Lubeluzole in Acute Ischemic Stroke Treatment
A Double-Blind Study With an 8-Hour Inclusion Window Comparing a 10-mg Daily Dose of Lubeluzole With Placebo

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Background and Purpose—This trial was a double-blind, placebo-controlled, phase III trial with an 8-hour inclusion window to assess the efficacy and safety of an intravenous loading dose of 7.5 mg followed by a daily intravenous dose of 10 mg lubeluzole for 5 days in acute ischemic stroke patients.

Methods—A total of 1786 patients were randomized: 901 to lubeluzole and 885 to placebo. Overall, 212 patients (23.5%) from the lubeluzole group and 213 (24.1%) from the placebo group discontinued the trial prematurely. In the lubeluzole group 201 patients (22.3%) discontinued because of adverse events compared with 193 patients (21.8%) in the placebo group.

Results—The primary population for the efficacy analysis comprised the core stroke patients (exclusion of older patients aged >75 years with severe stroke) in the 0- to 6-hour inclusion time window. The primary efficacy parameter was a 3-category functional status (Barthel Index 70 to 100/0 to 70/vegetative, dead) at week 12. In the lubeluzole group 207 patients (47.8%) were classified as mildly dependent/independent at week 12, 131 (30.3%) were moderately/severely dependent, and 95 (21.9%) were vegetative/dead. In the placebo group these numbers were 221 (54.4%), 112 (27.6%), and 73 (18.0%), respectively. Logistic regression analysis showed no statistically significant difference between the treatment groups (P=0.162). Additionally, for none of the secondary efficacy parameters (mortality at week 12, modified Rankin score, total Barthel score) was a statistically significant difference between the lubeluzole and placebo groups obtained. There were no statistically significant differences between the 2 treatments for all treated patients, patients included within the 6- to 8-hour window, and patients with severe strokes aged >75 years. Overall, of all treated patients, 401 (22.5%) died; 203 (22.5%) in the lubeluzole group and 198 (22.4%) with placebo. Of all subjects treated, 853 (95%) on lubeluzole and 826 (93%) on placebo reported an adverse event during their treatment period or within the next 2 days after discontinuation of treatment. The most frequently observed adverse events were fever (25.9% lubeluzole; 23.4% placebo), constipation (20.2%; 19.7%), and headache (17.6%; 21.2%). Imbalances were found for atrial fibrillation (1.8% lubeluzole; 1.1% placebo) and QT prolongation (0.9%; 0.2%).

Conclusions—This study failed to show an efficacy of lubeluzole in the treatment of acute stroke. On the other hand, lubeluzole treatment by the current dosage schedule was not associated with a significant safety problem. (Stroke. 2000;31:2543-2551.)

Key Words: clinical trials ■ lubeluzole ■ neuroprotection ■ stroke

In recent years, considerable efforts have been devoted to developing treatments for stroke aimed at restoring cerebral perfusion (thrombolysis) or at limiting neuronal damage (neuroprotection). Lubeluzole is a benzothiazole derivative that has been shown experimentally to preserve neurological function and reduce infarct volume in animal models of focal brain ischemia. The neuroprotective activity of lubeluzole is related to its ability to alter the biochemical cascade that leads to irreversible neural damage in the penumbra, by preventing an increase in extracellular glutamate and nor-
malizing neuronal excitability in the peri-infarct region.\(^4\) Experiments with cultured embryonic hippocampal neurons further indicate that the drug inhibits glutamate-induced nitric oxide–related neurotoxicity.\(^5,6\)

Results of a double-blind, placebo-controlled phase II trial involving 193 patients with acute ischemic stroke showed that lubeluzole, administered intravenously within 6 hours of stroke onset with a 1-hour 7.5-mg loading dose followed by 10-mg/d infusion for 5 days, was safe and resulted in a statistically significant reduction in mortality.\(^7\) In the same study, treatment with a higher lubeluzole dosage regimen of 15-mg loading dose followed by 20-mg/d infusion for 5 days was associated with a higher mortality rate that was attributable, at least in part, to an imbalance at randomization resulting in more patients with severe ischemic stroke being included in the high-dose group. On the basis of the results of this early phase II trial, a dosage regimen of 7.5-mg loading dose administered over 1 hour followed by a continuous infusion of 10 mg/d for 5 days was selected for use in subsequent phase III studies.

