Safety, Pharmacokinetics, and Pharmacodynamics of Escalating Repeat Doses of GSK249320 in Patients With Stroke

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Background and Purpose—Restorative therapies have the potential to improve function and reduce disability after stroke with a wide therapeutic window. The current study evaluated GSK249320, a monoclonal antibody that blocks the axon outgrowth inhibition molecule myelin-associated glycoprotein and also protects oligodendrocytes.

Methods—Patients with mild-moderate stroke were randomized to intravenous GSK249320 (1, 5, or 15 mg/kg per infusion, in escalating cohorts of 8–9 subjects) versus placebo (n=17). Infusion 1 was 24 to 72 hours after stroke; infusion 2 was 9±1 days later. The primary objective evaluated safety and tolerability, and the secondary objectives evaluated immunogenicity, pharmacokinetics, biomarkers, neurophysiology, and motor function.

Results—Baseline (n=42) characteristics were similar across treatment groups. No safety concerns were found based on adverse events, examination, vital signs, ECG, nerve conduction tests, brain imaging, motor function testing, and laboratory studies. Two of the 25 subjects dosed with GSK249320 developed transient antidrug antibodies after infusion 1. The pharmacokinetics profile was as expected for an IgG1 type monoclonal antibody. Serum levels of the biomarker S100β did not differ between groups. Global outcome measures were similar across groups. Modality-specific end points could be consistently measured in the first few days after stroke, and one of these, gait velocity, demonstrated a trend toward improvement with GSK249320 compared with placebo.

Conclusions—GSK249320 was generally well tolerated. No major safety issues were identified in this first study of a monoclonal antibody to modulate the neurobiology of brain repair after stroke. Future studies might explore the efficacy of GSK249320 as a restorative therapy for stroke.

Clinical Trial Registration—URL:http://www.clinicaltrials.gov. Unique Identifier: NCT00833989. (Stroke. 2013;44:1337-1342.)

Key Words: clinical trial ■ monoclonal antibody ■ myelin-associated glycoprotein ■ restorative ■ stroke recovery

Stroke remains a leading cause of adult disability in the United States for which few approved treatment options exist. Approximately 90% of patients survive the initial insult, living an average 6 to 7 years thereafter, with most having long-term significant impairments and disability.1 Intravenous tissue-type plasminogen activator was approved in the United States for treatment of acute ischemic stroke in 1996, but only ≈5% of the US patients receive this medication overall,2 and 25% in specialized centers;3 approximately half of those have long-term disability despite treatment.4,5

In the search for additional approaches to improve function and reduce disability after stroke, attention has been paid to restorative therapies.6 One such approach revolves around promoting axon outgrowth to augment brain repair. A key reason as to why axons do not regenerate after central nervous system injury is the lack of a permissive growth environment. Several growth inhibitors have been identified: myelin-associated glycoprotein (MAG), oligo-myelin glycoprotein, and Nogo-A. One potential strategy is to block the effect of these inhibitors.7

The current study pursued this strategy by using a monoclonal antibody, GSK249320, which is directed against MAG. GSK249320 is a humanized IgG1 monoclonal antibody to MAG that has a disabled Fc region; these features mitigate concerns related to (1) anti-MAG neuropathy, which is attributable to IgM-type antibodies, and (2) toxicity caused by activation of Fc-effector functions (eg, activation of complement attributable to C1q binding).

This specific approach was motivated by previous reports. After stroke in the aged brain, levels of MAG are prominently...
and spontaneously induced. Preclinical studies support the hypothesis that blockade of MAG promotes axonal growth, such as by introducing a dominant-negative form of the receptor, addition of an anti-MAG antibody, MAG immunodepletion, and inactivation of downstream effectors.

GSK249320 was found in preclinical studies to cross the blood–brain barrier (unpublished data, GlaxoSmithKline, 2013), neutralize MAG-mediated inhibition, promote axonal growth, and to protect oligodendrocytes from oxidative stress death. Studies in rodents and primates indicate that intravenous GSK249320 administration beginning 24 hours after experimental stroke improves behavioral outcome, without changing infarct volume (unpublished data). A study in 47 healthy human volunteers found no safety concerns with a single intravenous infusion up to 25 mg/kg GSK249320. Based on these findings, a study was initiated in stroke patients with primary objective to evaluate the safety and tolerability of 2 repeat intravenous infusions of GSK249320. Secondary objectives focused on immunogenicity, pharmacokinetics, biomarkers, neurophysiology, and motor function, and provided an opportunity to further evaluate the performance of modality-specific outcome measures, such as gait velocity, in a stroke trial that enrolled patients during acute hospitalization.

