"A randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, tolerability, and pharmacokinetic/pharmacodynamic effects of a targeted exposure of intravenous repinotan in patients with acute ischemic stroke"

Teal, Philip ; Davis, Stephen ; Hacke, Werner ; Kaste, Markku ; Lyden, Patrick D ; Fierus, Monika ; Peeters, André

ABSTRACT

mRECT demonstrated the feasibility of conducting a rigorous trial using a short therapeutic window demanding clinical and radiographic criteria to optimize patient selection and a Point-of-Care test to achieve a targeted exposure to repinotan. The study failed to demonstrate a clinical benefit of repinotan. The development of repinotan in acute ischemic stroke was discontinued.

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Philip Teal, Stephen Davis, Werner Hacke, Markku Kaste, Patrick D. Lyden, for the mRECT Study Investigators, Monika Fierus and for Bayer HealthCare AG

Stroke 2009;40;3518-3525; originally published online Sep 10, 2009;
DOI: 10.1161/STROKEAHA.109.551382

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A Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetic/Pharmacodynamic Effects of a Targeted Exposure of Intravenous Repinotan in Patients With Acute Ischemic Stroke

Modified Randomized Exposure Controlled Trial (mRECT)

Philip Teal, MD; Stephen Davis, MD; Werner Hacke, MD; Markku Kaste, MD; Patrick D. Lyden, MD, for the mRECT Study Investigators; Monika Fierus, MD, for Bayer HealthCare AG

Background and Purpose—Repinotan hydrochloride is a serotonin (5-HT)\textsubscript{1A} receptor full agonist with evidence of neuroprotection in animal models of permanent and transient focal ischemia. The purpose of this Phase IIb study was to investigate the efficacy, safety, and tolerability of a targeted exposure to repinotan in patients with acute ischemic stroke.

Methods—This was a double-blind, placebo-controlled, parallel-group, multicenter study of 681 patients stratified according to whether or not tissue plasminogen activator was administered and then randomly assigned to treatment with repinotan or placebo. A continuous 72-hour intravenous infusion of repinotan or placebo was to be started within 4.5 hours from the onset of ischemic symptoms. A Point-of-Care test was used to adjust the infusion rate if appropriate. The goal of Modified Randomized Exposure Controlled Trial (mRECT) was to show whether repinotan is statistically superior to placebo (\alpha\leq0.10) as measured by the response rate on the primary efficacy variable, Barthel Index (\geq85) at 3 months, using a Cochran-Mantel-Haenszel test.

Results—For the intention-to-treat population at 3 months, the response rate on the Barthel Index was 37.1\% (127 of 342) for patients on repinotan and 42.4\% (143 of 337) for patients taking the placebo (Cochran-Mantel-Haenszel probability value \textasciitilde0.149). No apparent safety concerns were identified.

Conclusions—mRECT demonstrated the feasibility of conducting a rigorous trial using a short therapeutic window demanding clinical and radiographic criteria to optimize patient selection and a Point-of-Care test to achieve a targeted exposure to repinotan. The study failed to demonstrate a clinical benefit of repinotan. The development of repinotan in acute ischemic stroke was discontinued. (Stroke. 2009;40:3518-3525.)

Key Words: acute stroke ■ neuroprotective agents ■ repinotan ■ stroke recovery ■ thrombolysis

Repinotan HCl is a selective, high-affinity, full serotonin receptor agonist at the 5HT\textsubscript{1A} receptor subtype. The neuroprotective efficacy of repinotan was established in preclinical studies using animal models (gerbil, mouse, and rat) of both permanent and transient ischemia.\textsuperscript{1} Results of Phase I clinical trials revealed prolonged elimination, increased maximum concentrations, and increased area under the plasma concentration versus time curve of repinotan in poor metabolizers for the sparteine–debrisoquine oxidation pathway.\textsuperscript{2,3} This finding suggests that repinotan biotransformation is mediated by cytochrome P450 2D6, which is poorly expressed or dysfunctional in approximately 10\% of the white and up to 2\% of the Asian and black populations. The highly variable pharmacokinetics of repinotan were confirmed in early Phase II studies in patients with stroke.\textsuperscript{4}

The tolerability, safety, and dose of repinotan were investigated in a Phase II double-blind, placebo-controlled study in which 240 subjects with acute hemispheric ischemia and a National Institutes of Health Stroke Scale (NIHSS) score of 4 to 25 were randomized to placebo or repinotan at 0.5, 1.25, or

Received March 3, 2009; accepted March 9, 2009.
From the University of British Columbia (P.T.), Vancouver, British Columbia, Canada; University of Melbourne (S.D.), Melbourne, Australia; the University of Heidelberg (W.H.), Heidelberg, Germany; the University of Helsinki (M.K.), Helsinki, Finland; the Veterans Administration Medical Center and University of California School of Medicine (P.D.L.), San Diego, Calif; and Bayer HealthCare AG (M.F.), Leverkusen, Germany.
Correspondence to Markku Kaste, MD, Professor and Chairman of Neurology, Emer, Head of Clinical Stroke Research, Department of Neurology, Helsinki University Central Hospital, University of Helsinki, PO Box 340, Huartmaninkatu 4, 00029 HUS Helsinki, Finland. E-mail markku.kaste@hus.fi
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Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.109.551382

