SA-NXY-0012

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: NXY-059
ACTIVE INGREDIENT: disufenton sodium

Trial title: CHANT (Cerebral Hemorrhage And NXY Treatment) A double-blind, randomized, placebo-controlled, parallel-group, multicenter, Phase IIb study to assess the safety and tolerability of 72 hours intravenous infusion of NXY 059 in adult patients with acute intracerebral hemorrhage (ICH).
Developmental phase: II (discontinued)
First subject recruited: 07 August 2004
Last subject completed: 19 January 2006
Approval date: 01 August 2006

OBJECTIVES

Primary objective:

To assess the safety and tolerability of NXY-059 compared to placebo in patients with acute intracerebral hemorrhage (ICH) by assessment of mortality (overall and by cause), the incidence of serious adverse events (SAEs), the incidence of adverse events (AEs), change from baseline in laboratory parameters, change from baseline in vital signs, incidence of abnormalities and change from baseline in electrocardiogram (ECG) parameters, and change from baseline in computed tomography (CT) / magnetic resonance imaging (MRI) scans.
Note: NXY-059 is also referred to as disufenton sodium.

Secondary objectives:

- To explore the efficacy of NXY-059 compared to placebo in patients with acute ICH by evaluating the recovery with respect to global disability, neurologic recovery, functional recovery and patient-reported outcomes.
- To investigate the pharmacokinetics (PK) of NXY-059 in patients with acute ICH.

METHODS

Study design

A double-blind, randomized, placebo-controlled, parallel-group, international, multicenter study designed to primarily evaluate safety and tolerability, and to secondarily study the efficacy on global disability and neurologic recovery of 72 h intravenous (iv) infusion of NXY-059 in acute

global disability and neurologic recovery of 72 h intravenous (iv) infusion of NXY-059 in acute ICH patients within 6 h of onset of symptoms. The total number of patients planned was 600 at 100 to 200 sites. Randomization was stratified for the total ICH score at admission (range of scores: 0, 1, 2, ≥3) and for country. By demonstrating the safety of NXY-059 in ICH patients, this study would provide important data to support initiation of therapy with NXY-059 in patients with suspected acute ischemic stroke (AIS) without delay (eg, prior to neuroimaging). The protocol specified a study visit at Day 90 ±7 days but, for analysis purposes, the time window was Day 90 ±10 days.

Target patient population and sample size
Males and females at least 18 years old with a clinical diagnosis of an acute stroke with limb weakness as part of the presenting deficit(s), and a CT/MRI scan showing an ICH. To be eligible for randomization, patients were required to have a total National Institutes of Health Stroke Scale (NIHSS) score ≥6 at admission, with the sum of scores on Items 5 and 6 to be ≥2, and full functional independence prior to the present stroke indicated by an estimated pre-morbid modified Rankin Scale (mRS) score of 0 or 1. Patients were also required to have onset of symptoms within 6 h of the planned start of infusion (SOI). Unconscious patients, indicated by a score of 3 on Item 1a (Level of Consciousness) on the NIHSS were excluded, as were patients with severe renal impairment (ie, calculated creatinine clearance [CLcrea] <30 mL/min).
The sample size was not based on any formal hypothesis testing. With a sample size of 300 patients per treatment group, there was a reasonable chance to detect AEs with an incidence of ≥1%.

Investigational product and comparator: dosage and mode of administration
NXY-059 concentrate for solution for infusion 400 mg/mL, diluted to 15 mg/mL with 0.9% sodium chloride, and placebo concentrate sodium chloride 80 mg/mL, diluted with 0.9% sodium chloride. Dose administration was a 72 h iv infusion comprised a 1-h loading dose (LD) 2270 mg/h and a 71-h maintenance dose (MD) up to 960 mg/h, adjusted for calculated (CLcrea), with maximum dose (960 mg/h) to patients with CLcrea >80 mL/min, and reduced infusion rates to patients with CLcrea 30-50 mL/min (480 mg/h), and >50-80 mL/min (660 mg/h), respectively.

Duration of treatment
Treatment duration of 72 h.

Criteria for evaluation (main variables)

Safety: Primary variables included the incidence of mortality (overall and by cause) and standard safety assessments such as AEs and SAEs, clinical laboratory data (hematology, clinical chemistry [including hepatic and renal variables], and urinalysis), vital signs, ECGs, physical examination, and change from baseline in CT/MRI scans with special attention to patients with progression of stroke, and New stroke SAEs specified by the protocol.

