SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: NXY-059

ACTIVE INGREDIENT: disufenton sodium

Trial title (number): SAINT I (Stroke – Acute Ischemic – NXY Treatment) A Double Blind, Randomized, Placebo Controlled, Parallel Group, Multicenter, Phase IIb/III Study to Assess the Efficacy and Safety of Intravenous NXY-059 in Acute Ischemic Stroke.

Developmental phase: III (discontinued)
First subject recruited: 11 June 2003
Last subject completed: 18 February 2005
Approval date: 06 March 2006

OBJECTIVES:

Primary objective:
To demonstrate the efficacy of NXY-059 compared to placebo in subjects with acute ischemic stroke (AIS). This objective was addressed first by the statistical testing of global disability as measured by the modified Rankin Scale (mRS) at last rating (primary variable); and second by the statistical testing of neurologic recovery as measured by the change from baseline in the total National Institutes of Health Stroke Scale (NIHSS) score at last rating (co-primary variable).

Note: NXY-059 is also referred to as disufenton sodium.

Secondary objectives:
- To explore the efficacy of NXY-059 compared to placebo on global disability, and functional and neurologic recovery as measured by the mRS and Barthel Index (BI) scores at Day 7, Day 30, Day 90 and BI at last rating, and measured by the total NIHSS score and change from baseline in NIHSS score at 24 h, end of infusion (EOI), Day 7, and Day 90. The total NIHSS score was also measured at last assessment.
- To evaluate the effects of NXY-059 compared to placebo on the ability of the patients to perform activities of daily living (ADL), mobility, and hand function as measured by the Stroke Impact Scale (SIS) physical domain SIS-16, and the SIS domain scores for communication, memory and thinking, emotional function, and social participation, at Day 90.
- To evaluate the effects of NXY-059 compared to placebo on patient's self-reported health status and health-related quality of life (HRQL) respectively, using the EQ-5D instrument at Day 90.
- To evaluate the safety and tolerability of NXY-059 compared to placebo.
- To characterize the pharmacokinetics (PK) of NXY-059 in patients with AIS.
- To evaluate the effects of NXY-059 compared to placebo on residence/location of care of patients with AIS during the 90-day follow-up period.

METHODS:

Study design
A randomized, double-blind, placebo-controlled, parallel group, international, multicenter study designed to demonstrate efficacy on global

A randomized, double-blind, placebo-controlled, parallel group, international, multicenter study designed to demonstrate efficacy on global disability and neurologic recovery, and to evaluate safety of a 72-h intravenous (iv) infusion of NXY 059 in AIS patients. The total number of patients planned was 1700 at approximately 200 centers. Randomization was stratified for the total NIHSS score at admission (range of scores: 6-9, 10-14, 15-19, and≥20), side of infarct (right or left), thrombolytic treatment with or intent to treat with recombinant tissue plasminogen activator (rt-PA), and country.

Target patient population and sample size

Males and females randomized to treatment, at least 18-years old, with a clinical diagnosis of an AIS and neuroimaging excluding other causes, and with limb weakness alone or in combination with other deficits. To be eligible for randomization, patients were required to have a total NIHSS score≥6 at baseline with the sum of scores on Items 5 and 6 (arm and leg motor function) to be≥2; and full functional independence prior to the present stroke (estimated pre-morbid mRS score = 0 or 1). Unconscious patients, indicated by a score of 2 or 3 on Item 1a (Level of consciousness) on the NIHSS were excluded, and so were also patients with severe renal impairment (a calculated creatinine clearance (CLcrea) <30 mL/min).

Using an alpha level of 5%, a power of 90% and an assumed mRS distribution of NXY-059 and placebo resulting in an approximate odds ratio (OR) of 1.3, a sample size of 850 treated patients per group was derived.

Investigational product and comparator

Dosage and mode of administration

NXY-059 concentrate for solution for infusion (400 mg/mL), diluted to 15 mg/mL, and placebo. Dose administration: 72-h iv infusion - 1 h loading dose (LD) 2270 mg/h and 71 h maintenance dose (MD) up to 960 mg/h adjusted for renal function defined by calculated CLcrea, with the maximum dose to patients with CLcrea >80 mL/min, and with reduced infusion rates to patients with CLcrea 30-50 mL/min, and >50-80 mL/min, respectively.

Study duration and duration of treatment

Treatment duration of 72 h and a follow-up period through Day 90.

Criteria for evaluation (main variables)

Efficacy: Primary variable was assessed by mRS score at last rating, and the secondary variables included mRS at Days 7, 30 and 90. Co-primary variable was assessed by change from baseline in total NIHSS score at last rating, and secondary variables included total NIHSS score and change from baseline in total NIHSS score at 24 h, end of infusion (EOI), Days 7, and 90, and in total NIHSS score at last rating. Other secondary efficacy variables included BI score at last rating, Days 7, 30 and 90; scores on the respective domains of the SIS and the SIS Visual Analog Scale (VAS), all at Day 90; and EQ-5D Weighted Index based on health states, and the EQ-5D VAS, both at Day 90.