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2.5 mg/day given by continuous intravenous infusion for 72 hours. Treatment was started within 6 hours of symptom onset. Evaluations were performed at 4 weeks and 3 months. Both the 0.5-mg/day and 1.25-mg/day doses were safe and well tolerated in this study with few subjects requiring discontinuation due to adverse events. Mortality over 3 months poststroke appeared to be more favorable for subjects receiving repinotan as compared with placebo. A higher incidence of serotonergic side effects was seen in the 2.5-mg/day dosage group. Due to the metabolic characteristics of repinotan, a substantial proportion of subjects with higher plasma levels of repinotan (“poor metabolizers” with regard to cytochrome P450 2D6) than in the remaining population was expected in this study. A repinotan-specific enzyme-linked immunosorbent assay was used to identify the subjects with plasma levels beyond a, conservatively defined, threshold, and these subjects were taken off medication. Therefore, the interpretation of the 2.5-mg/day dose appeared to be limited. Because the evaluation of outcome results indicated the best functional improvement in subjects receiving the 1.25-mg/day dose, further exploration of this dose in sufficiently sized efficacy studies was considered necessary. Furthermore, it was concluded that dose is a poor surrogate for exposure to repinotan. A population pharmacokinetic/pharmacodynamic model, based on preliminary efficacy from the Phase II study, as well as on pharmacodynamic assessments in healthy individuals and animal pharmacological studies suggested that the optimal repinotan exposure might be in the range of 5 to 20 μg/L.

To optimize repinotan exposure of patients with stroke, a Randomized Exposure Controlled Trial (RECT) design for a Phase III study of repinotan was developed. In this design, a Point-of-Care (POC) test was used, which indicated whether repinotan plasma concentrations had reached or exceeded a predefined threshold value, thus allowing for a reduction of the infusion rate to achieve the targeted repinotan plasma concentrations. While the RECT study was already recruiting, the data for repinotan were extensively re-evaluated, resulting in modifications to the study design. The changes were implemented after the randomization of 98 patients into RECT and included (1) reduction of the allowed treatment time window from 6 to 4.5 hours to increase the potential for neuroprotective effect; (2) a loading dose to reach target plasma concentrations sooner; and (3) patient assignment in a 1:1 ratio to treatment with repinotan or placebo (changed from 2:1 in RECT). The redesigned study was not powered to determine conclusive efficacy. From then on, it was referred to as Phase IIb modified RECT (mRECT) with the objective of proof of principle.

Materials and Methods

Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational study involving patients with acute ischemic stroke. Patients were enrolled on the basis of a 4.5-hour time window between the onset of stroke symptoms and initiation of study drug therapy. Intravenous tissue plasminogen activator (tPA) was permitted as standard medication. Patients were stratified according to whether or not tPA was administered and then randomly assigned in a blinded fashion to treatment with repinotan or placebo in a 1:1 ratio. A loading dose was used to achieve target drug levels more rapidly. The study involved sites in Europe, Israel, North America, and Australia.

Ethics and Data Quality Assurance

The protocol and protocol amendments for this study were prepared in accordance with Declaration of Helsinki regulations. Before implementation, the study protocol and protocol amendments were approved by each Independent Ethics Committee or Institutional Review Board. The study was conducted in accordance with Good Clinical Practice and all applicable regulatory regulations. Before any study procedure was performed and before a patient was enrolled in the study, the investigational nature and purpose of the study were explained to the patient or legal representative sufficiently detailed to make an informed decision about participating in the study. Before enrolling subjects into this study, investigators’ meetings were held in Australia, Canada, Europe, Israel, and the United States to review the protocol, the electronic case report form (CRF), procedures for obtaining informed consent and for reporting adverse events as well as training on the scales to be administered in the study. Certification records for all study staff administering the NIHSS were maintained, and the person conducting the NIHSS had to be recertified annually. The study was monitored at regular intervals to ensure compliance with the protocol, to review source documents, and to assess drug accountability.

