr 51 to 80 mL/min and 32 mL/h for ClCr of 30 to 50 mL/min), to achieve and maintain a target mean unbound steady state concentration of 260 μmol/L. Patients with estimated ClCr below 30 mL/min were to be withdrawn from treatment. Patients otherwise received standard of care for acute ICH.

Clinical Assessments

To assure no adverse impact on patient safety attributable to NXY-059, patients were assessed at enrolment, 24 and 72 hours, and 7 and 90 days after the start of infusion, using the National Institutes of Health Stroke Scale (NIHSS).[26,27] Follow-up assessments after 7, 30, and 90 days included functional measures: the modified Rankin Scale (mRS),[28] the Barthel Index (BI),[29] and the patient rated Stroke Impact Scale (90 days only).[30a] To improve the application of the disability and neurological scales, investigators were trained, tested, and certified in use of mRS, using a DVD-based method developed for the SAINT trials[30b] and the NIHSS using methods developed and validated by the National Institutes of Health.[27]

Imaging

Patients underwent a second neuroimaging scan at end of infusion (72 hours for those who completed the infusion). Additional scans were performed on patients that showed deterioration in their neurological status—worsening of 4 or more points on the NIHSS—any time from the start of investigational product infusion through 21 days. The qualifying and all follow-up scans were read centrally, blinded to treatment allocation. Hematoma volumes were estimated locally and centrally using the ellipsoid approximation.[31] The analysis of change in volume from baseline to 72 hours was adjusted for baseline volume. In addition, the central reader computed volumes using semiautomated planimetry and reconstruction. The presence of intraventricular hemorrhage was scored locally and centrally, as was the presence or absence of blood in the subarachnoid, subdural, or epidural spaces. The central reader used a detailed mapping grid to score the locations involved with hematoma to semiquantitatively describe lesion locations. Magnetic resonance images (MRI) were allowed in place of qualifying or follow-up CT scans if the MRI scanning protocol were approved in advance as sufficient to detect hemorrhage reliably.

Safety Assessments

During infusions, vital signs and adverse events were recorded. Routine laboratory tests were undertaken for central analysis at enrolment, and after 24 hours, 72 hours, and 7 days. Patients were contacted by telephone 30 days after the start of infusion to ascertain their status, query for any serious adverse events, and to obtain a rating on the modified Rankin Scale[32] and estimated Barthel index.[33] Follow-up ratings were obtained in person 7±2 days and 90±10 days after the start of infusion. Serious adverse events were collected from the signing of consent through study completion 90 days later.

Statistical Analysis

The sample size was determined based on projected recruitment rates at SAINT 2 study sites during the time planned for the study, rather than a power analysis based on a hypothesized event rate. With 600 patients assumed recruited, the study would have 80% power to detect a 5% absolute increase in adverse event reports, assuming a 2% rate in the placebo group. There was 90% power to detect a 6% increase. All patients in whom study infusion began were analyzed for safety, according to treatment received. If patients dropped out of the study because of death, the maximum score was assigned for their last rating on appropriate efficacy variables. For patients dropping out of the study before Day 90, for reasons other than death, the last available observation was used as last rating.

The primary analysis of all-cause mortality rate was performed with a logistic regression model adjusting for total ICH score and total NIHSS score at baseline. The difference between treatment groups was assessed with log-rank test. Cox proportional odds regression was used to assess the possible influence of prognostic factors. The treatment by exploratory factor interaction was investigated by use of logistic regression.

