Ancrod in Acute Ischemic Stroke
Results of 500 Subjects Beginning Treatment Within 6 Hours of Stroke Onset in the Ancrod Stroke Program

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Background and Purpose—Previous studies of multiple-day dosing with the defibrinogenating agent, ancrod, in acute ischemic stroke yielded conflicting results but suggested that a brief dosing regimen might improve efficacy and safety. The Ancrod Stroke Program was designed to test this concept in subjects beginning ancrod or placebo within 6 hours of the onset of acute ischemic stroke.

Methods—Five hundred subjects with acute ischemic stroke who could begin receiving study material within 6 hours of symptom onset were infused intravenously with either ancrod (0.167 IU/kg per hour) or placebo over 2 or 3 hours. The primary efficacy outcome was a dichotomized, modified Rankin score at 90 days with less stringent cut-points for higher prestroke modified Rankin score and pretreatment NIHSS total score (“responder analysis”). Safety variables included mortality, major bleeding, and intracranial hemorrhage.

Results—Although the desired changes in fibrinogen level were seen in >90% of ancrod subjects, interim analysis for futility led to the study being halted for lack of efficacy. Positive responder status in the interim dataset was seen in 39.6% of ancrod subjects and 37.2% of placebo subjects ($P=0.47$). Ninety-day mortality did not differ between the 2 groups (ancrod, 15.6%; placebo, 14.1%; $P=0.32$), and the incidence of symptomatic intracranial hemorrhage within the first 72 hours, although not significantly different in ancrod compared to placebo subjects ($P=0.19$), was approximately twice as high (3.9% vs 2.0%; $P=0.19$).

Conclusion—These results demonstrate that intravenous ancrod starting within 6 hours after symptom onset in a broad selection of subjects with ischemic stroke did not improve their outcome and revealed a trend to increased bleeding despite successful efforts to achieve rapid initial defibrinogenation and avoid prolonged hypofibrinogenemia. (Stroke. 2009;40:00-00.)

Key Words: ancrod • anticoagulant • cerebral infarction • defibrinogenation • fibrinogen • fibrinolytic agent • recovery of function • therapeutics • treatment outcome

Elevated fibrinogen levels are a known risk factor for coronary artery disease, peripheral arterial disease, and stroke, as demonstrated in a meta-analysis of 31 studies by the Fibrinogen Studies Collaboration.1 Less well-documented is the impact of fibrinogen level on outcome from stroke. A report by Tanne et al2 of data from the NINDS study of recombinant tissue plasminogen activator in acute ischemic stroke suggested that acute stroke patients with elevated initial fibrinogen levels did less well than those with lower levels. The serine protease, ancrod, is a defibrinogenating agent derived from the venom of the Malayan pit viper, Calloselasma rhodostoma, that has been marketed in some countries for occlusive vascular disease. Ancrod-induced defibrinogenation results in anticoagulation, reduced blood viscosity, and indirect fibrinolysis,3–5 leading, in recent years, to several studies of its potential benefit for the management of acute ischemic stroke.

Sherman et al published a study6 showing a good functional outcome for ancrod based on the proportion of subjects at 90 days who were alive and had Barthel Index total scores of 95 to 100 or at least as high as the prestroke score (for subjects with prestroke disability), covariate-adjusted for age and pretreatment Scandinavian Stroke Scale score. When started within 3 hours of stroke onset and continued for 5
days, 42.2% of ancrod subjects achieved a good functional outcome vs 34.4% of placebo subjects (P=0.04; effect size, 7.8%). In that trial the incidence of symptomatic intracranial hemorrhage (sICH) in the active group was only 2.5-times that of placebo (5.2% vs 2%; P=0.06). This was followed by a trial of ancrod started within 6 hours of stroke onset that failed to show benefit (good functional outcome of 42% in both groups).² Although failure was attributed to the longer time window, a larger per-patient dose of ancrod and liberal entry criteria for blood pressure probably contributed as well.³ Supporting the report by Tanne et al,² our recently published observation from these ancrod trials suggests that higher fibrinogen levels measured in placebo patients within 6 hours of stroke onset were associated with poor functional outcome.⁹

Post hoc analyses of these 2 ancrod trials as well as an earlier but smaller trial with a 6-hour window¹⁰ suggested that a modified dosing regimen designed to achieve rapid initial defibrinogenation should enhance efficacy and that avoidance of prolonged hypofibrinogenemia may reduce the incidence of hemorrhage.¹¹ This new dosing regimen led to the re-evaluation of ancrod for the treatment of acute ischemic stroke: the Ancrod Stroke Program (ASP), which was designed to test the hypothesis that this modified ancrod administration would achieve both efficacy (functional improvement) and safety in the setting of acute ischemic stroke. ASP began as 2 parallel randomized, double-blind trials, each planned for 650 subjects to begin within 6 hours of stroke onset a 2- or 3-hour infusion of the study material, based on pretreatment fibrinogen levels.

