Alteplase for the treatment of acute ischemic stroke in patients with low National Institutes of Health Stroke Scale and not clearly disabling deficits (Potential of rtPA for Ischemic Strokes with Mild Symptoms PRISMS): Rationale and design

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Abstract
Rationale: Over half of acute ischemic stroke patients have a low National Institutes of Health Stroke Scale of 0–5 and up to two-thirds may not appear clearly disabled at presentation. The efficacy of intravenous alteplase for the latter group is not known.

Aim: Potential of rtPA for Ischemic Strokes with Mild Symptoms (PRISMS) was designed to evaluate the safety and efficacy of intravenous alteplase for the treatment of acute ischemic stroke with National Institutes of Health Stroke Scale 0–5 and without clearly disabling deficits.

Sample size estimates: A maximum of 948 subjects were required to test the superiority hypothesis with 80% power, according to a one-sided 0.025 level of significance.

Methods and design: PRISMS was a multicenter, randomized, double-blind, placebo-controlled phase 3b clinical trial. Patients were randomized to the active arm (intravenous alteplase standard dose of 0.9 mg/kg, up to a maximum of 90 mg, plus oral aspirin placebo) or the control arm (intravenous alteplase placebo plus active oral aspirin dose of 325 mg).

Study outcome: The primary efficacy endpoint was favorable functional outcome, defined as a modified Rankin Scale score 0 or 1 assessed at 90-day postrandomization.

Keywords
Acute stroke therapy, intervention, ischemic stroke, methodology, protocols, alteplase

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Introduction and rationale
Over half of all patients with acute ischemic stroke (AIS) have a low National Institutes of Health Stroke Scale (NIHSS) of 0–5 at presentation.¹,² Up to two-thirds of those with low NIHSS will have deficits that appear nondisabling at presentation, and therefore are considered “mild” (Khoury and Kleindorfer, 2012, Personal Communication of supplemental data regarding La Rosa et al.).³,⁴ However, prospective observational cohort studies report significant rates (29–32%)
of 90-day disability (modified Rankin Scale (mRS) 2–6) in patients with mild stroke (Fischer and Mattle, 2010, Personal Communication of supplemental data regarding Fischer et al.).5,6

Among AIS patients who arrive within 3 h of symptom onset, a substantial proportion (40%) are not treated with alteplase primarily due to mild deficits at the time of treatment decision.7–9 Treatment rates of AIS patients with low NIHSS have increased in recent years, raising the question of the optimal management of patients with low NIHSS and deficits that appear nondisabling.10,11

Although alteplase is of established benefit for patients with low NIHSS scores associated with disabling deficits,12 it is unknown whether alteplase is beneficial for patients with low NIHSS scores associated with potentially nondisabling deficits (including both patients with persistently nondisabling deficits since onset or due to improvement to a nondisabling state). Eight of the nine prior major trials (NINDS Parts 1/2, ECASS 1/2/3, Atlantis Parts A/B, and EPITHET) explicitly excluded varying subsets of patients with the mildest deficits, and the ninth (IST 3) permitted their enrollment if there was physician equipoise regarding benefit, but did not collect data regarding specific deficits and perceptions of level of disability at presentation, precluding subgroup analysis.13,22,23

Currently, national clinical recommendations reflect this absence of definitive evidence regarding thrombolytic therapy in patients with low NIHSS scores and nondisabling deficits, stating that

…treatment of patients with milder ischemic stroke symptoms that are judged as nondisabling may be considered. Treatment risks should be weighed against possible benefits; however, more study is needed to further define the risk-to-benefit ratio. (Class IIb; Level of Evidence C)14,24

In designing the PRISMS trial, great consideration was given to the operational definition of stroke with low NIHSS and nondisabling symptoms. Eligibility based on an NIHSS threshold alone would capture some patients with clearly disabling symptoms. Drawing upon the work of a consensus panel,15 and seeking a clear, operationalized approach that accorded with the perspectives of patients, families, and physicians, the PRISMS Steering Committee defined PRISMS-eligible patients as those with NIHSS 0–5 and without “clearly disabling” deficits. Deficits were operationalized as “clearly disabling” if they would prevent return to employment or performance of basic activities of daily living at the time of the evaluation.