Adverse events and observed laboratory values were summarized and shift tables were generated to detect any clinically significant laboratory abnormalities in change of values from baseline to end of

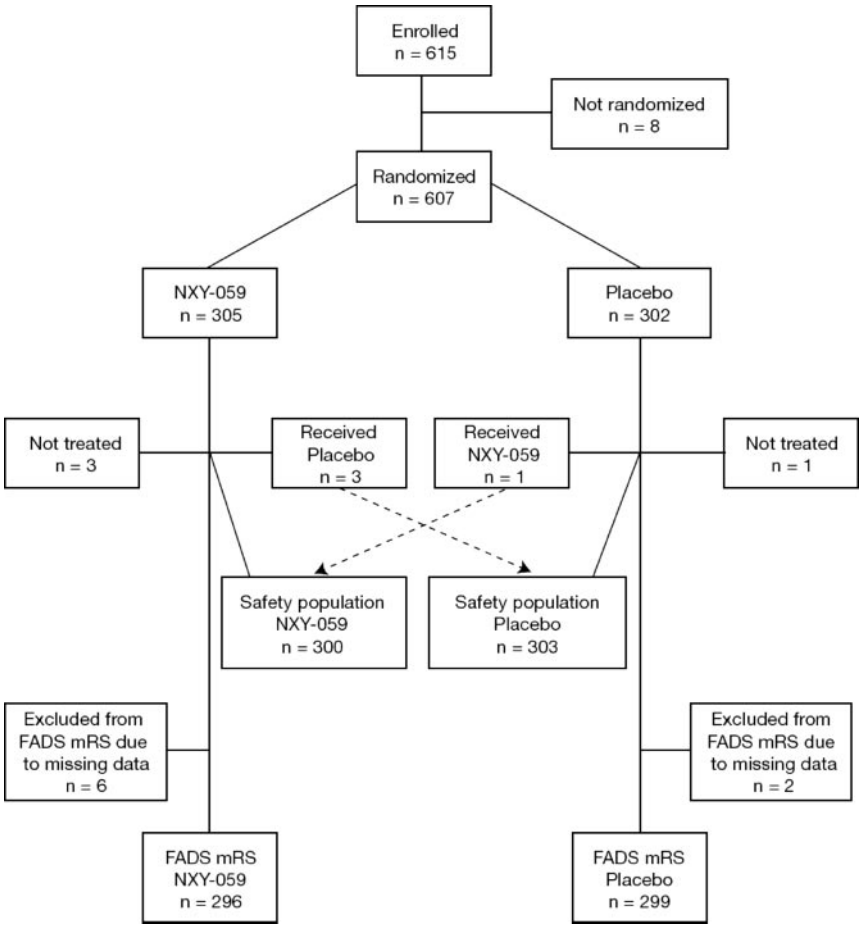

Figure 1. Trial profile and disposition of enrolled patients. FADS indicates full analysis data set. Other abbreviations as in the text.

infusion. Change from baseline in cerebral imaging (CT or MRI) was summarized and described at the end of infusion/72 hours. Also, changes from baseline to the time of any new stroke within 21 days were summarized.

The full categorized modified Rankin Scale scores were compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test with modified ridits. Logistic regression was applied to the modified Rankin Score data at last rating to assess for explanatory variables. Total NIHSS score and change from baseline in total NIHSS score were compared between treatment groups using a CMH test with modified ridit score.

Results

Recruitment into CHANT was completed in September 2005, with 603 patients treated (607 randomized; Table 2 and Figure 1). The number of patients randomized was 305 into NXY-059 treatment and 302 into placebo. One patient in each group was lost to follow-up. The central readings generally confirmed the investigator's readings, however in 1 NXY-059 and 3 placebo treated patients, the central read did not confirm the presence of primary ICH. Because of these exclusions or misrandomizations, the number of patients who received treatment was 300 NXY-059 and 303 placebo (Figure 1).

The 2 groups were generally well matched with respect to important baseline characteristics that influence outcome after ICH (Table 2) and with respect to medical history (Table 3). Atrial fibrillation was slightly more common in the NXY-059 group; diabetes and prior use of antithrombotics was slightly more common in the placebo group.

The overall unbound plasma concentration of NXY-059 at 66 to 72 hours was 295.8±109.9 μmol/L (mean±SD, n=203).

Mortality within 3 months of ICH was 61 (20.3%) for NXY-059–treated and 60 (19.8%) for placebo-treated patients; life table analysis showed no difference between the groups at any time after treatment (Figure 2). Time to death was not significantly different (P=0.86, log-rank test).

