Design and Baseline Results of the Monosialoganglioside Early Stroke Trial

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Background and Purpose: The Early Stroke Trial is a randomized, placebo-controlled, double-masked, multicenter study to assess the safety and efficacy of monosialoganglioside in patients who have suffered an ischemic stroke of the cerebral hemispheres.

Methods: Only patients who could be evaluated and treated within 5 hours after the onset of stroke were considered; within each center, subjects were stratified by age, sex, and clinical severity. Patients were randomly allocated to receive a specified sequence of intravenous and intramuscular doses of either monosialoganglioside or identical-appearing placebo for 21 days. Patients were followed up for 4 months after randomization. Neurological status was measured primarily by using the Canadian Neurological Scale. After assessing the effect of treatment on survival, the principal measure of efficacy will be the change in neurological status between baseline and the 4-month follow-up among survivors.

Results: Sixteen clinical centers, 15 in Europe and one in North America, entered a total of 792 eligible patients during a 36-month recruitment period (from May 1987 to April 1990). In our series there were more men than women, and the relative frequency of patients increased with advancing age. The most frequently associated cardiovascular conditions were hypertension, atrial fibrillation, and peripheral vascular disease. Approximately 46% of the patients were admitted to a hospital within 1 hour and 81% within 2 hours after the onset of stroke. About 22% first received the study treatment within 3 hours and 57%, within 4 hours.

Conclusions: This study demonstrates the feasibility of large-scale trials with the onset of treatment within 5 hours after an ischemic stroke. (Stroke 1992;23:519–526)

Key Words • cerebrovascular disorders • clinical trials • gangliosides

The acute treatment of ischemic stroke has so far been unsatisfactory, although a series of promising approaches to prevent or reduce ischemic injury in vitro and in animal models are being tested. Several obstacles are faced in transferring promising results from the laboratory to clinical practice. Most agents that act on the neuronal mechanisms following ischemia must be administered within minutes or hours after the onset of ischemia to be efficacious. However, it is difficult to recruit a large series of patients in which the diagnosis of ischemic stroke is confirmed and treatment initiated within a few hours after stroke. A second difficulty is to measure the clinical efficacy of a new drug. Because of limitations in the reliability and validity of current neurological or disability scales, clinical trials of large size are needed to test the efficacy of a potential new drug. To obtain large samples of patients, investigators are forced to design multicenter studies with increased organizational problems and higher costs. Among quantitative measures of neurological status, the Canadian Neurological Scale has been recently developed and tested. This scale is short and easy to administer and was found to have satisfactory reliability and validity.

We summarize the design, organization, and baseline results of a large-scale randomized clinical trial of monosialoganglioside (GM-1) in acute stroke. The study was designed to test whether the early administration of the drug, within 5 hours after the onset of symptoms, is both safe and efficacious. GM-1 is a glycolipid normally present in cell membranes of the mammalian nervous system. Experimental and clinical knowledge on the therapeutic potential of GM-1 were extensively reviewed elsewhere. Some recent trials suggest a therapeutic efficacy of GM-1 in acute neurological conditions such as spinal cord injury and subarachnoid hemorrhage. However, only preliminary studies with increased organizational problems and higher costs. Among quantitative measures of neurological status, the Canadian Neurological Scale has been recently developed and tested. This scale is short and easy to administer and was found to have satisfactory reliability and validity.

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clinical studies of GM-1 in acute or subacute stroke have been conducted thus far.\textsuperscript{10-14}

**Subjects and Methods**

The Early Stroke Trial (EST) included 16 clinical centers, a coordinating center, two data analysis centers, and appropriate committees (Appendix). There were eight clinical centers in Italy, two each in Austria and the Federal Republic of Germany, and one each in France, Spain, Switzerland, and the United States. The principal investigator of each clinical center was responsible for the conduct of the study; however, in most centers a clinical coordinator was also designated. A team of board-certified neurologists performed the trial activities of patient recruitment and evaluation, treatment administration, and outcome assessment in each center. Investigators were trained in the use of EST case report forms and assessment scales in a 3-day training program held in Abano Terme, Italy in the spring of 1987.