Safety: Secondary variables included incidence of mortality and standard safety assessments such as adverse events (AEs) and serious adverse events (SAEs), clinical laboratory data (hematology, clinical chemistry [including hepatic and renal variables], and urinalysis), vital signs, electrocardiograms (ECGs), and physical examination. Baseline neuroimaging scans were evaluated in all patients and follow-up scans were taken in patients with progressive stroke, new stroke, and concomitant treatment with rt-PA.

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 unbound fraction (fu) at 66 to 72 h; calculated unbound plasma concentration at 1 h and 66 to 72 h.

Statistical methods

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 standard error (SE) by treatment group was generated. P-values were generated for pre-specified analyses as

and in some cases the standard error (SE) by treatment group was generated. P-values were generated for pre-specified analyses as appropriate. For efficacy: the primary analysis methodology for binary or ordinal variables when performed used the Cochran-Mantel-Haenszel (CMH) test with modified ridit score and the main covariates in the model were treatment group, side of infarct, total NIHSS at baseline (categorized) and intent-to-treat or treated with rt-PA. Additionally, for selected analyses, a parallel logistic regression model was produced with the same main effects except baseline NIHSS was applied as a continuous variable to provide the odds ratio, 95% confidence interval (CI) with p-value. The primary statistical methodology when applied to continuous variables was the analysis of covariance (ANCOVA) with least square means (LSmeans) calculated and with the same main effects used for logistic regression analyses. The primary analysis of all-cause mortality rate was performed with a logistic regression adjusting for total NIHSS score at baseline (continuous), side of infarct, and intent-to-treat or treatment with rt-PA. The study was designed to use a sequential testing method on a series of efficacy measures, beginning with the primary analysis of the mRS at last rating and continuing through pre-specified measures until one resulted in a non-significant p-value. The complete sequential testing series for efficacy variables is presented in Table S2.

RESULTS:

Patient population

A total of 1722 patients were randomized into the study and of these, 1705 received treatment and were included in the safety evaluation (Table S1). The full analysis data set (FADS) included 1703 patients with 1699 patients evaluable for the analysis of the primary variable (ie, mRS at last rating). The 72-h infusion was completed by approximately 90% of the patients, and 81% completed the Day 90 visit. The most frequent reason for discontinuation from the study was adverse events: 148 patients (145 deaths) in the NXY-059 group and 142 patients (141 deaths) in the placebo group discontinued because of an adverse event.

Table S1 Patient population and disposition

Table S1 Patient population and disposition

Disposition and analysis populations		NXY-059	Placebo	Total
N randomized		861	861	1722
N randomized but not treated		8	9	17
Disposition of the safety population				
N analyzed for safety [a]		858	847	1705
N (%) of patients who	Completed treatment	777 (90.6%)	756 (89.3%)	1533 (89.9%)
	Discontinued treatment	81 (9.4%)	91 (10.7%)	172 (10.1%)
	Completed Day 90 visit	698 (81.4%)	689 (81.3%)	1387 (81.3%)
Other analysis populations				
N analyzed for efficacy (FADS) [b]		852	851	1703
N analyzed for efficacy (FADS-mRS)		850	849	1699
N analyzed for efficacy (PP-mRS)		762	761	1523
N analyzed for pharmacokinetics (PKFADS)		826	0	826

[a] Number of patients who received any dose of study drug treatment (by actual treatment received).

[b] Number of patients who received any dose of study drug treatment (by the treatment to which the patient was randomized) and with any efficacy data available after start of study drug treatment.

N is Number; FADS is Full analysis data set; mRS is modified Rankin Scale; PP is Per-protocol population; PKFADS is Full analysis data set for patients in pharmacokinetic evaluation.

In both groups, the proportion of women was approximately 45%. The mean age was 68.4 years, with a similar range within each group and with approximately one third of the patients in each age category (ie, 18 to 64, 65 to 74, and≥75 years of age). The demographic and baseline characteristics were balanced across the treatment groups and the patient population recruited was considered to be representative of the intended AIS population to be treated in clinical practice. Overall, 28.7% of the patients in the study were treated with rt-PA, the mean NIHSS score at admission was 12.6 (range=6 to 32), and the mean time from stroke symptom onset to start of infusion was 3 h, 46 min (range=1 h, 5 min to 6 h).

Efficacy results

Administration of NXY-059 as a 72-h infusion to AIS patients within 6 h of stroke symptom onset resulted in a statistically significant reduction in functional disability compared to administration of placebo (p=0.038) as measured by the mRS at last rating (the primary endpoint). In a logistic regression analysis adjusted for the same baseline variables as the primary analysis, the estimate of the OR was 1.20 (95% CI: 1.01-1.42). The evaluation of mRS at last rating using the PP population, performed as a sensitivity analysis to the primary analysis, demonstrated a statistically significant difference in treatment effect with NXY-059 relative to placebo (p=0.028) and lends further support to the effect seen in

statistically significant difference in treatment effect with NXY-059 relative to placebo (p=0.028) and lends further support to the effect seen in the primary analysis.