Study Population

Considered for inclusion were men and women ≥18 years of age who had experienced an acute ischemic stroke of hemispheric localization (excluding brainstem and cerebellum) of suspected thromboembolic origin and who were admitted to the hospital sufficiently early to initiate study drug treatment within 4.5 hours from the onset of the ischemic symptoms. Eligible patients were to have a NIHSS total score of 8 to 23 with a motor deficit ≥2 (for either one arm or leg) and level of consciousness ≤2 and at least one of the following: visual field deficit, neglect, or aphasia. If a patient had received tPA, the NIHSS must have been performed before the receipt of study drug but after infusion of tPA was initiated with no requirement to wait for and assess a potential rapid response to tPA. Time from arrival at the hospital emergency room to time of initiation of study drug therapy should not have exceeded 90 minutes for patients who were not receiving tPA. Patients who were receiving tPA should have had the study drug administered within 1 hour of the tPA initiation. Study drug treatment could have been started while the tPA was still infusing provided it was administered through a separate line. For patients who received tPA at another hospital and then were transferred to a hospital participating in this trial, the study drug must have been started within 4.5 hours after the onset of stroke symptoms (for the first 98 patients within 6 hours) and within 1 hour after arrival at the study hospital. Patients with infarction of more than one third of the middle cerebral artery territory or evidence of significant mass effect with shift of midline or major areas of sulcal effacement associated with loss of cortical definition (gray–white distinction), primary intracerebral hemorrhage, or lacunar infarct were excluded as were patients with clinical evidence of acute stroke due to lacunar infarct (pure motor hemiplegia, pure sensory deficit, ataxia/clumsy hand syndromes). Further exclusion criteria included clinically relevant pre-existing neurological deficit; generalized seizures having developed since the onset of stroke symptoms; systolic blood pressure >210 or <110 mm Hg; diastolic blood pressure >110 or <60 mm Hg; myocardial infarction within 3 months; unstable angina within 3 to 5 days before starting the infusion; unstable arrhythmia; severe conduction defect; bradycardia; uncompensated heart failure; history of myocarditis, cardiomyopathy, or aortic stenosis; prolonged QT interval; and the use of Class IA or Class III antiarrhythmic drugs. The cardiac exclusion criteria were taken as a cautionary measure after preclinical data were inconclusive in eliminating the possibility that repinotan has an effect on...
QTc interval prolongation. A re-evaluation of these data together with an analysis of the Phase I and earlier Phase II electrophysiologic (automated interval calculations) data with expert opinion suggested that these restrictions were appropriate in the absence of a definite study drug effect on QTc.

Study Treatments

An Interactive Voice Response System was used to coordinate the dispensing of study drug with the POC kit. Patients randomized to treatment received a continuous 72-hour intravenous infusion of repinotan or placebo at a rate of 40 mL/hr (loading dosage of repinotan 0.1 mg/hr) during the first 2 hours (0 to 2 hours) to achieve target drug levels more rapidly. The infusion rate was then decreased to 20 mL/hr (basic dosage of repinotan 0.05 mg/hr) for all patients over the next 4 hours (2 to 6 hours). The random code appeared on the concealed portion of the study medication label or on a blinded code break card. If unblinding occurred for any patient, study drug treatment was to be discontinued for that patient, the sponsor was to be notified immediately, and a written explanation provided. A POC test was used twice on each patient, at 6 and 12 hours poststart of infusion. The test result was to be read at 8 and 10 minutes after addition of the blood sample to the test device. This test, a competitive immunoassay, was used to obtain a visual, qualitative result of circulating levels of repinotan and was intended for professional and investigative use only. Depending on the test readout, dosage adjustments were made by reducing the infusion rate to achieve the target concentration range in the majority of patients. To maintain blinding, “placebo” devices were used to provide false-positive readouts in a number of patients treated with placebo. In such cases, the placebo “dose” was to be “adjusted” by reducing the infusion rate as if the subject received active treatment. Pharmacokinetic samples were collected before the start of the infusion and 2 hours, 6 hours, 12 hours, 24 to 36 hours, 72 hours, and 78 to 96 hours after the start of the infusion. They were used to inform the Data Monitoring Committee, to monitor the POC test performances, and to evaluate the relationship between repinotan concentrations and safety and efficacy. To ensure that the clinical study was conducted in a blinded manner, a number of clinical research organizations were contracted to perform separate tasks in the process.

Outcome Measures

The response to study drug treatment was based on serial examinations. Patients were monitored closely during the 72-hour treatment period and for 24 hours posttreatment for neurological status, safety, and pharmacokinetics. In addition, patients were to be assessed at 24 hours posttreatment, 4 weeks, and 3 months for neurological and functional outcome measures and adverse events. The Barthel Index (BI) and the modified Rankin Scale (mRS) were used for functional recovery and the NIHSS was used for neurological recovery. The original scores of these scales were recorded and converted to binary outcomes of successful response, yes or no, for purposes of analysis. The primary efficacy variable was the BI (success rate) at 3 months poststroke, as defined by a score of $\geq 85$. Successful response on the mRS was defined as a score of $0$, $1$, or $2$ at 3 months poststroke. Successful response on the NIHSS was defined as either an improvement of $\geq 4$ points from baseline or a return to normal ($0$ or $1$) from baseline at 3 months poststroke. Safety parameters included mortality, adverse events, changes in laboratory test values, and vital signs. Three baseline electrocardiograms were recorded and a further 5 during and after infusion time to capture and monitor any significant QTc effects. A centralized electrocardiographic data collection and expert reading organization was retained and used to read and interpret all electrocardiographic tracings from the study. This was done by a single trained expert using a standardized method. Pharmacokinetic samples were used to evaluate the relationship between repinotan concentrations and safety and efficacy outcome.