The coordinating center (Department of Clinical Research, Fidia S.p.A., Abano Terme, Italy) was responsible for the day-to-day administration and execution of the trial including the centralization, checking, and editing of data and the supervision of the clinical monitors. The coordinating center also provided 1) general status reports, including information on patient recruitment, follow-up assessments, and status of case report forms, to the clinical centers each month; 2) formal presentations to the Advisory Review and Treatment Effects Monitoring Committee (ARTEMC) and the Steering Committee every 6 months regarding quality and discipline of study execution, the deliberations of the Central Adjudication Committee, and any execution problems arising; and 3) presentations of study progress, protocol adherence, and logistic problems at the annual meetings of principal investigators and clinical coordinators.

The two data analysis centers (Department of Statistical Sciences, University of Padua, Padua, Italy and Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada) were responsible for conducting interim analyses and for preparing every 6 months appropriate summaries on drug safety and efficacy for the ARTEMC. These summaries were prepared for the two patient groups without specification of treatment; only when deemed indispensable were the treatment assignments of individual patients requested by the ARTEMC. The two data analysis centers will also be responsible for the final analyses.

The ARTEMC served as both the Safety Committee and as an advisory panel. The ARTEMC comprised one neurologist, one neurosurgeon, and two biostatisticians with special expertise in the conduct of stroke trials. Its responsibilities were 1) to advise the Steering Committee and the sponsor on design and performance of the trial, general policy issues, and operational procedures affecting the quality of the trial; 2) to review the performance of individual clinical centers, the coordinating center, and the data analysis centers; 3) to review the general status reports and reports from the Central Adjudication Committee and recommend corrective action when needed; and 4) to review interim analyses for evidence of adverse or beneficial treatment effects. The ARTEMC was, therefore, also responsible for protecting the welfare of the patients who participated in the trial.

The Central Adjudication Committee reviewed and validated the eligibility of patients entered into EST and the outcome events reported by the clinical investigators. The committee comprised three neurologists, two of whom were not involved in the execution of the trial, and two nonclinical methodologists. To discharge their responsibilities, the Central Adjudication Committee met for approximately 170 work days during the course of the study; details of the validation process are given below.

The Steering Committee had overall responsibility for the design, execution, analysis, and reporting of EST. The committee comprised a study chairman and a study coordinator, representatives of the clinical centers, one representative of the sponsor, one biostatistician, and one epidemiologist. The Steering Committee met approximately every 6 months to address and resolve policy issues encountered during the course of EST. In addition, the study chairman and the study coordinator visited the clinical centers to review their activity and to address local problems relating to the conduct of the trial.

All subjects with a focal cerebral deficit of acute onset, who were seen at one of the participating clinical centers, were considered for eligibility. Patients fulfilling the study inclusion criteria and passing the screen of exclusion criteria (Table 1) were eligible for EST. Patients giving informed consent, or those for whom the family gave informed consent, were enrolled into the trial. To keep a log of patients who met the inclusion criteria but failed to pass the screen of exclusion criteria at each center, we entered all patients considered throughout the recruitment period into a stroke registry.

For each subject included in the trial we collected the following baseline information: 1) demographic data; 2) results of physical, cardiovascular, and neurological examinations; 3) results of electrocardiography, hematologic tests, and urinalyses; 4) a brain computed tomogram without contrast medium; 5) a Canadian Neurological Scale\textsuperscript{15} score; 6) a Toronto Stroke Scale\textsuperscript{15} score; and 7) a Barthel activities of daily living scale\textsuperscript{16} score before the qualifying stroke, as assessed by history. Because of the EST exclusion criteria, this Barthel score was expected to be maximum in all patients recruited.

To investigate the extracranial and intracranial arterial patency within a few hours after the onset of stroke, patients underwent Doppler ultrasonography of the neck and intracranial arteries and in some specialized centers also cerebral angiography. These tests were to be undertaken as soon as possible, but not mandatorily before randomization. The investigators were instructed not to delay the onset of treatment only because of this ancillary evaluation.

