Background and Purpose—Based on neuroprotective efficacy in animal models, we evaluated the N-methyl D-aspartate (NMDA) antagonist Selfotel in patients with ischemic stroke, after doses up to 1.5 mg/kg were shown to be safe in phase 1 and phase 2a studies.

Methods—Two pivotal phase 3 ischemic stroke trials tested the hypothesis, by double-blind, randomized, placebo-controlled parallel design, that a single intravenous 1.5 mg/kg dose of Selfotel, administered within 6 hours of stroke onset, would improve functional outcome at 90 days, defined as the proportion of patients achieving a Barthel Index score of ≥60. The trials were performed in patients aged 40 to 85 years with acute ischemic hemispheric stroke and a motor deficit.

Results—The 2 trials were suspended on advice of the independent Data Safety Monitoring Board because of an imbalance in mortality after a total enrollment of 567 patients. The groups were well matched for initial stroke severity and time from stroke onset to therapy. There was no difference in the 90-day mortality rate, with 62 deaths (22%) in the Selfotel group and 49 (17%) in the placebo-treated group (RR=1.3; 95% CI 0.92 to 1.83; P=0.15). However, early mortality was higher in the Selfotel-treated patients (day 30: 54 of 280 versus 37 of 286; P=0.05). In patients with severe stroke, mortality imbalance was significant throughout the trial (P=0.05).

Conclusions—Selfotel was not an effective treatment for acute ischemic stroke. Furthermore, a trend toward increased mortality, particularly within the first 30 days and in patients with severe stroke, suggests that the drug might have a neurotoxic effect in brain ischemia. (Stroke. 2000;31:347-354.)

Key Words: controlled clinical trials ■ neuroprotection ■ stroke, acute ■ stroke, ischemic

The development of the N-methyl D-aspartate (NMDA) antagonists was based on the finding that an ischemic brain injury produces elevated levels of the excitatory neurotransmitter glutamate, which leads to excessive stimulation of the NMDA receptor.1 In the excitotoxic ischemic environment, NMDA receptor activation leads to neuronal injury, firstly due to an influx of sodium and water into the cells and secondly due to the accumulation of intracellular calcium. Rising intracellular calcium levels induce activation of proteases, phospholipases and protein kinases with eventual lysis of intracellular elements and cell death. Both competitive and noncompetitive NMDA antagonists have been developed. Selfotel (CGS 19755) is a competitive NMDA receptor antagonist that binds directly to the NMDA site of the glutamate receptor, inhibiting the action of glutamate in the excitotoxic environment of acute ischemia.2-3

The development of potentially effective neuroprotective agents such as the NMDA antagonists has particular appeal in acute stroke, because these compounds are not associated with an increased risk of hemorrhage and can therefore be administered without a screening CT scan. Selfotel was selected as a neuroprotective candidate because it was found to limit neuronal damage in a variety of animal stroke models.4-9 On the basis of dose escalation and safety studies in healthy volunteers, it was found that doses >1.5 mg/kg produced transient neurological symptoms, including sedation, dizziness, and confusion, without focal neurological abnormalities on examination.2 A phase 2A study involved dose escalation, placebo-controlled studies in stroke patients and led to the conclusion that an intravenous bolus dose of 1.5 mg/kg administered within 6 hours of onset of acute ischemic stroke appeared to be safe and possibly effective.3 Adverse experiences related to the central nervous system (chiefly, agitation, hallucinations, and confusion) occurred at higher doses of Selfotel.
Based on the animal, phase 1 and phase 2 data, a single dose of 1.5 mg/kg was selected to be tested in 2 concurrent, pivotal phase 3 ischemic stroke trials. In parallel with these stroke trials, 2 phase 3 trials were conducted in patients with traumatic brain injury. These trials were also terminated prematurely on the advice of the independent Data Safety Monitoring Board (DSMB), based on an overall mortality imbalance consistent with, although less impressive than, the stroke trial results. The Selfotel head injury trials will be reported separately.

Subjects and Methods

The primary objective of the trials was to determine the efficacy and safety of a single 1.5-mg/kg dose of Selfotel compared with placebo in acute ischemic stroke by evaluating the proportion of patients who achieved a reasonable level of functional independence at 90 days after stroke onset. This was defined as the proportion who achieved a Barthel Index score of $\geq 60$. The secondary objectives were to determine whether Selfotel improved the 30-day and 90-day neurological outcomes, through use of the National Institutes of Health Stroke Scale (NIHSS) and the Scandinavian Stroke Scale (SSS) scores, and to determine whether Selfotel, compared with placebo, reduced mortality from acute ischemic stroke.

The 2 trials had very similar protocols. One was conducted in Europe, Australia, Argentina, and Canada (protocol 10) and the other in the United States and Israel (protocol 07). These were called the ASSIST Trials (Acute Stroke Trials Involving Selfotel Treatment). The trials involved a multicenter, randomized, double-blind, placebo-controlled, parallel design that investigated the efficacy and safety of a single dose of Selfotel (1.5 mg/kg) in patients hospitalized for acute ischemic stroke, in which the drug was administered intravenously within 6 hours of the onset of symptoms (Appendix 2). It was planned that each trial enroll approximately 920 patients to obtain the 820 required patients (410 per treatment arm). In addition to the blinded monitoring by the staff involved in conducting the trials, the data were reviewed by an independent DSMB, consisting of qualified specialists (Appendix 1), who had unlimited access to the data on an ongoing basis. The treatment assignment was provided as A and B to the DSMB. The DSMB provided their assessments to a Steering Committee composed of representatives of the investigators and sponsor (Appendix 1).

