Background and Purpose—The goals of the present study were to assess the efficacy and safety of nalmefene (Cervene) in patients with acute (≤6 hours) ischemic stroke and to investigate the safety of combined recombinant tissue plasminogen activator and nalmefene in a separate subset of patients. Nalmefene, an opioid antagonist with relative κ receptor selectivity, has shown neuroprotective effects in multiple experimental central nervous system injury and ischemic models. Results from an earlier phase II study in patients with acute ischemic stroke suggested that nalmefene was safe and tolerable and may be effective for patients <70 years old.

Methods—This investigation was a phase III, placebo-controlled, double-blind, randomized study of a 24-hour infusion of nalmefene. Patients with acute ischemic stroke who had an onset of symptoms within 6 hours and a baseline score of $\leq 4$ on the NIH Stroke Scale were randomized to receive either 60 mg nalmefene administered as a 10-mg bolus over 15 minutes and then a 50-mg infusion over 23.75 hours or placebo. The primary efficacy outcome was the proportion of patients achieving a score of $\geq 60$ on the Barthel Index and a rating of “moderate disability” or better on the Glasgow Outcome Scale at 12 weeks. Assessments were performed at baseline (predose), hours 12 and 24, days 2 and 7, and week 12.

Results—A total of 368 patients were randomized at 42 centers, including 32 patients treated with recombinant tissue plasminogen activator and study drug. Nalmefene was well tolerated. Overall, there was no significant difference in 3-month functional outcome for nalmefene treatment compared with placebo on any of the planned analyses. A prospective secondary analysis also failed to find a treatment effect in patients $\geq 70$ years old.

Conclusions—Although nalmefene appears to be safe and well tolerated, this study failed to find any treatment benefit in stroke patients treated within 6 hours. (Stroke. 2000;31:1234-1239.)

Key Words: narcotic antagonists ■ stroke ■ therapy
Nalmefene treatment has been shown to reduce spinal cord ischemia injury\textsuperscript{23} and has been shown to improve metabolic recovery and limit reperfusion injury after global ischemia in rats.\textsuperscript{24} In addition, nalmefene has been shown to stereospecifically inhibit glutamate release after global experimental cerebral ischemia\textsuperscript{22} and to improve the cellular bioenergetic state in traumatic brain injury.\textsuperscript{26}

Nalmefene has previously been tested in 2 randomized trials in the United States. A previous phase Ia stroke trial found that nalmefene (0.1 mg/kg) administered as a bolus infusion followed by a 24-hour infusion starting within 6 hours of symptom onset in patients with acute ischemic cerebral infarction was well tolerated and may have improved 3-month outcomes.\textsuperscript{27} A larger phase Ib dose-comparison trial found that nalmefene was well tolerated in acute stroke patients up to 60 mg. Although no overall treatment effects were seen, subgroup analysis suggested that nalmefene may be beneficial in patients <70 years old.\textsuperscript{28}

The objectives of the present phase III study were to assess the safety and efficacy of 60 mg nalmefene versus placebo in patients with acute (<6 hours) ischemic stroke.

**Subjects and Methods**

This was a randomized, double-blind, multicenter, placebo-controlled clinical trial. Patients were randomized 1:1 and treated for 24 hours with either 60 mg nalmefene or placebo within 6 hours of an ischemic stroke. Patients received a bolus dose (50 mL/10 mg) of either nalmefene or placebo (normal saline) during 15 minutes, followed by a 24-hour maintenance infusion (500 mL/50 mg). The 60-mg dose was chosen on the basis of results of the prior dose-finding study,\textsuperscript{29} in which the 60-mg dose was determined to be safe and appeared to have the greatest potential for efficacy. The objectives of this phase III trial were to assess the efficacy and safety of nalmefene in patients with acute ischemic stroke. The primary efficacy outcome variable was the percentage of patients at 3 months with a Barthel Index (BI)\textsuperscript{29} of ≥60 and a moderate disability or better score on the Glasgow Outcome Score\textsuperscript{30} (BI+GOS) in the intent-to-treat (ITT) population. The “success rate” for each group was the percentage of patients who met these criteria. These functional end points have been used in other neuroprotective efficacy stroke trials.\textsuperscript{8} Secondary planned efficacy outcome measures were the National Institutes of Health Stroke Scale (NIHSS)\textsuperscript{31} total score at 3 months; NIHSS success rate (a decrease of ≥4 points from baseline) at 3 months, and success rates for BI at 3 months, GOS at 3 months, and combined BI+GOS at 3 months by patient age (< or ≥70 years).

