Gavestinel Does Not Improve Outcome After Acute Intracerebral Hemorrhage
An Analysis From the GAIN International and GAIN Americas Studies

E. Clarke Haley Jr, MD; John L.P. Thompson, PhD; Bruce Levin, PhD; Stephen Davis, MD; Kennedy R. Lees, MD; John G. Pittman, MS; Janet T. DeRosa, MPH; Paul Ordronneau, PhD; Devin L. Brown, MD; Ralph L. Sacco, MD; for the GAIN Americas and GAIN International Investigators*

Background and Purpose—Glycine Antagonist in Neuroprotection (GAIN) International and GAIN Americas trials were prospectively designed, randomized, placebo-controlled trials of gavestinel, a glycine-site antagonist and putative neuroprotectant drug administered within 6 hours of suspected ischemic or hemorrhagic stroke. Both trials reported that gavestinel was ineffective in ischemic stroke. This analysis reports the results in those with primary intracerebral hemorrhage.

Methods—The primary hypothesis was that gavestinel treatment did not alter outcome, measured at 3 months by the Barthel Index (BI), from acute intracerebral hemorrhage, based on pooled results from both trials. The BI scores were divided into 3 groups: 95 to 100 (independent), 60 to 90 (assisted independence), and 0 to 55 (dependent) or dead.

Results—In total, 3450 patients were randomized in GAIN International (N=11005) and GAIN Americas (N=1646). Of these, 571 were ultimately identified to have spontaneous intracerebral hematoma on baseline head computerized tomography scan. The difference in distribution of trichotomized BI scores at 3 months between gavestinel and placebo was not statistically significant (P=0.09). Serious adverse events were reported at similar rates in the 2 treatment groups.

Conclusions—These observations from the combined GAIN International and GAIN Americas trials suggest that gavestinel is not of substantial benefit or harm to patients with primary intracerebral hemorrhage. These findings are similar to results previously reported in patients with ischemic stroke. (Stroke. 2005;36:1006-1010.)

Key Words: hemorrhage ▪ neuroprotection ▪ stroke
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Secondary outcomes were safety and efficacy. Safety outcomes included treatment-emergent adverse events, serious adverse events, deaths, or temporary discontinuations of treatment. Efficacy outcomes included modified Rankin Scale (mRS) scores, Barthel Index (BI), and NIHSS scores after 24 hours.

**Statistical Analysis**

In each GAIN trial, the test of the primary null hypothesis used the extended Mantel–Haenszel \( \chi^2 \) test (1 degree of freedom), stratified by baseline stroke severity and age group, to combine the evidence from the 6 strata. This took account of the stratified randomization, which minimizes any confounding arising from age and NIHSS differences between strata. In the current analysis, the same approach was used. The statistical significance of the primary null hypothesis was established at the 0.05 level.

**Trial Profile**

![Trial Profile](image)

**Figure 1.** Trial profile.

**Hemorrhagic Stroke = 572**
- **International = 335**
- **Americas = 237**

**Intracerebral hemorrhage (ICH) = 571**

1. **Randomized to Gavestinel = 285**
   - **Withdrawn before Treatment = 2**
   - **Received Treatment = 283**
   - **Received rtPA = 3**
   - **Primary Efficacy Population With ICH = 260**
     - **Treated with Gavestinel = 279**
     - **Treated with Placebo = 1**
   - **Discontinued Treatment = 32**
   - **-Completed Mo 3 Barthel or died = 275**
   - **-Completed Mo 1 or Day 7 Barthel = 4**
   - **-Not followed to Day 7 = 1**

2. **Randomized to Placebo = 286**
   - **Withdrawn before Treatment = 6**
   - **Received Treatment = 286**
   - **Received rtPA = 2**
   - **Primary Efficacy Population With ICH = 284**
     - **Treated with Placebo = 282**
     - **Treated with Gavestinel = 2**
   - **Discontinued Treatment = 36**
   - **-Completed Mo 3 Barthel or died = 282**
   - **-Completed Mo 1 or Day 7 Barthel = 2**
   - **-Not followed to Day 7 = 0**

* Drug dispensing errors.
TABLE 1. Baseline Characteristics of Patients With Intracerebral Hematoma in GAIN Americas and GAIN International*

