SA NXY 0007

SUMMARY

ASTRAZENECAPHARMACEUTICALS

FINISHED PRODUCT: NXY-059

ACTIVE INGREDIENT: disufenton sodium

Trial title (number): SAINT II (Stroke – Acute Ischemic – NXY Treatment) A Double Blind, Randomized, Placebo Contr
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: 19 May 2003
Last subject completed: 19 September 2006
Approval date: 16 February 2007

OBJECTIVES

Primary objective:

To demonstrate the efficacy of NXY-059 compared to placebo in patients with acute ischemic stroke (AIS).

Secondary objectives:
To explore the efficacy of NXY-059 compared to placebo on global disability, functional recovery and neurologic statu
mRS score at Day 7, Day 30, Day 90; total NIHSS and change from baseline in total NIHSS at 24 hours, EOI, Day 7,
baseline in total NIHSS at last rating; score on the BI at Day 7, Day 30, Day 90 and last rating.

To evaluate the effects of NXY-059 in comparison to placebo on the ability of the patients to perform activities of da
and hand function as measured by the SIS-16 and the domain scores for communication, memory and thinking, emo
participation, respectively, of the Stroke Impact Scale (SIS) at Day 90 in patients with AIS.

To evaluate the effects of NXY-059 in comparison to placebo on patient's self-reported health status and health-relat
respectively, using the EQ-5D instrument at Day 90 in patients with AIS.

To evaluate the safety and tolerability of NXY-059 compared to placebo in patients with AIS.

To characterize the pharmacokinetics of NXY-059 in patients with AIS.

To evaluate the effects of NXY-059 compared to placebo on health care resource utilization during the index hospita
care resource utilization, residence/location of care and work status of patients with AIS during the 90-day follow-up
stroke.

METHODS

Study design

This was a double-blind, randomized, placebo-controlled, parallel group, multinational, multicenter study designed to
global disability and neurologic recovery, and to evaluate safety of 72-hour iv infusion of NXY-059 in patients with A

Target patient population and sample size

Males and females, age≥18 years, with clinical diagnosis of AIS and neuroimaging excluding other causes, and with l
combination with other deficits. To be eligible for randomization, patients were required to have total NIHSS score≥6
of scores on Items 5 and 6 (arm and leg motor function) to be≥2; and full functional independence prior to the prese
pre-morbid mRS score = 0 or 1). Unconscious patients, indicated by a score of 2 or 3 on Item 1a (Level of consciousn
excluded, as were patients with severe renal impairment (ie, with calculated creatinine clearance [CLcrea] <30 mL/m

The study was planned originally to treat 1700 patients. The sample size was increased by protocol amendment follo
SA-NXY-0006 (SAINT I). The amended planned number of treated patients was 3200 (1600 treated patients per gro
using an alpha level of 5%, a power of 80% and an assumed mRS distribution of NXY-059 and placebo resulting in a
(OR) of 1.2. The OR chosen for this calculation was the OR observed in SAINT I.

Investigational product and placebo: dosage, mode of administration and batch numbers

NXY-059 concentrate for solution for infusion (400 mg/mL), diluted to 15 mg/mL and administered as a 72-hour iv in
(LD) (2270 mg/hour) was administered for one hour followed by a 71-hour maintenance dose (MD) (up to 960 mg/h
adjusted for renal function defined by calculated CLcrea, with the maximum dose given to patients with CLcrea >80
infusion rates to patients with CLcrea 30-50 mL/min (480 mg/hour), and >50-80 mL/min (660 mg/hour), respectivel
continuous iv infusion of placebo.

Duration of treatment

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

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

Primary variable:

Patient's mRS score at last rating.

Secondary variables:

Total NIHSS score at last rating. (Note that it was originally planned to use change from baseline in total NIHSS scor
first secondary variable but this was changed by protocol amendment).

mRS score at Day 7, Day 30, Day 90; total NIHSS and change from baseline in total NIHSS at 24 hours, EOI, Day 7,
baseline in total NIHSS at last rating; score on the BI at Day 7, Day 30, Day 90 and last rating.

Scores on the respective domains of the Stroke Impact Scale (SIS) at Day 90.

Scores on the EQ-5D at Day 90.

Actual dose and target dose (based on calculated CLcrea); total plasma concentration at 1 hour and 66 to 72 hours;
concentration and fraction unbound in plasma (fu) at 66 to 72 hours; calculated unbound plasma concentration at 1

Patient's place of residence and work status at Day 90 and utilization of health care resources during the initial hospi
90 days after stroke.

SAFETY

Secondary variables:

Incidence of mortality and standard safety assessments such as adverse events (AEs) and serious adverse events (S
data (hematology, clinical chemistry, including hepatic and renal variables, and urinalysis), vital signs, electrocardiog
physical examination

physical examination.

