Glycine Antagonist in Neuroprotection for Patients With Acute Stroke
GAIN Americas: A Randomized Controlled Trial

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Context  Elucidation of the ischemic cascade has helped stimulate development of neuroprotective drugs aimed at limiting brain injury in the hours following an ischemic stroke. To date, none of these drugs has shown clinical efficacy.

Objective  To examine the efficacy of gavestinel (GV150526), an antagonist of the glycine site of the N-methyl-D-aspartate receptor, as a neuroprotective therapy for acute ischemic stroke when administered within 6 hours of symptom onset.


Setting  One hundred thirty-two hospital centers across the United States and Canada.

Patients  The primary efficacy population consisted of 1367 ischemic stroke patients with a predefined level of limb weakness and functional independence prior to stroke, stratified at randomization by age (≤75 vs >75 years) and initial stroke severity (National Institutes of Health [NIH] Stroke Scale scores of 2-5, 6-13, or ≥14).

Intervention  Patients were randomly assigned to receive an intravenous loading dose (800 mg) plus 5 maintenance doses (200 mg every 12 hours) of gavestinel (n=701) or placebo (n=666) for 3 days.

Main Outcome Measure  Functional capability at 3 months, measured by the Barthel Index (BI), with scores trichotomized as dead/0-55, 60-90, and 95-100, compared between the gavestinel and placebo groups.

Results  Treatment groups were well matched for baseline characteristics. For each group, median NIH Stroke Scale was 12, median age was 72 years, and median time to treatment was 5.2 hours. No statistically significant improvement on the 3-month BI trichotomy was demonstrated for gavestinel (P=.79). The proportion who were functionally independent (BI score=95-100) was 39% in the gavestinel group and 37% in the placebo group. No statistically significant difference in 3-month survival was observed using Kaplan-Meier curves (P=.11). No other secondary end point suggested an advantage for gavestinel. Among the 333 patients (24%) who received recombinant tissue-type plasminogen activator, there was also no benefit for gavestinel (P=.53). There were no serious safety issues.

Conclusion  In this study, gavestinel administered up to 6 hours after an acute ischemic stroke did not improve functional outcome at 3 months.

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For editorial comment see p 1760.
Table 1. Eligibility Criteria

**Inclusion criteria**
- Aged 18 years or older
- Symptoms consistent with acute stroke and present at time of the study treatment
- Treatment can be initiated within 6 hours of symptom onset
- Limb weakness present. If both arm and leg are affected, there must be drift within 10 seconds for the arm and 5 seconds for the leg; if only 1 limb is affected, the limb must touch the bed within 10 seconds for the arm or 5 seconds for the leg
- Previously independent (Modified Rankin score ≤ 1)
- Written informed consent given by the subject or a legally authorized representative
- If a woman, must be of non-childbearing potential, or if of childbearing potential, with negative pregnancy test at screen and confirmation of adequate contraception use

**Exclusion criteria**
- Obtunded, responding only with reflex motor or autonomic effects, or totally unresponsive, flaccid, areflexic
- Symptoms rapidly improving and likely to resolve completely within 24 hours
- Diagnosis or suspicion of subarachnoid hemorrhage
- Known serious life-threatening illness likely to lead to death in the next 3 months
- Symptoms consistent with severe congestive heart failure
- Presence of malignant hypertension
- Known history of significant renal impairment or hepatic disease
- Participation in a clinical trial with an investigational drug or internal device within the past 3 months
- Previous treatment with gavestinel
- Unlikely to be available for follow-up

The compound gavestinel (GV150526) was shown to have high affinity and high selectivity for the glycine site of the NMDA receptor complex, and inhibited NMDA-induced depolarization at low doses in preclinical studies. When administered up to 6 hours from stroke onset, gavestinol reduced infarct size by 50% in a rat middle cerebral artery occlusion model of ischemic stroke. In phase 2 studies, gavestinol was well tolerated when administered at projected neuroprotective doses. The phase 3 Glycine Antagonist in Neuroprotection (GAIN) trials, GAIN Americas and GAIN International, were undertaken using nearly identical protocols to determine whether patients treated with gavestinol within 6 hours of stroke onset have improved functional outcome (independence) at 3 months, and to further assess the compound’s safety in the clinical setting of acute stroke. Here we report the final results of GAIN Americas, which was conducted in the United States and Canada.