The 2 phase 3 studies had identical inclusion and exclusion criteria. Therefore, an interim analysis of futility was planned when the first 500 treated subjects across the 2 studies completed the 90-day follow-up. On reviewing that analysis, the Data Safety Monitoring Board recommended that the studies be halted for futility. Data from this interim population are the basis for this report.

### Subjects and Methods

ASP subjects were initially enrolled into 2 parallel double-blind, randomized, placebo-controlled studies: NTI-ASP-0502 (ASP-I) began in September 2004, and NTI-ASP-0503 (ASP-II) began in January 2005. Both studies were international and included sites in the US, Canada, Austria, the Czech Republic, Poland, Slovakia, Russia, Israel, South Africa, Taiwan, Australia, and New Zealand. Both studies were approved by all appropriate national authorities and ethics committees; written informed consent was obtained either from the subject or from representatives per local rules.

Entry criteria for ASP-I and ASP-II were identical (Table 1). Noncomatose subjects were eligible if they were at least 18 years of age (no upper limit) with a clinical diagnosis of ischemic stroke, were able to begin study treatment within 6 hours of symptom onset, had an initial NIHSS score of 5 to 25 (later changed to any score ≥5 with no upper limit), did not have hypertension even after antihypertensive medications (blood pressure ≤185/105 mm Hg), and did not have intracranial extravascular blood on pretreatment head neuroimaging (CT or MRI). Use of heparin, warfarin, and recombinant tissue plasminogen activator excluded subjects from enrollment, but aspirin and other antiplatelet agents were permitted. Ancrod was purified from the venom of the Malayan pit viper (Calloselasma rhodostoma). Identical-appearing clear vials of the study material containing either ancrod (70 WHO IU/mL) or placebo in 10 mmol/L sodium phosphate and 0.9% sodium chloride, pH 6.8, were packaged by an independent manufacturer and provided with unique vial numbers. A randomization scheme was prepared by an independent statistician contracted by the sponsor. The randomization was designed to stratify equal numbers of ancrod and placebo subjects to the 2 treatment groups by geographical region and pretreatment stroke severity (NIHSS 5–15 and ≥16). An age-based adaptive randomization process using a biased coin approach was also integrated to promote balanced enrollment by age (65 years or younger, 66–75, 76 years or older).¹² Vial assignment was performed in real time using an interactive voice response system.

Each vial was to be diluted into 250 mL saline and administered at the same infusion rate (0.6 mL/kg per hour) for 3 hours (infusing 0.5 IU/kg ancrod) for pretreatment fibrinogen levels ≥200 mg/dL or 2 hours (infusing 0.33 IU/kg ancrod) for pretreatment fibrinogen levels of 100 to 199 mg/dL; subjects with pretreatment fibrinogen levels <100 mg/dL were excluded. Blood samples were collected at prespecified time intervals for fibrinogen determination and sent to a central laboratory to assure constancy in the methodology for the fibrinogen assay.

Efficacy end points were based on the modified Rankin scale (mRS) and Barthel Index obtained at 10 and 90 days and the NIHSS obtained at prespecified time points over the first 72 hours and at 90 days. The primary efficacy outcome measure was a responder analysis of the mRS at 90 days, similar to that published by Adams et al.¹³ Responders were defined as follows: (1) subjects with a prestroke mRS of 0 to 1 and pretreatment NIHSS score of 5 to 15 who achieved a 90-day mRS of 0 to 1; (2) subjects with a prestroke mRS of 0 to 1 and pretreatment NIHSS scores ≥16 who achieved a 90-day mRS of 0 to 2; and (3) subjects with a prestroke mRS≥2 and any pretreatment NIHSS score who at 90 days returned to their prestroke mRS or better.