Statistical Methods

Determination of Sample Size

Assuming the success rate for the placebo group was 40% and the success rate for the repinotan group was 50% ($\Delta = 10\%$), $\beta = 20\%$ (80% power), $\alpha = 0.10$ (2-sided), and the invalidity rate = 10%, then it was determined that 340 randomized patients were needed for each group, or a total of 680 patients in the study.

Efficacy Analyses

Patients were valid for the intention-to-treat (ITT) analyses if they started on study drug infusion and had at least one postbaseline efficacy measure. Patients were included in the per protocol analysis if they were valid for the ITT population and met prespecified validity criteria. The primary efficacy analysis was conducted for the ITT population. A significant difference in the outcome measures between groups was tested for using a Cochran-Mantel-Haenszel test with a 2-sided $\alpha = 0.10$ comparing rates of success on the BI (a score of at least 85) at 3 months poststroke between repinotan and placebo groups stratified by tPA (yes/no) and country. The NIHSS and the mRS success rates were analyzed as secondary efficacy variables. Mantel-Haenszel and logistic regression analyses were performed on these variables as well. For all analyses on the BI, NIHSS, and mRS, patients who died were included as treatment failures by assigning them a “worst score.” The last observation carried forward (LOCF) visit was created using the efficacy value of the subject’s last visit. This was an actual value from a scheduled visit (ie, Day 4, Week 4, or Month 3), from an unscheduled visit, or an imputed value (if the patient died). As an additional secondary efficacy analysis, the 2 treatments’ survival curves were compared using a log rank test stratifying by tPA and country. As an additional secondary analysis, the BI was analyzed (as described previously) on the patients who had historical BI scores of $\geq 85$. The BI was also trichotomized to produce an ordinal response outcome. An ordered logistic regression using the proportional odds model was performed on this ordinal outcome by adopting model functions called cumulative logits as a secondary efficacy analysis. Additional and exploratory analyses on the BI and mRS were performed using different definitions of responders. A global test based on logit link function provides an estimate of the odds ratio for assessing a common treatment effect among correlated binary outcomes. The global test was performed as a secondary statistical method. The generalized estimating equations approach was used to obtain an estimated odds ratio of successful response based on 3 correlated binary outcomes: BI, NIHSS, and the mRS as defined previously.

Pharmacokinetics/Pharmacodynamics Analyses

SAS software Version 8.2 was used for data assembly, data description, exploratory analyses, contingency tables, and linear and logistic regression. Nonlinear mixed effect modeling (NONMEM software Version 5, Level 1.1 double precision) was used for the population pharmacokinetic modeling. Post hoc estimates of individual parameters and actual dosing history were used to predict concentrations of repinotan and patients’ exposure. The analysis of the effect of repinotan on BI used linear and logistic regression (SAS) and NONMEM was used for analyzing the effect of repinotan on QT interval, QTc.

Safety Analyses

Formal statistical tests were not planned for analyses of safety data. For categorical variables (adverse events, laboratory data, electrocardiogram), incidence rates were to be tabulated by treatment. Changes from baseline in vital signs, selected laboratory values, and electrocardiogram variables were to be summarized using descriptive statistics by treatment.

Trial Committees

A Steering Committee and an independent Data Monitoring Committee were established.
Results

The study was conducted between September 3, 2002, and September 13, 2004 (first patient’s first visit to last patient’s last visit) at 117 centers from 15 countries (Austria, Australia, Belgium, Canada, Finland, France, Germany, Hungary, Israel, Italy, Spain, Sweden, The Netherlands, United Kingdom, and the United States). In total, 681 patients were randomized (344 in the repinotan and 337 in the placebo groups). Ninety-five patients (14%) withdrew early from the study (52 in the repinotan and 43 in the placebo groups) with adverse events being the primary reason (35 patients in the repinotan and 23 in the placebo groups). No obvious treatment effects were observed. There was no difference in mean infusion time (66.20 hours in the repinotan group [n=342]; 66.39 hours in the placebo group [n=337]).

The Figure shows the number of patients included in the safety, ITT, and per protocol analyses.

There was little difference in the number of patients valid for safety and the number of patients valid for the ITT efficacy analyses, the summary of demographic data are given only for ITT patients. In total, 52% (356 of 679) of the patients were male. The breakdown by race was 91% (617 of 679) white, 3% (23 of 679) black, and 4% (24 of 679) Asian. Mean age was 70 years and mean body mass index was 26.8 kg/m². Sixty-one percent (207 of 342) of the patients allocated to repinotan and 60% (203 of 337) allocated to placebo were given tPA. Mean baseline NIHSS was 14.7 in both the repinotan and placebo groups. Overall, the treatment groups were balanced with respect to the demographic variables and other baseline characteristics (Table 1).