Efficacy: Secondary variables assessed by mRS score at last rating (Day 90 for completers) and at Days 7, 30 and 90; total NIHSS score and change from baseline in total NIHSS score at last rating (Day 90 for completers), and at 24 h, end of infusion (EOI), Days 7 and 90; Barthel Index (BI) score at last rating (Day 90 for completers), Days 7, 30 and 90; and scores on the domains of the Stroke Impact Scale (SIS) and the SIS-Visual Analog Scale (VAS) at Day 90.

Pharmacokinetics:
Secondary variables included: Dose, actual dose and target dose (based on calculated CLcrea); Total plasma concentration at 1 h and 66 to 72 h; unbound plasma concentration and fraction unbound in plasma (fu) at 66 to 72 h; calculated unbound plasma concentration at 1 h and 66 to 72 h.

Statistical methods
For safety (primary variable): The primary analysis of all-cause mortality rate was performed with a logistic regression adjusting for total NIHSS score at baseline (continuous), and ICH score (0, 1, 2, ≥3). For efficacy (secondary variables): The main analysis methodology for binary or ordinal variables was the Cochran-Mantel-Haenszel (CMH) test with modified ridit score. The main effects in the model were treatment group, ICH score (0, 1, 2, ≥3), and total NIHSS at baseline (categorized). Additionally, for selected analyses, a parallel logistic regression model was produced with the same main effects, except that baseline NIHSS was applied as a continuous variable, to provide the odds ratio (OR) and 95% confidence interval (CI) with a p-value. The primary statistical methodology for the mRS and NIHSS at last rating was the CMH test. All efficacy and safety variables were summarized with descriptive statistics. The ordinal and binary category variables were summarized within each category and treatment group with number and percentage. For continuous variables, the sample size, mean and standard deviation (SD) and, in some cases, the least square (LS) mean and standard error (SE) by treatment group were generated. P-values were generated for pre-specified analyses as appropriate.

RESULTS

Patient population
Of the 615 patients enrolled into the study, 607 were randomized to study treatment and 8 patients were not randomized due to eligibility criteria not fulfilled (7 patients) and AE (1 patient). Of these 607 patients randomized, 603 received treatment and were included in the primary safety evaluation. The full analysis data set for mRS (FADS-mRS) included 595 patients.

Table S1 Patient population and disposition

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		NXY-059	Placebo	Total
Population				
N randomized		305	302	607
N randomized but not treated		3	1	4
N misrandomized to treatment		3	1	4
Disposition		300	303	603
N of patients who	completed treatment	262	265	527
	discontinued treatment	38	38	76
	completed Day 90 visit	231	237	468
N analyzed for safety [a]		300	303	603
N analyzed for efficacy (FADS mRS)		296	299	595
N analyzed for efficacy (PP mRS)		248	251	499
N analyzed for pharmacokinetics (PKFADS)		281		

[a] NXY-059 (accounting for 305 randomized and 300 treated): 3 were not treated, 3 received placebo, and 1 patient randomized to placebo received NXY-059.
Placebo (accounting for 302 randomized and 303 treated): 1 was not treated, 1 received NXY-059, and 3 patients randomized to NXY-059 received placebo.

FADS is full analysis data set; N is number; PP is per-protocol population; PK is pharmacokinetics; mRS is modified Rankin Scale

The study population was representative of an ICH patient population with mild to moderate severity and was well balanced across the treatment groups for demographic and baseline characteristics, including neuroimaging variables. The patient population was predominantly male (64.5%), Caucasian (83.4%), and aged 66 years on average, with a history of hypertension (81.6%). The mean (range) NIHSS score at admission was 13.9 (6 – 33). The 72 h infusion was completed by 87.4% of the patients, and 77.6% completed the Day 90 visit.
Use of concomitant medications was well balanced across treatment groups. The use of any type of anticoagulant at the onset of the ICH was not different in the 2 groups (NXY-059 7.3%, placebo 6.9%). At the onset of the ICH, 23.5% of patients were taking antiplatelet agents and 6.9% of patients were taking vitamin K antagonists. The predominant cause of ICH as judged by the investigator was “spontaneous, associated with hypertension” (85.1%); ICH due to use of anticoagulants was 2.5%.