A large phase III trial conducted at 83 centers in the United States and Canada, with >700 ischemic stroke patients, demonstrated benefit of this lubeluzole regimen in treating acute ischemic stroke.\(^8\) Lubeluzole was associated with a significantly greater improvement at week 12 in neurological recovery (National Institutes of Health Stroke Scale), functional status (Barthel Index), and overall disability (Rankin Scale). Mortality at week 12 (the primary outcome measure) was nonsignificantly reduced with lubeluzole (20.7% versus 25.2%). The safety profile of lubeluzole was similar to that of placebo. In contrast, a European-Australian phase III trial of similar size found no effect of lubeluzole on mortality or clinical outcome.\(^9\)

An additional large, placebo-controlled trial with 0- to 6-hour and 6- to 8-hour inclusion windows was initiated to determine whether lubeluzole is effective in acute stroke.\(^6\) Since the therapeutic window for an effective neuroprotective drug in humans is not known,\(^10\)\(^–\)\(^12\) the study also sought to establish whether the time window to treatment could be extended. A meta-analysis of the previous 3 phase II and III trials indicated that a subgroup of younger patients and older patients with mild to moderate strokes might benefit from lubeluzole. In light of the aforementioned analysis, the protocol was adapted during the trial (without interim analysis) to specify the target population (the core stroke group) as patients with ischemic stroke excluding patients aged >75 years with severe strokes (defined by a global clinical impression) treated within 0 to 6 hours from symptom onset. The nontarget population was included in the safety analysis to exclude detrimental effects of active treatment. The trial was designed to evaluate the efficacy and safety of lubeluzole compared with placebo in the treatment of acute ischemic stroke with an 8-hour inclusion time window. The primary hypothesis was that lubeluzole would improve functional outcome at week 12 in the core stroke group treated within 6 hours of symptom onset.

### Subjects and Methods

We conducted a phase III, multicenter, double-blind, placebo-controlled trial, using a randomized block design in 2 strata, each with a separate randomized code list, defined by distinct entry windows of 0 to 6 hours and >6 to 8 hours after stroke onset. The patients in each stratum were randomly allocated to either lubeluzole or placebo treatment. Treatment had to start as soon as possible and in any case not later than 8 hours after the initial symptoms. The patients were followed until death or 12 weeks after the start of treatment, whichever came first.

Patient recruitment continued until a total of 800 patients in the core ischemic population (0 to 6 hours, excluding patients aged >75 years with severe strokes) were enrolled. Inclusion criteria were a clinical diagnosis of a cerebral hemispheric ischemic stroke; European Stroke Scale (ESS)\(^13\) score <70 at the start (ESS range, 0 to 100; the higher the score, the worse was the neurological deficit); age ≥18 years; and ability to commence trial medication within 8 hours after the onset of stroke symptoms. Patients awakening with stroke symptoms were considered to have had their stroke at the time they went to bed or at the time when last awake with normal neurological function. Availability of written or oral and witnessed informed consent according to national requirements of participating countries was necessary.

Exclusion criteria included a score <8 for level of consciousness on the ESS, indicating the patient was not alert or drowsy; complete or substantial resolution of the acute deficit by time of starting the trial medication; clinical presentation suggesting an etiology for the acute neurological deficit other than thromboembolic stroke; a Barthel Index\(^14\) score of 70 as a result of a previous stroke or other disease; presence of significant cognitive or psychiatric disorder; CT scan not consistent with the clinical diagnosis of an ischemic stroke; or concurrent illness of sufficient severity that the patient’s life expectancy was <12 weeks. Additional exclusion criteria were serious ventricular arrhythmias, second- or third-degree AV block or QT interval >450 ms at the start; acute and/or uncompensated heart failure; recent acute myocardial infarction (<6 weeks); clinically significant history of alcohol or drug abuse; pregnancy; and thrombolytic therapy.