Summary of Efficacy

The efficacy results are presented in detail in Table 2. For the ITT population at LOCF, response on the BI (defined as a score of at least 85) was 37.1% (127 of 342) for patients on repinotan and 42.4% (143 of 337) for patients taking the placebo. This difference was not statistically significant (Cochran-Mantel-Haenszel probability value=0.149). Response on the mRS (defined as a score of 0, 1, or 2) at LOCF was 32.2% (110 of 342) for patients on repinotan and 37.1% (125 of 337) for patients taking the placebo. This difference was not statistically significant (Cochran-Mantel-Haenszel probability value=0.169). Response based on NIHSS (defined as an improvement of at least 15 points) at 6 weeks in the ITT population was 38.7% (132 of 342) for patients on repinotan and 41.4% (139 of 337) for patients taking the placebo. This difference was not statistically significant (Fisher’s exact test).
Table 1. Demographics and Other Baseline Characteristics (ITT mRECT Population)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Repinotan (N=342)</th>
<th>Placebo (N=337)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>178 (52)</td>
<td>178 (53)</td>
</tr>
<tr>
<td>Female</td>
<td>164 (48)</td>
<td>159 (47)</td>
</tr>
<tr>
<td><strong>Age, years, mean ± SD</strong></td>
<td>70.3 ± 12.2</td>
<td>69.7 ± 12.4</td>
</tr>
<tr>
<td><strong>Race, N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>314 (92)</td>
<td>303 (90)</td>
</tr>
<tr>
<td>Black</td>
<td>13 (4)</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Asian</td>
<td>8 (2)</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Uncodeable</td>
<td>3 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td><strong>Region, N (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>8 (2)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>Europe</td>
<td>177 (52)</td>
<td>165 (49)</td>
</tr>
<tr>
<td>Israel</td>
<td>42 (12)</td>
<td>47 (14)</td>
</tr>
<tr>
<td>North America</td>
<td>115 (34)</td>
<td>113 (34)</td>
</tr>
<tr>
<td><strong>Weight, kg, mean ± SD</strong></td>
<td>76.9 ± 16.6</td>
<td>75.8 ± 15.0</td>
</tr>
<tr>
<td><strong>Height, cm, mean ± SD</strong></td>
<td>168.4 ± 9.0</td>
<td>169.0 ± 9.2</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m², mean ± SD</strong></td>
<td>27.1 ± 5.2</td>
<td>26.5 ± 4.3</td>
</tr>
<tr>
<td><strong>Systolic blood pressure, mm Hg, mean ± SD</strong></td>
<td>154.4 ± 22.9</td>
<td>153.3 ± 22.4</td>
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<tr>
<td><strong>Diastolic blood pressure, mm Hg, mean ± SD</strong></td>
<td>81.8 ± 14.6</td>
<td>80.9 ± 14.4</td>
</tr>
<tr>
<td><strong>Heart rate, beats/min, mean ± SD</strong></td>
<td>77.8 ± 16.4</td>
<td>78.5 ± 17.3</td>
</tr>
<tr>
<td><strong>Temperature, °C, mean ± SD</strong></td>
<td>36.4 ± 0.5</td>
<td>36.5 ± 0.6</td>
</tr>
<tr>
<td><strong>Respiration rate, breaths/min, mean ± SD</strong></td>
<td>19.0 ± 5.8</td>
<td>18.5 ± 4.1</td>
</tr>
</tbody>
</table>

Other baseline characteristics

| Patient given tPA, N (%)             | 207 (61)          | 203 (60)        |
| NIHSS, N, mean ± SD                 | 342 (14.7 ± 4.4)  | 335 (14.7 ± 4.3) |
| NIHSS, N, median                    | 342 (15)          | 335 (14)        |
| Prior neurological disability, N (%)| 23 (7)            | 24 (7)          |
| Prior strokes, N (%)                | 59 (17)           | 50 (15)         |

Table 2. Responder Rates (ITT Population)

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Repinotan</th>
<th>Placebo</th>
<th>CMH P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>53/317 (16.7%)</td>
<td>50/316 (15.8%)</td>
<td>0.807</td>
</tr>
<tr>
<td>Week 4</td>
<td>97/329 (29.5%)</td>
<td>103/320 (32.2%)</td>
<td>0.448</td>
</tr>
<tr>
<td>Month 3</td>
<td>124/329 (37.7%)</td>
<td>138/320 (43.1%)</td>
<td>0.141</td>
</tr>
<tr>
<td>LOCF</td>
<td>127/342 (37.1%)</td>
<td>143/337 (42.4%)</td>
<td>0.149</td>
</tr>
<tr>
<td>mRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 4</td>
<td>56/318 (17.6%)</td>
<td>56/318 (17.6%)</td>
<td>0.920</td>
</tr>
<tr>
<td>Week 4</td>
<td>89/329 (27.1%)</td>
<td>91/321 (28.3%)</td>
<td>0.559</td>
</tr>
<tr>
<td>Month 3</td>
<td>107/330 (32.4%)</td>
<td>121/320 (37.8%)</td>
<td>0.136</td>
</tr>
<tr>
<td>LOCF</td>
<td>110/342 (32.2%)</td>
<td>125/337 (37.1%)</td>
<td>0.169</td>
</tr>
</tbody>
</table>

CMH indicates Cochran-Mantel-Haenszel.