**Methods**

**Design**

PRISMS (NCT02072226) was designed as a phase 3b, multicenter, randomized, double-blind, placebo-controlled clinical trial intended to demonstrate the efficacy of intravenous (IV) alteplase for the treatment of mild AIS, as shown in Figure 1. Subjects were randomized to the active arm (IV alteplase standard dose of 0.9 mg/kg, up to a maximum of 90 mg, plus oral aspirin placebo) or the control arm (IV alteplase placebo plus active oral aspirin dose of 325 mg). The primary objective was to test the hypothesis that the active arm is superior to the control arm with respect to favorable functional outcome, defined as a mRS score of 0 or 1 at 90 days post randomization.

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**Figure 1. Study schema. ASA: aspirin; CT: computed tomography; IV: intravenous; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale.**
Patient population

AIS patients with NIHSS 0–5 and deficits judged not clearly disabling by the investigator, and in whom study treatment could be initiated within 3 h of onset, were to be enrolled at approximately 75 sites in North America. Deficits were operationalized as “clearly disabling” if the current deficits were judged to prevent return to work or performance of basic activities of daily living (i.e. bathing, ambulating, toileting, hygiene, and eating). Sites were provided with pocket cards (Figure 2) describing the typically eligible patient.

Noteworthy exclusion criteria included functional disability prior to the enrolling stroke (defined as a historical mRS score of 2 or more). Subjects with an inability to swallow, preventing the administration of oral aspirin or aspirin placebo and suggesting a disabling deficit, were also ineligible. Full eligibility criteria are listed in Table 1.

Randomization and treatment

Given the known time dependence of any potential benefit from alteplase, in order to minimize time to study drug administration, eligible patients were randomized via a step-forward procedure. The step-forward procedure was designed to ensure that a randomized treatment assignment is available prior to the arrival of each eligible subject, so that treatment can be initiated as soon as possible. Subjects were randomized in a 1:1 ratio via a combination of the urn and biased coin methods, balanced within site.

As part of site activation, the interactive web response system (IWRS) assigned drug kit IDs for the first eligible subject at each site. Within 8 h of treatment initiation, the site was required to enter the corresponding patient data into the IWRS, in order to obtain and flag the drug kit ID to be used for the next eligible subject at that site. If potential subjects were deemed
to meet prespecified eligibility criteria, the site pharmacist could premix study drug while informed consent was obtained. A subject was considered enrolled when the study drug bolus was administered. If the subject was not enrolled, the site was required to indicate in the IWRS that the corresponding drug kits were not used, and a new set of drug kit IDs was assigned.

**Table 1.** PRISMS eligibility criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tr>
<td>• Age 18 years (no upper limit)</td>
<td>• CT or MRI findings consisting of one of the following:</td>
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<tr>
<td>• Mild ischemic stroke = NIHSS ≤ 5 and not “clearly disabling”</td>
<td>• CT with clear large hypodensity &gt; 1/3 middle cerebral artery (MCA) territory or greater than 100 cc if not in MCA territory</td>
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<tr>
<td>• Not “clearly disabling” = patient can still do basic ADLs and/or return to work</td>
<td>• MRI with clear large hyperintensity on concurrent DW and FLAIR &gt; 1/3 MCA territory or greater than 100 cc if not in MCA territory</td>
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<tr>
<td>• Study treatment can be started within 3 h from last known well time</td>
<td>• Imaging lesion consistent with acute hemorrhage of any degree</td>
</tr>
<tr>
<td>• Informed consent</td>
<td>• Evidence of intraparenchymal tumor</td>
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CT: computed tomography; DW: diffusion-weighted; FLAIR: fluid-attenuated inversion recovery; ICH: intracranial hemorrhage; IV: intravenous; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; PRISMS: Potential of rtPA for Ischemic Strokes with Mild Symptoms.