The utility of this responder definition was tested before the ASP trial was broken and found to be robust using data from the Nimodipine for Ischemic Stroke Trial (NINDS) recombinant tissue plasminogen activator study.¹⁴ Secondary efficacy outcomes were assessed hierarchically, with neurological recovery (improvement of NIHSS at 90 days by ≥11 points or a reduction of the NIHSS to 0–1) followed by the Barthel Index total score. Safety end points included mortality, intracranial hemorrhage, major bleeding, and review of other physical and laboratory measurements.

### Table 1. Major Entry Criteria

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<th>Inclusion criteria</th>
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<td>Age ≥18 years</td>
<td>Signs and symptoms of acute ischemic deficit (any distribution)</td>
<td>Able to begin study material treatment within 6 hours of symptom onset</td>
<td>Pretreatment NIHSS ≥ 5</td>
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<td>Pretreatment mRS 0–1*</td>
<td>Written consent signed by the subject or his/her representative</td>
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### Exclusion criteria

- Neuroimaging evidence of intracranial, extracranial blood
- Coma (pretreatment NIHSS 1a ≈2)
- Improvement prior to study material administration to NIHSS <5
- Use or intended use of thrombolytic agent
- Previous stroke within prior 6 weeks
- Last pretreatment blood pressure >185/105
- Pretreatment fibrinogen <100 mg/dL
- Intrinsic or extrinsic coagulation disorders
- Medical condition likely to interfere with survival or evaluation through 90 days after stroke
- Previous exposure to ancrod or pit viper snake bites

*ASP-I initially permitted enrollment of subjects with prestroke mRS≥2.
For efficacy, the full analysis data set (FADS) population was used. The full analysis data set was defined as randomized subjects infused with any study material who had at least one measurement of efficacy for a given end point. Subjects in the full analysis data set population were grouped according to the study material assignment. The safety population was defined as all randomized subjects infused with any study material grouped according to the study material actually received (Figure 1).

A serious adverse event (SAE) of sICH was defined in ASP as evidence of extravascular blood on head neuroimaging temporally related to neurological worsening that, in turn, was judged by the investigator to be causally related to the hemorrhage. Asymptomatic intracranial hemorrhage was defined as evidence of extravascular blood on neuroimaging that was not associated with neurological worsening as judged by the investigator. Additional analyses utilized ECASS II criteria15 (including adjudication) and neuroradiological criteria differentiating 4 grades of intracranial hemorrhage as defined for ECASS.16 The primary analysis of intracranial hemorrhage incidence was performed on intracranial hemorrhages occurring within the first 72 hours after beginning the infusion. Major hemorrhagic events were defined as bleeding adverse events that met criteria for an SAE, transfusions for excessive bleeding, and sICH (ASP criteria).

The sample size in each study of 650 was predicated on a 2-tail alpha level of 0.05, power of at least 90%, a placebo response rate of 32%, and an ancrod response rate of 45%, yielding a treatment effect of 13%. The primary end point was to have been analyzed using logistic regression, corrected for age, pretreatment stroke severity, geographic region, and pretreatment fibrinogen level. A 2-sided alpha level of 0.05 was set for the significance of differences in efficacy end points.

An interim analysis of safety and key efficacy data were planned after a combined total of 500 treated full analysis data set subjects across both studies had either completed the day 90 evaluation or died. East software17 was used to conduct the interim analysis of the primary efficacy end point. The stopping boundary for futility used the O’Brien-Fleming boundary shape.18 The test of futility compared the primary end point across treatment groups at a 0.2266 signifi-
cance level; assuming the placebo group had a functional success rate of 32%, this would have corresponded to an approximate ancrod functional success rate of \( \leq 36.9\% \), an absolute difference of \( \leq 4.9\% \) between the rates for the 2 groups. Efficacy and safety end points were analyzed using a logistic regression model including terms for treatment group, study center, treatment-by-center interaction, and as continuous variables, age (years), pretreatment NIHSS score, and pretreatment fibrinogen level (mg/dL, centrally determined); individual adverse events and SAEs were analyzed using the Fisher exact test.

The studies were designed and funded by the sponsor, Neurobiological Technologies, Inc, and the analyses were conducted by a contractor to the sponsor with input from all of the authors. The study designs were provided before first subject enrollment at www.clinicaltrials.gov (NCT00141011 and NCT 00300196).

Results

By August 17, 2008, 500 subjects had been randomized and treated with study material (Figure 1). These were drawn from 508 subjects, 277 in ASP-I and 231 in ASP-II, who were randomized; 8 patients were randomized but not treated. Among the most common reasons for excluding screened patients presenting within 6 hours of onset were inability to begin study material within the 6-hour time window, mild deficits, rapidly improving deficits, and extravascular blood on the pretreatment head CT scan.