Heparin, warfarin, acetylsalicylic acid, dipryidamole, ticlopidine, or clopidogrel could be administered. If the first or second CT scan was performed after the start of the trial medication and CT was inconsistent with the clinical diagnosis of an ischemic stroke, the trial medication was discontinued. Patients were followed until death or week 12.

Patients received a 1-hour loading infusion of 7.5 mg lubeluzole or placebo followed by a continuous 5-day infusion of 10 mg lubeluzole or placebo per day. Treatment continued until the patient showed complete neurological recovery, as defined by an ESS score of 100 or for a maximum of 5 days and 1 hour. A CT scan was performed before or within 24 hours after the start of trial medication. A second CT scan was performed between days 4 and 7 to help confirm the clinical diagnosis of ischemic stroke. A CT scan was also performed if the patient showed clinically significant deterioration. All CT scans were evaluated by a blinded central reader. All concomitant medication taken during the trial and changes in dosages were recorded. Venous blood samples for drug analysis were taken just before the end of the 1-hour loading infusion and immediately before the end of the treatment. Adverse events were defined according to good clinical practice guidelines.

ESS, Barthel Index, modified Rankin Scale, and mortality were assessed before treatment, at 5 days at the end of treatment, and after 4 and 12 weeks. Investigators rated stroke severity using the clinical global impression of stroke before treatment. This early assessment of stroke severity included 3 distinct categories: mild, moderate, and severe. Efforts were made to ensure that the evaluations for a given patient were performed by the same observer throughout the course of the trial.

In the 2 phase III trials with a 0- to 6-hour inclusion time window,\(^6,9\) post hoc subgroup analyses suggested that beneficial effects of lubeluzole were not demonstrated in ischemic stroke patients aged >75 years with a severe stroke. The patient population after exclusion of those aged >75 years with severe stroke is hereafter referred to as the core patient population. If the reference improvement, represented by a common log odds ratio of 0.39, is
achieved, then the overall category probabilities were ($P > = (P_{0-6h} + P_{6-8h})/2$) 0.5095 for Barthel Index score 75 to 100, 0.3085 for Barthel Index score 0 to 70, and 0.1825 for dead patients. With $a=0.05$ and 80% power, 372 ischemic stroke patients in the 0- to 6-hour inclusion window were required in each group for the 3-category functional status at week 12. To further account for the 4.8% of patients who entered the earlier lubeluzole trials and were later found to have nonischemic stroke, it was estimated that 391 core patients per treatment group were required. Therefore, it was decided to enroll at least 800 core patients in the 0- to 6-hour window, which would provide adequate power to detect the treatment effect when either the logistic regression approach or the Mantel-Haenszel procedure was applied.

Statistical Analysis
The analyses for demographic and baseline characteristics described below were applied to each relevant population. The comparability between the 2 treatment groups was evaluated with respect to the demographic and baseline variables. For continuous variables (eg, age, body weight, inclusion time), an ANOVA with effects for treatment group, country, and inclusion time stratum (for all populations with subjects in both 0- to 6-hour and 6- to 8-hour inclusion time strata) were used. For ordinal categorical variables, treatment groups were compared by the Cochran-Mantel-Haenszel mean score test, controlling for country and inclusion time stratum. For nominal categorical variables (eg, race, sex), the Cochran-Mantel-Haenszel test for general association, controlling for country and inclusion time stratum, was used.

Efficacy Populations
All randomized subjects who received study medication were termed the all patient group. Two additional patient populations were analyzed: (1) The primary efficacy population comprised all core patients in the 0- to 6-hour stratum (Table 1). This included all patients who received treatment within 0 to 6 hours after the onset of stroke, except those aged >75 years with a severe stroke. (2) All core patients included all patients who received treatment within 0 to 8 hours after the onset of stroke, except those aged >75 years with a severe stroke. The 3 patient populations were analyzed in an “expansion setting,” with no adjustment for the significance level needing to be made.