Each baseline assessment form accompanied by appropriate documentation, including diagnostic information, hospital summaries, baseline laboratory data, etc., was reviewed by the Central Adjudication Committee without knowledge of treatment allocation or of clinical events occurring after randomization. Patients judged not to have the disease of interest were considered ineligible. Any apparent discrepancies or questions regarding the available documentation were discussed at a
TABLE 1. Inclusion and Exclusion Criteria for Patient Selection in Early Stroke Trial

Inclusion criteria
1. Focal cerebral deficit of acute onset
2. Signs and symptoms clinically attributable to ischemic stroke of cerebral hemispheres
3. Clinical evaluation and onset of study treatment within 5 hours after onset of stroke

Exclusion criteria
A. General characteristics
1. Age under 39 years
2. Age over 80 years
3. Pregnancy
4. Selection for early endarterectomy or any other experimental surgical procedure
5. Involvement in another drug trial

B. Clinical presentation
1. Unknown timing of qualifying stroke
2. Stupor or coma (Canadian Neurological Scale score of <1.5)
3. Canadian Neurological Scale score of >8.5
4. Previous stroke or other neurological disease with persistent focal cerebral signs or symptoms
5. Any disease or condition interfering with assessment of disability (including dementia and limb amputation)
6. Clinical or tomographic evidence of subarachnoid or cerebral hemorrhage, brain tumor, or other space-occupying lesion
7. Rapid resolution of symptoms before randomization

C. Life-threatening conditions*
1. Severe uncontrolled diabetes mellitus (fasting blood sugar of >300 mg/100 ml on most recent assessment, despite appropriate therapy)
2. Myocardial infarction in preceding 3 months
3. Life-threatening dysrhythmias
4. Severe renal failure (blood urea nitrogen of >100 mg/100 ml or creatinine of >2.5 mg/100 ml)
5. Severe respiratory insufficiency
6. Sepsis or severe infectious disease
7. Severe hepatic insufficiency or cirrhosis
8. Life-threatening cancer
9. Severe uncontrolled hypertension (diastolic pressure of >130 mm Hg despite appropriate medical therapy)

*Conditions that may have drastically limited survival during course of study.
quantity, and density identical to the ganglioside doses. Study drugs were supplied in identical glass ampules containing a 2 ml solution of either GM-1 or placebo.

Randomized patients underwent a series of fixed-time follow-up examinations. Blood pressure, pulse, and body temperature were reported twice a day in the first week, once a day during the second week, at 21 days, at 2 months, and at 4 months. An electrocardiogram was performed at day 7 and at 4 months. Hematologic tests and urinalyses were performed on days 10 and 21 and at 2 and 4 months; however, urinalyses were reported only when findings were abnormal. Concurrent medications, results of other diagnostic tests, intercurrent diseases, adverse events, and newly observed signs and symptoms were recorded daily in the first 15 days, at day 21, and at 2 and 4 months. The Canadian Neurological Scale and the Toronto Stroke Scale were repeated daily for the first 15 days, at 21 days, at 2 months, and at 4 months. The Barthel activities of daily living scale was administered at 7, 15, and 21 days and at 2 and 4 months. A brain computed tomogram was performed between days 5 and 7 and at 4 months. A chest radiogram was performed within 48 hours after the stroke and repeated when needed. After day 21, patient status and cause of death were assessed through follow-up visits at 2 and 4 months.

Death was classified as vascular or nonvascular. Among vascular deaths, we distinguished cerebral death caused by new strokes or complications of the qualifying stroke from cardiac death caused by myocardial infarction, congestive heart failure, acute pulmonary edema, or sudden death. Most nonvascular deaths were expected to be due to pneumonia, respiratory failure, or pulmonary embolism. Whenever permission from the family was obtained, an autopsy was performed on patients who died during hospitalization. All reported causes of death were reviewed by the Central Adjudication Committee using all available supporting documentation. Disagreements with the recorded cause of death were communicated to the investigators, who could provide further information to support their initial judgment.

Randomized patients were in general hospitalized for 21 days and then enrolled in the routine rehabilitation programs available at each center whenever necessary. Hospital discharge after 10 days was accepted if follow-up assessments and drug administrations until day 21 were performed, at home or at the rehabilitation institution, by a member of the clinical center team. Patients who, for any reason, interrupted treatment after randomization were followed up in the same way as those who did not and were included in all analyses.

The target sample size of 800 patients, to be randomized in two groups of 400 patients each, was selected considering as the principal outcome measure the change in Canadian Neurological Scale score between baseline and 4 months. Assuming a death rate in the 4 months following stroke of 25%, the two treatment groups were expected to decrease to approximately 300 analyzable patients. Therefore, the study was designed to have an 80% chance of demonstrating a statistically significant difference in outcome, at a one-sided significance level of 5%, if the true benefit of GM-1 was at least 0.2 times the standard deviation of the change in the Canadian Neurological Scale score (based on a t-test).