Sample size was determined with a pooled estimate of the primary efficacy variable from the prior studies (nalmefene 70%, placebo 55%).\textsuperscript{21,28} With these estimates in a 2-tailed test of equal proportions with a type I error rate of 5% and a power of 80%, the calculated number of patients was 165 per group.

The study was stratified according to whether patients had received recombinant tissue plasminogen activator (rtPA). When rtPA was administered, the patient must have received it within 3 hours to also be eligible for this study. For the purpose of efficacy evaluations, these patients were considered as a separate study population and were excluded from the ITT population.

All personnel at each study site and at Baker Norton who were involved in conducting and monitoring the trial were blinded to the study drug codes. Nalmefene was supplied in 5-mL vials identical in appearance to the placebo (normal saline 5-mL vials). All NIHSS examiners were certified according to NIH guidelines with use of a standard training video tape.\textsuperscript{32} The blinded members of an independent data safety monitoring board reviewed the adverse experiences in each treatment group on an ongoing basis.

All patients or their legal representatives signed an informed consent approved by the institutional review board of each study site. To be included in the study, patients had to be at least 21 years old with a diagnosis of acute ischemic stroke and an onset of symptoms within 6 hours before dosing. Stroke onset for patients who awoke with symptoms of a stroke was defined as the time when they were last known to be normal. A CT scan that excluded cerebral or subdural hematoma and subarachnoid hemorrhage was requested before randomization, and patients had to be awake or arousable to moderate stimulation.

Patients were excluded if the CT scan was inconsistent with an ischemic stroke, if they had a previous stroke with significant residual paresis on the same side as the current stroke, if they had a seizure between the onset of stroke symptoms and initial dose of study drug, or if they had concurrent life-threatening cardiac illnesses.

Patients with baseline systolic blood pressure <90 mm Hg or baseline diastolic blood pressure >120 mm Hg were excluded. Patients were also excluded if they were known to have hypersensitivity to narcotics or opiate antagonists or if they were currently taking narcotic analgesics on a daily basis. Finally, patients were also excluded if they had any unstable medical condition that the investigator thought would interfere with the conduct of the study.

Patients were monitored closely for the development of any neurological symptoms. An NIHSS and a BI were completed by certified investigators at baseline; 12, 24, 48, and 96 hours; 7 days; and 3 months after the initiation of study drug, and a GOS assessment was performed at days 1 and 7, weeks 4 and 8, and 3 months. Vital signs were obtained hourly for the first 6 hours and every 2 hours for the duration of the study infusion, and then the frequency varied depending on the standard of care for the stroke patient at each institution. General physical examinations were performed before treatment, at 24 and 48 hours, and on day 3 or the day of hospital discharge.

Trial design and data management and analysis were conducted by the sponsor, Baker Norton Pharmaceuticals. STATPROBE Inc contracted with Baker Norton to provide data management, programming, and statistical services for the study. The investigators did not participate in trial methodology planning or statistical analyses. The investigators were able to produce an independent interpretation of the results provided to them by the company in the preparation of the manuscript with the final report reviewed by the company. The primary efficacy assessment was based on an ITT population. The ITT population was defined as all randomized patients who completed the 15-minute initial bolus except those diagnosed initially with a hemorrhagic stroke and patients treated with rtPA. The number of patients responding to drug as determined with success rates was analyzed with the Mantel-Haenszel correlation statistic. The Cochran-Mantel-Haenszel procedure was used to test for a difference in response rates between the placebo group and the nalmefene group. The BI and NIHSS total scores at baseline and at follow-up evaluations were summarized with the use of descriptive statistics (mean, standard, interquartile range, and minimum-maximum). For the differences in NIHSS total scores from baseline to follow-up evaluations, the nalmefene treatment group was compared with placebo using ANOVA with treatment, center, and treatment-by-center interaction included as factors in the model. The GOS at follow-up evaluations was summarized descriptively with frequency counts and percents.

Safety analyses were carried out on all patients who received treatment. Adverse events were mapped to preferred terms and body system with a COSTART dictionary. The number and proportion of patients who reported adverse events (AEs), as well as the total number of reports of AEs, were determined by preferred term, by body system, and overall. The incidence of frequent AEs was compared between treatment groups with Fisher’s exact test. Based on the prior phase II trials, it was anticipated that nalmefene-treated patients would have a higher incidence of nausea and other digestive system symptoms.