The ASSIST trials enrolled patients aged 40 to 85 years with a clinical diagnosis of hemispheric acute ischemic stroke. Baseline neurological symptoms were documented with the SSS and the NIHSS scores. The duration between symptom onset and initiation of treatment with trial drug was to be of no more than 6 hours. In patients waking from sleep with neurological symptoms, the onset of symptoms was taken from the time that they were last seen to be neurologically normal. Patients were required to be ambulatory and functionally independent (Barthel Index score of $>95$) before the onset of the stroke and had to be hospitalized for the study. They were required to have significant motor deficit, demonstrated by a score of $\geq 2$ (some effort against gravity) in any limb on the NIHSS. Patients were classified using the Prognostic score of the SSS as having severe stroke (SSS $<16$) or mild to moderate stroke (SSS $\geq 16$). Although CT scanning was not mandated before therapy, CT had to be performed within 24 hours of stroke onset.

Patients were excluded if there were clinical signs of brain stem dysfunction or brain herniation, coma, seizures between the time of stroke onset and trial drug administration, a stroke syndrome related to a systemic condition (eg, vasculitis), or a history of any debilitating somatic or psychiatric condition that could interfere with neurological or functional assessment. Other exclusion criteria included a computed CT scan (if performed before dosing) that showed either hemorrhage or a noncerebrovascular brain disorder, concurrent enrollment in other investigational drug trials, the requirement for treatment with thrombolytic therapy or nimodipine, and finally, patients considered unlikely to be available for follow-up assessments. Patients with hemorrhagic stroke or noncerebrovascular pathology, treated before the CT scan, were included in the intention-to-treat (ITT) analysis.

Patients or next-of-kin had to be able to provide informed consent according to local or national legal requirements and institutional ethics committees. The trials involved males or nonpregnant females. A negative pregnancy test was required for females of childbearing potential before drug trial administration.

Eligible, consenting patients were then randomized to 1.5 mg/kg Selfotel or matching placebo in a 1:1 ratio. A single intravenous dose of trial drug was given over 2 to 5 minutes. If possible, patients were weighed in emergency departments or their weight was estimated on the basis of history and body nomogram. The great majority of patients were treated in stroke units in experienced stroke centers (Appendix 2).

After trial drug administration, patients were monitored for safety, neurological function, and functional status for 8 days, including a minimum of 4 hospitalization days. A second CT scan was to be performed at days 4 to 8 to confirm the final diagnosis. Surviving patients were then seen in clinic visits or in institutions on trial days 30 and 90. Efficacy was measured using the Barthel Index, the NIHSS, and the SSS by an evaluator not involved in the patients acute monitoring phase, to prevent potential unblinding due to possible Selfotel-associated adverse events. Investigators were trained in the administration of the scales used in the protocol.

All adverse experiences were reported during the acute monitoring phase of the trial (days 1 through 8). Serious adverse experiences were recorded continuously throughout the duration of the trial (until day 90). Adverse experiences considered to be part of the acute stroke process were not recorded unless the patients deteriorated after trial drug administration or required therapy. Physical examination, ECG, routine hematology, and blood chemistry were performed at baseline and during the monitoring and follow-up periods.

Statistical Methods

Efficacy analyses were performed on the ITT data set, which consisted of all randomized patients who received trial drug and had at least 1 postbaseline Barthel Index score or died within the 90-day period. The proportion of patients with a Barthel score $\geq 60$ was analyzed at 3 months (observed cases) and 3 months with last observation carried forward (LOCF) for all ITT patients. Mortality was analyzed at days 8, 30, and 90 for all ITT patients and for the 2 subgroups based on baseline stroke severity (mild to moderate and severe). Each analysis was performed by combining the results from the 2 trials with the Cochran-Mantel-Haenszel test.

Analyses were also performed to calculate the probability of success for each trial, based on the proportion of patients with a Barthel score $\geq 60$. This was defined as the likelihood of Selfotel demonstrating efficacy at the 0.05 significance level had the trial completed enrollment. Based on the observed rates, a Bayesian approach was used to generate, through simulations, hypothetical end point rates for the Selfotel and placebo groups. These hypothetical rates were then used to generate random outcomes for the remainder of the trial. In each case, these simulated outcomes were combined with the observed results to determine whether there was a significant outcome in favor of Selfotel.

Among the 5000 cases contained in the simulation, the proportion which yielded a significant difference in favor of Selfotel was calculated, and this was the estimated probability of success.

Results

As previously reported, the independent DSMB raised concerns based on the analysis of data on 476 patients. The present report includes the complete data from the 567 patients who had been enrolled in the ASSIST trials when the trials were terminated on the advice of the Steering Committee (Table 1).

Distribution of Patients and Demographic Characteristics by Treatment Group

In the 2 pivotal trials, 567 patients in total were enrolled at 94 centers worldwide. In all, 281 patients received 1.5 mg/kg
Selfotel and 286 received matching placebo. Randomization of patients, the proportions discontinuing drug prematurely and the numbers of patients evaluated in ITT and safety analyses are shown in Table 1.