Analyses will include all clinical centers; centers that recruited few patients or a series of patients unevenly distributed across strata will be pooled to reduce spurious variability. In all analyses, patients will be allocated to the stratum to which they belong, even though some patients were stratified incorrectly. Patients ruled ineligible by the Central Adjudication Committee will be excluded from all efficacy analyses.

We propose first to compare survival in the 4 months following stroke in the GM-1 and placebo groups.17 In the absence of a statistically significant treatment effect on survival, the main analysis will consider the change in Canadian Neurological Scale score between baseline and the 4-month follow-up assessment among survivors. If the score at the 4-month follow-up is not known for a surviving patient, it will be imputed using the last available score. The change in neurological score will be compared in the GM-1 and placebo groups using analysis of variance models including the following variables: treatment, center, stratum, Canadian Neurological Scale score at baseline, and age.18 Secondary analyses will be based on the Toronto Stroke Scale score and the Barthel activities of daily living scale score.

Safety will be assessed by comparing the rates of death, adverse experiences, newly observed signs and symptoms, and abnormal laboratory test results in the two groups.

Results

The original group of three clinical centers that initiated patient recruitment in May or June of 1987 was progressively expanded to a total of 16 clinical centers by June 1988. Two centers (Graz, Austria and Pavia, Italy) were discontinued before the end of the study because of low patient recruitment. The planned recruitment period of 24 months was extended to 36 months (from May 1987 to April 1990) to reach the target sample. Overall, 8,781 stroke subjects were entered into the study stroke registry; however, only 834 (9.5%) were eligible for recruitment. The loss was primarily due to patients’ being outside of the time frame. Details regarding the impact of specific inclusion and exclusion criteria on the original roster of potential patients will be reported elsewhere (manuscript in preparation). We were successful in recruiting eligible patients; 805 of the 834 patients (96.5%) gave informed consent and were recruited.

Of these 805 randomized patients, 13 were ruled ineligible by the Central Adjudication Committee and will be excluded from all efficacy analyses, but not from safety analyses. The ineligible patients were considered to have the following diagnoses: a subtentorial vascular lesion (10 patients), an angioma (one patient), and other conditions mimicking stroke (two patients). The number of eligible patients recruited from the 14 clinical centers that were active throughout the study ranged from 19 to 116. The total yield was 792 eligible patients (Table 2).

Of these 792 patients, 23 had minor deviations from the study protocol: nine were first treated later than 5 hours after the qualifying stroke, five had laboratory abnormalities suggestive of severe uncontrolled diabetes mellitus and one of acute renal failure, three were affected by a previous neurological disease with persis-
TABLE 2. Distribution of 792 Patients in Early Stroke Trial by Clinical Center*%

<table>
<thead>
<tr>
<th>Center</th>
<th>Country</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rome</td>
<td>Italy</td>
<td>116</td>
<td>14.6</td>
</tr>
<tr>
<td>Cagliari</td>
<td>Italy</td>
<td>113</td>
<td>14.3</td>
</tr>
<tr>
<td>Perugia</td>
<td>Italy</td>
<td>103</td>
<td>13.0</td>
</tr>
<tr>
<td>Bergamo</td>
<td>Italy</td>
<td>67</td>
<td>8.5</td>
</tr>
<tr>
<td>Chieti</td>
<td>Italy</td>
<td>54</td>
<td>6.8</td>
</tr>
<tr>
<td>Aosta</td>
<td>Italy</td>
<td>53</td>
<td>6.7</td>
</tr>
<tr>
<td>New Hyde Park</td>
<td>United States</td>
<td>53</td>
<td>6.7</td>
</tr>
<tr>
<td>Innsbruck</td>
<td>Austria</td>
<td>42</td>
<td>5.3</td>
</tr>
<tr>
<td>Lausanne</td>
<td>Switzerland</td>
<td>37</td>
<td>4.7</td>
</tr>
<tr>
<td>Madrid</td>
<td>Spain</td>
<td>37</td>
<td>4.7</td>
</tr>
<tr>
<td>Mainz</td>
<td>Federal Republic of Germany</td>
<td>33</td>
<td>4.2</td>
</tr>
<tr>
<td>Florence</td>
<td>Italy</td>
<td>25</td>
<td>3.2</td>
</tr>
<tr>
<td>Toulouse</td>
<td>France</td>
<td>25</td>
<td>3.2</td>
</tr>
<tr>
<td>Munich</td>
<td>Federal Republic of Germany</td>
<td>19</td>
<td>2.4</td>
</tr>
<tr>
<td>Graz†</td>
<td>Austria</td>
<td>9</td>
<td>1.1</td>
</tr>
<tr>
<td>Pavia†</td>
<td>Italy</td>
<td>6</td>
<td>0.8</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>792</td>
<td>100</td>
</tr>
</tbody>
</table>