Methods

Study Overview

Patients were screened, consented, randomized to intravenous GSK249320 or placebo, and received the first infusion within 72 hours of stroke onset. Multimodal testing was repeated over 112 days. All studies were approved by local institutional review boards.

Entry/Exclusion Criteria

Inclusion criteria included stroke onset 24 to 72 hours before therapy initiation; stroke radiologically confirmed as supratentorial and either (1) ischemic, with diameter >15 mm or volume >4 cc, or (2) intracerebral hemorrhage; NIHSS score of 3 to 21 (7–21 in Canada); weakness in arm (NIHSS Q5 score 1–3) or leg (NIHSS Q6 score 1–3) or both; age 18 to 90 (18–85 in Germany) years; and reasonable likelihood of receiving standard physical, occupational, and speech rehabilitation therapy. Exclusion criteria included unresponsive (NIHSS Q1a score >1); aphasia severe enough to confound evaluations; previous symptomatic stroke within 3 months; significant prestroke disability (modified Rankin Scale [mRS]>2); symptomatic depression; prestroke symptomatic peripheral neuropathy; prestroke neurological or psychiatric disease likely to confound clinical evaluations; previous demyelinating disease; other major chronic comorbidities; contraindication to transcranial magnetic stimulation (TMS) or MRI; ECG QTc >500 ms; concomitant participation in any investigational rehabilitation paradigm targeting stroke recovery; and pregnancy or lactation. Note that subsequent to the first 945 screen failures, entry criteria for total National Institutes of Health score, stroke subtype, and age were loosened to the above.

Intervention

Each patient was randomized to receive 2 intravenous infusions of either GSK249320 or placebo. Infusion 1 was given 24 to 72 hours after stroke onset, based on the fact that GSK249320 demonstrated the best functional recovery in animal models of stroke when first administered 24 hours after stroke. Infusion 2 was given 9±1 days after infusion 1 to match details of preclinical studies. Each infusion was administered over 60 minutes.

There were 3 sequential dose cohorts (1, 5, and 15 mg/kg), with 8 patients on active and 8 patients on placebo in cohort 1, and 8 patients on active and 4 patients on placebo in cohorts 2 and 3. Infusions were blinded; however, this trial is considered single-blind because the pharmacists preparing the infusions were unblinded to treatment allocation. Drug dose levels were selected based on animal data and first time in human data.

Study Assessments

Patients were followed for a minimum of 112 days and attended 7 visits during this time (days 1, 5, 10, 30, 60, 90, and 112). The primary outcome measure was safety, determined from adverse events, vital signs, physical and neurological examination, ECG, nerve conduction tests, brain MRI, and clinical laboratory testing. Secondary outcome measures included immunogenicity, based on serum measures of anti-GSK249320 antibodies; pharmacokinetics, based on blood draws; serum S100β as a biomarker of neural damage, oligodendrocyte protection, and blood–brain barrier disruption; measures of impairment and function; and neurophysiology, based on TMS measures.

Baseline assessments acquired before the first infusion included physical and neurological examination; vital signs; clinical laboratory testing; blood draw for immunogenicity, biomarker, and pharmacokinetics; ECG; NIHSS scoring; grip strength testing; Box and Blocks testing; and brain MRI. The safety measures of physical and neurological exams, vital signs, review of adverse events and concomitant medications, laboratory testing, and ECG were acquired serially through day 112; nerve conduction testing through day 30; brain MRI through day 60; and TMS through day 112. Three global end points (NIHSS, mRS, and Barthel Index) were assessed through day 90; 6 modality-specific end points (gait velocity, Fugl-Meyer arm motor scale, Fugl-Meyer leg motor scale, bilateral Box and Blocks test, Berg balance, and bilateral grip strength testing) were assessed through day 112; and Geriatric Depression Scale and Montreal Cognitive Assessment were assessed through day 90; validity has been established in stroke for each of these assessments except for Montreal Cognitive Assessment. Blood samples for immunogenicity and pharmacokinetics were acquired through day 112. Biomarker samples were acquired on days 1 and 5.

