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2 SYNOPSIS

Name of Sponsor: Asubio Pharmaceuticals, Inc.	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: SUN N4057 (Piclozotan) Injection 1 mg/mL	**Volume:**	
Name of Active Ingredient: SUN N4057 [3-chloro-4,5-dihydro-4[4-[4-(2-pyridyl)-1,2,3,6-tetrahydropyridin-1-yl]butyl]-1,4-benzoxazepin-5-one dihydrochloride dihydrate]	**Page:**	

Study Title:
A Phase 2b, Randomized, Double-Blind, Placebo-Controlled, Group-Sequential, Multicenter, Dose Finding Study of the Safety and Efficacy of SUN N4057 (Piclozotan) Administered for 72 Hours by Continuous Intravenous Infusion in Subjects with Acute Ischemic Stroke and Measurable Penumbra on MRI

Investigators and Study Centers: This was a multicenter study with 17 enrolling sites; 10 in the United States, 2 in Spain, 3 in Germany, and 2 in South Africa. An additional 25 sites were initiated but did not enroll subjects; 1 in Germany, 1 in South Africa, 1 in Spain, 17 in the United States, 3 in Belgium, and 2 in Israel.

Publication (reference): Not applicable.

Studied Period:

29 March 2005 (date of first subject enrollment)
19 October 2006 (date of early study termination)
16 January 2007 (date of last subject completed)

Phase of Development: 2b

Objectives: The primary objective was to determine the efficacy of a 72-hour infusion of SUN N4057 (piclozotan) in subjects with clinical findings of an acute ischemic stroke and a magnetic resonance image (MRI) demonstrating a measurable penumbra (perfusion-weighted imaging [PWI] minus diffusion-weighted imaging [DWI] volume). Efficacy was determined by comparing the percent change in stroke lesion volume from Screening to Day 28, with stroke lesion volume assessed by DWI at Screening and by fluid-attenuated inversion recovery (FLAIR) at Day 28, in the piclozotan group versus the placebo group.

The secondary objectives were:

- To compare the piclozotan group versus the placebo group for:
  - The proportion of subjects with no growth in stroke lesion volume between Screening and Day 28;
  - The clinical outcomes at Days 28 and 90 using the individual clinical scales (Modified Rankin Scale [mRS], Barthel Index [BI], and National Institutes of Health Stroke Scale [NIHSS]); and
  - The global test statistics at Days 28 and 90 using a composite of the results on the mRS, BI, and NIHSS.
- To assess the safety and tolerability of piclozotan in subjects with acute stroke.

Methodology: This was a multicenter, multinational, randomized, double-blind, placebo-controlled, sequential-group, preliminary trial to explore the efficacy of piclozotan in subjects with an acute ischemic stroke with a measurable penumbra, who received study drug within 9 hours after the onset of symptoms. Enrollment was to be managed so that 50% of subjects received study drug or placebo less than 6 hours after symptom onset and the remainder between 6 and 9 hours, inclusive, after symptom onset.

Randomization was stratified by time to treatment after event (<6 hrs, 6-9 hrs) and by geographical region. Originally the protocol specified that the study was to be conducted in two stages. Stage 1 was intended to assess the efficacy of two dose levels of piclozotan versus placebo in 112 randomized subjects, 93 of whom complete a Day 28 MRI (31 subjects in each of three treatment groups). If pre-determined efficacy and safety criteria were met, the original protocol indicated that piclozotan or placebo would be administered to additional randomized subjects in Stage 2 of the study, until an additional 94 subjects (47 in the continuing piclozotan

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treatment group and 47 in the placebo group) were randomized to provide an additional 80 subjects to complete a Day 28 MRI. The total number of subjects with Day 28 MRI data after both stages completed was expected to be 173: placebo group = 71 (31+40); the continuing piclozotan group = 71 (31+40); and the remaining piclozotan group = 31.

The Sponsor terminated the study prematurely due to slow enrollment, therefore Stages 1 and 2 were no longer applicable. Instead analysis was performed using the data from all subjects enrolled into the study as of study termination. These subjects were followed until their Day 90 visit or earlier (for those who discontinued prior to Day 90).