Efficacy Parameters
The primary efficacy parameter was a 3-category functional status according to the Barthel Index at the end of the 12-week observation period: independent or mildly dependent (75 to 100), moderately or severely dependent (0 to 70), and vegetative (ESS level of consciousness score <6 regardless of Barthel Index score) or dead. The main secondary parameter was the mortality rate at the end of the 12-week observation period. Other secondary parameters were survival time, modified Rankin score, and ESS score.

Mortality rate was determined at the 4- and 12-week observation periods. Survival time was defined as the length of time a patient lived since randomization or was censored at the analysis time point.

Functional outcome was measured from the modified Rankin Scale at each visit. The score was set to 6, indicating a state worse than the worst possible state (severe disability, score = 5) of the modified Rankin Scale at all time points after the patient’s death. A patient was considered to be in a vegetative state if he/she had an ESS level of consciousness score <6 (regardless of the Rankin Scale score). For the statistical analysis, the 7 modified Rankin Scale categories were collapsed into 3 categories: dead (score of 6) or vegetative, severe or moderate disability (score of 5, 4, or 3), and slight disability to no symptoms (score of 2, 1, or 0). The total ESS score at each visit was defined as the sum for all 14 items evaluated.

The total motor score at each visit was defined as the sum of all motor evaluations in the ESS scale, ie, items 6 to 14. The total nonmotor score at each visit was the sum of all other evaluations in the ESS scale. The week 12 visit was the primary time point. The total scores for surviving patients with missing or “not applicable” items were first rescaled so that the maximum possible score matched with that from patients with all items completed and was then rounded to the nearest integer.

Monitoring of Safety Data by the Data Safety Monitoring Board
The safety aspects of the trial were monitored by a Data Safety Monitoring Board (Appendix 2). The Data Safety Monitoring Board had ongoing access to information regarding serious adverse events, including all premature discontinuations of study drug, arrhythmias requiring interventions, seizures, and laboratory and ECG data. In addition, the percentage of ischemic stroke patients who were deceased at the end of the 12-week observation period, which was also an efficacy end point, was monitored for safety purposes.

Ethics
The trial protocol was reviewed and approved by local independent ethic committees or institutional review boards according to the requirements of the participating country. The trial was performed in accordance with the Declaration of Helsinki and its subsequent revisions. Informed consent was obtained from each patient (or from his or her legally authorized representative, according to the requirements of the participating country) before enrollment in the study.

Results
The trial commenced recruitment in May 1996 and completed follow-up in March 1998. One hundred thirty-one principal investigators from 5 countries participated in the trial (Appendix 1). A total of 1813 patients were recruited to the trial; 1786 of these were randomized: 901 to lubeluzole and 885 to placebo (Figure 1). The core stroke population comprised 857 patients: 441 in the lubeluzole group and 416 in the placebo group. Figure 1 gives an overview of the number of patients who prematurely discontinued the trial, as well as the reasons for discontinuation for the “all-treated” population and the primary efficacy population. In the all-treated group, 212 patients (23.5%) on lubeluzole and 213 patients (24.1%) on placebo discontinued the trial prematurely. The number of patients that discontinued because of adverse events was 201 (22.3%) in the lubeluzole group and 193 (21.8%) in the placebo group. Numbers of patients in the core and noncore populations are shown in Table 1.

