Original Contribution

Phase II Trial of the Sigma-1 Receptor Agonist Cutamesine (SA4503) for Recovery Enhancement After Acute Ischemic Stroke

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Background and Purpose—The σ-1 receptor (Sig-1R) agonist cutamesine (SA4503) enhanced functional recovery after experimental stroke with a treatment initiation window of 48 hours and chronic treatment for 28 days. We conducted a phase 2 clinical trial exploring the safety, tolerability, dose range, and functional effects of cutamesine in patients with ischemic stroke.

Methods—Subjects were randomized between 48 and 72 hours after stroke to receive cutamesine 1 mg/d, 3 mg/d, or placebo for 28 days. Effects on safety and function were assessed at baseline, at end of treatment (day 28), and at end of follow-up (day 56).

Results—In 60 patients, treatment with both cutamesine dosages was safe and well tolerated without significant differences in numbers of treatment emergent or serious adverse events. No significant effect was observed on the primary efficacy measure (change in National Institutes of Health Stroke Scale from baseline to day 56) or modified Rankin Scale and Barthel Index scores. Post hoc analysis of moderately and severely affected patients (baseline National Institutes of Health Stroke Scale, ≥7 and ≥10) showed greater National Institutes of Health Stroke Scale improvements in the 3 mg/d cutamesine group when compared with placebo (P=0.034 and P=0.038, respectively). A trend toward a higher proportion being able to complete a 10m timed walk was observed for cutamesine-treated subjects.

Conclusions—Cutamesine was safe and well tolerated at both dosage levels. Although no significant effects on functional end points were seen in the population as a whole, greater improvement in National Institutes of Health Stroke Scale scores among patients with greater pretreatment deficits seen in post hoc analysis warrants further investigation. Additional studies should focus on the patient population with moderate-to-severe stroke.


Key Words: clinical trial ■ randomized controlled trial ■ SA 4503 ■ stroke

Enhancement of functional recovery during the subacute and chronic phases of stroke represents a major therapeutic goal because a significant proportion of patients have persisting neurological deficits, even with optimal acute care and conventional rehabilitation. Preclinical in vivo models suggest that a time-limited window of neuroplasticity opens after stroke. New therapeutic approaches that stimulate these repair mechanisms may be able to exploit this opportunity, and a range of these is currently under investigation, including small molecules that target specific processes, small molecules that have a general stimulatory effect that may aid rehabilitation, growth factors, cell therapies, and physical modulation of neuronal networks. The σ-1 receptor chaperone protein (Sig-1R) mediated functional recovery in a model of neuronal plasticity relevant to stroke. Sig-1Rs mainly reside in the endoplasmic reticulum and are enriched in the mitochondria-associated endoplasmic reticulum membrane but can change their intracellular location in response to cellular stress. The biochemical function of the Sig-1R is that of a molecular chaperone, stabilizing proteins in response to cellular stress.
and facilitating the folding of proteins, such as brain-derived neurotrophic factor. Moreover, Sig-1Rs promote cell survival in reactive-oxygen–dependent apoptosis by increasing the expression of Bcl-2, associate with ion channels and receptors at the plasmalemma to stabilize their native conformation under cellular stress conditions, and regulate dendritic spine formation. Specific activation of the Sig-1R thus affects multiple physiological pathways, and these mechanisms offer a rationale for the functional recovery and cognitive effects of Sig-1R agonists observed in models of central nervous system injury and functional impairment.

Cutamesine (1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl) piperazine dihydrochloride, SA4503), an orally available, central nervous system active, selective agonist of the Sig-1R, enhanced functional recovery after experimental stroke in rats when treatment commenced 48 hours after stroke and continued for 1 month, without affecting infarct size. Treatment with cutamesine in vivo increased the levels of the synaptic proteins neurexin and neurexin in the peri-infarct area, whereas in vitro the compound stimulated neurite outgrowth in primary cortical neuronal cultures. Stimulation of axonal sprouting and neurogenesis is associated with improved recovery from experimental stroke. Cutamesine enhances the expression of brain-derived neurotrophic factor in vivo and in vitro, by regulating the processing to mature, secreted brain-derived neurotrophic factor. Delayed administration of a small-molecule ligand of the brain-derived neurotrophic factor tropomyosin receptor kinase B (TrkB) promoted recovery after hypoxic-ischemic stroke with a delayed treatment initiation window. Cutamesine, by virtue of its specific activation of the Sig-1R, affects multiple molecular pathways and such a pleiotropic mechanism may be necessary to improve functional recovery after experimental stroke. An orally administered agent with delayed treatment initiation is an attractive therapeutic candidate for stroke.