Investigators reported adverse events in 265 (88.3%) NXY-059–treated patients and in 266 (87.8%) placebo-treated patients, or 1094 events in the NXY-059 group compared with 1121 events in the placebo group. The pattern of adverse events was similar in the 2 groups. Serious adverse events were reported by investigators in 138 (46.0%) NXY-

TABLE 3. Medical History

Medical History	NXY-059, n=300 n (%)	Placebo, n=303 n (%)
Hypertension	240 (80)	252 (83.2)
Previous ischemic stroke	34 (11.3)	33 (10.9)
Myocardial ischemia	18 (6.0)	27 (8.9)
Atrial fibrillation, past or current	35 (11.7)	25 (8.3)
Diabetes mellitus	49 (16.3)	63 (20.8)
Prior use of antiplatelets	65 (21.7)	77 (25.4)
Prior use of anticoagulants	22 (7.3%)	21 (6.9%)

Selected items from the medical histories are summarized for each treatment group. There are no differences between the study groups.

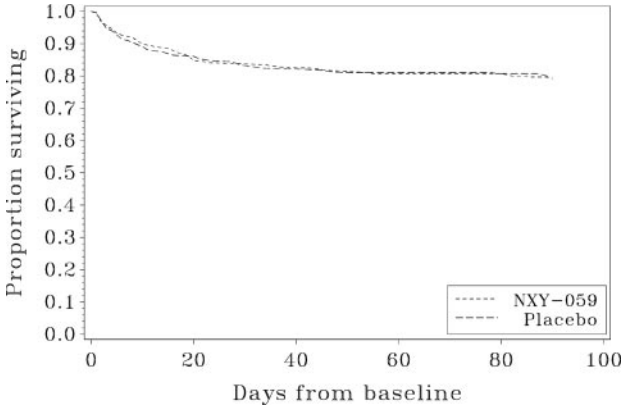

Figure 2. Life table analysis of mortality in the CHANT trial.

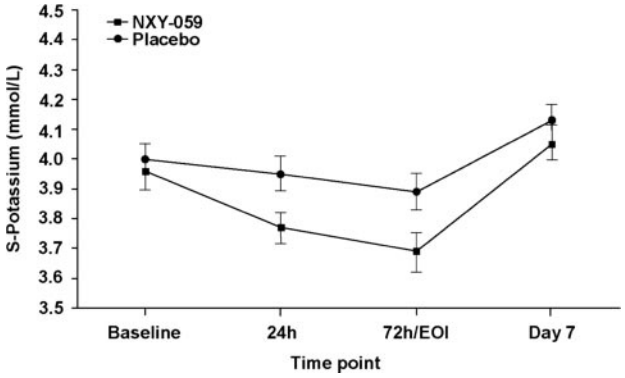

Figure 3. Serum potassium after enrollment into CHANT. At baseline and then after enrolment at 24 hours, 72 hours, or the end of the study drug infusion (EOI), or at 7 days, the mean (95% CI) serum potassium was calculated for each group. Although the differences are statistically significant after 24 and 72 hours, there were no adverse events or other clinical manifestations associated with this finding.

059–treated patients (202 events) compared with 121 (39.9%) placebo–treated patients (173 events). There was no consistent pattern to this difference and it was to a larger extent because of serious adverse events occurring beyond 1 week after end of study drug infusion. The incidence of the most common serious adverse events during the study is shown in Table 4. The most frequent event was stroke in evolution, and its incidence was similar in the 2 treatment groups (NXY-059 21.7% versus placebo 22.4%). Treatment was discontinued because of an adverse event in 18 (6.0%) NXY-059–treated and 20 (6.6%) placebo-treated patients; there were no differences in the incidence and type of serious adverse events leading to death (data not shown). There was no relationship between adverse events, serious adverse events, or mortality and creatinine clearance or steady-state plasma NXY-059 concentration (data not shown).