**Results**

A total of 368 patients (186 nalmefene, 182 placebo) were randomized between May 1, 1996, and January 15, 1998, at

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The efficacy results for ITT patients are shown in Table 3. The primary outcome measure (BI ≥60 and at least moderate disability on the GOS) at 3 months did not differ for nalmefene treatment (66.9%) compared with placebo (62.3). There also was no treatment effect seen for all ITT patients on the secondary outcome variables of BI success, GOS success, NIHSS success rate, and 3-month NIHSS total score (see Table 3). In addition, no significant differences were seen in the primary outcome measure when adjustments were made for baseline NIHSS scores and time-to-treatment differences.

A prospective secondary analysis of treatment effect by age (< or ≥70 years) was performed. This planned analysis was based on a significant treatment effect seen in patients <70 years old in the prior dose-finding study. Nalmefene-treated patients <70 years old had milder baseline strokes (mean 10.7±7.1, median 7.0) compared with placebo patients (mean 12.2±6.5, median 11.0; P=0.048). The primary response (BI+GOS) rates for patients <70 years old were 81.8% for nalmefene and 73% for placebo (P=0.26). Although a similar trend in favor of nalmefene is seen on the secondary measures, no significant differences were seen.

<table>
<thead>
<tr>
<th>TABLE 1. Patient Demographics at Baseline (ITT Population)</th>
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<tbody>
<tr>
<td>Nalmefene</td>
</tr>
<tr>
<td>Male, %</td>
</tr>
<tr>
<td>Male, %</td>
</tr>
<tr>
<td>Age, y*</td>
</tr>
<tr>
<td>Time to treatment, h</td>
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<tr>
<td>Baseline NIHSS</td>
</tr>
<tr>
<td>Weight, lb</td>
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<tr>
<td>Diabetes, %</td>
</tr>
<tr>
<td>Smoking, %</td>
</tr>
<tr>
<td>Atrial fibrillation history, %</td>
</tr>
<tr>
<td>Hemiparesis (left), %</td>
</tr>
<tr>
<td>Stroke type, %</td>
</tr>
<tr>
<td>Thrombotic</td>
</tr>
<tr>
<td>Embolic</td>
</tr>
<tr>
<td>Lacunar</td>
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<tr>
<td>*Values are mean±SD.</td>
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<tr>
<td>†Significant difference from placebo.</td>
</tr>
</tbody>
</table>

45 centers. Among these, 23 nalmefene-treated patients and 15 placebo patients received rtPA and were excluded from the ITT population, leaving 163 nalmefene-treated and 167 placebo ITT patients (330 total). The percentage of patients who completed the 24-hour infusion was 95% for nalmefene and 96% for placebo (NS). The results of the patient demographics for the ITT population are shown in Table 1. There were no significant differences in patient age, stroke severity (NIHSS), history of hypertension, or presumed stroke type as assessed at hospital discharge. Stroke subtype was determined by the investigator on the basis of the TOAST classification. Final stroke subtypes were not verified by an events committee, and no confirmatory imaging studies were obtained. The time to treatment was significantly longer in the nalmefene group, whereas diabetes tended to be more common in the placebo group.

For all enrolled patients, the overall mortality rates at 3 months in the treated group was 15.6% (29 of 186) compared with 16.5% (30 of 182) in the placebo group. There were no deaths that were thought to be related to nalmefene treatment. The proportion of patients with serious AEs was comparable (nalmefene 16.5% and placebo 17.0%). There also was no treatment effect seen for all ITT patients on the secondary outcome variables of BI success, GOS success, NIHSS success rate, and 3-month NIHSS total score (see Table 3). In addition, no significant differences were seen in the primary outcome measure when adjustments were made for baseline NIHSS scores and time-to-treatment differences.

A prospective secondary analysis of treatment effect by age (< or ≥70 years) was performed. This planned analysis was based on a significant treatment effect seen in patients <70 years old in the prior dose-finding study. Nalmefene-treated patients <70 years old had milder baseline strokes (mean 10.7±7.1, median 7.0) compared with placebo patients (mean 12.2±6.5, median 11.0; P=0.048). The primary response (BI+GOS) rates for patients <70 years old were 81.8% for nalmefene and 73% for placebo (P=0.26). Although a similar trend in favor of nalmefene is seen on the secondary measures, no significant differences were seen.