**METHODS**

The GAIN Americas trial, conducted at 132 medical centers in the United States and Canada, was a randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gavestinel in patients with a clinical diagnosis of acute stroke.

**Patients**

The eligibility criteria for the trial are outlined in Table 1. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). Total baseline NIHSS scores could range from 2 to 41, due to the limb weakness inclusion and level of consciousness exclusion criteria. Eligible patients with hemorraghic stroke were included in order to provide information about the safety and preliminary efficacy of gavestinel among patients with intracerebral hemorrhage (ICH). Patients who received intravenous recombinant tissue-type plasminogen activator (rt-PA) within 3 hours of stroke onset, and who met the eligibility criteria after rt-PA infusion, were enrolled. All patients, or their legally authorized representatives (in accordance with local regulations), provided written informed consent to enter the trial. All participating centers obtained approval for the consent form and the study protocol from their local ethics or institutional review boards prior to randomizing patients.

**Randomization**

The treatment assignment schedule was generated by the statistician on the independent safety and efficacy data monitoring committee (SEDMC) and was given to the centralized randomization service. Patients were randomly assigned (1:1) to receive either gavestinol or placebo, with stratification by age (≤ 75 or > 75 years) and stroke severity (NIHSS scores categorized as 2-5, 6-13, ≥ 14) yielding 6 strata. These NIHSS categories were selected based on their associations with 6-month functional outcome in a large, population-based study. Treatment allocations were obtained by pharmacists at the study sites by telephoning the randomization service, which used an interactive voice-response system.

**Treatment**

The study drug was provided in prenumbered packs of amber vials containing gavestinol sodium or vehicle placebo (Glaxo Wellcome Inc, Research Triangle Park, NC). The contents of the vials were diluted in 5% dextrose (D5W) due to the poor solubility of gavestinol in saline. Since gavestinol is light sensitive, the infusion bag and tubing were covered with opaque green plastic sleeves during preparation and administration. The sleeves also helped prevent unblinding of study personnel by keeping them from seeing the pale yellow color of the diluted gavestinol solution. Accidental unblinding of personnel involved in patient care were recorded in the case report form.

The study drug was given intravenously over 3 days. Patients received either placebo or a total of 1800 mg of gavestinol administered as a loading dose of 800 mg (400 mg in 250 mL of...
D5W over 30 minutes, then 400 mg in 250 mL of D5W over 3.5 hours, followed by 5 maintenance doses of 200 mg each in 150 mL of D5W over 15 minutes at 12, 24, 36, 48, and 60 hours after the start of the loading dose.

Assessments

Baseline assessments included demographics, medical history, cerebrovascular event history, prestroke level of independence by the Modified Rankin Scale (MRS), stroke severity by the NIHSS, and stroke subtype by the Oxfordshire Community Stroke Project classification. Study personnel were trained and certified in using the NIHSS through video training procedures. The presence of ICH was determined from a brain computed tomography (CT) scan taken within 18 hours of stroke onset, or a magnetic resonance imaging (MRI) scan taken within 6 hours. Digitized images were read by a blinded committee of 3 independent neuroradiologists. At day 7 or at hospital discharge, whichever came sooner, stroke subtype was classified by the criteria used in the Trial of ORG10172 in Acute Stroke Treatment (TOAST). Routine hematologic and clinical chemistry parameters were measured at baseline and after treatment completion. A central laboratory performed the analyses. Study treatment was terminated if creatinine values exceeded 2.0 mg/dL (178.8 μmol/L), or if bilirubin, aspartate aminotransferase, or alanine aminotransferase values exceeded 4 times the upper limit of reference range on these or locally obtained laboratory tests. Electrocardiograms were obtained at baseline and during the treatment phase and were read at a central blinded reading center.