Study medication was administered as a continuous intravenous (IV) infusion for up to 72 hours (Hour 0 through Hour 72). Subjects were evaluated for up to 72 hours after completion of the study medication infusion, and underwent post-treatment evaluations at Days 28 and 90. Subjects were evaluated by a telephone interview at Day 60 for completion of the mRS and BI scales and for the presence of any adverse events (AEs).

Number of Subjects (planned and analyzed):
A total of 206 subjects were planned; 43 subjects were randomized and received at least one dose of study medication and were analyzed for safety; of these 43 subjects, only 41 had a post-Baseline safety assessment and were therefore included in the modified intent-to-treat population and analyzed for efficacy.

Diagnosis and Main Criteria for Inclusion/Exclusion:
This study included male and female subjects, between 18 and 85 years of age at randomization, who demonstrated localized cortical signs of stroke. Subjects must have received study drug within 6 hours (50% of subjects) or between 6 to 9 hours after onset of symptoms. Subjects were required to have an NIHSS score ≥6 and ≤22 or at least 2 on the aphasia item of the NIHSS with corresponding findings on MRI consistent with a presentation of aphasia.

MRI findings had to be consistent with acute ischemic stroke with substantial cortical involvement in the middle cerebral artery (MCA) region. The ischemic lesion had to be visible on DWI with a diameter ≥2 cm and ≤8 cm; PWI diameter ≥3 cm; screening PWI abnormality exceeding the screening DWI abnormality (mismatch) by 50% in volume or >1 cm in diameter.

Main exclusion criteria included the presence of reduced level of consciousness, forced eye deviation or total gaze paresis, dense hemiplegia of upper and lower extremities, pre-stroke mRS score ≥2, rapid neurological improvement between screening and start of drug infusion, persistent hypertension (systolic blood pressure [SBP] >220 mmHg and/or diastolic blood pressure [DBP] >120 mmHg), seizure during stroke, receipt or eligible to receive thrombolytics, or another significant neurological disease or previous occurrence of stroke.

In addition, the following MRI findings were exclusionary: intracranial hemorrhage; subacute stroke in symptomatic region; significant mass effect, edema, or midline shift. A subject with a contraindication to MRI (eg, ferrous implants, cardiac pacemakers, claustrophobia, or severe agitation) was also to be excluded.

Test Product, Dose and Mode of Administration, Batch Number:

Piclozotan – target plasma concentration of 70 to 85 ng/mL, IV infusion, lot/batch number [redacted]

Piclozotan – target plasma concentration of 110 to 125 ng/mL, IV infusion, lot/batch number [redacted]

Duration of Treatment: Study medication administered as a continuous 72-hour IV infusion (a 1-hour loading dose followed by a 5-hour loading dose and a 66-hour maintenance dose).

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Reference Therapy, Dose and Mode of Administration, Batch Number:
Placebo (0.9% sodium chloride, IV infusion), obtained through hospital pharmacy (no batch number available for the sodium chloride).

Criteria for Evaluation:

Efficacy: MRIs were performed at Screening, Hour 12, and Day 28 in order to determine the absolute change and percent change in stroke lesion volume between Screening and Day 28. The proportion of subjects who had no growth in stroke lesion volume as assessed by DWI on MRI at Screening to stroke lesion volume assessed by FLAIR on Day 28 in each treatment group was evaluated as a secondary endpoint.

In addition, clinical scores were captured. Clinical scores obtained included the mRS (pre-stroke [as estimated by the subject's family], post-treatment Days 28, 60, and 90), the NIHSS (at Screening, at Hours 48 and 96, and post-treatment Days 28 and 90), and BI (post-treatment Days 28, 60, and 90).

Furthermore, a global test statistic (GTS), based on the results of the mRS, the BI, and the NIHSS at Days 28 and 90, was used as a global clinical outcome measure. However, as outlined in the protocol this trial was not powered to detect a statistically significant difference between the groups with regard to the clinical outcome measures.