To reduce variance in outcome measures, all scorers were trained before study initiation. Training videos were provided for the Berg balance and Fugl-Meyer motor scales. TMS procedures and analysis were standardized across sites. Formal certification was required for mRS and NIHSS.

Data Analysis

Adverse events and other safety parameters were tabulated and examined. Estimates of the effect of GSK249320 at each dose relative to placebo were calculated for motor function and global end points. A repeated measures model was fitted, with treatment, visit, treatment X visit interaction, and baseline as fixed effects. Visit was fitted on the repeated statement. Scores on mRS were analyzed at each visit using χ² testing. Montreal Cognitive Assessment and Geriatric Depression Scale at day 90 were analyzed using analysis of covariance, with treatment as the fixed effect and day 5 score as a covariate. The relationships between GSK249320 plasma exposures and any markers of safety or biological activity were subjected to exploratory pharmacokinetic/pharmacodynamic analyses. Study MRI scans were reviewed by an experienced neuroradiologist at the GlaxoSmithKline Clinical Imaging Center, including measurement of infarct volume on acute diffusion-weighted images. For analysis of pharmacokinetic data, an initial assessment of dose proportionality was explored for the area under the curve from time zero (predose) extrapolated to infinite time, area under the curve from time zero to last time of quantifiable concentration within a subject across all treatments, and maximum observed concentration (Cmax) using graphical presentations. An assessment of dose proportionality was made.

Enrollment was planned at 40 patients based on safety, feasibility, and the need to provide sufficient placebo-treated subjects to characterize the outcome measures in terms of variability and placebo response. Two additional subjects were enrolled in cohort 2 as per protocol after withdrawal of subjects in cohorts 1 and 2, increasing total enrollment to 42. Missing data were not imputed. Data management responsibilities and statistical analyses were handled by GSK.
Results

Study Conduct
A total of 3359 patients were screened, with the most common reason for screen failure being a non-stroke (for example, transient ischemic attack instead). A total of 42 subjects were enrolled, all of whom received ≥1 dose of investigational product and had the first infusion 24 to 72 hours after stroke as planned, and 38 (90%) subjects received both doses of investigational product (Figure 1). The treatment blind was accidentally broken for 1 subject during the study (15 mg/kg group) on day 11. All strokes were ischemic apart from 1 patient in the 15 mg/kg group with hemorrhagic stroke. Baseline characteristics were similar across treatment groups (Table 1). Thirty-six (86%) subjects completed the study, and 6 (14%) subjects withdrew from the study prematurely. One subject in the GSK249320 15 mg/kg group was withdrawn because of investigator discretion. Five subjects (3 placebo, 1 in the 5 mg/kg group, 1 in the 15 mg/kg group) withdrew consent, 2 because of medical worsening and 3 for personal reasons (eg, doing too well or did not have time). No subjects were withdrawn because of an adverse event. The amount of physical therapy, occupational therapy, or total therapy did not significantly differ between treatment arms at any time point.

There were 5 protocol deviations: a subject with active depression was enrolled (5 mg/kg group), infusion 2 was given to a subject (5 mg/kg group) 2 days beyond the allowable protocol window, and a dosing error for a subject (5 mg/kg group) resulted in that subject receiving a 1 mg/kg dose for the first administration. Additionally, 2 subjects received an excess amount of investigational product (1 in the placebo group and 1 in the 5 mg/kg group). Nothing suggested an adverse effect of these events on safety findings.