Primary Outcome

The primary outcome was functional capability in activities of daily living at 3 months as measured by the Barthel Index (BI). Barthel Index scores were trichotomized as follows: 95-100 = “independence” (little or no help required), 60-90 = “assisted independence” (some help required), and 0-55 = “dependence” (help required with most or all activities). Deaths were analyzed along with the 0-55 group. The BI cut points were chosen based on prior studies that established that scores of 60 and 95 defined meaningful clinical subgroups. Guidelines for administering the BI were reviewed at pre-study training meetings. To minimize bias in the assessment of the primary outcome, the person performing the BI at 3 months could not be a person involved in caring for the patient during the initial hospitalization.

Secondary Outcomes

Secondary outcomes included level of independence determined by BI at 7 days or hospital discharge (whichever came sooner) and at 1 month, and both stroke severity determined by NIHSS and level of handicap determined by MRS at 1 and 3 months. Other outcomes included survival through 3 months and a global test, composed of dichotomies of the BI (95-100, 0-90/dead), NIHSS (0-1, 2-42/dead), and MRS (0-1, 2-5/dead) measured at 3 months. This was a modified version of the global test used in the National Institute of Neurological Disorders and Stroke (NINDS) trial of rt-PA for acute stroke in that it omitted the Glasgow Outcome Scale. Reduction in ischemic lesion volume growth from baseline to 3 months by diffusion-weighted MRI, health care resource use through 3 months, and functional outcome and quality of life using the Stroke Impact Scale at 1 and 3 months were additional prespecified secondary outcomes that will be reported separately.

Safety Monitoring

Adverse events, both serious and nonserious, were recorded. Certain adverse events were designated as “events common to stroke patients” in the protocol. These included progression of stroke, hemorrhagic transformation, brain herniation, aspiration pneumonia, deep vein thrombosis, and recurrent stroke. For such events that also met the standard definition of a serious adverse event, the requirement for immediate reporting by investigators was waived (with prior regulatory approval) unless the event proved fatal or the investigator otherwise felt the event required urgent notification. Other types of serious adverse events followed usual reporting requirements. The SEDMC reviewed all safety data after the first 150 patients were enrolled, and then after each subsequent 250 patients were enrolled. Fatal events were reported to the SEDMC as they occurred.

Statistical Methods

The primary efficacy analysis included all ischemic stroke patients who received at least 1 dose of study drug. Randomized patients who did not go on to receive any study treatment were excluded. Following the intent-to-treat principle, patients who received any medication were analyzed in the treatment group to which they were randomized, regardless of treatment received. Treated patients who were lost to follow-up or withdrew consent prior to their 3-month assessments were assigned their last posttreatment BI score.

Barthel Index score distributions in active and placebo groups were compared using the extended Mantel-Haenszel χ² test (1 df) stratified by baseline stroke severity and age group, at the 2-sided, 5% level of significance. The scores used for the extended Mantel-Haenszel test were 2 for BI 95-100, 1 for BI 60-90, and 0 for BI 0-55 or dead. These scores were optimal under a proportional adjacent odds model. The null hypothesis was that distributions of the trichotomized outcome would be the same in both treatment groups. Given the scoring, positive z values were interpretable as gavestinel superior to placebo, and negative z values as placebo superior to gavestinel. The trial was powered at 90% at 2-tailed α = .05 for an (unstratified) outcome distribution for the trichotomized BI, as shown in Table 2. This allowed for a 10 percentage-point difference between treatment groups in the best outcome category in favor of gavestinel and a 6 percentage-point difference in the worst category. The outcome distribution in the placebo group was based on the Clomethiazole Acute Stroke Study. A sample size of 673...
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evaluable, nonhemorrhagic patients per treatment group was required to detect the stated differences. Assuming 10% of randomized patients would have an ICH, and no more than 5% would be unevaluable, a total sample size of 1580 acute stroke patients was required.

Two interim analyses and a final analysis were scheduled. These used a 2-sided test with equal allocation of type I error (.025 in either direction), but with asymmetrical stopping boundaries. Due to the conservative nature of the stopping boundaries for the interim analyses, only a slight adjustment (at the fourth decimal place) was needed in the P values required by the group-sequential design. For the routine reporting of P values below, nominal P values were used, ie, no further adjustments for group-sequential testing were applied.