Safety results (Primary)
Administration of NXY-059 was well tolerated and generally safe in patients with ICH. The overall mortality in the NXY-059 group was 20.3% (61 deaths) compared to 19.8% (60 deaths) in the placebo group, and was not statistically different in a logistic regression analysis (p=0.981, OR 0.99 with 95% CI 0.65 to 1.52). Time to death, analyzed with a logrank test, also was not significantly different (p=0.860).

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The incidence of AEs and the pattern of AEs were similar in the NXY-059 and placebo groups (Table S2), with the exception of hypokalemia, which was reported more frequently in patients receiving NXY-059 compared to those receiving placebo (17.7% vs 13.2%) (Table S3); none of these events of hypokalemia was reported as an SAE.

Table S2 Overall AE experience (Safety population)

AE category	NXY-059 (N=300)	Placebo (N=303)
Number of patients with AE(s)	265 (88.3%)	266 (87.8%)
Number of AEs	1094	1121
Number of patients with SAEs	138 (46.0%)	121 (39.9%)
Number of patients with SAE(s) assessed as causally related to study treatment	1 (0.3%)	3 (1.0%)
Number of patients who died	61 (20.3%)	60 (19.8%)
Number of patients with non-fatal SAE(s)	100 (33.3%)	78 (25.7%)
Number of patients discontinued from treatment due to an AE [a,c]	18 (6.0%)	20 (6.6%)
Number of patients discontinued from the study due to an AE [b,c]	62 (20.7%)	61 (20.1%)

[a] The proportion of patients discontinued from treatment due to a fatal SAE was 3.7% in the NXY-059 group and 3.6% in the placebo group.

[b] The proportion of patients discontinued from study due to a fatal SAE was 20.0% in the NXY-059 group and 19.8% in the placebo group. One NXY-059 patient (E3005507) had an SAE (stroke in evolution) before start of infusion, was discontinued from the study, and later died. This patient is counted in the overall deaths, but is not counted in the discontinuations from study due to an AE because all AEs that began prior to start of infusion were excluded from all summary tables and analyses.

[c] A patient could have treatment discontinued but continue in study, or complete treatment but be subsequently discontinued from the study, or appear in both categories of discontinuations.

AE is adverse event; SAE is serious adverse event

Table S3 **Number of patients with adverse events by preferred term and most frequent (>5% in NXY-059 group), overall study period (safety population)**

Preferred term	NXY-059 (N = 300)	Placebo (N = 303)
Pyrexia	86 (28.7%)	87 (28.7%)
Stroke in evolution	66 (22.0%)	71 (23.4%)
Hypokalaemia	53 (17.7%)	40 (13.2%)
Constipation	51 (17.0%)	50 (16.5%)
Headache	42 (14.0%)	45 (14.9%)
Agitation	27 (9.0%)	22 (7.3%)
Vomiting	26 (8.7%)	33 (10.9%)
Hypertension	25 (8.3%)	34 (11.2%)
Nausea	24 (8.0%)	26 (8.6%)
Urinary tract infection	23 (7.7%)	27 (8.9%)
Anxiety	21 (7.0%)	18 (5.9%)
Pneumonia	20 (6.7%)	27 (8.9%)
Hyperglycaemia	18 (6.0%)	10 (3.3%)

Sorted by most frequent in NXY-059 group.
% is proportion of patients in each category within treatment group and analysis population (N).

The number of patients with SAEs was higher (138 patients, 46.0%) in the NXY-059 group compared to the placebo group (121 patients, 39.9%). However, no individual or group of related SAE preferred terms accounts for this difference.

- All SAEs: The most common SAEs in the overall study period, with a similar incidence in both treatment groups, were stroke in evolution and pneumonia.
- Fatal SAEs: For the overall study period and during infusion, the incidence and types of fatal SAEs were similar in the 2 groups. The most common fatal SAEs were stroke in evolution and pneumonia and the incidence of each was similar in the treatment groups.
- Non-fatal SAEs: There were more patients with non-fatal SAEs in the NXY-059 group compared to placebo for the overall study period (33.3% vs 25.7%), and during infusion (17.7% vs 14.2%). Stroke in evolution was the most common nonfatal SAE, and its incidence was similar in the NXY-059 and placebo groups for the overall study period (13.0% vs 12.5%). No individual or group of related non-fatal SAE preferred terms accounts for this difference in the incidence of non-fatal SAEs.