Pharmacokinetics: Pharmacokinetic (PK) samples were collected, at Hours 1, 6, and 72 to determine peak piclozotan concentrations at the end of the first and second loading dose (Hours 1 and 6, respectively) and the end of the maintenance dose (Hour 72). A PK sample was also to be collected any time the study drug infusion was temporarily or permanently stopped due to an AE or QTc prolongation.

Safety: Safety was assessed by comparing the incidence of treatment-emergent adverse events (TEAEs), changes in physical examination, vital signs, electrocardiograms (ECGs), and clinical laboratory tests from pretreatment (Screening or Baseline) to each assessment time post-randomization, between the treatment groups.

Statistical Methods:
Data handling, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations were performed primarily using SAS (version 9.1.3 or later) for Windows. Statistical testing was performed at the 0.05 level using two-tailed tests. Due to the small number of subjects at each site, the data from all study sites were pooled into two regions, ie, United States (US) vs. non-US. Three analysis populations were defined for this study: a safety population, a modified intent-to-treat (MITT) population, and an efficacy evaluable population.

Efficacy Analysis: The original primary efficacy endpoint was the proportion of subjects with no growth in stroke lesion volume from Baseline to Day 28. Due to the early termination of the study by the Sponsor and the resulting small sample size, the primary efficacy endpoint was changed prior to database lock and study unblinding, to the mean change in stroke lesion volume from Baseline to Day 28. The actual values, observed changes, and percent changes from Baseline in the stroke lesion volume were summarized by treatment group at each time point. Within-treatment changes from Baseline and percent changes were assessed using paired t-test. Between-treatment changes were assessed using an analysis of covariance (ANCOVA) model, or Wilcoxon Rank-sum test.

A responder analysis was performed to determine the number and proportion of subjects who had no growth in their Screening stroke lesion volume at Day 28 and the data were tabulated by treatment group. The proportions were compared using a pair-wise Cochran–Mantel–Haenszel (CMH) test stratified by enrollment status

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(<6 hours or between 6 to 9 hours) and pooled site (US region or non-US region). Since the power of this study design was based on a different criterion, the *P*-value from the CMH test serves only as a reference value.

The actual values as well as changes from Baseline in the NIHSS and the mRS were analyzed similarly to the stroke lesion volume change at each post-Baseline visit. The actual values of the BI were descriptively summarized at each post-Baseline visit by treatment group, and between-treatment difference was assessed using the above mentioned ANCOVA model. In addition, the mRS was analyzed using a method presented by Lees et al (*N Engl J Med*. 2006;354:588-600). Global Test Statistic was summarized at Day 28 and Day 90 by the number and proportion of subjects who would be considered responders to treatment as determined by a predefined level of improvement in the NIHSS, mRS, or BI. The results were tabulated by treatment group.

Pharmacokinetics: The PK parameters, as well as total infusion time, dose per kg, and total dose infused were summarized descriptively by treatment group with the number of non-missing values and the median, mean, standard deviation (SD), minimum, and maximum. The percent coefficient of variation (%CV) and geometric mean were also displayed. A line graph depicting mean ± SD plasma concentrations over time was produced for each active treatment group. The relationship between C_1 and efficacy data and between C_1 and incidence of nausea/vomiting was examined. Within-treatment differences were assessed using a t-test. Between-treatment differences were assessed using an ANCOVA model.

Safety Analysis: Safety was assessed from AEs, laboratory values, vital signs, 12-lead ECG, physical exam, and use of concomitant medications.

Summary and Conclusions:

Efficacy Results:

The early termination of this study after enrollment of 43 subjects obviated the planned interim analysis and left the planned final analysis underpowered. Results of the final analysis of the available data are summarized as follows:

The primary efficacy analysis of the change from Baseline in stroke lesion volume, as measured by DWI, at Day 28 showed no difference between placebo and piclozotan treatment groups.

Response rate, as measured by the proportion of subjects with growth or no growth in lesion volume, was not greater in the piclozotan treatment groups than in the placebo group.