Prestated secondary analyses examined the secondary outcome measures described above using the extended Mantel-Haenszel test for the BI outcomes and the Mantel-Haenszel test\textsuperscript{24} for the NIHSS and MRS outcomes. The global test used the same model as the NINDS trial but our method of estimation used multinomial theory and weighted least squares to estimate and test the common odds ratio.\textsuperscript{25} Prespecified subgroup analyses of BI distributions at 3 months stratified by time to treatment (≤4, >4 hours), use of rt-PA, and baseline age and NIHSS score also used the extended Mantel-Haenszel test. Safety analyses included all treated patients (hemorrhagic and ischemic stroke) grouped according to treatment actually received, rather than as assigned at randomization. As per study protocol, efficacy for ICH will be determined in a pooled analysis combining ICH patients from both GAIN trials.

RESULTS

Enrollment began in April 1998 and ended in October 1999 with 132 sites (100 in the United States, 32 in Canada) contributing patients. Follow-up was completed in January 2000. The trial profile is summarized in FIGURE 1. Of the 1646 patients randomized, 41 did not receive study treatment. The most common reasons for failing to treat were consent obtained too late or withdrawn (n=11), rapid improvement of symptoms (n=7), drug administration delays (n=6), or other eligibility criteria violations (n=17). Of the 1605 patients treated, 237 were classified as having hemorrhagic strokes (236 ICH, 1 other) by the image adjudication committee. The remaining 1368 patients constituted the ischemic stroke group. Follow-up was complete on 1343 (98.2%) of these patients; 25 patients withdrew consent or were lost to follow-up before 3 months. None were withdrawn from the study by investigators for adverse events. Earlier posttreatment assessments were carried forward for the missing 3-month data in 24 cases. One patient was excluded from the analysis because consent was withdrawn prior to any follow-up assessment. The primary efficacy population (N=1367) there-
fore included 701 ischemic stroke patients randomized to gavestinel and 666 randomized to placebo.

In this population, 77 violations of inclusion or exclusion criteria were reported in 74 patients (36 randomized to gavestinel, 38 to placebo). The most frequent violations were late (>6 hours) study drug administration (53 instances, 3.9% of patients) and use of an investigational drug or device in the past 3 months (13 instances, 0.9% of patients). Forty-five patients (6.4%) in the gavestinel group and 41 patients (6.1%) in the placebo group stopped treatment prematurely for reasons other than death. Of these, 37 were discontinues due to adverse events (18 gavestinel, 19 placebo) and 10 due to elevated laboratory values (6 gavestinel, 4 placebo). Thirty patients died before treatment was completed: 21 (3.0%) in the gavestinel group and 9 (1.4%) in the placebo group. Clinical sites reported 5 cases where the treatment blinding was accidentally broken during the course of treatment.

Table 3 summarizes the baseline characteristics of the 2 treatment groups. There were no major imbalances, but fewer patients in the gavestinel group had a history of previous transient ischemic attack. The proportion of patients older than age 75 years was 39.1% in the gavestinel group and 38.0% in the placebo group. Median time to treatment was 5.2 hours in both the gavestinel and placebo groups, with 17% and 19%, respectively, treated within 4 hours of stroke onset.

The primary outcome analysis is summarized in Figure 2. Patients treated with gavestinel did not show a statistically significant improvement in independence at 3 months compared with patients treated with placebo, after adjustment for age and baseline NIHSS score. No treatment effect was detected, even after adjusting for the baseline NIHSS score and the cohort's characteristics. No significant differences were found on any of the secondary end points (Table 4), including survival through 3 months (Figure 3). In addition, no significant difference was found using the global statistic (odds ratio [OR], 1.05; 95% confidence interval [CI], 0.85-1.31; P = .64).