The mean serum potassium fell transiently in both treatment groups, with a nadir occurring by 72 hours after infusion began and recovering to baseline levels by 1 week (Figure 3). The decrease was greater in the NXY-059–treated patients. Hypokalemia was reported as an adverse event more frequently in patients receiving NXY-059 compared with placebo (17.7% versus 13.2% during the study, 13.7% versus 10.6% during infusion). There was no difference in other routine laboratory values and no difference in incidence of abnormalities and change from baseline in ECG parameters and vital signs.

There was no difference between the treatment groups for functional or neurological outcome. The distribution of the modified Rankin scores was similar in both groups at all time points (Figure 4). Similarly, there were no differences between the groups in the NIHSS, Barthel Index, and Stroke Impact Scale (data not shown).

Average hematoma volumes in the groups were similar at baseline: 22.4±20.1 mL (range 0.9 to 123.1 mL) in the NXY-059 group and 23.3±22.8 mL (0.5 to 144.4 mL) in the placebo group (mean±SD). Hematoma growth was slightly less in the NXY-059 group versus placebo, comparing baseline to 72 hours after treatment onset (Table 5), but not significantly different. Similarly, edema growth was comparable in both groups at baseline and after 72 hours of drug infusion (Table 5). There were no differences in volumes or hematoma growth noted when comparing patients presenting within 3 hours from onset to those presenting later. From the semi-quantitative brain maps, new brain areas were scored on the 72-hour scans (indicating hemorrhage extension) in 75 (26.0%) of NXY-059–treated patients, compared with 71 (24.5%) of placebo-treated patients. Considering only the patients with a serious adverse event report consistent with neurological deterioration or hemorrhage expansion, new brain regions were scored on the follow-up scans in 21/70 NXY-059 patients compared with 25/63 placebo-treated patients (not significant, chi-square). A ventricular drain was inserted in 20 NXY-059 and 11 placebo treated patients. Surgical evacuation of the ICH was performed in 4 NXY-059 and 5 placebo patients.

TABLE 4. No. (%) of Patients With Adverse Events During the Overall Study Period

Serious Adverse Event	NXY-059 (n=300)	Placebo (n=303)
Stroke in evolution	65 (21.7%)	68 (22.4%)
Pneumonia	17 (5.7%)	17 (5.6%)
Pulmonary embolism	7 (2.3%)	4 (1.3%)
Hemorrhagic stroke	6 (2.0%)	4 (1.3%)
Respiratory failure	6 (2.0%)	4 (1.3%)
Pneumonia aspiration	6 (2.0%)	8 (2.6%)
Arteriovenous malformation	5 (1.7%)	3 (1.0%)
Sepsis	4 (1.3%)	5 (1.7%)
Depressed level of consciousness	3 (1.0%)	0 (0.0%)
Ischemic stroke	3 (1.0%)	3 (1.0%)
Respiratory distress	3 (1.0%)	2 (0.7%)
Urinary tract infection	3 (1.0%)	0 (0.0%)
Neurological symptom	2 (0.7%)	3 (1.0%)
Respiratory tract infection	2 (0.7%)	3 (1.0%)

Adverse events were collected from investigator reports. This table lists the most common reported events, in order of frequency, from the overall study period (90 days). There are no significant differences. Similar tables covering just the study drug infusion period, or just the first week after enrollment, similarly showed no differences.

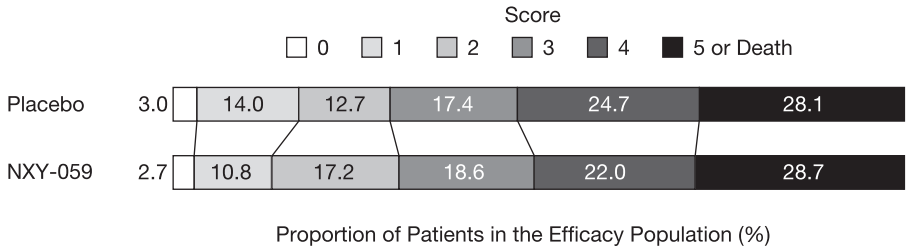

Figure 4. Functional outcome: modified Rankin Scale at 90 days. There was no difference in the distribution of modified Rankin Scale scores between the 2 treatment groups. Numbers within the panels are percentages, rounded to nearest decimal.