Here, we describe the results of an initial clinical study of cutamesine in which we examined the safety and preliminary efficacy of this compound in patients with ischemic stroke. The clinical trial design was closely modeled on the preclinical studies with respect to the treatment initiation window, treatment duration, and receptor occupancy levels necessary for stroke recovery.

Methods

Overall Study Design

A multicenter, international, randomized, double-blind, placebo-controlled phase 2 study was conducted to investigate safety and tolerability of oral treatment with cutamesine (1 or 3 mg/d) versus placebo in subjects who had experienced an ischemic stroke between 48 and 72 hours before randomization; exploratory objectives included upper and lower extremity motor function, functional disability, and depressive symptoms. Fifteen centers enrolled patients: 7 in the Czech Republic, 4 in Spain, and 4 in the United Kingdom. A list of all participating investigators is given in the online-only Data Supplement. The study was approved by the Institutional Review Boards or the ethical review process relevant to each country and performed according to the principles of current Good Clinical Practice. All participating subjects gave informed consent.

Subjects were assigned to receive either 1 or 3 mg cutamesine capsules or matching placebo capsules according to a computerized randomization schedule using an interactive voice response system, with an active:placebo ratio of 2:1 in each dose cohort. Both subjects and study personnel responsible for treatment were blind to the treatment assigned to each subject. An independent data and safety monitoring board reviewed data available after all subjects in the 1 mg/d cohort had completed the day 56 study completion visit and determined that it was safe to proceed to the 3 mg/d dose cohort. The data and safety monitoring board reviewed safety and tolerability data on an ongoing basis throughout the trial and held several scheduled meetings during the trial to discuss data quality and safety. The members of the data and safety monitoring board are listed in the online-only Data Supplement.

Subjects received cutamesine-containing gelatin capsules or matching placebo orally once daily for 28 days and were followed thereafter until day 56 after stroke. On days 2, 7, and 14 of treatment, subjects underwent safety assessments. On days 28 and 56, subjects underwent full batteries of safety and functional assessments.

Rehabilitation therapies were permitted as clinically indicated and the number of hours and types of therapy completed were recorded by subjects or caregivers in a diary throughout the study period. The planned enrollment was 60 subjects divided equally between 2 sequential cohorts. The first subject was screened on May 27, 2008. The first randomization occurred on June 24, 2008. The last subject completed on June 24, 2009.

Main Inclusion and Exclusion Criteria

The study included men or women aged ≥18 years with ischemic stroke between 48 and 72 hours before randomization confirmed by computed tomography or MRI and a National Institutes of Health Stroke Scale (NIHSS) score of ≥4 (total score) or ≥2 on the arm or leg motor function scores of the NIHSS. Subjects had to be medically stable within the 24 hours before randomization. Excluded were subjects with a transient ischemic attack or who were unable to take medication by mouth at the time of baseline assessments. Thrombolysis during the acute phase of stroke before study enrollment was allowed. A full description of inclusion and exclusion criteria is given in the online-only Data Supplement.

Objectives of the Trial and Criteria for Evaluation

The primary objective of the trial was to evaluate the safety and tolerability of cutamesine, assessed by treatment emergent adverse event (TEAE) incidence including clinical laboratory tests.

The secondary objective was to evaluate the effects of cutamesine on neurological function by assessing changes in NIHSS scores from baseline to day 28 and day 56, respectively. Investigators performing the NIHSS had to be certified by completion of an online video-based education process or had to provide proof of a recent comparable certification.

Exploratory objectives included further potential efficacy measures of motor function recovery (10m timed walk), disability (modified Rankin Scale), and activities of daily living (Barthel Index) by comparing baseline performance with day 28 and day 56 performances, respectively. A further exploratory objective evaluated the potential effects on poststroke depression. The 15-item version of the Geriatric Depression Scale was used to measure level of depressive symptoms.

Statistical Methods and Population Definitions

The number of subjects (20 evaluable subjects per treatment arm) was considered appropriate for an initial evaluation of safety and tolerability and for an exploratory evaluation of potential treatment benefits. The study was not powered to detect differences between treatment groups on functional outcome measures.