The groups were well matched with regard to demographic variables. There were no notable differences at randomization between the groups (Table 2) for age, gender, weight, and mean time from stroke onset to treatment (4.5 hours in each treatment group). Of the 567 patients, 13% were treated within 3 hours, a similar proportion in both groups. Baseline neurological severity was comparable in the Selfotel and placebo-treated groups with a mean NIH Stroke Scale score of 14.2 (Selfotel) and 13.9 (placebo). Approximately one third of each group were classified as having mild to moderate stroke severity and two thirds were categorized as having had a severe stroke, based on the prognostic score of the SSS12 (Table 2). The proportion of patients with a normal baseline CT scan was the same in both groups (Table 2).

The groups were well matched for prior medical conditions, with risk factors evenly distributed between the treatment groups. These included hypertension (Selfotel 60.7%, placebo 60.4%), atrial fibrillation (Selfotel 32.9%, placebo 24.1%), prior transient ischemic attack or stroke (Selfotel 27.9%, placebo 31.7%), diabetes (Selfotel 20.7%, placebo 16.9%), and myocardial infarction (Selfotel 16.0%, placebo 23.4%).

Adverse Experiences
Most adverse experiences were neurological in type and more common in the Selfotel-treated group (Table 3). Significantly higher proportions of Selfotel-treated patients experienced agitation, hallucinations or confusion. There were similar proportions of patients with neurological adverse experiences in those who died in the Selfotel- and placebo-treated groups.

The term “cerebrovascular disorder” (Table 3) included patients who demonstrated neurological progression after treatment with study drug and those who exhibited a further depression of conscious state with the development of stupor or coma. Overall, the proportion of patients with neurological progression or depressed conscious state was higher in the Selfotel-treated than placebo-treated patients. For stupor and coma alone, a total of nearly 10% of Selfotel patients were affected, compared with 2% of placebo-treated patients (P<0.001).

Posttreatment Investigations
A similar proportion of patients (82% Selfotel, 87% placebo) had evidence (days 7 to 10) of an acute stroke lesion on the posttreatment CT scan. There were 8% primary cerebral hemorrhages in the Selfotel and 7% in the placebo-treated group. The remainder were ischemic lesions, most commonly involving the middle cerebral territory (Selfotel 72%, placebo 81%). A similar proportion of patients had evidence of mass effect on the postdosing CT scan (Selfotel 53%, placebo 54%). Both at baseline (22% Selfotel, 15% placebo) and at subsequent recordings (24% Selfotel, 17% placebo) there was a greater incidence of atrial fibrillation in the Selfotel-treated patients (P<0.05). There was no significant change in hematology or blood chemistry posttreatment.

Minor differences in postdosing medications were noted between the 2 groups. Notably, more Selfotel-treated patients received sedative medications (Selfotel 39%, placebo 17%; P<0.01). The most commonly used sedative drugs were haloperidol and lorazepam.
TABLE 4. Primary Outcome: Proportion of Patients With Total Barthel Index Score of ≥60

<table>
<thead>
<tr>
<th>Stroke Severity</th>
<th>Selfotel, %</th>
<th>Placebo, %</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/moderate</td>
<td>83</td>
<td>83</td>
<td>0.981</td>
</tr>
<tr>
<td>Severe</td>
<td>48</td>
<td>43</td>
<td>0.352</td>
</tr>
<tr>
<td>All patients</td>
<td>61</td>
<td>58</td>
<td>0.490</td>
</tr>
<tr>
<td>3 mo LOCF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/moderate</td>
<td>79</td>
<td>78</td>
<td>0.852</td>
</tr>
<tr>
<td>Severe</td>
<td>35</td>
<td>35</td>
<td>0.981</td>
</tr>
<tr>
<td>All patients</td>
<td>50</td>
<td>50</td>
<td>0.853</td>
</tr>
</tbody>
</table>

LOCF indicates last observation carried forward.
*By pooled protocols and intent-to-treat analysis.

Efficacy

Primary Outcome Analysis

The trials were terminated prematurely based on the advice of the independent DSMB. Hence, the analyses reflect data from 31% of the planned patient enrollment. An additional analysis that was not prespecified was conducted to estimate the probability of success of the trials had enrollment been completed.

Results based on the ITT data from the 2 trials were pooled for analysis of the primary outcome variable, the proportion of patients with a total Barthel Index score of ≥60. There were no statistically significant differences in the primary outcome measure between the treatment groups or in the analyses of sub-groups by stroke severity (Table 4). Separate analyses of the patients with 3-month outcome data and 3-month last observation carried forward (LOCF), by stroke severity, also showed no statistically significant differences between the treatment groups (Table 4).

Secondary Outcome Analysis

Neurological outcomes at days 30 and 90 (ITT) included the total NIHSS score and the standardized percent changes from baseline NIHSS score, the total SSS score and the standardized percent changes from the baseline SSS score. No significant differences were evident in 30- or 90-day neurological outcomes.