Discussion

This trial of NXY-059 treatment for acute ICH achieved the prespecified primary end point of safety: we detected no important differences between the groups with respect to adverse events, serious adverse events, or mortality (Table 4). CHANT was planned to run in SAINT 2 study sites, and the sample size was based on recruitment projections in those sites, not on a hypothesized event rate. With the numbers of patients recruited, the study had, for example, 80% power to detect a 5% absolute increase in adverse event reports, assuming a 2% rate in the placebo group. There was 90% power to detect a 6% increase. Small increases in adverse event frequency would require far greater numbers for detection. The groups were well balanced with respect to all important variables that might influence safety, and hence the data suggest NXY-059 appears to have a good safety profile in ICH patients. Although CHANT is the largest study completed to date of an investigational agent in ICH patients, the number of studied patients is small in relation to the potential clinical use of the drug.

In the CHANT trial, NXY-059 was associated with statistically significantly increased rates of hypokalemia, although the absolute reduction in serum potassium was small relative to placebo. An analogous finding was observed in the SAINT 1 trial of NXY-059 for ischemic stroke.[20] No data are available to suggest a mechanism for this effect. There was no associated adverse event or serious adverse event that occurred with the observed reduction in serum potassium, so the effect lacks any clinical significance in these study populations. Nonetheless, surveillance of serum potassium and other electrolytes are recommended as part of standard acute stroke management, with or without NXY-059 treatment.

TABLE 5. Hematoma and Edema Volume Change From Baseline at 72 Hours

Variable	NXY-059 (n=287)	Placebo (n=288)	*P* Value
Hematoma Volume change, mL	4.5 (1.5)*	6.7 (1.5)	0.188
Edema Volume change, mL	16.7 (1.4)	17.8 (1.4)	0.442
Total, mL	20.6 (2.6)	23.7 (2.6)	0.260

Baseline and 72 hours scans were compared for evidence of hemorrhage and edema. The difference between 72 hours and baseline volume was calculated for each patient, and the group means calculated after correcting for baseline volume. The resulting mean growth in lesion volume was compared between the 2 groups; there were no statistically significant differences.

*Least Squares Mean (SE).

NXY-059 had no effect on functional outcome, as measured by several accepted and valid rating scales (Figure 4). These data suggest that even if some subtle increase in the frequency of adverse events was overlooked in this trial, no adverse impact on functional outcome could be detected. Further, NXY-059 therapy did not exacerbate the natural enlargement of ICH over 72 hours after treatment; hemorrhage enlargement is an independent prognostic determinant of mortality and functional outcome.[22] If anything, the data are more consistent with attenuation of hemorrhage growth.

CHANT is the largest clinical trial to test the safety or efficacy of a neuroprotectant in patients with ICH. Three other trials of drugs with mechanisms very different from NXY-059—GAIN, CLASS-H, and IMAGES—used similar methods, and also found no effect, beneficial or harmful.[34–36] GAIN included 571 patients with presenting characteristics similar to CHANT; the agent studied, gavestinel (GV150526), blocks the glycine site of the n-methyl-D-aspartate receptor. In GAIN-ICH, mortality was 20% overall and similar in the 2 groups. The relatively smaller CLASS-H trial tested the safety of a GABA agonist, clomethiazole, in 96 ICH patients, compared with placebo in 102 ICH patients. In CLASS-H, the groups were imbalanced with respect to important variables that influence outcome, and the mortality was nominally higher in the clomethiazole group, compared with placebo, although multivariable logistic regression suggested the difference was attributable to the baseline imbalances, not the drug. In the IMAGES trial, magnesium was administered to 125 ICH patients and placebo to 122 ICH patients. The odds ratio for unfavorable outcome was 0.82 (95% CI 0.44 to 1.53). Taking CHANT, IMAGES, GAIN, and CLASS-H together, however, despite the fact that NXY-059 has a very different mechanism of action, suggests that putative neuroprotectants—at least for the classes of agents studied—to date appear to exhibit a good safety profile in ICH patients. No efficacy signal is apparent in the accumulated experience with neuroprotection to date.