Safety
GSK249320 was generally well tolerated. No clinically significant trends were present in heart rate, systolic blood pressure, or diastolic blood pressure after dosing, with similar patterns present across treatment groups. Overall, an adverse event was reported in 31 (73.8%) subjects, most commonly insomnia, constipation, pyrexia, and diarrhea; and this did not vary according to treatment group. A serious adverse event was reported in 10 (23.8%) subjects, which also did not vary by treatment group and was as expected for the patient population; none was fatal. Three events were deemed potentially drug related by the local investigator: 2 were in the same patient (15 mg/kg group), consisting of acute renal failure (mild intensity, days 18–38) and stroke (moderate intensity, days 38–58), and the third was an event of dysgeusia reported in a patient in the 5 mg/kg group. There were no events suggestive of infusion site reactions, allergic or hypersensitivity reactions, or peripheral or central demyelination with GSK249320 treatment. No adverse event resulted in discontinuation of drug. Events common to stroke were tabulated separately, present in 66.7% of subjects, and did not vary according to treatment group; the most common events were depression/mood disorder and joint or soft tissue pain.

Laboratory Results
No clinically significant trends were observed for postdosing clinical chemistry and hematology parameters, which were similar across treatment groups. ECG findings also evolved over time similarly across groups. Nerve conduction testing found no suggestion of peripheral demyelination related to GSK249320. TMS found no results that might suggest clinical worsening among subjects who received GSK249320, and will be presented in detail elsewhere. MRI review raised no concerns, including no suggestion of increased risk of central demyelination secondary to GSK249320 treatment.

Figure 1. CONSORT diagram.
Biomarker Results
Levels of the S100β protein were detectable in all subject samples at all time points. No significant change in S100β levels over time was apparent in any of the 4 subject groups, however, and levels did not differ between placebo- and GSK249320-treated subjects. There was a trend for higher serum levels of S100β in relation to NIHSS score at baseline ($\rho=0.29$; $P=0.089$).

Pharmacokinetic Results
Pharmacokinetic analysis of subjects who received GSK249320 and blood sampling per protocol found that the geometric mean of terminal half-life across all subjects was 22.5 days. GSK249320 plasma concentrations were linear with increasing dose for the area under the curve and for Cmax, after both first and second drug administration. The initial volume of distribution was 30.5 mL/kg, the volume of distribution at steady state was 54.8 mL/kg, and clearance was 0.0757 mL/kg per hour.

Immunogenicity Results
Of the 25 subjects who were dosed with GSK249320, 2 (8%) developed transient antidrug antibodies after infusion 1 (1 in the 1 mg/kg group and 1 in the 5 mg/kg group). In addition, 1 subject had preexisting antibodies, with a titer of 600, that were only present in the day 1 predose sample collection and consequently not related to treatment. None of the immunogenicity-positive responses were associated with alterations in the pharmacokinetic profile or adverse event findings.

Clinical Outcome
There were no apparent trends suggestive of clinical worsening in subjects receiving GSK249320. NIHSS total scores improved over time and did not suggest harm with GSK249320 treatment. Findings for the day 90 global outcome measures, NIHSS and mRS, did not differ across treatment groups (Table 2).

The modality-specific end points, many of which have not been extensively used in stroke trials that enroll patients during the acute stroke hospitalization period, could be collected in most patients early after stroke. At visit 1, 24 to 72 hours after stroke, the first assessment of the Box and Blocks test was obtained in all 42 subjects; grip strength test was obtained in 41 subjects. For the 41 subjects who received a visit 2 examination, which occurred 5 to 9 days after stroke, the first assessment of Fugl-Meyer scores could each be obtained in 40 subjects; Montreal Cognitive Assessment score in 39 subjects; and gait velocity, Berg balance, and Geriatric Depression Scale in 38 subjects. The gait velocity data suggested a trend toward benefit with GSK249320 treatment that warrants further exploration in future trials. A mixed model repeated measures analysis of mean change in gait velocity found greater gains for GSK249320 (all doses combined) compared with placebo at days 30 ($P=0.006$), 90 ($P=0.018$), and 112 ($P=0.012$), largely driven by results in the 1 mg/kg and 5 mg/kg groups (Figure 2). The only other modality-specific measure to show such a finding was the lower extremity Fugl-Meyer score at day 30 ($P=0.027$). Note, however, that 5 of the 10 sites that enrolled subjects assessed gait velocity incorrectly, with 4 sites