The safety population was defined as all randomized subjects who received ≥1 dose of study medication or placebo; the intent-to-treat population was defined as all subjects in the safety population who received ≥1 efficacy evaluation after starting treatment. Analyses of baseline characteristics and safety measures were performed using the safety population.
Efficacy analyses evaluated the change in functional outcome parameters from baseline to the end of the treatment period (day 28) and from baseline to the study completion visit (day 56) and were performed using the intent-to-treat population. The intent-to-treat analysis used last observation carried forward for missing observations. The primary efficacy analysis evaluated change in the total NIHSS from baseline to the end of the treatment period (day 28) and from baseline to the study completion visit (day 56) using ANCOVA. Factors for the ANCOVA statistical model included treatment (placebo, 1 mg/d cutamesine or 3 mg/d cutamesine), with baseline scores, subject age, and timing of treatment initiation after stroke onset as covariates. Comparisons between cutamesine and placebo were performed, and 95% confidence intervals (CIs) were constructed for differences between cutamesine and placebo.

Results

Demographic Characteristics, Medical History, and Selected Study Parameters

There were 60 evaluable subjects in this study, 31 men and 29 women; subject disposition is shown in Figure 1. All subjects were white. The 3 treatment groups had similar demographic profiles and medical comorbidities (Table 1). The mean time

Table 1. Demographic Characteristics, Time of Treatment Initiation, Medical History, and Concomitant Medications of the Safety Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=22)</th>
<th>Cutamesine 1 mg (n=19)</th>
<th>Cutamesine 3 mg (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening, y, mean±SD (range), y</td>
<td>65.4±12.9 (25–81)</td>
<td>67.1±12.4 (43–83)</td>
<td>66.9±11.0 (47–86)</td>
</tr>
<tr>
<td>Sex, women (%)</td>
<td>11 (50%)</td>
<td>10 (53%)</td>
<td>8 (42%)</td>
</tr>
<tr>
<td>Treatment initiation time from stroke onset, h, mean±SD (range), h</td>
<td>60.2±7.6 (50–72)</td>
<td>56.8±8.6 (48–74)</td>
<td>59.8±7.3 (48–72)</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (68)</td>
<td>15 (79)</td>
<td>16 (84)</td>
</tr>
<tr>
<td>Myocardial infarction/IHD</td>
<td>6 (27)</td>
<td>5 (26)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>CABG/angioplasty</td>
<td>1 (5)</td>
<td>2 (11)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Previous ischemic stroke/TIA</td>
<td>2 (9)</td>
<td>1 (5)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (23)</td>
<td>9 (47)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>3 (14)</td>
<td>3 (16)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (32)</td>
<td>3 (16)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Concomitant medications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>11 (50)</td>
<td>9 (47)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>14 (64)</td>
<td>13 (68)</td>
<td>15 (79)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>6 (27)</td>
<td>4 (21)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thrombolysis (alteplase)</td>
<td>10 (46)</td>
<td>4 (21)</td>
<td>6 (32)</td>
</tr>
</tbody>
</table>

This population included all randomized subjects who received ≥1 dose of study medication or placebo. CABG indicates coronary artery bypass graft; IHD, ischemic heart disease; and TIA, transient ischemic attack.
from stroke onset to starting treatment was 56.8 hours for the 1 mg/d cutamesine group, 59.8 hours for the 3 mg/d cutamesine group, and 60.2 hours for the placebo group.

**Primary Outcomes: Safety and Tolerability**
The incidence and nature of TEAEs within the safety population for each of the 3 treatment groups are shown in Table 2. At least 1 TEAE was reported in 17 (90%) of the 19 subjects in the 1 mg/d cutamesine group, 15 (79%) of the 19 subjects in the 3 mg/d cutamesine group, and 17 (77%) of the 22 subjects in the placebo group. There was no clear relationship of TEAE incidence to treatment or dose. The number of TEAEs considered at least possibly related to study drug did not differ significantly between groups, being reported in 3 (16%) subjects receiving 1 mg/d cutamesine, 1 (5%) receiving 3 mg/d cutamesine, and 2 (9%) receiving placebo. There was 1 death 6 days after randomization because of cerebral hemorrhage, in a subject receiving 3 mg/d cutamesine. This event was considered unrelated to the study drug by the treating clinician. One serious adverse event was reported for 1 subject in the 1 mg/d cutamesine group (respiratory failure). This event was considered unrelated to the study drug. Two subjects in the 3 mg/d cutamesine group had a serious adverse event: one stroke that occurred after carotid endarterectomy and 1 instance of hemorrhagic transformation of stroke 1 day after randomization, neither considered to be drug related. No serious adverse events were reported in subjects receiving placebo. Other than the death in 1 subject, none of the TEAEs led to premature discontinuation in any group.