Because there were no meaningful differences between ASP-I and ASP-II and the plan had been to combine the 2 studies for analysis, the following is based on the combined analysis of the interim 500-subject population. The ancrod and placebo groups were similar at baseline (Table 2) with respect to age, gender, pretreatment NIHSS total score, time-to-treat, blood pressure, and history of diabetes mellitus, and tobacco use. The mean dose of study material (IU/kg for ancrod) received in each group was identical and very close to the intended dose of 0.5 IU/kg over 3 hours or 0.33 IU/kg over 2 hours.

There was no difference between ancrod and placebo in the primary efficacy end point at 90 days; similar proportions of subjects achieved responder status in each group (ancrod 39.6% vs placebo 37.2%; \( P = 0.47 \); Table 3). No trends suggested benefit in subgroups based on age or pretreatment NIHSS. The proportion of subjects who achieved the first secondary end point based on improvement in the NIHSS was also similar in each group (ancrod 37.3% vs placebo 38.9%). The NIHSS total score for ancrod subjects did not improve more than for placebo between baseline and 24 hours (difference in mean scores: ancrod 1.4 vs placebo 2.1).

Mortality at 90 days was not different between the groups (ancrod 15.6% vs placebo 14.1%; \( P = 0.32 \); Table 3). Stroke was the most common cause of death, accounting for 38% of deaths in each treatment group. The time to death was similar between groups (data not shown; \( P = 0.71 \)).

Using the ASP criteria, sICH occurred within the first 72 hours in 10 ancrod subjects (3.9%) compared with 5 placebo subjects (2.0%; \( P = 0.19 \); Table 3). sICH in the ancrod subjects developed early, with 6 of the 10 hemorrhages occurring within the first 24 hours, 7 within 48 hours, and the remaining 3 between 48 and 72 hours. In contrast, only 2 of the 5 sICH in placebo subjects occurred within the first 48 hours. Asymptomatic hemorrhages within the first 72 hours were similar in the 2 groups (ancrod 6.7% vs placebo 6.5%; \( P = 0.85 \)). Adjudication of sICH was performed by a subcommittee of the Steering Committee based on ECASS II criteria,12 resulting in fewer subjects in each group with an sICH, but the difference between the 2 groups was more marked and was statistically significant (ancrod 3.5% vs placebo 0.4%; \( P = 0.021 \)). Using neuroradiological criteria from ECASS,13 there was very little difference between the 2 treatment groups among the 4 grades of intracranial hemorrhage. Within the first 10 days, there was an increased incidence of major hemorrhagic events in the ancrod subjects (6.3% vs 2.9%; \( P = 0.054 \)); the difference for major hemorrhage within the first 72 hours was more marked and was statistically significant (5.5% vs 1.6%; \( P = 0.028 \)).

There was a trend for more frequent adverse events in the placebo group (93.5%) than in the ancrod group (89.0%;
Adverse events leading to subject withdrawal were uncommon, occurring in only 3 placebo-treated subjects and 1 ancrod-treated subject. Table 4 displays the 10 most common adverse events. Although not reflected in Table 4, there was a statistically significant increase in the incidence of infections in the ancrod subjects (38.8% ancrod vs 29.0% placebo; \( P = 0.023 \)). This increase was the result primarily of an increased incidence of pneumonia (9.0% vs 6.5%; \( P = 0.069 \)), upper respiratory tract infections (2.7% vs 0.4%; \( P = 0.069 \)), and bronchitis (2.4% vs none; \( P = 0.031 \)). More ancrod subjects had adverse event terms reflecting renal failure (renal failure, acute renal failure, and renal impairment) than placebo (2.7% vs 0.4%; \( P = 0.034 \)), and hematuria was more common in ancrod than placebo subjects (7.8% vs 4.9%; \( P = 0.20 \)).

There was a trend for more frequent SAEs in the ancrod-treated subjects (38.0%) than in placebo-treated subjects (33.1%; \( P = 0.26 \); Table 3). SAEs that occurred in at least 1% of the safety population are also shown in Table 4. Stroke-in-evolution as an SAE occurred with approximately equal
frequency in ancrod and placebo subjects (4.7% vs 3.7%; \(P=0.66\)), similar to SAEs of hemorrhagic transformation of the index stroke (1.6% vs 0.4%; \(P=0.37\)). The increased incidence in infections noted as adverse events is also reflected as an SAE, with >2-fold but insignificant increase in pneumonia for the ancrod subjects (5.1% vs 2.0%; \(P=0.092\)).