*Centers are listed in order of number of patients entered and, for equal members, in alphabetical order.
†Centers discontinued before end of study because of low patient recruitment.

ent focal signs or symptoms, two were demented, two were comatose, and one had lung cancer. Seven of the nine subjects treated later than 5 hours after the stroke were treated within 6 hours; the remaining two were treated within 7 hours. These 23 cases will be included in all safety and efficacy analyses.

The demographic and clinical characteristics of the study cohort at entry into EST are shown in Table 3. As in most hospital series of stroke patients, there were more men than women and the relative frequency of patients increased with advancing age. Almost 50% of the patients enrolled were older than 69 years at the time of the stroke. The most common cardiovascular conditions in the history of patients were (in order of frequency) hypertension, atrial fibrillation, and peripheral vascular disease. Approximately 18% of the patients had a history of transient ischemic attack, and less than 1% had undergone cerebrovascular surgery. Smoking (at least 10 cigarettes per day for at least 1 year) was reported in approximately 33% of the patients; alcohol abuse (at least 2 1 wine or 250 ml spirit per day for at least 1 year) in 8%. The distribution of the patients by stratification variables is given in Table 4. The two largest strata were women >65 years old with severe deficits (18.7%) and men >65 years old with severe deficits (17.9%). The smallest stratum was women ≤65 years old with severe deficits (4.7%).

Table 5 shows the distribution of the patients by time of the qualifying stroke and by time of events between the stroke and the onset of study treatment. Only approximately 5% of the patients could be first treated within 2 hours after the qualifying stroke; about 22% were first treated within 3 hours and 57%, within 4 hours. By contrast, hospital referral was rapid. Approximately 46% of the patients were admitted within 1 hour (or had the stroke while in the hospital for another disease) and 81%, within 2 hours. Apparently, most of the delay between stroke and the onset of treatment was due to the baseline assessment of patients within the clinical centers. Doppler ultrasonography of the neck and intracranial arteries was performed in 654 patients (82.6%); in 82.1% of them, the test was performed within 5 hours. Cerebral angiography was performed in 191 patients (24.1%); in 81.7% of them, the test was performed within 5 hours after the onset of stroke.

Discussion

The EST is randomized and has a large patient base, and no investigator, adjudicator, or representative of the sponsor had access to the treatment code at any time during the study. Indeed, the treatment code was disclosed only after a computer tape of the final data base had been handed to the ARTEMC, to ensure that no further modifications of key data were made. Therefore, the process of making decisions about the eligibility of patients, the causes of death, and the validity of outcome measures was unbiased. Also, the principal analyses to be carried out were decided before disclosure of the treatment code.
TABLE 4. Severity of Qualifying Stroke in 792 Patients in Early Stroke Trial

<table>
<thead>
<tr>
<th>Canadian Neurological Scale score</th>
<th>Total</th>
<th>≤65 yr</th>
<th>&gt;65 yr</th>
<th>Total</th>
<th>≤65 yr</th>
<th>&gt;65 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5–3.0</td>
<td>169</td>
<td>21.3</td>
<td>27</td>
<td>3.4</td>
<td>60</td>
<td>7.6</td>
</tr>
<tr>
<td>3.5–5.0</td>
<td>194</td>
<td>24.5</td>
<td>31</td>
<td>3.9</td>
<td>60</td>
<td>7.6</td>
</tr>
<tr>
<td>Severe stratum (1.5–5.0)</td>
<td>363</td>
<td>45.8</td>
<td>58</td>
<td>7.3</td>
<td>120</td>
<td>15.2</td>
</tr>
<tr>
<td>5.5–7.0</td>
<td>266</td>
<td>33.6</td>
<td>67</td>
<td>8.5</td>
<td>89</td>
<td>11.2</td>
</tr>
<tr>
<td>7.5–8.5</td>
<td>163</td>
<td>20.6</td>
<td>51</td>
<td>6.4</td>
<td>53</td>
<td>6.7</td>
</tr>
<tr>
<td>Less severe stratum (5.5–8.5)</td>
<td>429</td>
<td>54.2</td>
<td>118</td>
<td>14.9</td>
<td>142</td>
<td>17.9</td>
</tr>
<tr>
<td>Total</td>
<td>792</td>
<td>100.0</td>
<td>176</td>
<td>22.2</td>
<td>262</td>
<td>33.1</td>
</tr>
</tbody>
</table>