We studied the safety of NXY-059 in an ICH population with similar severity of symptoms to that accumulated in the ischemia trials, SAINT-I and SAINT-2. Overall, these results suggest that NXY-059 is well tolerated with no safety concerns observed in ICH patients studied to date. No differences in the frequency of adverse events, serious adverse events, or mortality emerged from the study data. We found no treatment effect on functional outcome, either positive or negative, as measured by valid stroke rating scales. Hematoma volumes were similar in the 2 groups at

baseline and 72 hours after treatment. There is no suggestion that NXY-059 benefits ICH patients.

Appendix

The following participated in the CHANT study. Steering Committee: K.R. Lees, Glasgow, United Kingdom (chair); P. Lyden, San Diego, United States (Principal Investigator, CHANT); T.J. Ashwood, Södertälje, Sweden (sponsor representative); A. Davalos, Barcelona, Spain; S. Davis, Melbourne, Australia; H.-C. Diener, Essen, Germany; J. Grotta, Houston, United States; A. Shuaib, Edmonton, Canada; W.W. Wasiewski, Wilmington, United States (sponsor representative). Data and Safety Monitoring Board: S. Pocock, London, United Kingdom (chair); H. Adams, Iowa, United States; P. Bath, Nottingham, United Kingdom; D. Oakes, Rochester, United States; N.-G. Wahlgren, Stockholm, Sweden. Study Team Leader: K. Svensson, Södertälje, Sweden. Study Team Physicians: H.-G. Hårdemark, G. Åhlberg, Södertälje, Sweden; L. Rodichok, Wilmington, United States. Study Team Statisticians: H.H. Svensson, Södertälje, Sweden; V. Alderfer, U. Emeribe Wilmington, United States. Clinical Coordinating Center: UCSD Clinical Trials Coordinating Center, P. Lyden, Coordinating Investigator, K. Rapp, Project Manager. Contract Research Organizations: Perceptives Informatics (IVRS system and neuroimaging); Diagnostic Technology and Services Research Technology Limited (Central ECG reader); Covance Central Laboratory Services SA (Central Laboratory).

Clinical Centers

CHANT Study Investigators (Enrollment)