**Secondary Outcomes: Functional Effects**
The prespecified primary efficacy outcome measure was the adjusted mean change from baseline in total NIHSS score. There was a dose-related separation of the cutamesine treatment groups from placebo at the end of treatment (day 28) and at the end of follow-up (day 56; Table 3). However, this difference was not statistically significant. To explore whether modified entry criteria in a future trial would enhance the probability of identifying a treatment response, we performed exploratory post hoc analyses on subgroups of the intent-to-treat population defined by NIHSS baseline thresholds of ≥7, ≥8, ≥9, and ≥10. Data on the subgroups with NIHSS ≥7 and ≥10 are shown. These 2 populations included 33 and 21 subjects, respectively. Subjects with a NIHSS score of ≥7 at baseline showed a statistically significant difference between the 3 mg/d cutamesine group and placebo, with a mean score difference of −2.6 points (95% CI, −5.0, −0.2; \( P = 0.034 \)) from baseline total NIHSS at the end of treatment. A significant difference between the 3 mg/d cutamesine group and the placebo was also seen for NIHSSs≥9 (difference, −3.3; 95% CI, −6.3, −0.3; \( P = 0.035 \)) and a trend toward a difference for NIHSSs≥8 (difference, −2.4; 95% CI, −5.0, 0.3; \( P = 0.075 \)). The treatment difference at the end of follow-up was sustained but smaller (difference, −2.0; 95% CI, −4.7, −0.7) and was not statistically significant (\( P = 0.140 \)). No consistent differences were observed in analyses of the 1 mg dose group. Among subjects with a NIHSS score ≥10 at baseline, a significant difference in change from baseline total NIHSS scores between the 3 mg/d cutamesine group and placebo was observed both at the end of treatment (difference, −3.7; 95% CI, −7.1, −0.2; \( P = 0.038 \)) and at the end of follow-up (difference, −4.7; 95% CI, −9.0, −0.3; \( P = 0.037 \)).

### Table 2. TEAE in the Safety Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n=22), n (%)</th>
<th>Cutamesine 1 mg (n=19), n (%)</th>
<th>Cutamesine 3 mg (n=19), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>17 (77)</td>
<td>17 (90)</td>
<td>15 (79)</td>
</tr>
<tr>
<td>Possibly related TEAE</td>
<td>2 (9)</td>
<td>3 (16)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Other SAE</td>
<td>0</td>
<td>1 (5)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Discontinuation of study drug, other than death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MedDRA system organ class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>10 (46)</td>
<td>9 (47)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>10 (46)</td>
<td>8 (42)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>10 (46)</td>
<td>9 (47)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>4 (18)</td>
<td>5 (26)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>3 (14)</td>
<td>7 (37)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Investigations</td>
<td>4 (18)</td>
<td>4 (21)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>2 (9)</td>
<td>3 (16)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>3 (14)</td>
<td>4 (21)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>3 (14)</td>
<td>3 (16)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>6 (27)</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>4 (18)</td>
<td>2 (11)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>0</td>
<td>1 (5)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>0</td>
<td>2 (11)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>0</td>
<td>2 (11)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>0</td>
<td>2 (11)</td>
<td>0</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>0</td>
<td>0</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>0</td>
<td>0</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

Summary of TEAEs and incidence of TEAEs by system organ class as defined by MedDRA. There was no clear relationship of TEAE incidence to treatment or dose. MedDRA indicates Medical Dictionary for Regulatory Activities; SAE, serious adverse event; and TEAE, treatment emergent adverse event.
Patients displayed a wide range of walking impairment, and various degrees of walking assistance need to perform the 10m timed walk. Therefore, we categorized these data into those subjects who were able to perform the task, independently or with help, and those who could not perform this task (Figure 2). When compared with the placebo group, a nonsignificantly higher proportion of subjects treated with 3 mg/d cutamesine could complete a 10-m walk at day 28 (82% versus 55%; odds ratio [cutamesine:placebo], 4.0; 95% CI, 0.9, 18.8; \( P = 0.079 \); logistic regression model) and at day 56 (88% versus 67%; odds ratio [cutamesine:placebo], 4.8; 95% CI, 0.7, 32.7; \( P = 0.106 \); logistic regression model).

The 3 mg/d cutamesine group performed better than the placebo group in modified Rankin Scale (Table I in the online-only Data Supplement) and Barthel Index (Table II in the online-only Data Supplement) both at the end of treatment and at the follow-up periods, respectively. However, these differences between cutamesine arms and placebo were not statistically significant.

In the Geriatric Depression Scale, an improvement from baseline in depression symptoms was seen in all 3 treatment groups (Table III in the online-only Data Supplement) without significant difference between the groups. However, the baseline Geriatric Depression Scale scores were low, indicating that the study population was not notably depressed.