Major protocol deviations occurred in 86 lubeluzole patients (9.5%) and 74 placebo patients (8.4%). The majority of these deviations concerned noncompliance with respect to treatment (54 lubeluzole and 51 placebo patients).
Figure 1. Patient disposition in the trial. PLAC indicates placebo; LUB, lubeluzole; F.U., follow-up; and CNS, central nervous system. *1 Patient died at day 87, and 1 patient died at day 94; *2 1 patient died at day 105; (a) 58 patients died before day 84, 1 after day 84; (b) 1 patient died before day 84; (c) 1 patient died before day 84; (d) 1 patient died before day 84; (e) 49 patients died before day 84, 1 after day 84; (f) 1 patient died before day 84; (g) 106 patients died before day 84, 2 after day 84; (h) 1 patient died before day 84; (i) 116 patients died before day 84, 2 after day 84.
Table 2 summarizes the baseline demographic and stroke data for all treated patients. Statistically there was no difference between the 2 treatment groups. Clinically relevant comorbidities are shown in Table 3. Again, there was no difference between the 2 groups.

The results for the primary end point (functional status assessed by Barthel Index at week 12) for the core stroke patients in the 0- to 6-hour inclusion stratum are summarized in Table 4 and Figure 2. Logistic regression demonstrated no statistically significant difference between the lubeluzole and placebo groups ($P=0.16$).

Twelve-week mortality in the core stroke patients (0 to 6 hours) was 164 (19.1%): 92 (20.9%) in the lubeluzole group versus 72 (17.3%) in the placebo group ($P=0.36$). Modified Rankin scores at week 12 for the core stroke group (0 to 6 hours) are shown in Table 4. Logistic regression results showed no statistically significant difference between the lubeluzole and placebo groups ($P=0.504$). In the core stroke population (0 to 6 hours), Barthel score at week 12 was 57.0 ($\pm 1.95$) (mean $\pm$ SEM) for the lubeluzole group versus 62.6 ($\pm 1.92$) for the placebo group ($P=0.13$). The change from baseline in ESS scores was 15.8 ($\pm 1.54$) for the lubeluzole group versus 18.2 ($\pm 1.52$) for the placebo group ($P=0.42$).

Functional status at the primary end point (week 12) for all treated patients is shown in Table 5. Logistic regression showed no statistically significant difference between the lubeluzole and placebo groups ($P=0.19$). Overall 12-week mortality in all treated patients was 401 (22.5%): 203 (22.5%) in the lubeluzole group versus 198 (22.5%) in the placebo group (logistic regression: $P=0.81$). Modified Rankin scores at week 12 are also shown in Table 5, again with no difference between lubeluzole and placebo groups ($P=0.71$).

Total Barthel score at week 12 was 52.5 ($\pm 1.37$) (mean $\pm$ SEM) in the lubeluzole group versus 54.4 ($\pm 1.39$) in the placebo group ($P=0.20$). ESS motor scores were similar:

Table 3. Comorbidities

<table>
<thead>
<tr>
<th>Relevant Concomitant Disorder</th>
<th>Lubeluzole</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>Hypertension</td>
<td>576 (63.9)</td>
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<td>Ischemic heart disease</td>
<td>406 (45.1)</td>
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<td>Atrial fibrillation</td>
<td>281 (31.2)</td>
<td>269 (30.4)</td>
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<tr>
<td>Congestive heart failure</td>
<td>272 (30.2)</td>
<td>252 (28.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>207 (23.0)</td>
<td>198 (22.4)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>100 (11.1)</td>
<td>81 (9.2)</td>
</tr>
<tr>
<td>Hepatic impairment</td>
<td>36 (4.0)</td>
<td>36 (4.1)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>199 (22.1)</td>
<td>210 (23.7)</td>
</tr>
<tr>
<td>Previous transient ischemic attack</td>
<td>105 (11.7)</td>
<td>96 (10.8)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>304 (33.7)</td>
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Safety Evaluation

All 1786 patients enrolled in the trial were evaluated for safety. The results for all treated patients within the 8-hour inclusion window (“all treated 0 to 8 hours”) are shown here. The results of all other populations analyzed, ie, all core patients within a 6-hour inclusion window (“core stroke 0 to 6 hours”), all treated patients aged 75 years with severe strokes. Additionally, the global test did not indicate any significant differences between lubeluzole and placebo.