Of the three clinical assessments performed, improvements were shown primarily in NIHSS and BI scores, but no differences were observed between treatment groups. The GTS showed no difference among treatment groups.

Pharmacokinetic Results:

Four unexplainable concentration values >1000 ng/mL (8230, 3790, 1020, and 6370 ng/mL) were excluded from PK analyses. Median concentration values were reported because of the presence of other outliers. Following the exclusion of the outliers listed above, the median concentrations at Hour 6 were 75.3 ng/mL and 130.0 ng/mL, which were within ±10% of the targeted concentrations of 80 and 120 ng/mL for the low- and high-dose group, respectively. In general, the median concentrations at Hour 1 and Hour 72 were slightly lower and higher, respectively, for the low- and high-dose groups. The geometric means were also close to the target doses at Hour 6 (76.7 and 110.4 ng/mL, respectively), while mean plasma concentrations were more variable. The low-dose group had a mean of 123.3 ± 163.60 ng/mL compared to 117.6 ± 38.06 ng/mL in the high-dose group at this time point; variability in the low-dose group was due to outliers, which ranged from the minimum

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9.9 ng/mL to the maximum 555.0 ng/mL.

At Hour 72, the median concentrations for the low- and high-dose groups were 89.9 and 157.0 ng/mL, respectively, while the means were 82.7 ± 47.26 and 236.7 ± 207.65 ng/mL, with variability in the high-dose group due largely to an outlier of 720.0 ng/mL.

Median C_{max} piclozotan concentration for the low-dose group was 93.4 ng/mL and was observed at 30.6 ± 35.10 hours (T_{max}). A median C_{max} of 171.0 ng/mL, observed at a T_{max} of 49.5 ±33.79 hours, was calculated for the high-dose group.

Summary of Selected Pharmacokinetic Parameters, Safety Population

Parameter	Low Dose	High Dose	Combined Doses
C_1 (ng/mL)			
N	9	8	17
Mean	63.9	110.5	85.9
SD	13.58	54.17	44.18
Median	67.0	112.0	74.9
Min, Max	41.5, 78.3	40.8, 207.0	40.8, 207.0
%CV	21.12	49.0	51.5
Geometric Mean	62.5	97.6	77.1
C_6 (ng/mL)			
N	9	9	18
Mean	123.3	117.6	120.5
SD	163.60	38.06	115.26
Median	75.3	130.0	90.9
Min, Max	9.9, 555.0	43.6, 160.0	9.9, 555.0
%CV	132.7	32.4	95.7
Geometric Mean	76.7	110.4	92.0
C_{72} (ng/mL)			
N	9	8	17
Mean	82.7	236.7	155.2
SD	47.26	207.65	162.04
Median	89.9	157.0	119.0
Min, Max	3.4, 171.0	64.5, 720.0	3.4, 720.0
%CV	57.1	87.7	104.4
Geometric Mean	60.0	184.9	101.9
C_{max} (ng/mL)			
N	10	9	19
Mean	139.9	244.2	189.3
SD	149.87	186.42	171.87
Median	93.4	171. 0	132.0
Min, Max	41.5, 555.0	130.0, 720.0	41.5, 720.0
%CV	107.1	76.3	90.8
Geometric Mean	105.4	207.5	145.3

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T_{max} (h)			
N	10	9	19
Mean	30.6	49.5	39.6
SD	35.10	33.79	34.88
Median	6.0	71.8	68.8
Min, Max	0.3, 72.7	1.0, 73.8	0.3, 73.8
%CV	114.5	68.3	88.2
Geometric Mean	8.7	26.0	14.6

Note 1: Date and time for subject 036-001 (low-dose group) at Hour 1 were corrected after database lock.
Note 2: Four outlier concentration values >1000 ng/mL occurred for subjects 029-005 and 039-006 and were excluded from analysis.

Safety Results:

In this population of 43 subjects with acute ischemic stroke, all but 2 subjects (both in the placebo group) experienced AEs, the majority of which were mild or moderate in severity. The most commonly reported AEs were nausea, urinary tract infection, pyrexia, constipation, pneumonia, vomiting, agitation, and depression, all of which would not be unexpected in this patient population. Severe AEs occurred more frequently in subjects in the piclozotan groups compared with placebo subjects (35.7% versus 20.0%). The AEs most often considered by the Investigators to be related to study drug were nausea and vomiting.