The 3 mg/d cutamesine and the placebo group received similar hours of daily rehabilitation therapy during the 28-day treatment period and throughout the 56-day study duration (Table IV in the online-only Data Supplement). Subjects in the 1 mg/d cutamesine group recorded fewer hours of rehabilitation therapy when compared with the 3 mg/d cutamesine and placebo groups.

**Discussion**

We report here the first randomized, controlled study of the Sig-1R agonist cutamesine in stroke. Orally administered cutamesine commenced between 48 and 72 hours after onset and continued for 28 days was considered safe and generally well tolerated relative to placebo at both the 1 and the 3 mg/d dosages. The nature and frequency of TEAEs were as expected from the medical history of enrolled subjects and

**Table 3. Effects of Cutamesine or Placebo Treatment on Neurological Recovery (NIHSS)**

<table>
<thead>
<tr>
<th>ITT/LOCF</th>
<th>All Subjects</th>
<th>NIHSS ≥7</th>
<th>NIHSS ≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Cutamesine 1 mg</td>
<td>Cutamesine 3 mg</td>
</tr>
<tr>
<td>End-of-treatment visit</td>
<td>n</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td>10.7±4.8</td>
<td>8.1±4.4</td>
</tr>
<tr>
<td>Adjusted change from baseline</td>
<td></td>
<td>−3.8±0.6</td>
<td>−4.0±0.6</td>
</tr>
<tr>
<td>Treatment effect</td>
<td></td>
<td>...</td>
<td>−0.2 (−1.9, 1.4)</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>...</td>
<td>0.802</td>
</tr>
</tbody>
</table>

NIHSS were recorded at baseline, at the end-of-treatment visit (day 28), and at the end-of-follow-up visit (day 56). NIHSS is given as mean±SD for baseline and mean±SE for adjusted change from baseline. Treatment effect (cutamesine–placebo) is shown as mean (95% confidence intervals). The prespecified primary efficacy outcome measure was the analysis of NIHSS (total score) in all subjects. Effects on populations with NIHSS ≥7 and NIHSS ≥10 at baseline, respectively, were performed post hoc. Adjusted change from baseline was calculated using an ANCOVA model, with a factor for treatment, and covariates for baseline score, patient age, and timing of treatment initiation after stroke onset. These analyses were performed on the ITT using LOCF. ITT indicates intent-to-treat population; LOCF, last observation carried forward; and NIHSS, National Institutes of Health Stroke Scale.

**Figure 2. Effects of cutamesine or placebo treatment on motor function recovery (10-m walk).** Shown are the percentages of subjects of the intent-to-treat population who were able to complete the 10-m walk independently or with assistance at baseline, day 28, and day 56. Statistical analysis using a logistic regression model, with a single factor for treatment, and covariates for patient age, and timing of treatment initiation after stroke onset: 3 mg/d cutamesine vs placebo (82% versus 55%; odds ratio [cutamesine:placebo], 4.0; 95% CI, 0.9, 18.8; \( P = 0.079 \); logistic regression model) and at day 56 (88% versus 67%; odds ratio [cutamesine:placebo], 4.8; 95% CI, 0.7, 32.7; \( P = 0.106 \); logistic regression model).
mostly reflect sequelae of the recent stroke. No patterns suggestive of drug-related adverse events were detected in this limited sample.

Because changes in NIHSS score may be a more useful metric than modified Rankin Scale and Barthel Index scales for early phase clinical trials particularly in moderately severe stroke (ie, baseline NIHSS score, 7–15), we used improvement in NIHSS from baseline as a measure of functional improvement in this study. Conventional functional scales (modified Rankin Scale and Barthel Index) were included as secondary end points. No statistically significant treatment differences were detected as per the prespecified statistical analysis plan. Trends toward better functional performance with cutamesine, most notably neurological outcome as measured by NIHSS in the 3 mg/d cutamesine group when compared with placebo in exploratory post hoc analysis of subjects with moderate to severe neurological impairment at baseline, were observed but must be interpreted with caution. Although we observed differences favoring cutamesine in subgroups defined by different NIHSS thresholds of between 7 and 10 points at this dose, we did not adjust for multiple statistical comparisons.

This trial was designed to gain initial clinical experience with cutamesine in a patient population with stroke, and the results will inform future trial design in several areas. On the basis of greater difference in NIHSS scores among cutamesine-treated subjects in the moderate to severe patient subgroups, a higher NIHSS cut off score at baseline will be considered.