Table 6. Adverse Events in Placebo and Lubeluzole Treatment Groups (All Patients)

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Lubeluzole (n=885)</th>
<th>Placebo (n=885)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>4 (2.0)</td>
<td>8 (4.0)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>14 (6.9)</td>
<td>13 (6.6)</td>
</tr>
<tr>
<td>CNS hemorrhages</td>
<td>3 (1.5)</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>CNS-related deaths without hemorrhages</td>
<td>92 (45.3)</td>
<td>76 (38.4)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>10 (4.9)</td>
<td>11 (5.6)</td>
</tr>
<tr>
<td>Hemorrhagic transformation</td>
<td>5 (2.5)</td>
<td>8 (4.0)</td>
</tr>
<tr>
<td>Infection</td>
<td>30 (14.8)</td>
<td>33 (16.7)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4 (2.0)</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>Other</td>
<td>26 (12.8)</td>
<td>26 (13.1)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>3 (1.5)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>9 (4.4)</td>
<td>7 (3.5)</td>
</tr>
<tr>
<td>Systemic hemorrhage</td>
<td>1 (0.5)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (1.0)</td>
<td>1 (0.5)</td>
</tr>
</tbody>
</table>

Values are number (%). CNS indicates central nervous system.

TABLE 5. Functional Status (Barthel Index and Rankin Scale Scores) in All Treated Patients at Week 12

<table>
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<tr>
<th>Status</th>
<th>Lubeluzole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent and mildly dependent</td>
<td>380 (42.8)</td>
<td>401 (46.5)</td>
</tr>
<tr>
<td>(Barthel 70–100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately/severely dependent</td>
<td>302 (34.0)</td>
<td>265 (30.7)</td>
</tr>
<tr>
<td>(Barthel 0–70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetative (ESS score ≥6) or dead</td>
<td>205 (23.1)</td>
<td>197 (22.8)</td>
</tr>
<tr>
<td>Mildly disabled/no symptoms</td>
<td>282 (31.8)</td>
<td>280 (32.4)</td>
</tr>
<tr>
<td>(Rankin 0, 1, 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately/severely disabled</td>
<td>400 (45.1)</td>
<td>386 (44.7)</td>
</tr>
<tr>
<td>(Rankin 3, 4, 5)</td>
<td></td>
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<tr>
<td>Vegetative (ESS score ≥6) or dead</td>
<td>205 (23.1)</td>
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Values are number (%).
more hemorrhagic transformations leading to death in placebo (8; 4.0%) than in lubeluzole patients (5; 2.5%). More central nervous system–related deaths not associated with hemorrhage were observed in the lubeluzole group (45.3% versus 38.4%). Table 7 summarizes all deaths reported, including 4 patients in each group who died after day 84. In the lubeluzole group, 2 patients died as a result of cardiac arrest (days 85 and 91), another patient died at day 85 (other reason), and a patient died at day 105 (infection). In the placebo group, 2 patients died at day 87 (pulmonary embolism and other reason), 1 patient at day 94 (infection), and 1 at day 102 (congestive heart failure).

In the primary patient population (core stroke, inclusion 0 to 6 hours), there were more hemorrhagic transformations leading to death in the placebo group: 6.7% versus 3.2%. More central nervous system–related deaths without hemorrhages were observed in the lubeluzole group (45.2% versus 37.3%).

In summary, this trial of lubeluzole treatment (7.5-mg loading dose followed by 5 days at 10 mg/d) did not improve functionality at week 12 in the primary efficacy population (patients treated to 6 hours excluding elderly severe patients but including primary hemorrhagic strokes). Equally, no significant differences were observed for the secondary end points and the secondary efficacy populations. These findings are not in accord with the hypotheses formulated after the post hoc analysis of the earlier trials. On the other hand, lubeluzole treatment administered by the current dosing schedule was not associated with a significant safety problem.

Discussion

The present large trial failed to show any benefit of lubeluzole in acute ischemic stroke, adding another substance to the long list of other agents that failed to show benefit in stroke. The distribution of biological features and severity of stroke was well balanced between the 2 treatment groups, and there was no evidence of any significant imbalance in prognostic factors between the lubeluzole and placebo groups.