Incidence of intracranial hemorrhage in patients treated concomitantly with recombinant tissue Plasminogen Activato

Change in neuroimaging scans in patients with progressive stroke, new stroke, and concomitant treatment with rt-PA

Statistical methods

Safety variables were analysed with the safety population, efficacy variables were analysed with the full analysis data pharmacokinetic variables were analysed with the PKFADS. Sensitivity analyses of the primary variable (mRS score a total NIHSS score at last rating, were made with the per protocol (PP) analysis set. All patients who received any dos treatment were included in the safety population. The FADS follows the intent-to-treat (ITT) ideal in that patients are treatment group to which they were randomized, even if they received the other treatment in error. FADS contained except those not treated with study drug and those without any efficacy data available after start of study drug. The population is a subset of FADS, and consists of data from patients who did not have major violations/deviations from includes all patients randomized to the NXY-059 treatment group who received study drug except for those missing missing all plasma concentration data.

All variables are summarized with descriptive statistics. Binary or ordinal variables were analysed using the Cochran- test with modified ridit score, adjusting for stratification variables (treatment group, side of infarct, total NIHSS at ba intent-to-treat or treatment with rt-PA). Further analysis was done for ordinal and binary variables using logistic regr associated 95% confidence intervals (CI) are presented. Continuous variables were analyzed with ANCOVA test, and 95% CI are presented. The primary analysis of all-cause mortality rate was performed with logistic regression. Logist ANCOVA tests were adjusted for total NIHSS score at baseline, side of infarct, and intent-to-treat or treatment with r score at baseline was used for adjusting all logistic regression and ANCOVA tests except for one sensitivity analysis o which used logistic regression adjusted for categorized total NIHSS score at baseline. The study was designed to use method on a series of efficacy measures, beginning with the primary analysis of the mRS at last rating and continuin measures until one resulted in a non-significant p-value.

Patient population

In total, 3306 patients were randomized into the study and of these, 3241 received treatment and were included in t (**Error! Reference source not found.**). The FADS (treated patients with any last rating efficacy data) included 323 patients evaluable for the analysis of the primary variable, mRS at last rating (FADS-mRS). The proportions of patien 72-hour infusion and the Day 90 visit were similar in the two treatment groups and 94.8% had an EOI assessment.

Table S1 Patient population and disposition

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Disposition and analysis populations		NXY-059	Placebo	Total
N randomized		1646	1660	3306
N randomized but not treated		40	25	65
Disposition of the safety population				
N analyzed for safety [a]		1610	1631	3241
N (%) of patients who	Completed treatment	1423 (88.4%)	1432 (87.8%)	2855 (88.1%)
	Discontinued treatment	187 (11.6%)	199 (12.2%)	386 (11.9%)
	Had EOI assessment	1542 (95.8%)	1532 (93.9%)	3074 (94.8%)
	Completed Day 90 visit	1284 (79.8%)	1309 (80.3%)	2593 (80.0%)
Other analysis populations				
N analyzed for efficacy (FADS) [b]		1604	1629	3233
N analyzed for efficacy (FADS-mRS)		1588	1608	3196
N analyzed for efficacy (PP-mRS)		1417	1442	2859
N analyzed for pharmacokinetics (PKFADS)		1562		1562

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

The mean age was 68.9 years and 45.5% of patients were female (FADS). Medical history included hypertension (76 disease (33.0%), diabetes (24.4%)and atrial fibrillation (28.9%). Prior medications included antiplatelets (35.8%), a and HMG CoA reductase inhibitors (24.0%). The 3 most common concomitant medications were antiplatelets (88.3% ACE inhibitors (48.0%).

Overall, 44.0% of the patients in the study were treated with rt-PA, the mean NIHSS score at admission was 13.0 (r mean time from stroke symptom onset to start of infusion was 3 hours, 48 minutes (range=0 hours, 45 minutes to 7 48.0% of patients had their infarct on the left side.

The demographic and baseline characteristics were balanced across the treatment groups and the patient population considered to be representative of the intended AIS population to be treated in clinical practice.

RESULTS

Efficacy results

NXY-059 given as a 72-hour infusion to AIS patients within 6 hours of stroke symptom onset did not reduce function placebo (p=0.331) as measured by the mRS at last rating (the primary endpoint) (**Error! Reference source not fo** regression analysis adjusted for the same baseline variables as the primary analysis, the estimate of the OR was 0.9 The corresponding analyses of mRS at last rating separating patients who died from those with severe disability, also NXY-059 from placebo (CMH test, p=0.535).