<table>
<thead>
<tr>
<th>TABLE 2. Adverse Events Thought to Be Related to Study Drug</th>
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<tbody>
<tr>
<td>Body System</td>
</tr>
<tr>
<td>Preferred Term</td>
</tr>
<tr>
<td>Cardiovascular, %</td>
</tr>
<tr>
<td>Digestive, %</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Metabolic/nutritional, %</td>
</tr>
<tr>
<td>Nervous, %</td>
</tr>
<tr>
<td>Agitation</td>
</tr>
<tr>
<td>Hallucinations</td>
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<tr>
<td>Dizziness</td>
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</tbody>
</table>

There was no significant difference between drug and placebo for any event. Values are given as percentage.

<table>
<thead>
<tr>
<th>TABLE 3. Response to Treatment at Week 12 (ITT Population)</th>
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<tbody>
<tr>
<td>Outcome Variable</td>
</tr>
<tr>
<td>BI+GOS success, %†</td>
</tr>
<tr>
<td>BI success, %‡</td>
</tr>
<tr>
<td>GOS success, %§</td>
</tr>
<tr>
<td>NIHSS success (4 point ↓), %</td>
</tr>
<tr>
<td>NIHSS success (0, 1), %¶</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
</tbody>
</table>

*P value to test a difference in proportion of success between the nalmefene and placebo groups with the Cochran-Mantel-Haenszel statistic to control for investigator.
†The combined outcome is failure if 1 or both of BI+GOS are failure; otherwise, BI+GOS equals success.
‡BI success equals a score of ≥60 or a return to baseline BI if baseline value was <60.
§NIHSS success equals a decrease of ≥4 points from baseline.
¶NIHSS success equals a final NIHSS score of 0 or 1.
There also were no significant treatment effects seen in patients \( \geq 70 \) years old with the primary response (BI+GOS) rates being: 56.7% for nalmefene and 55.8% for placebos.

In an exploratory post hoc analysis, the effect of treatment by gender was evaluated. Male patients treated with nalmefene tended to have milder strokes at baseline (mean 11.7±7.3, median 9.5) than did men in the placebo group (mean 12.9±6.7, median 12.0; \( P=0.29 \)). A trend in favor of nalmefene was seen for all measures with the primary response being 69.5% for nalmefene and 61.6% for placebo. In contrast, female patients treated with nalmefene tended to have more severe strokes at baseline (mean 12.8±7.8, median 12) than did women in the placebo group (mean 11.7±6.6, median 10; \( P=0.33 \)). All measures were very similar in female patients (eg, BI+GOS 64.2% for nalmefene and 63.0% for placebo), although mortality rates tended to be higher in the nalmefene group (19.8% versus 12.3%).

There were 23 patients in the nalmefene group and 15 in the placebo group who received rtPA and therefore were a priori excluded from the ITT population. All 38 patients received rtPA within 3 hours and met all approved criteria for treatment. The nalmefene and placebo patients were well matched with baseline demographics similar to the ITT population. The primary outcome measure (BI+GOS) at 3 months were not different for rtPA/nalmefene treatment (73.9%) compared with rtPA/placebo treatment (66.7%) (\( P=0.85 \)). The secondary outcome variables were also similar (BI: rtPA/nalmefene 78.3%, rtPA/placebo 73.3%; GOS: rtPA/nalmefene 78.3%, rtPA/placebo 66.7%; NIHSS: rtPA/nalmefene 73.9%, rtPA/placebo 66.6%). However, there is a possibility of a type II error with these results given the small patient numbers and high placebo recovery rates.

Discussion
The results of the present study indicate that the competitive \( \kappa \) receptor opiate antagonist nalmefene can be administered safely to patients with acute stroke in doses up to 60 mg during 24 hours. There were no serious AEs considered to be related to treatment. There was a higher incidence of nausea in the nalmefene-treated patients, but this was easily managed with antiemetic medications and did not interfere with completion of the infusion. Patients who received nalmefene did not have an increased incidence of hallucinations or agitation.