There were 111 deaths in the 567 patients, an overall mortality rate of 20%. A nonsignificant increase in deaths occurred in the Selfotel treated patients (22%) compared with the placebo-treated patients (17%) over the whole trial (RR = 1.3; 95% CI 0.92 to 1.81; P = 0.14). However, statistically significant differences between the treatment groups were evident, with higher mortality evident in the Selfotel-treated patients at both day 8 (P = 0.02) and day 30 (P = 0.05), although these analyses were conducted post hoc and not prespecified (Table 5).

Analysis of Kaplan-Meier survival curves (Figure 1) suggested an early trend toward separation between the Selfotel- and placebo-treated patients that commenced within 24 hours of randomization and appeared to persist for 2 to 3 weeks. However, this trend toward greater early mortality in the Selfotel group was not significant by log-rank test (P = 0.17).

As expected, the mortality was higher in patients with severe stroke than in patients with mild/moderate stroke (Table 5). However, this difference was more pronounced in Selfotel-treated patients (57/187, 30%) than in placebo-treated patients (40/185, 22%); P = 0.05. This difference was larger at the end of the first week of the trial (day 8): Selfotel 17%, placebo 9%; P = 0.03. These analyses were also not prespecified and were conducted post hoc.

TABLE 5. Relative Risk of Mortality for Stroke Patients Receiving Selfotel Versus Placebo, by Stroke Severity

<table>
<thead>
<tr>
<th>Indication</th>
<th>Selfotel, % (n/N)</th>
<th>Placebo, % (n/N)</th>
<th>Relative Risk</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>22.1 (62/280)*</td>
<td>17.1 (49/286)</td>
<td>1.292</td>
<td>(0.923, 1.809)</td>
</tr>
<tr>
<td>Severe patients</td>
<td>30.5 (57/187)</td>
<td>21.6 (40/185)</td>
<td>1.410</td>
<td>(0.994, 1.999)</td>
</tr>
<tr>
<td>Mild/moderate patients</td>
<td>4.3 (4/92)</td>
<td>8.9 (9/101)</td>
<td>0.488</td>
<td>(0.156, 1.531)</td>
</tr>
<tr>
<td>Deaths by day 8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>11.4 (32/280)*</td>
<td>5.9 (17/286)</td>
<td>1.923</td>
<td>(1.093, 3.382)</td>
</tr>
<tr>
<td>Severe patients</td>
<td>16.6 (31/187)</td>
<td>9.2 (17/185)</td>
<td>1.804</td>
<td>(1.035, 3.144)</td>
</tr>
<tr>
<td>Mild/moderate patients</td>
<td>0.6 (0/92)</td>
<td>0.0 (0/101)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

*Includes one Selfotel patient (Patient 402 in Protocol 10) who had no baseline stroke severity score and died on day 2.
Probability of Success

Analysis of the probability of success was conducted independently for each protocol based on the proportion of patients with a Barthel Index score of ≥60. Based on the observed data, protocol 07 had a 32% chance and protocol 10 had a <1% chance of demonstrating efficacy had the trials completed enrollment. This apparent difference might be explained by the much smaller sample size of the protocol 07 trial when enrollment to the trial was terminated.

Discussion

The ASSIST trials were terminated by the Steering Committee on the advice of the independent DSMB after approximately 30% of patients had been enrolled and followed up for 90 days. Although the overall mortality difference between the groups did not achieve formal statistical significance, there was a trend toward increased mortality in the Selfotel group at day 90. Of greater concern, significantly increased mortality was evident in the patients with severe stroke, particularly at days 8 and 30, although this subgroup analysis was not prespecified. Furthermore, the probability of demonstrating efficacy in the individual trials, had they proceeded to completion, was exceedingly small. This was particularly apparent on review of the data from protocol 10, in which the majority of patients (389) had been entered.

The Selfotel-treated and placebo-treated patients were well matched at baseline. The ASSIST trials showed no difference between the treatment groups in the proportion of patients who achieved a Barthel Index score of ≥60 at 90 days, this level of function being correlated with the ability to manage most activities of daily living independently.

These results indicate that 1.5 mg/kg Selfotel administered intravenously within 6 hours of onset of acute ischemic stroke is not beneficial. Furthermore, a potentially harmful effect, particularly in patients with severe stroke, is indicated by the data. Most of the excess deaths in the Selfotel-treated group occurred within the first 8 days of stroke onset, raising the possibility of a pharmacologically adverse effect. In addition, the neurological adverse experiences thought to be drug related were more common in the Selfotel-treated patients, as was also evident in the phase 2a randomized trial. No firm conclusions can be drawn about an association between these adverse experiences and the apparent increase in mortality in Selfotel-treated patients in the first few days after stroke, particularly in patients with severe ischemia. However, these observations raise the possibility that the drug might be neurotoxic in human brain ischemia.

Alternatively, the psychological and sedative adverse effects of Selfotel may have mimicked stroke progression to coma and adversely influenced clinical management and outcome during the crucial early days. The development of various degrees of depression of conscious state was much more common in the Selfotel-treated group. Future stroke trials involving sedative compounds should include specific measures to ensure that any such confounding effect is prevented.