Table S2 mRS score at last rating, CMH test (FADS-mRS)

Table S2 **mRS score at last rating, CMH test (FADS-mRS)**

Treatment group	n	0	1	2	3	4	5/deaths
NXY-059	1588	9.8% (156)	17.6% (279)	14.0% (223)	14.7% (233)	17.8% (283)	26.1% (414)
Placebo	1607[a]	10.3% (166)	18.4% (295)	14.7% (236)	15.0% (241)	17.4% (280)	24.2% (389)
Difference		-0.5%	-0.8%	-0.7%	-0.3%	0.4%	1.9%
				Overall	p-value[b] =	0.331	

a One placebo patient (E2002048) had missing value for side of infarct, and so is excluded from the analysis.
b p-value for the extended Cochran-Mantel-Haenszel mean score statistic (row mean difference) using modified ridit score and controlling for total NIHSS score at baseline (categorized), side of infarct, and intent-to-treat or treatment with rt-PA; 5 patients in the intent-to-treat with rt-PA randomization strata did not receive rt-PA.

Last rating is Day 90 for completers, last available observation for patients who are lost to follow-up, and worst score (5) for patients who died.

The evaluation of mRS at last rating using the PP population, performed as a sensitivity analysis, supported the lack primary analysis(p=0.247). Similarly, sensitivity analyses of the primary variable at other timepoints (Day 7, Day 30, by stroke severity at baseline and by time from stroke onset to start of study drug infusion, showed no evidence of a

Because the analysis of the primary variable was not statistically significant, all subsequent variables in the hierarchy analysed in accordance with the statistical analysis plan. However, statistical analysis of all secondary efficacy outcor those related to the mRS, NIHSS, Barthel Index (BI), Stroke Impact Scale (SIS) and the EQ-5D scale supported the l

Pharmacokinetic results

The doses used were targeted to achieve a mean steady-state unbound NXY-059 plasma concentration of 260 µmol/ the patients >150 µmol/L and <5% of the patients >400 µmol/L. The mean target unbound plasma concentration o was achieved with a 1-hour LD and maintained by a 71-hour MD across the 3 CL_{crea} groups. Steady-state unbound p NXY-059 >150 µmol/L were achieved in 96.5% of patients and >400 µmol/L occurred in 16.2% of patients. The me NXY-059 when overdose patients and outlier values were excluded was 303, 301 and 319 µmol/L in the CL_{crea} group 50 mL/min, respectively, and the overall mean was 307 µmol/L.

Safety results

The overall AE experience in the study is summarized in **Error! Reference source not found.**. NXY-059 appeared AIS patients. The incidences of overall mortality, SAEs, DAEs, and AEs were similar between the NXY-059 and the pl

Table S3 Overall AE summary (Safety)

Table S3 Overall AE experience (Safety)

	NXY-059 (N=1610)
AEs	
Number of patients with AE(s)	1356 (84.2%
Number of AEs	5876
Number of patients with AE(s) assessed as causally related to study treatment	117 (7.3%)
Number of patients with an AE in at least 1 specific diagnosis/symtpom group	618 (38.4%)
SAEs	
Number of patients with SAEs	637 (39.6%)
Number of SAEs	956
Number of patients with SAE(s) assessed as causally related to study treatment	12 (0.7%)
Number of patients with SAE(s) starting after study period	0 (0.0%)
Number of SAE(s) starting after study period	0
Fatal SAEs	
Number of patients who died	267 (16.6%)
Number of patients who died after study period	0
Non-fatal SAEs	
Number of patients with non-fatal SAE(s)	469 (29.1%)
Number of non-fatal SAEs	686
DAEs[a]	
Number of patients discontinued from treatment due to an AE	72 (4.5%)
Number of patients discontinued from treatment due to fatal AE	31 (1.9%)
Number of patients discontinued from treatment due to non-fatal AE	47 (2.9%)
Number of patients discontinued from study due to an AE	272 (16.9%)
Number of patients discontinued from study due to fatal AE	263 (16.3%)
Number of patients discontinued from study due to non-fatal AE	15 (0.9%)

[a] Patients can contribute to both "discontinued from treatment" and "discontinued from stu means that a patient can discontinue treatment and be discontinued from the study for the patients can have both a fatal and a non-fatal AE leading to discontinuation

% is proportion of patients in each category within treatment group and analysis population (N

Study period is up to Day 100

AE is adverse event; SAE is serious adverse event, DAE is discontinuation due to an adverse e

The most common AEs in the study are summarized in **Error! Reference source not found.**. Apart from hypokale more frequently during treatment with NXY-059 (12.1% vs 9.2%), there were no clinically important differences bet groups in the incidence and pattern of AEs. Similarly, there were no clinically important differences between the 2 tr incidence and pattern of SAEs or DAEs.