Overall, no treatment effect was seen on functional outcome at 3 months on any of the outcome measures, with approximately two thirds of both placebo and nalmefene-treated patients having a successful recovery. There are several potential reasons for this lack of a treatment effect; the most likely is that this dose of nalmefene does not provide significant neuroprotection when administered at \( \approx 5 \) hours. A second possibility is that the trial was underpowered to detect a difference. This trial was designed to detect a 15% between group difference. It would have taken \( >600 \) patients per group to detect the 5% difference that was observed. Finally, the high recovery rate in the placebo group may have caused a type II error by producing a “ceiling effect.” Other acute stroke trials have reported similar difficulties with high spontaneous recovery rates and potential type II errors when patients with mild strokes (NIHSS score \( \geq 4 \)) were allowed to be enrolled.\(^{34-35}\) For this reason, many current stroke trials are now targeting patients with moderate to large strokes (NIHSS score \( \geq 8 \)).\(^{34}\)

No significant treatment effects were seen on any of the outcome measures in patients \(<70 \) years old. Although a trend favoring nalmefene treatment is seen on all measures, this appears to be secondary to the nalmefene patients having milder strokes at baseline. These results illustrate that potential confounding baseline differences may occur when subgroup analyses are performed in clinical trials. Therefore, the present study did not confirm the positive treatment effects for patients \(<70 \) years old seen in our dose-finding study.\(^{28}\) In that study, the pooled BI+GOS success rates in patients \(<70 \) years old were 81% for nalmefene and 65% for placebo (\( P=0.015 \)). Unfortunately, these final results were not known until enrollment in the present study was near completion. For this reason, no prespecified age criterion was used (eg, enrollment limited to patients \(<70 \) years old). Therefore, the present study was relatively underpowered to detect treatment differences in patients \(<70 \) years old. The study is also underpowered to determine whether treatment within 3 hours of stroke would be beneficial, because \( <25\% \) of the patients were enrolled before 4 hours. Further exploration in younger patients with ischemic stroke who are treated within a shorter time window is needed before a final determination of the therapeutic efficacy of nalmefene can be determined.

In comparisons of our trial results with those of other studies, it should be noted that the primary definition of a “successful recovery” in the present trial is more liberal than that used in the NINDS TPA trial (“successful recovery” defined as BI \( \geq 95 \)).\(^{36}\) This in part explains the differences in spontaneous “good outcomes” seen in the 2 trials: present study placebo group 62%, NINDS trial placebo group 38%.

Because nalmefene and NMDA receptor antagonists share a similar underlying efficacy mechanism (ie, decreasing excessive neuronal excitation), it is interesting to compare the results of the present study with the results of the trials with NMDA receptor antagonists. Although both nalmefene and NMDA receptor antagonists showed promising preclinical and early phase clinical trial efficacy,\(^{37,38}\) larger NMDA receptor antagonists trials failed to detect treatment benefits, with therapeutic doses limited by significant CNS or cardiovascular side effects.\(^{10,39}\) The present study did not show any significant CNS or cardiovascular events associated with nalmefene, and consequently the dose that was used was not limited by side effects. However, both classes of neuroprotective agents failed to show treatment benefits in patients enrolled up to 6 hours. Whether any of these agents would be beneficial if used within 3 hours of stroke has not been investigated.

In conclusion, these data show that nalmefene at a dose of 60 mg can be administered safely to patients with acute ischemic stroke with relatively few side effects. Unfortunately, no significant benefit was observed with treatment even in a subgroup of patients \(<70 \) years old. The present study does not adequately address the therapeutic potential of nalmefene in patients treated concurrently with tPA within 3 hours of symptom onset.
Acknowledgments
This work was supported by Baker Norton Pharmaceuticals, Inc. The authors wish to thank Valerie Roska for her assistance with the manuscript.

Appendix
Cervene Study Investigators
The following are the study investigators (with number of patients in parentheses), with their affiliation and location.

- Milton Alter, MD, PhD (9); NeuroTrials, Wynnewood, Pa. Carmel Aron, MD (3); Loma Linda University, Loma Linda, Calif. Richard Atkinson, MD (8); Neurological Consultants Medical Group, Sacramento, Calif. Philip Calanchini, MD (5); California Pacific Medical Center, San Francisco, Calif. J. Robert Clark, MD (6); Future Scripts, Inc, Spokane, Wash. Wayne Clark, MD (64); Oregon Stroke Center, Department of Neurology, Portland, Ore.
- Gretchen Tietjen, MD; Deaconess Health Systems, St Louis, Mo.
- Herman BH, Goldstein A. Antinociception and paralysis induced by intrathecal dynorphin A. J Pharmacol Exp Ther. 1985;232:27–32.

References
Cervene (Nalmefene) in Acute Ischemic Stroke: Final Results of a Phase III Efficacy Study
Wayne M. Clark, Eric C. Raps, David C. Tong and Roger E. Kelly
for the Cervene Stroke Study Investigators

Stroke. 2000;31:1234-1239
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