No differences were noted in the incidence of discontinuation of treatment due to an AE or of discontinuation from study due to an AE.

The effect of NXY-059 treatment on the evolution of ICH was evaluated by neuroimaging and by SAE reporting. All neuroimaging scans were assessed by a central reader blinded to treatment

SAE reporting. All neuroimaging scans were assessed by a central reader blinded to treatment. No differences were found in the evolution of hematoma or edema volumes, the extent of ventricular blood, or the degree of hydrocephalus. As expected in ICH patients, the edema and hematoma volume increased from baseline to 72 h for both groups. Although the increase was smaller in the NXY-059 group compared to placebo, the 95% CI of the observed difference among treatment groups included 0, suggesting no treatment effect. Extension of the hemorrhage into adjacent location(s) and/or appearance of new hemorrhage in a separate location(s) was equally frequent in both groups.

To further evaluate the effect of NXY-059 on ICH, a group of related SAE preferred terms indicating progression of stroke were reviewed. The incidence of stroke progression was similar in the 2 groups for the overall study period. Additionally, the incidence of surgical hematoma evacuation was similar between the groups.

There were no differences in the AE incidence between treatment groups for the predefined specific diagnosis/symptom groups of respiratory tract infections, cardiac failure, ventricular arrhythmias, ischemic heart disease (IHD), myocardial infarction (MI), non-intracranial hemorrhage, infusion site reactions or hepatic impairment. The overall reporting of preferred terms related to renal impairment was higher in the NXY-059 group (4.0%, 12 patients) than in the placebo group (2.3%, 7 patients), and was mainly reported during infusion (6 NXY-059 patients and 1 placebo patient). There was 1 fatal SAE related to renal failure in the placebo group, and none in the NXY-059 group. The clinical significance of these findings is uncertain given the relatively small numbers of patients involved.

Analyses based on pre-specified subgroups (eg, age, gender, CLcrea, Cu,ss >400 μmol/L), did not reveal any clinically meaningful differences from the overall population in the AE profile of NXY-059 relative to the appropriate comparator group.

With the exception of serum potassium, no clinically relevant differences between treatment groups were observed in clinical laboratory assessments, including serum creatinine, liver function tests, or urinalysis. A total of 169 patients had a serum potassium value below 3.5 mmol/L at 24 h and/or 72 h, 111 patients (37.0%) in the NXY-059 group and 58 patients (19.1%) in the placebo group. However, no differences in serum potassium between the groups were noted by the Day 7 assessment.

No significant differences were noted in changes from baseline in vital signs, ECGs and QTc intervals between the NXY-059 and placebo groups.

Efficacy and pharmacokinetic results (secondary)

The study did not demonstrate a difference between NXY-059 and placebo on functional, neurologic or patient reported outcomes as measured by the mRS (OR 1.01, 95% CI 0.75 to 1.35), NIHSS, BI or SIS. These findings suggest that NXY-059 did not demonstrate a detrimental or beneficial effect on these outcome measures as assessed at 90 days in ICH patients in this study.

The doses used were targeted to achieve a mean steady-state unbound NXY-059 plasma concentration of 260 μmol/L with at least 90% of the patients >150 μmol/L and <5% of the patients >400 μmol/L. The mean target unbound plasma concentration of NXY-059 (260 μmol/L)

patients >400 μmol/L. The mean target unbound plasma concentration of NXY-059 (260 μmol/L) was rapidly achieved with a 1-h LD followed by a 71-h MD and maintained consistently across the 3 CLcrea cut-offs. Steady-state unbound plasma concentrations of NXY-059 >150 μmol/L were achieved in 94.6% of patients and >400 μmol/L occurred in 13.3% of the patients. The mean calculated Cu,66-72h of NXY-059 when overdose patients and outlier values were excluded was 299.4, 280.5, and 311.4 μmol/L in the CLcrea cut-off groups >80, >50-80, and 30-50 mL/min, respectively, and the overall mean was 295.8 μmol/L.

REFERENCE

Lyden P., Shuaib A., Lees K.R., Davalos A., Davis S.M., Diener H.-C., et al 2007. Safety and Tolerability of NXY-059 for Acute Intracerebral Hemorrhage. The CHANT trial. Stroke 38:2262-2269.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing NXY-059 (disufenton sodium), Healthcare Professionals should view their specific country information.