Because of their theoretical role in the attenuation of neurotoxicity in acute brain ischemia and their promise based on animal results, a number of other phase 2 and phase 3 NMDA antagonist clinical trials have recently been conducted. The noncompetitive NMDA antagonist dextrorphan was evaluated in a pilot study within 48 hours of the onset of hemispheric infarction. Neurological side effects were similar to those seen in the ASSIST trials. The noncompetitive NMDA antagonist aptiganel appeared promising on the basis of studies with diffusion-weighted MRI and a phase 2 trial. However, the phase 3 trial was prematurely terminated. Two phase 3 trials of another NMDA antagonist, eliprodil, were also terminated because of lack of efficacy. Detailed examination of the combined results of these trials may shed light on the true risk-benefit ratio of NMDA antagonists. This will be the subject of a Cochrane Collaboration review.

These negative results of trials of a range of NMDA antagonists have raised doubts about the clinical role for this class of acute stroke drug. It is puzzling that a number of NMDA antagonists, including Selfotel, appear to be attractive candidates for neuroprotection in animal models but have been convincingly shown to be ineffective in adequately powered and well-designed clinical trials. A variety of explanations have been suggested. It has been proposed that the injurious effect of NMDA antagonists could outweigh the theoretical benefits of glutamate blockade and modification of the excitotoxic stroke environment.

Other possible explanations include the problems in translating the animal stroke models to human brain ischemia and the poor penetration of neuroprotective drugs into the critically impaired perfusion of the ischemic penumbra. A recent animal study suggested that brain ischemia might in fact enhance the adverse effects of NMDA antagonists.

Stroke in humans is more complex and heterogeneous than in animal infarct models. Variability of stroke subtypes; the influence of important physiological variables such as blood pressure, temperature, and oxygenation; and the dosage limitations in humans due to adverse effects are all possible explanations for the difficulty in translating positive animal studies to clinical trial results.

The precise time windows for neuroprotective strategies are unknown. Most of the animal models that demonstrate attenuation of infarct size with NMDA antagonists have used treatment thresholds of minutes up to a couple of hours. In contrast, most of the clinical stroke trials have tested patients up to 6 hours, which may be too long. With a time window of 6 hours, there is a tendency for patients to cluster up to the deadline time. Only 13% of patients in the ASSIST trials were treated within 3 hours, and this small number did not allow a meaningful analysis of any possible effect of earlier treatment. The only clearly positive stroke trials to date with intravenous therapy used reperfusion strategies with either tPA or ancord, both with a 3-hour time window. Grotta recently suggested that a 3-hour time window may be the therapeutic limit for either neuroprotection or reperfusion strategies, based on animal models utilizing a wide range of acute interventional approaches. Hence, neuroprotective trials with a 3-hour threshold are warranted.

Finally, recent experimental evidence suggests that neuroprotection, as a single acute stroke treatment strategy, may be unlikely to succeed without concomitant reperfusion therapy. Heiss et al used positron-emission tomography to measure initial cerebral blood flow within 3 hours of stroke onset and MRI to measure morphological outcome in a series of stroke
patients. They concluded that most of the brain tissue infarcted was attributable to severe initial ischemia and that secondary mechanisms, such as excitotoxicity, had a relatively minor effect on infarct size. Hence, modest attenuation of infarct size by a neuroprotective agent may not translate into a clinically significant difference in functional outcome. Combinations of thrombolytic and neuroprotective therapies appear to be an attractive strategy. First, neuroprotective drugs may extend the therapeutic window for thrombolysis. Second, thrombolysis, which promotes acute reperfusion, is likely to facilitate higher concentrations of a neuroprotective agent in the critically underperfused penumbral region. Large trials that test combination therapies, however, are likely to first depend on the confirmation in humans of an effective neuroprotective agent.

Appendix I

Committee Structures

Steering Committee
Prof Stephen M. Davis (Dept of Neurology, Royal Melbourne Hospital, Grattan Street, Parkville, Vic 3050, Australia). Prof Kennedy R Lees (Clinical Director, University of Glasgow, Gaddie Institute, Western Infirmary, Glasgow G11 6NT, United Kingdom). Dr Gregory W Albers (701 Welch Rd. Building B, Suite 325, Palo Alto, CA 94002). Prof Hans Christoph Diener (University of Essen, Hufelandstrasse 55, 45122 Essen, Germany). Prof John Norris (Sunnybrook Health Service Centre, University of Toronto, 207 Bayview Ave, Toronto, Ontario M4N 3M5, Canada). Dr Subri Markaki (Novartis Pharmaceuticals, 59 Route 10, East Hanover, NJ 07936). and Prof Goertil Karlsson (Clinical Research Manager, Novartis Pharma AG, CH-4002 Switzerland).

Data and Safety Monitoring Board
Prof J. Donald Easton (Dept of Neurology, Rhode Island Hospital, Brown University, 110 Lockwood St, Room 324, Providence, RI 02903). Prof Alain Autret (Head, Clinique Neurologique, Hospital Bretonneau, F-37044 Tours Cedex, France). Prof J.W.F. Bekx (Dept of Neurosurgery, University Hospital, Oostersingel 59, NL – 9700 RB Groningen, the Netherlands). Prof William F. Collins (Yale Medical School, Dept of Neurological Surgery, PO Box 208039, New Haven, CT 06520-8039). Prof Andreas Laupacis (Director, Clinical Epidemiology Unit, Department of Research, Ottawa Civic Hospital. Room 22, Clinical Sciences Building, 1053 Carling Ave, Ottawa, Ontario K1Y 4E9, Canada). Dr Michael Selam (George Washington University, 2150 Pennsylvania Ave, Washington, DC 20037), and Dr Nancy Tomkyn (7550 205th Ave NE, Redmond, WA 98053).