There was no evidence of interaction with previous intravenous thrombolytic treatment, which was given in a significant proportion of subjects. Therefore, any future study will likely allow thrombolysis before randomization. The treatment duration was modeled after preclinical data, but it is conceivable that molecular processes leading to enhanced recovery may be operational for several months after the onset of stroke and thus a longer treatment duration may be considered. This becomes relevant because the hypothesized mechanism of action of cutamesine suggests that it may enhance the effects of rehabilitation therapy. The highly variable duration of rehabilitation therapy indicates a challenge of controlling this in future clinical trials. We did not analyze treatment response in this trial with therapy dose as a covariate, and future trials should attempt to address this limitation: however, because therapy is a complex multimodal intervention tailored to the needs of an individual, quantifying such inputs will remain a challenge. Efforts will be necessary in a future study to understand and interpret the interdependencies of multimodal sensorimotor stimulation by rehabilitation and cutamesine treatment for improved stroke recovery better.

Enhancement of stroke recovery with treatment initiation in the subacute phase of stroke is a relatively new area of stroke clinical research, and the clinical paradigms are likely to differ from those used in investigations of acute neuroprotection or thrombolysis.

Several early trials with small molecules and biology that may enhance recovery have used differing strategies and reported varying results. Small molecules studied included n-amphetamine, levodopa, sildenafil, and most recently fluoxetine. In the fluoxetine for motor recovery after acute ischemic stroke (FLAME) trial, treatment initiation with fluoxetine was delayed to 5 to 10 days after stroke and enhanced motor function recovery after 90 days was observed.

Furthermore, various growth factor molecules investigated include a combination of β-human chorionic gonadotropin and erythropoietin, recombinant human erythropoietin, and granulocyte colony-stimulating factor. A small trial with β-human chorionic gonadotropin/erythropoietin initiated treatment 24 to 48 hours after stroke while an initial trial with granulocyte colony-stimulating factor delayed treatment initiation after stroke ≤30 days. However, those studies were primarily concerned with establishing safety. Larger multicentre trials such as those with erythropoietin or granulocyte colony-stimulating factor (AX200 for Ischemic Stroke trial) adopted a more standard neuroprotectant trial approach, commencing treatment within 6 or 9 hours of stroke, respectively, and found no effect on efficacy measures.

Given these initial trials, issues that are, as yet, not clearly defined include optimal patient characteristics (clinical and imaging) that identify a potential responder population; appropriate timing for treatment initiation, likely to vary according to the specific therapeutic intervention being studied; treatment duration; and the interaction of pharmacological treatment with conventional rehabilitation therapies. The FLAME trial demonstrated that stroke recovery enhancement is possible by pharmacological intervention and that a feasible clinical trial protocol can be developed in this patient population. Moreover, the population of this present study consisted of neurologically stable patients for whom the acute phase of the stroke has passed. Consequently, only few serious adverse events were observed. A stroke recovery approach with delayed enrollment of neurologically stable patients may thus offer an alternative avenue for clinical development in stroke.

In conclusion, the clinical data and experience gained in this initial study in patients with stroke will inform the design of a future larger study of cutamesine therapy to enhance recovery after ischemic stroke.

**Acknowledgments**

We thank Drs Shevaldishev and Takao for managing the implementation of this trial.

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**Disclosures**

Drs Muir, Santamarina, and Skoloudik participated in this clinical study as country coordinators and investigators. W. Sato and Dr Mita are on the board of directors of M’s Science Corporation. Dr Urfer is a former member of the board of directors of M’s Science Corporation.

**References**


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Roman Urfer, Hans J. Moebius, David Skoloudik, Estevo Santamarina, Wakao Sato, Shiro Mita and Keith W. Muir

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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2014/09/30/STROKEAHA.114.005835.DC1
SUPPLEMENTAL MATERIAL

Phase II trial of the Sigma-1 Receptor Agonist Cutamesine (SA4503) for Recovery Enhancement after Acute Ischemic Stroke

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Supplemental Methods

Diagnosis and main criteria for inclusion:

The study included males or females 18 years of age or older who had experienced an ischemic stroke (computed tomography [CT] or magnetic resonance imaging [MRI] consistent with diagnosis of stroke) 48-72 hours before randomization; had significant impairment of neurological function, defined as a total score of $\geq 4$ on the NIHSS, or $\geq 2$ on the upper or lower extremity motor function scores (Questions 5 and 6) of the NIHSS; could reasonably be expected to be available for all study visits; were previously independent, as confirmed by a score of $<2$ on the Modified Rankin Scale; were medically and neurologically stable within 24 hours prior to randomization (including stable neurological exam, normal or normalizing complete blood count [CBC] and urinalysis, stable vital signs, lack of myocardial infarction [MI], afebrile, and the investigator’s judgment as to stability of the subject’s condition); and had laboratory values within the following limits: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) $<2$ times the upper limit of normal (ULN), bilirubin $\leq 1.5$ times the ULN, hemoglobin $\geq 9.0$ gm/dL, platelet count $\geq 100,000$/mm$^3$, and creatinine clearance $>50$ mL/min.