Drug Concentration and Relationship to Response on the BI

A total of 1531 repinotan concentrations were included in the pharmacokinetics and pharmacokinetics/pharmacodynamics analyses. Concentrations were highly variable. Patients treated with repinotan had plasma concentrations (geometric mean [95% CI]) of 7.3 (6.7 to 8.1), 6.9 (6.3 to 7.6), and 5.7 (5.1 to 6.4) μg/L at 6 hours, 12 hours, and 72 hours, respectively. Patients were classified into 2 subpopulations of clearance: a subpopulation of 70% of patients with higher clearance (9.1 L/hr) and a subpopulation of 30% with lower clearance (1.6 L/hr). In the pharmacokinetics/pharmacodynamics analyses, the BI as a continuous variable or as a dichotomous response showed that the efficacy outcome was mainly affected by the NIHSS at baseline (decrease of response as NIHSS score increases), the delay between the onset of stroke symptoms and the start of study drug infusion (decrease of response as the delay increases), the age of the patient (decrease of response with increasing age), and the blood pressure (decrease of response as blood pressure increases). Patients treated with tPA showed a more favorable outcome. Measures of total drug exposure (repinotan area under the curve of 0 to 72 hours, area under the curve of 0 to infinity) or plasma concentration at the end of infusion (72 hours) were not identified as relevant covariates for BI score, BI as a continuous variable, that is, a correlation between repinotan exposure and effect was not demonstrated. Among the tested exposure parameters for repinotan, only area under the curve of 0 to 12 hours was found to affect the BI, and the concentration at 6 hours, and the area under the curve of 0 to 12 hours affected the success rate whereby a nonstatistically consistent across the levels of the subgroups and analysis populations.

least 4 points from baseline) at LOCF was 66.7% (228 of 342) for patients on repinotan and 69.6% (233 of 335) for patients taking the placebo. This difference was also not statistically significant (Cochran-Mantel-Haenszel probability value = 0.413). mRS adjusted for baseline NIHSS, BI adjusted for baseline NIHSS and age, and mRS adjusted for baseline NIHSS and age were also analyzed and the results were similar as those shown in Table 2.

Results from the per protocol population were very similar to those based on ITT patients (data not shown), although with slightly more pronounced differences favoring placebo. In general, the difference between treatment groups was...
significant trend ($P=0.09$) was observed for a worsening in outcome when the exposure to repinotan increased.

**Drug–Drug and Drug–Disease Interactions**

There were very similar results between the repinotan and placebo groups for patients not treated with tPA (Table 3). The overall negative trend against repinotan therefore raises the possibility of an interaction between repinotan and tPA. Before this study, the possible interaction between repinotan and tPA was addressed in vivo using a model of thrombin-induced platelet accumulation in rabbit cerebral vasculature. In addition to this in vivo model, a number of experiments have been performed in vitro to examine the possible interaction. The overall conclusion from these preclinical studies was that there is no indication of an interaction between repinotan and tPA that could affect its thrombolytic potency or fibrin specificity.8

Because the subjects were only randomized in the study after they had received tPA (or the decision had been made not to administer tPA), other confounding factors in the tPA-treated subgroup cannot be ruled out. Finally, there is the possibility that this is simply a chance finding.

**Summary of Tolerability and Safety**

Adverse events are coded according to the Medical Dictionary for Regulatory Activities, Version 7.1. Incidence is defined as the number of patients reporting the event after the start of study drug infusion. Table 4 provides an overview of events and survival for the mRECT safety population. Twenty-one percent (71 of 343) of patients on repinotan and 20% (67 of 337) patients taking the placebo died. The incidence of any adverse event was 98% (335 of 343) in patients on repinotan and 97% (326 of 337) in patients taking the placebo. Adverse events were assessed as related to the study drug by the investigator; an assessment of possible or probable was considered drug-related. The incidence of any drug-related adverse event was 21% (73 of 343) in patients on repinotan and 22% (74 of 337) in patients taking the placebo. Any serious adverse event had an incidence of 43% (149 of 343) in patients on repinotan and 40% (136 of 337) in patients taking the placebo. Ten percent (33 of 343) of patients in the repinotan and 7% (24 of 337) in the placebo groups reported an adverse event leading to discontinuation. The type and frequency of adverse events occurring in at least 10% of any treatment group were very similar, except agitation—a serotonergic side effect—which was reported in 53 patients (15%) on repinotan and 29 (9%) on placebo.