After so many failed trials with neuroprotective substances, one is inclined to question the relevance of data from animal experiments to the condition of human stroke. Lubeluzole has shown efficacy in the photochemical stroke model as well as in traditional rat models of transient and permanent middle cerebral artery occlusion. A number of important differences between the animal studies and this trial may account for the failure to demonstrate efficacy in patients who achieved a plasma concentration >70 ng/mL after the loading dose, which would support the notion that neuroprotective concentrations of lubeluzole were not achieved.

Further pharmacokinetic/pharmacodynamic analysis of all the data from phase II and III lubeluzole trials would be instructive in understanding the differences seen between the trials and assessing whether the development of other benzothiazoles as neuroprotective agents is warranted.

The low dose was chosen because of dose-limiting side effects, a recurring problem in the development of neuroprotective agents. Lubeluzole differs from other neuroprotective compounds in that the primary dose-limiting toxicity was QT interval prolongation rather than central nervous system adverse effects.

This trial was unusual in using a post hoc sub group analysis to define some aspects of the trial protocol. Theoretically, it is most likely that patients with moderate stroke benefit most from therapy. Patients with mild strokes might recover without treatment, and patients with severe strokes might not improve at all with any kind of therapy. Therefore, it was decided to include only patients with an ESS score <75. Older patients with severe strokes were included to determine safety in this group because if lubeluzole had shown efficacy, the safety in this group would need to be established. The hypothesis generated from post hoc analysis of previous lubeluzole studies, that older patients with severe stroke might experience harm, was not substantiated in the present study and cautions against overinterpretation of subgroup analysis of other acute stroke trials. With the same rationale, patients with cerebral hemorrhages were included. CT scan was not mandatory before inclusion to allow a rapid onset of treatment with the study drug. The number of patients with cerebral hemorrhages, however, was too small to detect any differences between active drug and placebo.

One reason for failure may be that very large numbers of patients are needed to show benefit of a particular treatment. In trials of myocardial infarction and stroke trials using aspirin, patient numbers of approximately 20 000 have often been required to show a clear benefit of treatment. For financial and logistic reasons, these megatrials can only be performed with simple protocols and brief data collection. The history of development of lubeluzole supports the requirement of the Food and Drug Administration and the European authorities to present data from 2 independent trials for approval of a new drug or treatment. The phase II trial of lubeluzole showed a positive result in terms of reduced mortality. One of the phase III trials showed a significant benefit in terms of neurological impairment, while the other trial with a similar design had a negative result. Finally, this large trial answered the question of whether the chosen dose...
of lubeluzole was effective. Whether higher doses of benzothiazoles without cardiac toxicity would show neuroprotective efficacy in humans remains unclear.

One should also consider the recently presented hypothesis that without early reperfusion, either spontaneous or induced by thrombolysis, it is not possible to only marginally reduce the size of the final infarction because the critical hypoperfusion accounts for the largest proportion of the final infarct.27 If this is true, it seems unlikely that any single neuroprotective agent will appreciably limit the size of the evolving infarct substantially. Future trials should concentrate on the combination of thrombolysis with neuroprotective substances. A recent randomized, double-blind trial studying the combination of thrombolysis with neuroprotective agent will terminally premature the size the sponsor. With the small numbers available, there was no difference between the 2 treatment groups.28 However, this should not preclude the undertaking of future trials with combination therapy.

Appendix 1
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Appendix 2
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Janssen Research Foundation
T. Wessel; I. Vingerhoets; H. Bueds; K. Verstraeten; L. Braeken; P. Janssen Research Foundation; L. Hantson; R. Guttierrez; J. Terri.

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References
Lubeluzole in Acute Ischemic Stroke Treatment: A Double-Blind Study With an 8-Hour Inclusion Window Comparing a 10-mg Daily Dose of Lubeluzole With Placebo

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