**Stroke mimic adjudication**

Prior to database lock and unblinding, a subset of Steering Committee members reviewed the final diagnoses for all enrolled patients with either: (1) local site final diagnosis of neurovascular mimic, or (2) local site diagnosis of imaging-negative ischemic
stroke or transient ischemic attack (TIA). The central review group analyzed all relevant clinical records and data, blinded to treatment assignment. When central review group members had perspectives discordant with the local site final diagnosis, discussion was held between the site PI and central review group members. The site PI then made a final diagnostic determination.

**Primary outcome – Efficacy**

The primary endpoint was a mRS score of 0 or 1, reflecting favorable functional outcome, evaluated at 90 days post randomization.

**Prespecified secondary and exploratory outcomes**

The efficacy of IV alteplase was also evaluated by the full ordinal scale of the mRS and global favorable recovery using the Global Statistic (mRS 0 or 1, NIHSS 0 or 1, Barthel Index 95 or 100, and Glasgow Outcome Scale 1).\(^20\)

The primary safety endpoint was symptomatic intracranial hemorrhage (sICH) defined as any neurological decline attributed to ICH within 36 h, modified from the NINDS trials.\(^21\) Secondary safety outcomes include any ICH within 36 h, overall mortality within 90 days, and stroke-related and neurological deaths within 90 days.

Exploratory outcomes are listed in Table 2.

**Safety monitoring**

All adverse events (AEs), including serious AEs and nonserious AEs of special interest (AESIs), regardless of relationship to study drug, were reported until 30 days from study drug administration. After 30 days, the following events were captured: serious AEs, nonserious AESIs, and AEs resulting in withdrawal from study. AESIs consisted of sICH events (if not otherwise reported), stroke recurrence, or suspected transmission of an infectious agent via a medicinal product. Baseline laboratory, vital sign, neurological exam, and imaging data were collected to ensure that eligibility requirements were met. Follow-up (22–36 h) neuroimaging (MRI preferred if clinical standard of care) was required to assess for hemorrhage.

**Data monitoring body**

An independent Data Monitoring Committee (iDMC), composed of external advisors, provided ongoing review of accumulating safety data; the iDMC was also charged with review of the formal futility analysis, planned to take place after 50% of subjects had completed follow-up.

**Sample size determination**

The PRISMS trial was designed to detect a 9% absolute difference in the proportion of subjects with favorable outcome with 80% power, using a one-sided type I error rate of 0.025 to test the superiority hypothesis, under the assumption that 65% of control subjects will experience a favorable outcome, and allowing for one interim futility analysis. It was anticipated that a higher rate of favorable outcome in controls would allow for more power to detect a lower treatment effect. The interim futility analysis was to be conducted according to an O’Brien–Fleming-type boundary, after 50% of the sample had completed the 90-day assessments. These assumptions resulted in a sample size of 856 subjects. Because the analysis would be conducted according to the ITT principle, the sample size was further adjusted to account for dilution of the treatment effect associated with 5% nonadherence (due to loss to follow-up, consent withdrawal, treatment crossovers, and neurovascular (stroke/TIA) mimics). The maximum sample size was therefore 948 subjects.

**Statistical analysis**

The PRISMS trial was designed to test the primary endpoint via a Cochran–Mantel–Haenszel test, stratified by age (<65 versus ≥ 65), time from onset to treatment (0–2 versus > 2 h), and pretreatment NIHSS score (0–2 versus 3–5).

**Study organization and funding**

The initial protocol was designed by the academic team and brought to Genentech, Inc. for consideration. After requested modifications, Genentech, Inc. sponsored the study, distributed study drug, and provided oversight of study management. A Steering Committee, composed of sponsor representatives and external scientific advisors, provided recommendations regarding study conduct and analysis throughout the trial recruitment phase through regularly scheduled in-person and teleconference meetings. The Steering Committee remained blinded to treatment arm during the subject recruitment and follow-up phases; after database lock and completion of prespecified analyses, the Steering Committee became unblinded and participated in the review and interpretation of study results. All imaging was interpreted by two independent blinded neuroradiologists at the central imaging core.
The PRISMS trial was designed to definitively evaluate the efficacy of alteplase administered within 3 h of onset of ischemic stroke with NIHSS 0–5 and without clearly disabling deficits at presentation, as compared to aspirin, to improve functional outcomes at 90-day post-randomization. If positive, the trial would likely mandate the treatment of all AIS patients with an objective deficit, regardless of severity or level of disability, who are otherwise eligible for IV alteplase. If negative, it would minimize risk to patients for whom there would be no significant clinical benefit of this therapy.