<table>
<thead>
<tr>
<th></th>
<th>Gavestinel</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>280</td>
<td>284</td>
</tr>
<tr>
<td>Age, mean±SD</td>
<td>67.5±12.0</td>
<td>68.5±12.2</td>
</tr>
<tr>
<td>Proportion male, No. (%)</td>
<td>165 (58.9)</td>
<td>173 (60.9)</td>
</tr>
<tr>
<td>Proportion white, No. (%)</td>
<td>222 (79.3)</td>
<td>229 (80.6)</td>
</tr>
<tr>
<td>Baseline blood pressure:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic, mm Hg (mean±SD)</td>
<td>172.0±27.4</td>
<td>169.9±26.8</td>
</tr>
<tr>
<td>Diastolic, mm Hg (mean±SD)</td>
<td>92.8±16.4</td>
<td>92.3±16.5</td>
</tr>
<tr>
<td>Baseline NIHSS score, median (interquartile range)</td>
<td>15.0 (9.0–18.0)</td>
<td>13.0 (9.0–18.0)</td>
</tr>
<tr>
<td>Time from onset to treatment, min (median, interquartile range)</td>
<td>278.0 (235.0–330.0)</td>
<td>290.0 (240.0–330.0)</td>
</tr>
<tr>
<td>Hemorrhage characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small, ≤2.5 cm, No. (%)</td>
<td>66 (23.6)</td>
<td>58 (20.6)</td>
</tr>
<tr>
<td>Large, &gt;2.5 cm, No. (%)</td>
<td>214 (76.4)</td>
<td>224 (79.4)</td>
</tr>
<tr>
<td>Intraventricular extension, No. (%)</td>
<td>79 (28.2)</td>
<td>75 (26.4)</td>
</tr>
</tbody>
</table>

*None of the differences between gavestinel and placebo groups is statistically significant at \( P<0.05 \) 2-sided. All comparisons take stratification into account. A 2-way analysis of variance for treatment group by stratum was used for age and baseline blood pressure, a stratified Wilcoxon test for baseline NIHSS score and time from onset to treatment, and a Mantel–Haenszel test across strata for proportion male, proportion white, and hemorrhage characteristics.

All comparisons of baseline characteristics in gavestinel versus placebo groups take stratification into account. A 2-way analysis of variance for treatment group by stratum was used for continuous variables, a stratified Wilcoxon rank-sum test for ordinal measures, and a Mantel–Haenszel test across strata for categorical variables.

Results

From March 1998, through October 1999, 3450 patients were randomized in GAIN International (N=1804) and GAIN Americas (N=1646). Of these, 572 were judged by the Image Adjudication Committee to have hemorrhagic stroke on the baseline head computerized tomography scan (Figure 1). One was not located intracerebrally, leaving 571 actual intracerebral hemorrhages. Two patients did not receive treatment and were excluded from the analysis. Additionally, 5 patients (3 gavestinel and 2 placebo) were excluded because they had received tissue plasminogen activator before randomization. One patient randomized to gavestinel instead received placebo, whereas 2 patients randomized to placebo received gavestinel. For the primary efficacy analysis, which used intent-to-treat principles, there were 280 patients assigned gavestinel versus 284 patients assigned placebo. The safety analyses included all randomized and treated patients according to the drug they actually received: 284 gavestinel patients versus 285 placebo patients. Seven patients were missing 3-month BI scores. Earlier post-treatment assessments were carried forward for 6 of these (4 gavestinel and 2 placebo). One gavestinel patient was completely lost to follow-up and was imputed to have the lowest possible BI score.

Table 1 outlines the baseline characteristics of the patients in each treatment group. There was an approximate balance in the age, race, sex, and time from onset of symptoms to initiation of treatment. There were similar proportions of patients who had small versus large hematomas and intraventricular extension of the hemorrhage. Despite the stratified randomization, the gavestinel group had a median 2 point higher baseline NIHSS score than placebo patients did. None of the differences in baseline characteristics was statistically significant.

Mortality was not significantly different between the 2 groups (stratified Wald test z score=−0.878, \( P=0.380 \); relative hazard ratio=0.843, 95% confidence interval=0.575 to 1.235). In the efficacy population, 51 of 280 (18%) gavestinel-treated patients died within 3 months compared with 58 of 284 (20%) placebo patients. In the safety population (n=569), 54 of 284 (19%) gavestinel patients died compared with 59 of 285 (21%) placebo patients.

Figure 2 shows the distribution of BI scores at 3 months in the 2 treatment groups divided into the prespecified cutoffs for independence, assisted independence, and dependence or death. Overall, the difference in distribution of 3-month BI scores favored gavestinel but did not reach statistical significance \( (P=0.091) \). The proportion of patients receiving tissue plasminogen activator did not significantly alter the results \( (P=0.128) \). Analyses of the secondary outcomes, including the modified Rankin Scale and NIH Stroke Scale, failed to disclose any statistically significant differences (Appendix 2).

The proportion of patients who reported serious adverse events was similar in both groups (Table 2). There were no important differences between the groups in the incidence of nonserious adverse events, except that the proportion of patients with elevated bilirubin (a known side effect of gavestinel) was 14% in the gavestinel group compared with 5% in the placebo group. All bilirubin elevations were transient.

Figure 2. Distributions of BI scores and mortality at 3 months. Differences in outcome were not statistically significant (extended Mantel–Haenszel \( \chi^2 \) test).