Appendix II

Study Centers and Principal Investigators

Australia
J. Frayne, Dept of Neurology, Alfred Hospital, Commercial Road, Prahran VIC 3181; G. Donovan, Dept of Neurology, Austin and Repatriation Medical Centre, Studeley Road, Heidelberg VIC 3084; A. Black, Dept of Neurology, Queen Elizabeth Hospital, Woodville SA 5011; B. Chambers, Dept of Neurology, Heidelberg Repatriation Hospital, Banksia Street, Heidelberg West VIC 3018; S. Davis, Dept of Neurology, Royal Melbourne Hospital, Grattan Street, Parkville VIC 3050; G.J. Hankey, Dept of Neurology, Royal Perth Hospital, Wellington Street, Perth WA 6001; A. Corbett, Dept of Neurology, 6th Floor–Ward 620, Concord Repatriation General Hospital, Concord NSW 2139; C. Anderson, Repatriation General Hospital, Daws Road, Daw Park SA 5041, and Dept of Neurology, Flinders Medical Centre, Flinders Drive, Bedford Park SA 5042.

Belgium

Canada
B. Anderson, Section of Neurology, St Boniface General Hospital, 409 Tache Rd, Winnipeg, Manitoba, R2H 2A6; M. Beaudy, Centre hospitalier de Jonquière, 2230 de l’HÔpital, Jonquière, Québec G7X 7X2; L. Berger, Hôpital Charles LeMoyne, 121, boul Taschereau, Greenfield Park, Québec J4V 2H1; R. CÔtê, L’HÔpital Général de Montréal, Division de Neurologie, Room L7408, 1650 Cedar Avenue, Montréal, Québec H3G 1A4; R. Duke, Hamilton General Hospital, 237 Barton St, Hamilton, Ontario L8M 3K4; V. Limsák, Dept of Clinical Neurological Sciences, University Hospital, 339 Windemere Rd, London, Ontario N6A 5A5; D. Howse, Division of Neurology, Kingston General Hospital, Queen’s University, 76 Stuart St, Kingston, Ontario K7L 2V7; K. M. Hoyte, Dept of Clinical Neuroscience, University of Calgary, Calgary General Hospital, 201–803 1st Ave NE, Calgary, Alberta T2E 7C5; J.W. Norris, Stroke Research Unit E-426, Sunnybrook Health Science Center, 2075 Bayview Ave, Toronto, Ontario M4N 3M5; F. Silver, The Toronto Hospital, Western Division, 399 Bathurst St, Toronto, Ontario M5T 2S8; Ph. Ted, Division of Neurology, Vancouver General Hospital, 215-2775 Heather St, Vancouver, BC Columbia V5J 3J5.

Germany
H.C. Diener, Universitätsklinikum Essen, Neurologische Universitätsklinikum und Poliklinik, Hufelandstrasse 55, 45147 Essen; A. Haass, Univ-Nervenklinik, Abteilung Neurologie, Oscar-Orth-Strasse, 66421 Homburg/Saar; W. Christe, Virchow-Klinikum, Medizinische Fakultät der Humboldt-Universität zu Berlin, Neurologisches Abteilung, Augustenburger Platz 1, 13353 Berlin; C. Kessler, Klinik und Poliklinik für Neurologie der Univ Greifswald Ellernholzstrasse 1–2, 17489 Greifswald; R. Haberk, Klinikum Grosshadern, Neurologische Abteilung, Marchioninistraße 15, 81377 Muenchen; B. Ringelstein, Klinik und Poliklinik für Neurologie der Univ Rueuester Albert-Schweitzer-Str 33, 48129 Muenster; K.M. Einhaeupel, Univ-Klinikum Charité, Med Fakultät der Humboldt-Universität, Neurologische Klinik und Poliklinik, Schumannstr 20–21, 10117 Berlin; J.-P. Malin, Universitätsklinikum Bergmannsheil, Neurologische Klinik und Poliklinik, Bürkite-de-la-Camp-Platz 1, 44789 Bochum; U. Gallenkamp, Neurologie im Kreiskrankenhaus Luedenscheid, Paulmannshoehner Str 14, 58515 Luedenscheid.

Spain
J. Alvarez Sabin, Hospital Valle Hebrón, Avda Valle Hebrón, 08035 Barcelona; J. Matías Guita, Servicio de Neurología, Hospital General de Alicante, Maestro Alonso, 109, 03010 Alicante; E. Diez-Tejedor, Ciudad Sanitaria La Paz, Hospital General, Pa de la Castellana, 261, 28046 Madrid; J. Castillo Sánchez, Departamento de Neurología, Hospital General de Galicia, Galera, s/n, 15705 Santiago de Compostela; A. Gil Peralta, Hospital Virgen del Rocio, Avda Manuel Siuret, s/n, 41013 Sevilla; F. Rubio, Hospital Principes de España (Hospital de Bellvitge), Feixa Llarga, s/n, 08907 Hospitalat de Llobregat, Barcelona.