Main criteria for exclusion:

The study excluded subjects who were pregnant or breast feeding, were of childbearing potential and unwilling to use adequate birth control for the duration of the study, were currently receiving anti-epileptic agents, anxiolytic agents (except for benzodiazepines in stable doses that were started prior to stroke, or short term in the first hours after admission to the hospital), amphetamines, or sigma-1 receptor agents or medications inhibiting CYP3A4 or CYP2D6; had transient ischemic attack (TIA); had stroke in progression; had received anti-psychotic medications within the previous 6 months; had a prior history of seizure or suspected seizure, head injury with loss of consciousness (within the past year), head injury due to penetrating wound, abnormal motor function (prior to stroke), dementia, myocardial infarction (MI) within the last 6 months, hospitalization for major psychiatric illness within the last 5 years, evidence of alcohol or drug dependence or abuse which, based on the investigator's judgment, could have affected the subject's ability to participate in this trial, any major surgical intervention within last 6 months, diagnosis or evidence of chronic hepatitis or human immunodeficiency virus (HIV), current conditions of unstable cardiac, hepatic, or renal disease (evidenced as creatinine clearance of $<50$ mL/min), or other major medical disorder, terminal illness, or severe neurological diseases other than stroke; had participated in any study of an investigational drug, device, or other treatment within 30 days prior to enrolment; or were unable to take medication by mouth (i.e., were using a feeding tube) at the time of baseline assessments.
## Supplemental Tables

### Supplemental Table I:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Cutamene 1 mg</th>
<th>Cutamene 3 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End-of-treatment visit</strong></td>
<td>N 20</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Scores 0 or 1 at baseline, n (%)</td>
<td>1 (5.0)</td>
<td>0</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Scores 0 or 1 at Visit 6, n (%)</td>
<td>4 (20.0)</td>
<td>5 (26.3)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Odds ratio (Cutamene:Placebo)</td>
<td>—</td>
<td>1.37</td>
<td>1.26</td>
</tr>
<tr>
<td>95% CI</td>
<td>—</td>
<td>0.29, 6.54</td>
<td>0.26, 6.20</td>
</tr>
<tr>
<td>p-value from logistic regression</td>
<td>—</td>
<td>0.692</td>
<td>0.778</td>
</tr>
<tr>
<td><strong>End-of-follow-up visit</strong></td>
<td>N 21</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Scores 0 or 1 at baseline, n (%)</td>
<td>1 (4.8)</td>
<td>0</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>Scores 0 or 1 at Visit 8, n (%)</td>
<td>4 (19.0)</td>
<td>8 (42.1)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>Odds ratio (Cutamene:Placebo)</td>
<td>—</td>
<td>2.68</td>
<td>1.72</td>
</tr>
<tr>
<td>95% CI</td>
<td>—</td>
<td>0.62, 11.49</td>
<td>0.38, 7.88</td>
</tr>
<tr>
<td>p-value from logistic regression</td>
<td>—</td>
<td>0.185</td>
<td>0.485</td>
</tr>
</tbody>
</table>

**Table I:** Effects of cutamine or placebo treatment on modified Rankin Scale (mRS). Data shown for intent-to-treat population with categorization of mRS score of 0 and 1, versus 2, 3, 4, and 5, at baseline, end-of-treatment (Day 28) and end-of-follow-up (Day 56) visits, respectively. A logistic regression model was fitted with factors for treatment (placebo, 1 mg/day cutamine, or 3 mg/day cutamine) and baseline score, with patient age and timing of treatment initiation after stroke onset as covariates. Odds ratios and 95% confidence intervals (CI) were constructed for differences between cutamine and placebo.