*Subcategory percentages do not add to 100% due to rounding.
TABLE 2. Selected Serious Adverse Events in Intracerebral Hematoma Patients in GAIN Americas and GAIN International

<table>
<thead>
<tr>
<th>Event</th>
<th>Gavestinel n=284 (%)</th>
<th>Placebo n=285 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression of stroke</td>
<td>82 (29)</td>
<td>88 (31)</td>
</tr>
<tr>
<td>Hemiation</td>
<td>23 (8)</td>
<td>26 (9)</td>
</tr>
<tr>
<td>Serious respiratory*</td>
<td>5 (2)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>51 (18)</td>
<td>63 (22)</td>
</tr>
</tbody>
</table>

*p: Pneumonia, aspiration, pulmonary edema, etc. SAE indicates serious adverse event.

Discussion

This pooled analysis represents the largest clinical trial of a putative neuroprotectant drug in patients with primary intracerebral hemorrhage. This group of stroke patients has long been neglected in stroke research. Previous studies have largely focused on surgical interventions.\(^1\)\(^4\)\(^5\) Unfortunately, no statistically significant benefit of gavestinel treatment begun within 6 hours of intracerebral hemorrhage was seen in this trial. These results are consistent with the reported observations in ischemic stroke patients treated with gavestinel\(^3\)\(^4\).

The patients enrolled in this study were a highly selected subgroup of patients with intracerebral hemorrhage. To be eligible, patients had to be fully alert or only slightly drowsy, and had to have at least a mild motor deficit. That \(\approx 20\%\) of patients died within 3 months suggests that if patients with intracerebral hemorrhage are selected with similar neu- rological criteria at baseline, their outcomes may not be worse than patients with similar deficits from ischemic stroke\(^3\)\(^4\). Similarly, the overall rate of serious adverse events \((\approx 20\%)\) reported in this hemorrhagic stroke population was similar to the rate reported in the ischemic stroke population.

Although this was a large clinical trial in intracerebral hemorrhage by historical standards, it is possible that a beneficial treatment effect of gavestinel may have been missed because of a type 2 error. The observed adjacent odds ratio and 95% confidence interval was 1.22 (0.98 to 1.52) with the current sample size. If the placebo outcomes remained the same and assuming proportional adjacent odds, the proportion of favorable outcomes in the gavestinel group would have had to be an absolute 14% greater (ie, 42% versus 28% for BI \(\geq 95\)) to have been detectable with 90% power in a study of this size. For good power to detect smaller differences, a much larger sample size would have been required. However, the relatively small absolute 5% difference in favor of gavestinel observed in the current study, combined with the indifferent results obtained from the 2 larger studies in patients with acute ischemic stroke, offer little encouragement for further clinical trials of this compound in patients with intracerebral hemorrhage.

Appendix 1

Image Adjudication Committee: Rudiger von Kummer, MD (Chair), University of Technology, Dresden, Germany; Stefano Bastianello, MD, PhD, State University of Rome, Rome, Italy; Thomas Tomswick, MD, FACR, University of Cincinnati, Cincinnati, Ohio.

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GAIN Americas Steering Committee: Ralph Sacco, MD, (Chair), New York, NY; Stephen Phillips, MD, Halifax, Canada; Clarke

APPENDIX 2. Secondary Outcomes at 3 Months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Gavestinel n=280</th>
<th>Placebo n=284</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modified Rankin Scale</td>
<td></td>
<td></td>
<td>0.73*</td>
</tr>
<tr>
<td>No symptoms</td>
<td>16 (5.7%)</td>
<td>18 (6.3%)</td>
<td></td>
</tr>
<tr>
<td>Symptoms, no disability</td>
<td>41 (14.6%)</td>
<td>33 (11.6%)</td>
<td></td>
</tr>
<tr>
<td>Mild disability</td>
<td>39 (13.9%)</td>
<td>34 (12.0%)</td>
<td></td>
</tr>
<tr>
<td>Moderate disability</td>
<td>39 (13.9%)</td>
<td>39 (13.7%)</td>
<td></td>
</tr>
<tr>
<td>Moderately severe disability</td>
<td>74 (26.4%)</td>
<td>77 (27.1%)</td>
<td></td>
</tr>
<tr>
<td>Severe disability</td>
<td>21 (7.5%)</td>
<td>25 (8.8%)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>50 (17.9%)</td>
<td>58 (20.4%)</td>
<td></td>
</tr>
<tr>
<td>NIHSS Median, interquartile range</td>
<td>5 (2–14)</td>
<td>6 (2–17)</td>
<td>0.31†</td>
</tr>
<tr>
<td>Global test, (Barthel (\geq 95))</td>
<td>1.067 (0.758–1.402)</td>
<td>0.71‡</td>
<td></td>
</tr>
<tr>
<td>Odds ratio, (95% confidence interval)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Stratified Generalized Mantel-Haenszel \(\chi^2\) test
†Stratified Wilcoxon rank-sum test.
‡Stratified global test.

Haley, MD, Charlottesville, Va; John Thompson, PhD, New York, NY; Bruce Levin, PhD, New York, NY; nonvoting members: Paul Ordonez, PhD and Rose Snipes, MD, Glaxo Wellcome, Inc, Research Triangle Park, NC.

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