France
J. Boullit, Centre Hospitalier Général, Service de Neurologie, Route de Paris, 01012 Bourg en Bresse; J.-M. Vallat, Hôpital Dupuytren, Service de Neurologie, 2, avenue Alexis Carrel, 87042 Limoges; M.-H. Mahagne, Hôpital Saint-Roch, Service des Urgences Médicales, 5, rue Pierre Devoluy, BP 319, 06006 Nice; J.-P. Caussanel, Centre Hospitalier Général, Service de Neurologie, Route de Tarbes, BP 382, 32008 Auch; J.-P. H. Caussanel, Service de Neurologie, Boulevard de l’Hôpital, 71018 Macon; M. Weber, Hôpital Saint-Julien, Service de Neurologie, 1 rue Foller, 54000 Nancy; P. Chouteau, Hôpital Saint-Vincent, Service de Clinique Médicale, Boulevard de Belfort, 59044 Lille; B. Mihout, Hôpital
Charles Nicolle, Service de Neurologie, 1, rue de Germon, 76031 Rouen; J.-M. Bland, Hôpital Guî de Chauliac, Service de Neurologie, 2, ave Bertin Sans, 34059 Montpellier; F.A.P. Nouallhat, Centre Hospitalier Intercommunal, Service des Urgences Médicales, 10, rue du Champ Gaillard, 78303 Poissy.

United Kingdom
K.R. Lees, Dept of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, 44 Church St, Glasgow G11 6NT; M. Ardrön, Dept of Integrated Medicine, Leicester Royal Infirmary, Leicester LE1 SW.

Italy
A. Mamoli, II Divisione Neurologica, Ospedali Riuniti di Bergamo, Largo Barozzi, 1, 24100 Bergamo; F. Sasanelli, Reparto di Neurologia Ospedale Predabissi, Via Pandina, 1, 20077 Melegnano (MI); N. Canal, Clinica Neurologica, Ospedale San Raffaele, Via Olgetta, 20, 61032 Milano; E. Botacchi, Divisione Neurologica, Ospedale Regionale Aosta, Viale Ginevra, 3, 11100 Aosta; M. Poloni, Clinica Neurologica I, Ospedale S. Paolo, Via A. Di Rudini, 8, 20114 Milano.

Netherlands
J. Boiten, AZ Maastricht, P. Debelaan 25, postbus 5800, NL-6202 Maastricht; J. Nihom, Medisch Spectrum Twente, Locatie Haaksbergenstraat, Haaksbergenstraat 55, 7513 ER Enschede.

South America
M. Fernandez Pardal, Hospital Britânico de Buenos Aires, Unidad Neurológia, Perdriel 64, Buenos Aires 1280; R.O. Dominguez, Clinica del Sol, Coronel Diaz 2211, Buenos Aires 1425; R. Menichini, Sanatorio Británico de Rosario, Unidad Neurológia, Paraguay 40, Rosario 2000; R. Manzi, Sanatorio Pasteur, Chacabuco 675, Catamarcia 4700.

Sweden
A. Waegner, Dept of Neurology, The Karolinska Hospital, 17176 Stockholm.

Israel
N. Bornstein, Tel Aviv Medical Center, Ichilov Hospital, 6 Weizman St, Tel Aviv, 64239 Israel.