Australia: S. Davis, Melbourne (4); C. Staples, Brisbane (1); C. Levi, New Castle (1); C. Bladin, Melbourne (8); G. Donnan, Melbourne (2); D. Crimmins, Gosford (4); R. Gerraty, Melbourne (3). Belgium: G. Vanhooren, Brugge (2); P. De Deyn, Antwerpen (6); V. Thijs, Leuven (5); C. Willems, Hasselt (2); E. Urbain, Montignies-sur-Sambre (2). Brazil: A. Massaro, Sao Paulo (1); M.A. Friedrich, Porto Alegre (2). Bulgaria: P. Stamenova, Sofia (4); D. Minchev, Varna (2); V. Platikanov, Pleven (7); T. Notcheva, Russe (9). Canada: A. Shuaib, Edmonton (10); D. Selchen, Mississauga (10); P. Teal, Vancouver (3); S. Phillips, Halifax (2); C. Voll, Saskatoon (4); D. Howse, Thunder Bay (2); L. Berger, Greenfield Park (3); D. Gladstone, Toronto (4). Czech Republic: J. Bauer, Prague (4); M. Bar, Ostrava-Poruba (9); D. Vaclavik, Ostrava-Vitkovice (10); H. Lachmann, Prague (9); O. Skoda, Pelhrimov (5). France: C. Lucas, Lille (3); P. Amarenco, Paris (16); P. Labauge, Nimes (1); F. Ziegler, Belfort (1); T. Moulin, Besancon (3); J. Bouillat, Bourg En Bresse (4); A. Bonafe, Montpellier (2); D. Sablot, Perpignan (3); B. Guillon, Saint Herblain (4). Germany: H.C. Diener, Essen (2); J. Glahn, Minden (4); D. Schneider, Leipzig (11); C. Weiller, J. Liepert, Hamburg (4); A. Hetzel, T. Els, Freiburg (8); P. Vogel, Hamburg (5). Hong Kong: L. Wong, Hong Kong (5); P.W. Ng, Hong Kong (1). Hungary: N. Szegedi, Budapest (20); L. Csiba, Debrecen (4); S. Horváth, Kistarcsa (5); A. Csányi, Györ (8); J. Nikl, Zalaegerszeg (1); B. Clemens, Debrecen (17). Italy: G. Micieli, Pavia (5); G. Agnelli, Perugia (1). New Zealand: A. Barber, Auckland (4). Portugal: L. Cunha, Coimbra (7); M. Correia, Porto (3); V. Salgado, Amadora (10); G. Gonçalves, Coimbra (3). Singapore: I. Ng, Singapore (15); N. Chou, Singapore (5); J. Thomas, Singapore (3). Slovak Republic: M. Brozman, Nitra (8); M. Nyéky, Roznava (2); J. Vyletelka, Zilina (6); M Dvorák, Levoca (11); E. Kurca, Martin (4); J. Herényiová, Lucenec (1). South Africa: J. Gardiner, Cape Town (1); J. Thorne, George (1); J. Roos, Somerset West (5); M. Isaacs, Morningside (1). South Korea: J.-S. Kim, Seoul (6); B.-C. Lee, Anyang-Si (5). Spain: J. Serena Leal, Gerona (18); J Roquer, Barcelona (6); E. Díez Tejedor, Madrid (2); J. Matias Guiu, J.M. Molto Jorda, Alicante (5); A. Chamorro, Barcelona (14); F. Nombella, Madrid (3); J. Castillo, Santiago (5); J.R. González Marcos, Sevilla (8); A. Dávalos, Badalona (17); J. Alvarez Sabin, Barcelona (16); F. Rubio, Barcelona (2). United Kingdom: K. Lees, Glasgow (3); G. Ford, Newcastle-on-Tyne (1). United States: M. Nash, Decatur, Ga (13); N. Iannuzzi III, Winston-Salem, NC (9); J. Grotta, Houston, Tex (7); B. Cucchiara, Philadelphia, Pa (6); J. Harris, Ft. Lauderdale, Fla (6); T. Hemmen/P. Lyden, San Diego, Calif (6); W. Holt, Port Charlotte, Fla (6); M. Tremwell, Ft. Smith, Ariz (6); C. Chang, Honolulu, Hawaii (5); D. Chiu, Houston, Tex (5); H. Sachdev, San Jose, Calif (4); L. Wechsler, Pittsburgh, Pa (4); E. Wilson, Bristol, Tenn (4); B. Demaerschalk, Phoenix, Ariz (3); J. Kooiker/J. McDowell, Olympia, Wash (3); K. Levin, Ridgewood, NJ (3); J. Sander, Toledo, Ohio (3); R. Silbergleit, Ann Arbor, Mich (3); R. Stephens, Concord, Calif (3); R. Brooks, Schenectady, NY (2); N. Culligan, Danbury, Conn (2); B. Dandapani, Melbourne, Fla (2); J. Gebel, Louisville, Ky (2); C. Graffagnino, Durham, NC (2); J. Hanna, Cleveland, Ohio (2); D. Heiselman, Akron, Ohio (2); K. Ng, Ocala, Fla (2); W. Truax, Marrero, La (2); P. Akins, Sacramento, Calif (1); S. Arkin, Kansas City, Mo (1); F. Chang, Ft. Wayne, Ind (1); C. Gomez, Birmingham, Ala (1); M. Jacoby, Des Moines, Iowa (1); L. Larsen, Holmdel, NJ (1); A. Majid, East Lansing, Mich (1); S. Mallenbaum, Virginia Beach, Va (1); G. Newman, Madison, Wis (1); N. Papamitsakis, Edison, NJ (1); A. Turel Jr, Danville, Pa (1).

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