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics</th>
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<tbody>
<tr>
<td>Placebo</td>
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<tr>
<td>No. subjects randomized</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Sex (F/M)</td>
</tr>
<tr>
<td>Previous stroke</td>
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<tr>
<td>Previous TIA</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>Current smoker</td>
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<tr>
<td>Previous myocardial infarct</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Stroke in MCA territory</td>
</tr>
<tr>
<td>Infarct volume, cc</td>
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<tr>
<td>Time from stroke onset to first dose, h</td>
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<tr>
<td>Received acute reperfusion therapy for index stroke</td>
</tr>
<tr>
<td>Baseline NIHSS score</td>
</tr>
<tr>
<td>Percentage arm motor deficit at baseline (NIHSS Q5&gt;0)</td>
</tr>
<tr>
<td>Percentage leg motor deficit at baseline (NIHSS Q6&gt;0)</td>
</tr>
</tbody>
</table>

IA indicates intra-arterial; MCA, middle cerebral artery; MERCI, Mechanical Embolus Removal in Cerebral Ischemia; NIHSS, National Institute of Health Stroke Scale; and TIA, transient ischemic attack.

Results are mean±SD, median (range), or percentage. Acute reperfusion therapy includes intravenous tissue-type plasminogen activator, IA tissue-type plasminogen activator, MERCI, and Penumbra. No baseline characteristic varied according to treatment group.
instructing subjects to walk as fast as possible instead of at a normal pace, and 1 site instructing subjects to both walk as fast as possible and at a normal pace.

Discussion
Restorative therapies have the potential to be accessed by a large percentage of stroke patients and therefore might be useful complements to reperfusion and rehabilitation approaches to stroke therapy. One form of restorative therapy aims to improve function by promoting axon outgrowth to augment brain repair. GSK249320 is a monoclonal antibody that blocks the growth inhibiting glycoprotein MAG and protects oligodendrocytes, and that was found to improve behavioral outcomes in rodent and primate studies. The current study translated GSK249320 in accordance with Stroke Therapy Academic Industry Roundtable (STAIR) guidelines; in particular, preclinical studies found that GSK249320 was associated with significant gains in motor recovery compared with placebo in several stroke models, in both rodent and primate studies. The current study found that, across 3 escalating dose levels, GSK249320 was generally well tolerated in human subjects with moderate stroke.

The primary outcome measure was safety, and all 3 dose levels of GSK249320 performed well in this regard. Review of adverse events, vital signs, physical and neurological exams, ECG, nerve conduction tests, brain imaging, clinical outcomes, and laboratory studies did not disclose any concerns. One theoretical concern was induction of demyelinating lesions on introduction of antibodies directed against MAG. However, these were not detected in peripheral or central nervous system, in accordance with the design of the GSK249320 antibody. In addition, GSK249320 was not found to be strongly immunogenic or to cause any infusion site reactions, allergic responses, or hypersensitivity reactions.

Pharmacokinetic data demonstrated the half-life of GSK249320 in stroke patients to be similar to the 21 days estimated in healthy volunteers and typical of an IgG1 type of monoclonal antibody. The linearity with dose observed in the healthy volunteer study was also confirmed in this stroke patient study. Furthermore, population analyses showed limited variability and good agreement with the parameter estimates in the healthy volunteer study.

S100β is a glial cell marker secreted from disrupted oligodendrocytes in ischemic tissue and was included in the current study to assess the oligodendrocyte protection properties of GSK249320, neurological damage, and blood–brain barrier dysfunction. Oligodendrocyte protection is relevant to stroke recovery; for example, oligodendrocyte integrity is important to the function of new axon sprouts as well as axons that lose myelin during ischemia. Detection of S100β in all serum samples across groups suggests consistent blood–brain barrier leakage across subjects. However, S100β levels did not increase over the measurement period, as reported previously, possibly because of sampling of S100β at relatively late time points in the current study. Because no reduction in serum S100β levels was demonstrated in relation to GSK249320 treatment and no differences in serum S100β levels were observed between placebo- and GSK249320-treated patients, verification of the oligodendrocyte protection mechanism of GSK249320 could not be concluded in the current study. The trend toward increasing serum S100β levels with greater stroke severity is consistent with previous reports.