### Supplemental Table II:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Cutamene 1 mg</th>
<th>Cutamene 3 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End-of-treatment visit</strong></td>
<td>N 20</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>26.0 (27.3)</td>
<td>34.5 (28.3)</td>
<td>39.7 (27.2)</td>
</tr>
<tr>
<td>Adjusted change from baseline, mean (SE)</td>
<td>24.0 (6.1)</td>
<td>38.0 (6.2)</td>
<td>35.2 (6.5)</td>
</tr>
<tr>
<td>Treatment effect (SA4503-placebo), mean (95% CI)</td>
<td>—</td>
<td>140 (3.6, 31.6)</td>
<td>111 (-6.9, 29.2)</td>
</tr>
<tr>
<td>p-value for treatment effect</td>
<td>—</td>
<td>0.12</td>
<td>0.22</td>
</tr>
<tr>
<td><strong>End-of-follow-up visit</strong></td>
<td>N 21</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>25.0 (27.0)</td>
<td>34.5 (28.3)</td>
<td>39.7 (27.2)</td>
</tr>
<tr>
<td>Adjusted change from baseline, mean (SE)</td>
<td>35.3 (5.7)</td>
<td>43.0 (5.9)</td>
<td>44.9 (6.2)</td>
</tr>
<tr>
<td>Treatment effect (SA4503-placebo), mean (95% CI)</td>
<td>—</td>
<td>7.7 (8.9, 24.3)</td>
<td>9.6 (-7.4, 26.7)</td>
</tr>
<tr>
<td>p-value for treatment effect</td>
<td>—</td>
<td>0.36</td>
<td>0.26</td>
</tr>
</tbody>
</table>

**Table II:** Effects of cutamine or placebo treatment on Barthel index (BI). Data shown for intent-to-treat population (LOCF). Change from baseline to the end of the treatment visit (Day 28) and from baseline to the end-of-follow-up visit (Day 56) was analyzed by ANCOVA with a factor for treatment (placebo, 1 mg/day cutamine, or 3 mg/day cutamine), and covariates for baseline score, patient age, and timing of treatment initiation after stroke onset. CI, confidence interval; SD, standard deviation; SE, standard error of the mean.
Supplemental Table III:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Cutamesine 1 mg</th>
<th>Cutamesine 3 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End-of-treatment visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>18</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>3.2 (3.7)</td>
<td>3.6 (3.3)</td>
<td>3.3 (2.5)</td>
</tr>
<tr>
<td>Adjusted change from baseline, mean (SE)</td>
<td>0.6 (0.7)</td>
<td>0.7 (0.7)</td>
<td>0.7 (0.8)</td>
</tr>
<tr>
<td>Treatment effect (SA4503 - placebo), mean (95% CI)</td>
<td>—</td>
<td>0.2 (-1.9, 2.3)</td>
<td>0.1 (-2.0, 2.3)</td>
</tr>
<tr>
<td>p-value for treatment effect</td>
<td>—</td>
<td>0.85</td>
<td>0.91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Cutamesine 1 mg</th>
<th>Cutamesine 3 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End-of-follow-up visit</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>19</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>3.5 (3.8)</td>
<td>3.6 (3.3)</td>
<td>3.3 (2.5)</td>
</tr>
<tr>
<td>Adjusted change from baseline, mean (SE)</td>
<td>0.2 (0.6)</td>
<td>-0.4 (0.6)</td>
<td>0.6 (0.6)</td>
</tr>
<tr>
<td>Treatment effect (SA4503 - placebo), mean (95% CI)</td>
<td>—</td>
<td>-0.6 (-2.3, 1.1)</td>
<td>0.4 (-1.3, 2.2)</td>
</tr>
<tr>
<td>p-value for treatment effect</td>
<td>—</td>
<td>0.5</td>
<td>0.63</td>
</tr>
</tbody>
</table>

**Table III:** Effects of cutamesine or placebo treatment on Geriatric Depression Scale (GDS). Data shown for intent-to-treat population (LOCF). Change from baseline to the end of the treatment visit (Day 28) and from baseline to the end-of-follow-up visit (Day 56) was analyzed by ANCOVA with a factor for treatment (placebo, 1 mg/day cutamesine, or 3 mg/day cutamesine), and covariates for baseline score, patient age, and timing of treatment initiation after stroke onset. CI, confidence interval; SD, standard deviation; SE, standard error of the mean.

Supplemental Table IV:

<table>
<thead>
<tr>
<th></th>
<th>Placebo (h)</th>
<th>Cutamesine 1 mg (h)</th>
<th>Cutamesine 3 mg (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>21</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Days 1 - 28 mean (SD)</td>
<td>3.0 (2.4)</td>
<td>2.3 (2.3)</td>
<td>3.2 (2.8)</td>
</tr>
<tr>
<td>Days 1 - 56 mean (SD)</td>
<td>3.2 (2.5)</td>
<td>2.3 (2.4)</td>
<td>3.4 (2.6)</td>
</tr>
</tbody>
</table>

**Table IV:** Mean duration of daily rehabilitation therapy. The amounts of rehabilitation therapy were recorded at each treatment and follow-up visit based on the subject’s / caregiver’s rehabilitation diary. Values given are mean (SD) hours for the ITT population. SD, standard deviation.