This treatment effect on the mRS was evident at the earliest time point assessed (Day 7) through the end of the study (Day 90). The effect was also evident across the full range of baseline stroke severities, use with or without rt-PA, and across the 6 h time window from stroke symptom onset to initiation of treatment. In addition to the modest overall treatment effect, NXY-059 treatment resulted in a better score than placebo for all dichotomizations of the mRS. Treatment with NXY-059 demonstrated a statistically significant effect over placebo for 2 of these dichotomizations: 4.4% more patients achieved a complete recovery with no symptoms from their acute ischemic stroke (mRS=0 vs 1-5/death; p=0.003; OR=1.54; 95% CI 1.15-2.07) and 3.7% more patients were able to walk independently and were less dependent on others for bodily needs (mRS=0-3 vs 4-5/death; p=0.024; OR=1.27; 95% CI 1.01-1.58).

The co-primary endpoint, the change from baseline in total NIHSS score at last rating, analyzed by the pre-specified ANCOVA test (parametric method) did not demonstrate an effect of NXY-059 on neurologic recovery (p=0.864). However, the skewed bimodal distribution of the NIHSS results and the disproportionate weight given to deaths did not support the use of this analysis method. In addition, the total (final) NIHSS score was more representative of a patient's final outcome and more clinically relevant than the change from baseline in the NIHSS score when comparing differences in outcome across the entire scale. Consequently, a post hoc, nonparametric CMH analysis of the total (final) NIHSS score was done (with worst score of 42 imputed for death), and showed a p-value of 0.099 for the effect of NXY-059 versus placebo at last rating. In addition, when NIHSS scores at each time point were evaluated using this methodology (CMH test on the total NIHSS score), NXY-059 demonstrated significant ($p<0.05$) effects over placebo at all time points (24 h through Day 90) based on observed total NIHSS scores (ie, with deaths not imputed).

Although results for the other secondary measures of functional disability (BI) and patient-reported health-related quality of life (SIS and EQ-5D) were almost universally in favor of NXY-059 (ie, point estimates in the NXY-059 group better than in the placebo group), they did not demonstrate statistically significant effects of NXY-059 compared to placebo, with the exception of the SIS-Visual Analog Scale and the Day 7 and Day 30 assessments for the BI.
The results of the primary analysis of the efficacy variables (mRS, NIHSS, BI, SIS, and EQ-5D) at Day 90 or last rating are summarized in Table S2 according to the sequential testing method pre-specified in the protocol and statistical analysis plan. The primary mRS analysis was statistically significant, but analysis of the subsequent endpoint (change from baseline at last rating in NIHSS score) was not. Therefore, all p-values presented in Table S2, after change from baseline at last rating in total NIHSS score, represent only nominal p-values. For mRS and BI, percentage and number of patients is presented in Table S2. For other variables, the least squares mean (LSmean) and standard error (SE) are given.

Table S2 **Overview of efficacy according to pre-specified sequential testing, at Day 90 or last rating**

Group order	Outcome variable, [a] Analysis population	Category	NXY-059 [b]	Placebo [b]	NXY-059 vs Placebo [c]	p-value [d]
1	mRS, FADS-mRS		850	849		
		0	15.4% (131)	11.0% (93)	4.4%	
		1	18.0% (153)	20.0% (170)	-2.0%	
		2	11.4% (97)	11.7% (99)	-0.3%	
		3	14.2% (121)	12.7% (108)	1.5%	
		4	16.9% (144)	20.6% (175)	-3.7%	
		5/death	24.0% (204)	24.0% (204)	0.0%	0.038 *
2	Change from baseline in total NIHSS, FADS-NIHSS		851	851		
			-1.8 (0.5)	-1.7 (0.5)	-0.1 (-1.4,1.1)	0.864
3	BI (dichotomized), FADS-BI		850	848		
		0-<95	56.7% (482)	59.2% (502)	-2.5%	
		≥95-100	43.3% (368)	40.8% (346)	2.5%	
						0.140
4	SIS-16, FADS-SIS excluding mortality		669	676		
			66.2 (1.1)	63.4 (1.1)	2.8 (-0.3,5.9)	0.077
5	EQ-5D weighted index, FADS-EQ-5D		819	816		
			0.47 (0.013)	0.43 (0.013)	0.04 (-0.00,0.07)	0.057
6	EQ-5D VAS, FADS-EQ-5D excluding mortality		670	671		
			64.48 (0.904)	62.02 (0.904)	2.45 (-0.06,4.96)	0.055
7	SIS-social participation, FADS-SIS excluding mortality		668	672		
			57.5 (1.2)	55.8 (1.2)	1.7 (-1.7,5.0)	0.328
	SIS-communication, FADS-SIS excluding mortality		669	674		
			80.1 (0.9)	79.1 (0.9)	1.0 (-1.6,3.7)	0.433