Secondary outcome measures also included both global and modality-specific outcome measures. Global outcome

### Table 2. Final Outcome Measure Results

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>1 mg/kg</th>
<th>5 mg/kg</th>
<th>15 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global outcome measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score</td>
<td>2.0</td>
<td>1.5</td>
<td>2.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Percentage modified Rankin Scale score 0–1</td>
<td>21%</td>
<td>25%</td>
<td>38%</td>
<td>33%</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>95</td>
<td>100</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td><strong>Modality-specific outcome measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fugl-Meyer leg motor scale</td>
<td>25.2±10.0</td>
<td>25.0±9.5</td>
<td>31.4±3.5</td>
<td>25.5±13.8</td>
</tr>
<tr>
<td>Fugl-Meyer arm motor scale</td>
<td>48.7±24.5</td>
<td>46.5±27.1</td>
<td>52.1±18.0</td>
<td>37.7±31.0</td>
</tr>
<tr>
<td>Box and Blocks test</td>
<td>22.9±14.9</td>
<td>25.3±22.4</td>
<td>31.3±20.7</td>
<td>25.8±24.1</td>
</tr>
<tr>
<td>Berg balance</td>
<td>41.8±19.4</td>
<td>50.3±7.0</td>
<td>50.4±10.0</td>
<td>35.7±23.4</td>
</tr>
<tr>
<td>Grip strength</td>
<td>15.6±14.5</td>
<td>18.1±20.6</td>
<td>17.1±11.5</td>
<td>17.6±19.7</td>
</tr>
</tbody>
</table>

Values are mean±SD, except for the NIHSS and Barthel Index, which are median. The Fugl-Meyer leg motor scale ranges from 0 to 34; the Fugl-Meyer arm motor scale ranges from 0 to 66; the Berg Balance scale ranges from 0 to 56; for each of these scales, a higher score is better. The Box and Blocks score is the number of blocks transported by the affected upper extremity in 60 s. Grip strength is reported in kg.

Figure 2. Gait velocity is provided over the 112 days of study conduct for each of the 4 treatment groups. The change in gait velocity was significantly greater for GSK249320 compared with placebo at days 30 (P=0.006), 90 (P=0.018), and 112 (P=0.012), driven by 1 mg/kg and 5 mg/kg group results.

The primary outcome was safety, and all 3 dose levels of GSK249320 performed well in this regard. Review of adverse events, vital signs, physical and neurological exams, ECG, nerve conduction tests, brain imaging, clinical outcomes, and laboratory studies did not disclose any concerns. One theoretical concern was induction of demyelinating lesions on introduction of antibodies directed against MAG. However, these were not detected in peripheral or central nervous system, in accordance with the design of the GSK249320 antibody. In addition, GSK249320 was not found to be strongly immunogenic or to cause any infusion site reactions, allergic responses, or hypersensitivity reactions.

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Secondary outcome measures also included both global and modality-specific outcome measures. Global outcome
measures (Table 2) were similar across treatment groups and, in general, were as expected for a study of moderate stroke. The 6 modality-specific end points, each of which has established validity in the setting of stroke and many of which have not been commonly used in the acute stroke setting, could be consistently collected in the first days after stroke, although patients with severe aphasia were excluded. One reason for including modality-specific secondary outcome measures was that some of these approximated the motor-intensive behavioral end points used in the preclinical studies. The results suggest a potentially favorable effect of GSK249320 on gait velocity (Figure 2), a measure of lower limb motor recovery, and on lower extremity motor Fugl-Meyer, a measure of sensorimotor function. Both findings might reflect type I error and require validation. However, half of the sites did not collect gait velocity data correctly, despite clear testing details in the procedures manual and protocol, indicating that this detail was not fully assessed at site initiation visits, and highlighting the importance of training for novel end points.

Restorative therapies in the acute stroke setting generally have a time window of a day or more and therefore have the potential to improve outcome in a large percentage of patients. The current study found that 2 intravenous infusions of one such therapy, GSK249320 initiated 24 to 72 hours after stroke onset, is well tolerated. This is a novel approach to brain repair after stroke because there is limited experience using a monoclonal antibody to modify poststroke neurobiology in humans. The current results support the safety of this pharmaceutical compound and the value of further studies in patients with acute stroke.

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Disclosures
Dr Cramer has served as a paid consultant to GlaxoSmithKline. The other authors have no conflicts to report.

Study Sites
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