This first trial in this understudied patient population presented some unique recruitment challenges including delays to ED presentation by the patient, delayed diagnosis of presenting event as stroke by clinicians, less frequent stroke team activation, and lack of clinical equipoise among some subinvestigators at sites who had routinely offered or not offered treatment to these patients. Efforts to increase recruitment included frequent site contact by the sponsor’s Medical Science Liaisons, webinars by steering committee members, a brochure and slide presentation designed to introduce the trial to patients in a standardized manner, and a web-based interactive patient selection educational tool. However, recruitment lagged behind target and, on 21 December 2016, after 313 subjects had been randomized, the sponsor terminated enrollment due to delayed recruitment timelines.

In light of the early termination, prior to database lock and unblinding of the study team, the statistical analysis plan was updated to focus on estimation of treatment effects and confidence intervals rather than hypothesis tests. It was prespecified that the risk difference would be obtained from a linear model with the binary mRS 0–1 outcome as the response, and treatment, age, time from last known well to treatment, and baseline NIHSS as covariates. Quadratic terms for the continuous covariates would be added to the model if the Wald p-value for the quadratic term is <0.1.

The PRISMS trial represents the first randomized controlled trial in this population of strokes with low NIHSS and without clearly disabling deficits. The results will contribute to our understanding of the benefit, in terms of functional, cognitive and behavioral outcomes, and risk associated with alteplase treatment in mild stroke patients.

**Declaration of conflicting interests**

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SD Yeatts reports personal fees from...
Genentech for role as a member of the Steering Committee of the PRISMS Trial, during the conduct of the study. JP Broderick reports fees from Genentech to the Department of Neurology and Rehabilitation Medicine for his role as a member of the Steering Committee of the PRISMS Trial, during the conduct of the study. A Chatterjee reports personal fees from Genentech for role as a member of the Steering Committee of the PRISMS Trial, during the conduct of the study. EC Jauch reports personal fees from Genentech for role as a member of the Steering Committee of the PRISMS Trial, during the conduct of the study. SR Levine reports personal fees and non-financial support from Genentech for role as a member of the Steering Committee of the PRISMS Trial during the conduct of the study; grants from Genentech, from outside the submitted work. JG Romano reports personal fees from Genentech for role as a member of the Steering Committee of the PRISMS Trial, during the conduct of the study; grants from Genentech to the University of Miami to support his role as PI of the Mild and rapidly Improving Stroke Study. JL Saver served as an unpaid member of the Trial Steering Committee under a no-remuneration contract with Genentech, advising on the design and conduct of the PRISMS trial. Dr. Saver also served as an unpaid site investigator in the PRISMS trial, for which the University of California received payments on the basis of clinical trial contracts for the number of subjects enrolled. Outside of the submitted work, Dr. Saver reports receiving contracted hourly payments and travel reimbursement from Medtronic, Stryker, and Neuravi, and Boehringer Ingelheim (prevention only) for service on Trial Steering Committee(s), making recommendations regarding best approaches to rigorous trial design and conduct. The University of California has patent rights in retrieval devices for stroke. A Vagal reports grants from Genentech to University of Cincinnati, during the conduct of the study. B Purdon and J Devenport report being full time employees of Genentech. P Khatri reports payment to university department for research efforts from Genentech (lead PI of PRISMS), Neurospring (Co-investigator of CREATE grant), Lumosa (DSMB and consultant) and NIH/NINDS. She also reports fees from Biogen (DSMB), Medpace/Novartis (coinvestigator). She was an unpaid consultant to EmstopA and received travel support from Neuravi (academic workshop).

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