The study has shown that repinotan has no effect on QTcB and causes an increase of QTcF proportional to concentration with large between-subject variability. In some subjects, the increase of QTcF may be clinically significant.

**Discussion**

The present study was designed to maximize the therapeutic effect of repinotan in the treatment of patients with acute ischemic stroke by maintaining steady-state drug concentrations in plasma between 5 to 20 μg/L, that is, within the expected optimum therapeutic range, using a POC test. We treated patients with severe stroke in this study reflected by a mean admission NIHSS of 14.7 points and a mortality rate of 20% to 21%. In the heterogenous group of patients in this study, response to repinotan was similar to the response to placebo for each of the outcome measures and in each of the populations and subgroups. In the ITT population, the response on the primary efficacy variable, the BI was 37% for repinotan and 42% for placebo, a difference that was not statistically significant. Similarly, responses based on the mRS and the NIHSS were consistent with that observed for
the BI and suggested no difference between the treatment groups. Results of other responder variables adjusted for baseline status (ie, mRS adjusted for baseline NIHSS, BI adjusted for baseline NIHSS and age, and mRS adjusted for baseline NIHSS and age) also failed to suggest any treatment effects. Results based on the per protocol analysis population were similar to the results from the ITT analysis. The frequency and severity of safety outcomes were similar in the repinotan and placebo treatment groups and were overall balanced and within the expected range. In summary, mRECT failed to demonstrate clinical benefit of repinotan. Post hoc analyses looking at time to treatment, target pharmacokinetic population, and stroke severity also either did not show a treatment difference or showed a trend in disfavor of repinotan. In view of the disappointing study results, the development of repinotan in acute ischemic stroke was discontinued. The reasons for the lack of treatment effect in this study are not clear. Robust preclinical data suggested a neuroprotective drug effect of repinotan. However, the various animal models of neuroprotection are still lacking clinical validation, and their predictive value so far appears to be questionable. mRECT was a rigorous and well-conducted trial. With the POC test in combination with the loading dose, a significant number of patients have been exposed to repinotan in the expected therapeutic range (5 to 20 μg/L), albeit in general at the lower end. However, in the absence of a clear exposure/response relationship, this is unlikely to be a reason for drug failure because higher exposure was not associated with an improved outcome. Demanding clinical and radiographic criteria were applied to enroll a patient population expected to have the greatest benefit from treatment with a putative neuroprotectant. Randomization was very effective with no confounders at baseline. Sixty percent of patients received tPA, by far the highest proportion in any neuroprotectant trial to date. This demonstrates that well-organized sites are capable of providing demanding acute care, including intravenous tPA, the POC approach as well as the administration of study drug within a challenging time window of 4.5 hours from the onset of stroke symptoms and within 1 hour of tPA initiation for patients eligible for thrombolysis.

Appendix

Steering Committee
P. Teal, Vancouver, BC, Canada (chair); S. Davis, Melbourne, Australia; W. Hacke, Heidelberg, Germany; M. Kaste, Helsinki, Finland; P. D. Lyden, San Diego, Calif; and Buyer HealthCare representatives as nonvoting members.

Independent Data Monitoring Committee
K. R. Lees, Glasgow, UK (chair); J. M. Orgogozo, Bordeaux, France; and J. R. Whitehead, Reading, UK.