United States
G. Albers, Stanford University Medical Center, 300 Pasteur Dr, H3160, Stanford, CA 94305 / Palo Alto Veterans Administration Medical Center, 3801 Miranda Ave, Palo Alto, CA 94304 / El Camino Hospital, 2500 Grant Rd, Mountain View, CA 94040 / Santa Barbara Cottage Hospital, PO Box 689, Santa Barbara, CA 93102 / Valley Care Medical Center, 111 E Stanley Blvd, Livermore, CA 94550; J. Barton, St Luke’s Medical Center, Dept of Pharmaceutical Services, 2900 W Oklahoma Ave, Milwaukee, WI 53215; B. Bogdanoff, Crozer Chester Medical Center, Suite 533, 1 Medical Center Blvd, Upland, PA 19013; J. Brillman, Allegheny General Hospital, Medical College of Pennsylvania, Allegheny Campus, 320 E N Ave, Pittsburgh, PA 15212; T. Burke, Madigan Army Medical Center, Tacoma, WA 98431-3000; W. Clark, Oregon Health Sciences University, Dept of Pharmacy, OP16A, 3181 SW Sam Jackson Park Rd, Portland, OR 97201-3098 / Portland VAMC, Pharmacy, 119P, 3710 SW Veterans’ Hospital Rd, Portland, OR 97217 / Sacred Heart General Hospital, 1255 Hilyard St, Eugene, OR 97401 / Providence Medical Center, 4805 NE Glisan, Portland, OR 97213; J. Couch, University Hospital, 800 NE 13, Room EB 400, Oklahoma City, OK 73104 / Presbyterian Hospital, 700 NE 13, Oklahoma City, OK 73104 / Veterans Hospital, 921 NE 13, Oklahoma City, OK 73104; M. Dietz, Alpine Clinical Research Center, 1000 Alpine Ave, Suite 200, Boulder, CO 80304 / Boulder Community Hospital, 1100 Balsam Ave, Boulder, CO 80304; S. Fox, Morristown Memorial Hospital, 100 Madison Ave, Morristown, NJ 07962; J. Frey, Barrow Neurological Institute, St. Joseph’s Hospital and Medical Center, 350 W Thomas Rd, Phoenix, AZ 85013-4496; R. Gotshall, Group Health Hospital, 200 15th Ave E, Seattle, WA 98112 / Eastside Hospital, 2700 152nd Ave NE, Redmond, WA 98052; R. Greenlee, Jr, Zale Lipshy University Hospital, 5151 Harry Hines Blvd, Dallas, TX 75235 / Parkland Memorial Hospital, 5201 Harry Hines Blvd, Dallas, TX 75235; J. Grotta, University of Texas Health Science Center, Dept of Neurology, MSB 7.044, 6431 Fannin, Houston, TX 77030 / Hermann Hospital, 6411 Fannin, Houston, TX 77030 / Memorial Southwest Hospital, 7737 SW Freeway, Houston, TX 77074 / Memorial Northwest Hospital, 1635 N Loop W, Houston, TX 77008; S. Hanson, Methodist Hospital, 6500 Excelsior Blvd, St Louis Park, MN 55426; E. Hooper, University of Louisville Hospital, Dept of Emergency Medicine, 530 S Jackson St, Louisville, KY 40202; J. Hromes, Kennestone Hospital, 677 Church St, Marietta, GA 30060; J. Johnson, Tulsa Regional Medical Center, 744 W 9th, Tulsa, OK 74127; R. Johnson, Neurological Associations of Washington, 1600 116th Ave NE, Suite 302, Bellevue, WA 98004 / Overlake Hospital, 1035 116th Ave NE, Bellevue, WA 98004 / T. Kent, University of Texas Medical Branch, Room 9.128 John Sealy Annex, 301 University Blvd, Galveston, TX 77555-0539 / St Mary’s Hospital, 404 St Mary’s Blvd, Galveston, TX 77555; L. Kran, Mercy Medical Center, 701 10th St SE, Cedar Rapids, IA 52403; F. LaFranchise, Memorial Medical Center Inc, 4700 Waters Ave, Savannah, GA 31404; R. Libman, Long Island Jewish Medical Center, Dept of Neurology, New Hyde Park, NY 11040; P. Lyden, UCSD Stroke Center (8466), Outpatient Center, 3rd Floor, #3, 200 W Arbor Dr, San Diego, CA 92103-8466; J. Meissner, Saint Marys Hospital, Mayo Clinic and Foundation, 1216 Second St SW, Rochester, MN 55902; A. Miller, Maimonides Medical Center, 4800 Tenth Ave, Brooklyn, NY 11219; S. Nazarian, John L. McClellan Memorial Veterans Hospital, Neurology Service 127/LR, 4300 W 7th St, Little Rock, AR 72205; C. Sadowsky, Palm Beach Neurological Group, 5205 Greenwood Ave, Suite 200, W Palm Beach, FL 33407 / St Mary’s Hospital, 901 45th St, W Palm Beach, FL 33407; J. Schauben/S. Perry, University Medical Center, University of Florida Health Science Center–Jacksonville, 655 W Eighth St, Jacksonville, FL 32209; H. Skaggs, Seton Medical Center, 1201 W 38th St, Austin, TX 78705; P. Swanson/W. Longstreth, University of Washington Medical Center, Div of Neurology, RG 27, 1950 NE Pacific, Seattle, WA 98195 / Harborview Medical Center, Div of Neurology, ZA 95, 325 Ninth Ave, Seattle, WA 98104; A. Turel, Geisinger Medical Center, 100 N Academy Ave, Danville, PA 17822-1405; C. Wohlgemuth, Lehigh Valley Hospital, Cedar Crest and 1-78, PO Box 689, Allentown, PA 18105-1556.

Acknowledgments
This study was funded by Ciba-Geigy (now Novartis Pharma AG). The Steering Committee consisted of independent academic investigators, together with a neurologist (Dr Markabi) and a scientist (Dr Karlsson) employed by Ciba-Geigy. We acknowledge the additional contributions of other Ciba-Geigy personnel, including Dr Herbert Faleck, Dr Deborah Murphy, and Dr Audrey Wong.

Academic investigators on the ASSIST Steering Committee, together with a neurologist (Dr Markabi) and a scientist (Dr Karlsson) employed by Ciba-Geigy. We acknowledge the additional contributions of other Ciba-Geigy personnel, including Dr Herbert Faleck, Dr Deborah Murphy, and Dr Audrey Wong.

The academic investigators on the ASSIST Steering Committee wish to express their appreciation of Novartis Pharma AG, sponsor of the ASSIST trials, for providing ongoing resources and a commitment to publish the negative results of the trials, despite commercial pressures elsewhere.

References
26. Grotta J. The current status of neuronal protective therapy: why have all neuronal protective drugs worked in animals but none so far in stroke patients? *Cerebrovasc Dis.* 1994;4:115–120.
Selfotel in Acute Ischemic Stroke: Possible Neurotoxic Effects of an NMDA Antagonist
Stephen M. Davis, Kennedy R. Lees, Gregory W. Albers, Hans Christoph Diener, Sabri Markabi, Goeril Karlsson and John Norris
for the ASSIST Investigators

Stroke. 2000;31:347-354
doi: 10.1161/01.STR.31.2.347

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/31/2/347

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/