Percent of total number of patients in trial.

TABLE 5. Chronology of Events in 792 Stroke Patients in Early Stroke Trial

<table>
<thead>
<tr>
<th>Events</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of stroke (24-hour clock)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0:01–6:00</td>
<td>35</td>
<td>4.4</td>
</tr>
<tr>
<td>6:01–12:00</td>
<td>369</td>
<td>46.6</td>
</tr>
<tr>
<td>12:01–18:00</td>
<td>253</td>
<td>31.9</td>
</tr>
<tr>
<td>18:01–24:00</td>
<td>135</td>
<td>17.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from stroke to hospital admission (hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke while in hospital for another disease</td>
<td>25</td>
<td>3.2</td>
</tr>
<tr>
<td>≤1:00</td>
<td>341</td>
<td>43.1</td>
</tr>
<tr>
<td>1:01–2:00</td>
<td>276</td>
<td>34.8</td>
</tr>
<tr>
<td>2:01–3:00</td>
<td>118</td>
<td>14.9</td>
</tr>
<tr>
<td>3:01–4:00</td>
<td>25</td>
<td>3.2</td>
</tr>
<tr>
<td>4:01–5:00</td>
<td>5</td>
<td>0.6</td>
</tr>
<tr>
<td>&gt;5:00</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>0.1</td>
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<tr>
<td>Time from stroke to first assessment by investigator (hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1:00</td>
<td>257</td>
<td>32.4</td>
</tr>
<tr>
<td>1:01–2:00</td>
<td>278</td>
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<td>2:01–3:00</td>
<td>186</td>
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<td>3:01–4:00</td>
<td>56</td>
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<td>4:01–5:00</td>
<td>12</td>
<td>1.5</td>
</tr>
<tr>
<td>&gt;5:00</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>Time from stroke to onset of study treatment (hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:01–2:00</td>
<td>38</td>
<td>4.8</td>
</tr>
<tr>
<td>2:01–3:00</td>
<td>140</td>
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<tr>
<td>3:01–4:00</td>
<td>274</td>
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<tr>
<td>4:01–5:00</td>
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<td>41.8</td>
</tr>
<tr>
<td>&gt;5:00</td>
<td>9</td>
<td>1.1</td>
</tr>
<tr>
<td>Time from stroke to first computed tomogram (hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1:00</td>
<td>52</td>
<td>6.6</td>
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<tr>
<td>1:01–2:00</td>
<td>200</td>
<td>25.3</td>
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<td>2:01–3:00</td>
<td>256</td>
<td>32.3</td>
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<td>3:01–4:00</td>
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<td>4:01–5:00</td>
<td>74</td>
<td>9.3</td>
</tr>
<tr>
<td>5:01–6:00</td>
<td>9</td>
<td>1.1</td>
</tr>
<tr>
<td>&gt;6:00</td>
<td>6</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Following a previously suggested methodological approach, we will exclude from the principal efficacy analyses patients who were randomized but were subsequently ruled to be ineligible by the Central Adjudication Committee. This approach should increase the ability of the study to detect a significant difference between GM-1 and placebo if GM-1 is indeed efficacious. However, since eligibility decisions were implemented without information on treatment and outcome, no bias should result. There will be full disclosure in the EST efficacy report of all outcome events in ineligible randomized patients.