Results for prespecified subgroups of interest are shown in Table 5. The distributions of the BI at 3 months were compared within each of the 6 age and NIHSS strata. A significant difference was found in only 1 stratum among the

Table 3. Demographic and Baseline Characteristics for the Primary Efficacy Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gavestinel (n = 701)</th>
<th>Placebo (n = 666)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Mean (SD), y</td>
<td>70.0 (12.8)</td>
<td>70.0 (12.6)</td>
</tr>
<tr>
<td>Median, y</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>NIHSS score Mean (SD)</td>
<td>12.7 (6.3)</td>
<td>13.0 (6.4)</td>
</tr>
<tr>
<td>Median</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Age and NIHSS strata, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤75, 2-5</td>
<td>65 (9.3)</td>
<td>64 (9.6)</td>
</tr>
<tr>
<td>≤75, 6-13</td>
<td>198 (28.2)</td>
<td>181 (27.2)</td>
</tr>
<tr>
<td>≤75, ≥14</td>
<td>164 (23.4)</td>
<td>168 (25.2)</td>
</tr>
<tr>
<td>&gt;75, 2-5</td>
<td>31 (4.4)</td>
<td>25 (3.8)</td>
</tr>
<tr>
<td>&gt;75, 6-13</td>
<td>106 (15.1)</td>
<td>97 (14.6)</td>
</tr>
<tr>
<td>&gt;75, ≥14</td>
<td>137 (19.5)</td>
<td>131 (19.7)</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>335 (47.8)</td>
<td>316 (47.4)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>594 (84.7)</td>
<td>578 (86.8)</td>
</tr>
<tr>
<td>Black</td>
<td>54 (7.7)</td>
<td>46 (6.9)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>24 (3.4)</td>
<td>21 (3.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>23 (3.3)</td>
<td>18 (2.7)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (0.9)</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Stroke risk factors, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>468 (66.8)</td>
<td>469 (70.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>166 (23.7)</td>
<td>171 (25.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>178 (25.4)</td>
<td>175 (26.3)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>142 (20.3)</td>
<td>163 (24.5)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>216 (30.9)</td>
<td>197 (29.6)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>163 (23.2)</td>
<td>165 (24.8)</td>
</tr>
<tr>
<td>Heavy alcohol (≥2/d)</td>
<td>54 (7.7)</td>
<td>53 (8.0)</td>
</tr>
<tr>
<td>History of CV event, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>137 (19.5)</td>
<td>139 (20.9)</td>
</tr>
<tr>
<td>Previous TIA†</td>
<td>117 (16.7)</td>
<td>150 (22.5)</td>
</tr>
<tr>
<td>Time to treatment Mean (SD), h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, h</td>
<td>5.0 (1.0)</td>
<td>5.0 (1.0)</td>
</tr>
<tr>
<td>Treated ≤4 h, No. (%)</td>
<td>116 (16.6)</td>
<td>125 (18.8)</td>
</tr>
<tr>
<td>Treated with rt-PA, No. (%)</td>
<td>166 (23.7)</td>
<td>167 (25.1)</td>
</tr>
<tr>
<td>TOAST subtype of stroke, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large vessel atherothromboembolic</td>
<td>240 (34.2)</td>
<td>231 (34.7)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>215 (30.7)</td>
<td>212 (31.8)</td>
</tr>
<tr>
<td>Small vessel (lacunar)</td>
<td>126 (18.0)</td>
<td>104 (15.6)</td>
</tr>
<tr>
<td>Infarct (unknown cause)</td>
<td>90 (12.8)</td>
<td>100 (15.0)</td>
</tr>
<tr>
<td>Infarct (other)</td>
<td>20 (2.8)</td>
<td>9 (1.4)</td>
</tr>
<tr>
<td>No infarct</td>
<td>10 (1.4)</td>
<td>10 (1.5)</td>
</tr>
</tbody>
</table>

*Not all column percentages total 100 due to rounding. NIHSS indicates National Institutes of Health Stroke Scale; MI, myocardial infarction; CV, cerebrovascular; TIA, transient ischemic attack; rt-PA, recombinant tissue-type plasminogen activator; OCSP, Oxfordshire Community Stroke Project; and TOAST, Trial of ORG10172 in Acute Stroke Treatment.

1P = .004. No other P values were <.05.
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Younger patients with milder strokes (age ≤75 years, NIHSS 2-5). After adjustment for age, baseline NIHSS, sex, time to treatment, use of rt-PA, and stroke subtype (lacrinar vs nonlacunar), the difference for this stratum persisted (P<.001, Wald test statistic for logistic regression with an assumed common log OR). Among those treated within 4 hours of stroke onset, no significant differences were demonstrated for those receiving gavestinel vs placebo.