The incidence of serious adverse events (SAEs) was 2/15 (13.3%), 3/14 (21.4%), and 4/14 (28.6%) subjects in the placebo, low-dose, and high-dose groups, respectively. Four subjects in the piclozotan groups had treatment-related SAEs, including 3 subjects in the low-dose group with progressing stroke and pneumonia, bradycardia, and nausea and vomiting; and 1 subject in the high-dose group with aspiration pneumonia and pulmonary edema (outcome was death).

Four subjects died; one death, a 76-year-old male subject with aspiration pneumonia and pulmonary edema was considered treatment related. Aspiration pneumonia is a risk that could be associated with the known emetic side effects of piclozotan, and preventive measures for aspiration were discussed in the protocol. The other 3 deaths (2 from neurological deterioration and 1 from cardiac arrest after hemorrhagic transformation) were not considered treatment related by the investigators. Two of the 3 discontinuations due to non-serious AEs were because of vomiting.

Clinical laboratory and hematology data evaluated in this study showed no remarkable trends in changes from Baseline. Shifts in individual results to abnormal levels also did not reveal patterns of concern.

For vital signs, a mean decrease of 0.4 ± 0.72ºC in body temperature was noted in the high-dose group at Hour 1, but no other evidence of mean temperature decreases was seen during the study. Blood pressure (BP) and respiration rates were variable, but did not appear to be altered in a treatment- or dose-related manner.

Within-group comparisons showed that there was a significant change (P<0.05) in QTcB from Baseline to subsequent values at 6, 12, and 24 hours within the high-dose group, while no differences were recorded between treatment and placebo groups. Similar patterns were reported for QTcF and QTcR. None of the comparisons in changes from Baseline in QT/QTc analyses showed any significant differences between treatment groups at any time point. ECG measurements showed considerable variability, although there were few notable differences between treatment groups. QT intervals were corrected for heart rates using the Bazett, Fridericia, and linear regression corrections. Single ECGs performed at Baseline provided highly variable

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baseline-corrected changes, which were not distributed evenly across the treatment groups. The high-dose piclozotan group had a markedly lower mean Baseline QT/QTc value compared to the placebo and low-dose group, and the tendency of a regression toward the mean was thought to have a potential to confound the interpretation of changes from Baseline under these circumstances. In addition, the size of the study groups was too small to permit use of the categorical change results to exclude a possible prolongation in QT/QTc interval in the combined piclozotan groups compared to placebo, and due to variability and limited Baseline measures, any possible drug effects remain to be fully characterized. Finally, the percentage of subjects with AEs potentially linked to QTc prolongation was comparable between piclozotan-treated groups and the placebo-treated group. There were no instances of Torsades de Pointes or any SAEs possibly related to QTc prolongation.

No notable changes were observed in physical examination results or concomitant medications.

Evaluation of the relationship of plasma concentration to nausea and vomiting showed no significant differences in plasma concentration and no dose-related increase in nausea and vomiting among the subjects with these symptoms. Plasma concentration also did not appear to be associated with QT or QTc prolongation.

Conclusions:

Efficacy Conclusion

This study failed to demonstrate evidence of efficacy due to its premature discontinuation because of poor enrollment; as such, no efficacy conclusions can be drawn.

Pharmacokinetic Conclusion

Though there was high variability due to the presence of outliers, the target concentrations of 80 and 120 ng/mL for the low- and high-dose groups, respectively, were generally achieved, based on the median concentration values. This finding is consistent with the plasma exposures in a previous study (SPI-102) using the same piclozotan dosing regimens.

Safety Conclusion

Piclozotan demonstrated an acceptable safety profile in this hospitalized patient population. There were no significant changes in vital signs or clinical laboratory measurement values, and most AEs were deemed not related to study drug.

Final Report Date: 09 May 2008

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