Study Investigators
The following centers contributed data to mRECT: Australia: D. Crimmins, Gosford, New South Wales; S. Davis, Melbourne, Victoria; G. Donnan, Heidelberg, Victoria; D. Dunhabin, Hobart, Tasmania; J. Frayne, Melbourne, Victoria; D. Freilich, Footscray, Victoria; C. Levi, New Lambton Heights, New South Wales; M. Williams, Southport, Queensland. Austria: F. Aichner, Linz; M. Brainin, Kloten; Belgium: W. Lang, Wien. Belgium: Ceulemans, Bornem; A. Peeters, Brussels. Canada: P. Bailey, St. John, Newfoundland; M. Beaudy, Chicoutimi, Quebec; A. Bellavance, Greenfield Park, Quebec; L. Berger, Greenfield Park, Quebec; A. Demchuk, Calgary, Alberta; V. Hachinski, London, Ontario; F. Kemble, Victoria, British Columbia; D. Novak, Penticton, British Columbia; S. Phillips, Halifax, Nova Scotia; D. Selchen, Mississauga, Ontario; A. Shuaib, Edmonton, Alberta; F. Silver, Toronto, Ontario; P. Teal, Vancouver, British Columbia; C. Voti, Saskatchewan, T. Winder, Lethbridge, Alberta. Finland: M. Kaste, Helsinki; M. Rantalata, Lahti; J. Sivenius, Kuopio; I. Tarvainen, Mikkeli. France: M.-H. Mahagne, Nice; F. Rouanet, Bordeaux. Germany: M. Dichtgans, Munich; H. C. Diener, Essen; K. Einhaupl, Berlin; T. Els, Freiburg; C. Gerloff, Tubingen; J. Glahn, Minden; M. Gotzler, Magdeburg; B. Griebing, Bad Neustadt; R. Haberl, Munich; G. Hamann, Munich; J. Heckmann, Erlangen; G. Iickenstein, Regensburg; C. Kessler, Greifswald; M. Klein, Berlin; R. Landwehr, Kaiserslautern; W. Muller, Wurtzburg; M. Nickel, Nurnberg; P. Ringleb, Heidelberg; D. Schneider, Leipzig; R. Schneider, Aschaffenburg; J. Schulz, Tubingen; M. Sitter, Frankfurt; J. Sobesky, Koln; F. Stogbauer, Muenster. Hungary: A. Valkovic, Miskolc. Israel: N. Bornstein, Tel Aviv; B. Gross, Naharuya; Y. Lampl, Holon; R. Milo, Ashkelon; J. Streicher, Petach Tikva; D. Tanne, Tel Hashomer; B. Weller, Haifa; D. Yarmitsky, Haifa. Italy: P. Bassi, Milan; P. Bovi, Verona; D. Consoli, Vibo Valentia; V. Gallai, Perugia; D. Guidetti, Reggio Emilia; C. Marini, L’Aquila; G. Mazzotta, Perugia; G. Miceli, Pavia; R. Sterzi, Como; D. Toni, Roma; V. Tosso, Vicenza. The Netherlands: G. J. Luijkx, Groningen; P. Vos, Nijmegen. Spain: J. Castillo, Santiago de Compostela; J. R. Gonzalez, Barcelona; J. M. Llacer Andrs, Valencia; E. Mostacero, Zaragoza; J. A. Sabin, Barcelona; E. D. Tejedor, Madrid. Sweden: N.-G. Wahlgren, Stockholm; P. Wester, Umea. United Kingdom: M. Ardon, Leicester; R. McWalter, Dundee; K. Muir, Glasgow. United States: E. Albakri, Tampa, Fla; I. Alfaullah, Robbinsdale, Minn; D. Brock, Philadelphia, Pa; M. Brody, Del Ray Beach, Fla; C. Chang, Honolulu, Hawaii; D. Chiu, Houston, Texas; T. Devlin, Chattanooga, Tenn; D. Dietrich, Great Falls, Mt; B. Grayman, Upland, Pa; D. Hanley, Baltimore, Md; J. Hanna, Cleveland, Ohio; J. Harris, Ft Lauderdale, Fka; N. Iannuzzi III, Winston-Salem, NC; M. Jacoby, Des Moines, Iowa; R. Johnson, Bellevue, Wash; K. Levin, RidgeWood, NJ; H. Luten, Portland, Ore; P. Lyden, San Diego, Calif; P. Mazzaro, Beaufort, SC; K. Ng, Ocala, Fla; N. Papamitsakis, Edison, NJ; C. Perkins, Stony Brook, NY; H. Sachdev, San Jose, Calif; J. Schim, Oceanside, Calif; S. Sen, Chapel Hill, NC; S. Starkman, Los Angeles, Calif.

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Pharmacokinetic and Pharmacodynamic Analyses
Eliane Fuseau and Olivier Petricoul, EMF Consulting, Aix-en-Provence, France.

Acknowledgments
The contributions of the principal and coinvestigators at each of the study sites are gratefully acknowledged. We acknowledge the intellectual contributions of Antoni Davalos, MD; Larry B. Goldstein, MD; Daniel F. Hanley, MD; Gian Luigi Lenzi, MD; Jean-Marc Orgogozo, MD; and Ralph Sacco, MD, MSc, to the protocol design. Furthermore, P. Rombout, DriDevO, CL Klimmen, The Netherlands, is gratefully acknowledged for developing simulation models for repinotan on which the study design has been based. EMF.
Consulting, Aix-en-Provence, France, is gratefully acknowledged for performing the pharmacokinetic and pharmacodynamic analyses.

Source of Funding
The study was sponsored and all drug supplies were provided by Bayer HealthCare, Wuppertal, Germany.

Disclosures
S.D. is on the steering committees for the FAST (Factor 7 in intracerebral hemorrhage)–Novo Nordisk and SAINT (AstraZeneca) trials. He has provided advice or given lectures on behalf of Sanofi Aventis, BMS, Pfizer, and Boehringer Ingelheim. M.K. has received honoraria and has served as a consultant. P.D.L. has received significant financial research support. M.F. was employed with Bayer Healthcare AG, Leverkusen, Germany, which contributed to the sponsoring of this trial.

References