Thrombolytic therapy with intravenous rt-PA was administered to 333 patients: 166 (24%) in the gavestinel group and 167 (25%) in the placebo group. Time to treatment with the study group and 167 (25%) in the placebo patients: 166 (24%) in the gavestinel vs placebo.

ences were demonstrated for those receiving gavestinel vs placebo.

Figure 2. Barthel Index at 3 Months (Primary Efficacy Outcome)

Table 4. Secondary Efficacy Outcomes

<table>
<thead>
<tr>
<th>End Point</th>
<th>Gavestinel (n = 701)</th>
<th>Placebo (n = 668)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barthel Index at 7 days/discharge†</td>
<td>95-100</td>
<td>121 (17)</td>
<td>98 (15)</td>
</tr>
<tr>
<td></td>
<td>60-90</td>
<td>115 (16)</td>
<td>113 (17)</td>
</tr>
<tr>
<td></td>
<td>0-55 or dead</td>
<td>464 (66)</td>
<td>453 (68)</td>
</tr>
<tr>
<td>Barthel Index at 1 month†</td>
<td>95-100</td>
<td>215 (31)</td>
<td>208 (31)</td>
</tr>
<tr>
<td></td>
<td>60-90</td>
<td>135 (19)</td>
<td>116 (17)</td>
</tr>
<tr>
<td></td>
<td>0-55 or dead</td>
<td>350 (50)</td>
<td>342 (51)</td>
</tr>
<tr>
<td>NIH Stroke Scale at 3 months‡</td>
<td>0-1</td>
<td>197 (28)</td>
<td>179 (27)</td>
</tr>
<tr>
<td></td>
<td>2-42 or dead</td>
<td>504 (72)</td>
<td>487 (73)</td>
</tr>
<tr>
<td>Modified Rankin Scale at 3 months‡</td>
<td>0-1</td>
<td>200 (29)</td>
<td>170 (26)</td>
</tr>
<tr>
<td></td>
<td>2-5 or dead</td>
<td>499 (71)</td>
<td>491 (74)</td>
</tr>
</tbody>
</table>

Some column percentages may not total 100 due to rounding. *Extended Mantel-Haenszel χ² test. †Mantel-Haenszel test.

COMMENT

To date, the GAIN Americas trial (N = 1367) and the GAIN International trial (N = 1455) are the largest trials of a neuroprotectant for acute stroke. Both were adequately powered to detect a difference in the primary end point and to provide definitive conclusions about the study medication’s efficacy for ischemic stroke. Despite promising preclinical studies with gavestinel, neither GAIN trial demonstrated any treatment benefit for this compound.26 In GAIN International, 34% of gavestinel-treated patients and 35% of placebo-treated patients were independent at 3 months, compared with 39% and 37%, respectively, in GAIN Americas. Mortality at 3 months was 20% in GAIN International and 21% in GAIN Americas. The serious adverse event experience was also similar in the 2 trials, with neither showing the drug to cause harm. Unlike other types of NMDA receptor antagonists, gavestinel had no significant neurologic or cardiovascular adverse effects.

In GAIN Americas, the only subgroup analysis that showed a favorable 3-month outcome for gavestinel was among younger patients with mild strokes (age ≤75 years, NIHSS 2-5). After adjustment for possible baseline confounders, this finding persisted. However, a benefit for this subgroup was not found in GAIN International. A treatment effect was reported for patients younger than 70 years in the nalmefene phase 2 study,27 but was not confirmed in its phase 3 study.28 The favorable out-
come for gavestinel in this 1 subgroup in our study remains unexplained.

The other prespecified secondary analyses revealed no other subgroups of benefit. Even among patients treated within 4 hours of stroke onset (n = 241), no beneficial effect for gavestinel was suggested. Patients who received combined therapy of gavestinel and rt-PA did not show a significant improvement compared with those who received placebo and rt-PA. These 333 patients, with 166 receiving both gavestinel and rt-PA, represent the largest experience with a neuroprotectant in combination with thrombolytic therapy to date. However, since study procedures called for completing the rt-PA infusion before randomization into GAIN, some patients who responded rapidly to rt-PA might not have been enrolled in GAIN. The only other study combining a neuroprotectant (lubezulole) with rt-PA was terminated early by the sponsor.29 The results among 89 patients enrolled in that trial (randomized 1:1 to rt-PA, plus lubezulole or placebo) showed that the combination was feasible, safe, and might increase efficacy over rt-PA alone. Other neuroprotective agents need to be assessed for potential benefit in combination with rt-PA.