There was a trend for central nervous system SAEs being slightly increased in the ancrod-treated subjects (15.7% vs 13.9%; \(P=0.62\)), resulting primarily from nonsignificant increased incidences of cerebral hemorrhage, stroke-in-evolution, and hemorrhagic transformation of the index stroke. Table 4 lists the central nervous system-related SAEs that occurred in \(\geq 3\) subjects in either treatment group.

The dosing regimen used in these studies was designed to achieve rapid initial defibrinogenation (0 to 3-hour defibrinogenation rate \(\geq 30\) mg/dL per hour) and avoid prolonged hypofibrinogenemia (9 to 72-hour time-weighted fibrinogen level \(>70\) mg/dL); Figure 2 shows that this was generally achieved. Subjects who received ancrod were categorized in terms of success at meeting these criteria and whether success was related to key efficacy and safety outcomes. Calculated defibrinogenation rates were available in 194 ancrod subjects; most (177; 91.2%) achieved the desired rate of initial defibrinogenation, \(>30\) mg/dL per hour, and 71 of those achieved the primary efficacy end point (40.1%). The response rate in those with lower defibrinogenation rates was 10 of 17 (58.8%). Calculated mean 9 to 72-hour fibrinogen levels were available in 240 ancrod subjects; nearly all (235, 97.9%) had levels greater than the target floor of 70 mg/dL, and 9 of those experienced sICH (3.8%). None of the 5 subjects with lower mean fibrinogen levels had sICH.

**Discussion**

Ancrod is a serine protease that has been shown to rapidly decrease serum fibrinogen levels in healthy volunteers and stroke patients. A previous study of intravenous ancrod for acute treatment of ischemic stroke suggested that, when started within 3 hours of stroke onset, ancrod improved outcome.\(^6\) In an early study of 132 subjects starting treatment within 6 hours of stroke onset, there was evidence of efficacy when the data were analyzed using a patient-weighted analysis.\(^10\) The larger ESTAT study using a 6-hour window, however, failed to confirm this finding, and there was a significant increase in mortality and sICH with ancrod in ESTAT.\(^7\)

The ASP studies were designed based on a retrospective review of these studies.\(^11\) The highest initial infusion rate used in the previous studies, 0.5 IU/kg administered over a short duration (3 hours), was chosen to rapidly reduce fibrinogen and prevent long periods of low fibrinogen levels. Initially rapid defibrinogenation was achieved in \(>91\)% of ancrod subjects, and avoidance of prolonged hypofibrinogenemia was achieved in \(>97\)% of ancrod subjects for whom data were available.

The interim study population was well-balanced for the key prognostic factors for stroke outcome (eg, age and pretreatment stroke severity). Ancrod did not improve outcome and was associated with a nonsignificant increase in sICH and major bleeding events and a significantly increased incidence of infection. The lack of efficacy in this population may be the result of the time to treat, which on average was \(>5\) hours. Ancrod may still possess efficacy when administered within 3 hours as demonstrated in the STAT study.\(^6\)

The dosing period of 3 hours in this program differs from that used in previous studies of ancrod in acute ischemic stroke,\(^6,7,10\) when dosing continued over several days. An early treatment effect in the present study therefore might have been diluted by the lack of continued treatment. Inconsistent with this hypothesis, however, is the observation that unlike STAT, when neurological scores improved in the first 24 hours, more in ancrod than placebo subjects, no such early treatment effect was seen in the interim ASP database.