The Canadian Neurological Scale was selected as the principal measure of neurological status in EST.5 We used the 1986 version of the scale because only this was available at the time the trial was planned; a modified version was proposed in 1989.6 The interrater reliability of the scale was tested on two different samples and was found to be satisfactory.56 In addition, the scale was found to have good internal consistency.6 Content validity of the scale was assessed by a panel of stroke experts who agreed on the specific items to be included and their relative weights. Items were selected because of their relevance to acute stroke and their ease of assessment.6 The scale was found to be accurate compared with the standard neurological examination (concurrent validity) and to predict outcomes in stroke patients (predictive validity).6 The Canadian Neurological Scale was found to correlate better with the standard neurological examination of stroke patients than the Glasgow Coma Scale (discriminant validity).6,23 Finally, the Canadian Neurological Scale was found to be sensitive in detecting changes over time in neurological status compared with a series of standard neurological examinations (convergent validity). The authors showed that a change in score of 1.0 point or more was highly sensitive, sufficiently specific, and had a maximum negative predictive value compared with the assessment of change in neurological status by standard clinical evaluation.6 Because we investigated the difference in recovery of function following stroke between GM-1- and placebo-treated patients, we were most interested in the ability of the scale to detect changes over time.

Approximately 47% of the patients recruited experienced their stroke between 6:01 AM and noon. The higher occurrence of stroke in the morning has been previously reported and might be linked to increased
platelet aggregability and increased plasma catechol-
amine levels.24 However, our hospital series was se-
lected and may not reflect the circadian variation in the
general population. Our findings could simply reflect
the higher probability for a stroke patient to be hospi-
talized, diagnosed, and randomized within 5 hours in
the morning than at other times of the day.

Although only approximately 10% of the subjects
entered into the stroke registry were eligible for in-
clusion in the trial, we experienced a high recruitment rate
among those eligible. EST therefore demonstrates the
feasibility of trials of acute treatments for ischemic stroke.
With some reorganization of stroke services and refer-
ral practices, and with the involvement of many
centers in various countries, it was possible to overcome
the loss of eligible patients due to the drastic restriction
in time between stroke and treatment.2 The clinical
centers successfully reduced the time between hospital
referral and onset of treatment by improving coordina-
tion of personnel at the emergency room, the depart-
ment of neuroradiology, and the department of neurol-
yology or other clinical departments. The time between
stroke and hospital referral could not be modified since
it is determined by the awareness of physicians and of
the general population that treatments for stroke in the
acute phase are available. Interestingly, 81% of patients
who were ultimately recruited into EST reached a hospital
within 2 hours after stroke onset. This suggests that,
although the organization of a coordinated team
within the hospital is indispensable, the key issue re-
mains early hospital referral. Treatment of ischemic
stroke within a few hours after the onset of symptoms
may prove to be a successful approach.1

Appendix

Clinical Centers (in order of number of patients entered).
Dipartimento di Scienze Neurologiche, Università degli Studi
"La Sapienza" di Roma, Roma, Italy: C. Argentino, D. Toni,
M. Rassura, M.L. Sacchetti, and C. Fieschi; I Divisione di
Medicina Generale, Centro per l’Arteriosclerosi, Ospedale
"Brotzu," Cagliari, Italy: S. Muntoni, G. Dessi, M. Sanna,
M.B. Botta, M. Serri, P. Cannas, P.P. Loi, and M.T. Casula;
Unità Operativa di Perugia, Perugia, Italy: (Cattedra di Ger-
ontologia e Geriatria) U. Senin, G. Aisa, G. Valigi, and G.
Menculini, (Clinica Neurologica) V. Gallai, A. Alunni Gaggi-
noni, P.L. Brustenghi, F. Xavier Del Gatto, A. Dello Mastro,
and representatives of the clinical centers.

Central Adjudication Committee. Chairman, A. Carolei
(Siena, Italy). G. Sancesario and C. Argentino (Rome, Italy).
R. Bruno and E. Olivi (Abano Terme, Italy).

Advisory Review and Treatment Effects Monitoring Comittee.
Chairman, M. Walker (Bethesda, MD). D. Easton
(Providence, RI), M. Gent and R. Roberts (Hamilton, Canada).

Clinical Monitors. Fidia S.p.A., Abano Terme, Italy: C. Mar-
nazzco, G. Salvato, and A. Innocenti; Fidia Pharmaceutical Corp.,
Fidia Farmapharmac, Munich, FRG: F. Berni and J. Kleasing;

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