There were some important and unique design features included in the GAIN studies. Randomization was centralized and stratified into 6 strata by age and stroke severity, thus providing well-balanced treatment groups, which have been lacking in some trials.23,30,31 Exclusion of strokes that did not include an NIHSS motor component score of at least 2 decreased the chances of having too many mild strokes with a high spontaneous recovery rate, thus causing a type II error. Another unique feature was the use of the trichotomized BI as a primary outcome measure. In previous stroke trials, various cutoff scores have been used for the BI, but less than 60 has been the time-honored categorization for definite dependence.32 The additional BI cutoff score of 93 was chosen on the basis of the NINDS study as a measure of definite independence.19

Stroke forums, such as the Stroke Therapy Academic Industry Roundtable II, have emphasized the importance of a highly involved steering committee working in partnership with the industry sponsor. In the GAIN Americas trial, the protocol was developed by an independent academic steering committee working with the pharmaceutical sponsor. Moreover, this academic-industry collaborative group remained active in the ongoing supervision of the trial, while the GAIN Americas database was managed and analyzed at an academic center.

The efficacy of neuroprotectants in preclinical animal studies has not been corroborated by human acute stroke trials to date.23,28,30,31,33-35 Part of the reason may lie in fundamental differences between stroke in the animal models (mainly rodents) and in humans. The experimental conditions of animal models do not accurately reflect the variability found in clinical stroke patients with comorbid conditions. The failures of neuroprotective compounds in hu-
mains to date has led to the formulation of recommendations for minimum standards for the preclinical testing of putative neuroprotective drugs. These recommendations include requirements for collecting data on the adequate penetration of drug across the blood-brain barrier, efficacy in multiple species including primates, and reproducibility by independent laboratories.

We considered several factors that might explain our neutral results. First, did we misjudge the therapeutic window of opportunity? In animal models of middle cerebral artery occlusion, gavestin reduced infarct volume by 50% when given up to 6 hours from the onset of ischemia. In our data, there was no suggestion of benefit even among patients treated within 4 hours. Inadequate penetration of the drug into the brain was also considered. In a preliminary study of central nervous system penetration in 1 acute stroke patient, gavestin was detected in the cerebrospinal fluid 2 hours after the start of intravenous administration of the drug and gradually increased. However, no testing has been done to establish whether the compound reaches the infarct core or penumbra. We also considered whether the study population included too many mild and lacunar strokes. The majority of patients in the GAIN study had larger infarcts with some involvement of the cortex, where NMDA receptors are concentrated and where the drug was expected to have the most beneficial effect. We also considered whether our failure to detect a treatment effect was due to insensitivity of the outcome scales. Although the scales used in this trial are easy to use, have good reliability, and have been used in many acute stroke trials, there is still debate on how they should be used and interpreted in clinical trials. These scales may be not sensitive enough to detect small treatment differences, and have “ceiling” effects in detecting differences at higher levels of functioning. Moreover, the BI does not assess cognitive or perceptual functions, which have a marked influence on global outcome following stroke. Given the concordant findings using multiple outcome measures in the GAIN trials, it is unlikely that choosing another outcome scale would have altered our conclusions.

The GAIN Americas trial, the largest phase 3 acute stroke trial conducted in North America, had some unique design features and was well executed. The study failed to show a neuroprotective effect for gavestin when administered within 6 hours of acute ischemic stroke. This glycine antagonist joins the growing list of neuroprotectants that have not shown improved outcomes for patients with acute stroke, despite promising preclinical results. We still believe neuroprotection remains a viable strategy for acute stroke treatment and should continue to be studied.

Author Contributions: Dr Sacco, as principal investigator of the GAIN Americas Trial, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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GLYCINE ANTAGONIST FOR ACUTE STROKE

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