Although sICH was relatively uncommon in this study, the incidence of sICH using ASP criteria in the ancrod subjects was twice that seen with placebo (a difference that failed to reach statistical significance). The overall incidence of sICH was even lower when characterized with ECASS II criteria,\(^15\) but the difference between ancrod and placebo was more marked and was statistically significant. There was virtually no ancrod–placebo difference, however, using ECASS neuroradiological criteria.\(^16\) These discrepancies highlight the sensitivity of sICH reporting to the definitions used. Nonetheless, the fact that sICH by ASP and ECASS II criteria increased at all and that major bleeding increased significantly was unexpected because the analysis of previous data suggested that the risk of hemorrhage with ancrod was related to prolonged low fibrinogen levels, and these did not occur in this study. An association of efficacy to initial defibrinogenation rates and sICH to maintenance fibrinogen levels in the ancrod subjects could not be determined in this study because so few ancrod subjects failed to achieve the desired targets. There are 2 unexpected safety findings: the increased incidence of infections and the increased incidence of renal failure. There was a significant increase in the incidence of all infections attributable in large measure to the increases in pulmonary and upper respiratory tract infections. Ancrod is
not known to induce immunodeficiency or inhibit white blood cell production or function; thus, the mechanism leading to this finding is unclear. There was also a significant increase in adverse events related to renal failure in the ancrod subjects. Although ancrod is excreted in the kidneys, these observations have not been previously reported. Both ancrod subjects with SAEs of renal failure had progressive stroke and multisystem organ failure; both died, but renal failure was not the primary cause of death in either of the subjects. Whether the observations of increased incidence of renal failure and infections are chance occurrences or true safety signals is unclear. Nevertheless, based on the data from this cohort of patients, any future investigations with ancrod should include close surveillance for infections and renal impairment as well as bleeding.

Two of the previous stroke studies with ancrod showed a benefit from ancrod, whereas 1 did not. The briefer but more intense dosing used in ASP was expected to improve both efficacy and safety, but that was not the case. Reasons for failure to show efficacy in ASP are most easily attributed to the delay in treatment, the same rationale used to explain the negative ESTAT results. Other factors, however, may have contributed to the failure of ESTAT, including inclusion of subjects with blood pressures up to 220/120 mm Hg and a greater overall dose than that used in STAT, but these factors were controlled in ASP. Moreover, the time-to-treat in one of the earlier studies was virtually identical to that in ASP. Unlike most acute stroke trials, ASP enrolled subjects with very severe strokes (pretreatment NIHSS >25), no upper age limit, and initially severe prestroke disability (mRS >2), and this may have reduced the likelihood of a positive trial even though the primary efficacy end point and analysis accounted for these variables. Although patient selection might explain the results in ASP, the brain’s intolerance of long periods of ischemia (mean time-to-treat of 5 hours) may simply have exceeded any mild benefit from ancrod, and the positive result in the 1994 study of ancrod started within 6 hours of onset with patient-weighted analysis might thus have been related to patient selection in that smaller study. The positive results of ECASS III, in which treatment began between 3 and 4.5 hours after stroke onset, suggest that intravenous recombinant tissue plasminogen activator benefits selected stroke patients who can begin treatment within 4.5 hours of symptom onset, but extending the time interval for reperfusion treatment to 5 or 6 hours may simply not be feasible.

Defibrinogenation with enzymes like ancrod still holds promise for a variety of thrombotic conditions, but a beneficial effect in stroke patients has been convincingly demonstrated only in patients beginning multi-day treatment within 3 hours of stroke onset and not with mean treatment intervals of 5 hours as in ASP.

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Disclosures

Drs Levy, Wasienski, and Spatarea were employees of the sponsor, NTI. Dr Levy and Wasienski own stock in NTI. Dr del Zoppo received honoraria from NTI. Professor Kaste received travel expenses and honoraria from Boehringer Ingelheim, Paion AG, Forest Laboratories, and Lundbeck for serving as a member of Steering Committees of ECASS, ECASS II, ECASS III, DIAS, DIAS 2, and DIAS 4, and as a speaker and as a consultant. Dr Diener received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from: Abbott, AstraZeneca, Bayer Vital, BMS, Boehringer Ingelheim, Coaxia, D-Pharm, Fresenius, GlaxoSmithKline, Janssen Cilag, MSD, MindFrame, NTI, Novartis, Novo-Nordisk, Paion AG, Parke-Davis, Pfizer, Sanofi-Aventis, Sankyo, Servier, Solvay, Thrombogenics, Wyeth, and Yamaguchi. H.C. Diener has no ownership interest and does not own stock in any pharmaceutical company. Professor Ringelstein has received travel expenses and honoraria from Boehringer Ingelheim, Syngis, NTI, Novartis, Novo-Nordisk, Sanofi-Aventis, Solvay, Bayer Vital, M’s Science, Sevier, UCB, and Trommsdorff for serving
as a member of Steering Committees, Safety Committees in clinical trials, and as a speaker and consultant. Professor Ringelstein has no ownership interest and does not own stocks of any pharmaceutical company.

References


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Stroke. published online October 29, 2009;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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/early/2009/10/29/STROKEAHA.109.565119.citation

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