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CLINICAL STUDY REPORT FOR TR701-112 EMA ANALYSIS PLAN

A PHASE 3 RANDOMIZED, DOUBLE-BLIND, MULTICENTER STUDY COMPARING THE EFFICACY AND SAFETY OF 6-DAY ORAL TR-701 FREE ACID AND 10-DAY ORAL LINEZOLID FOR THE TREATMENT OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS

1 TITLE PAGE

Protocol Number	TR701-112
Test Drug	TR701 free acid (FA)
Indication	Acute Bacterial Skin and Skin Structure Infections
Development Phase	Phase 3
Study Dates	First patient enrolled 23 August 2010 Last patient last visit 30 September 2011
Sponsor Responsible Medical Officer	[redacted]
Sponsor Signatory	[redacted] Trius Therapeutics, Inc. 6310 Nancy Ridge Drive San Diego, CA 92121 Office: [redacted] Fax: [redacted] Mobile: [redacted] E-mail: [redacted]
GCP Statement	This study was conducted in accordance with current United States Food and Drug Administration regulations, International Conference on Harmonisation Good Clinical Practice guidelines, the European Union Directive 2001/20/EC for clinical trials conducted in the European Union, and the Institutional Review Board/Ethics Committee, and local ethical and legal requirements.
Date of Report	05 December 2012

2 SYNOPSIS FOR EMA ANALYSIS PLAN

Name of Sponsor/Company Trius Therapeutics, Inc 6310 Nancy Ridge Drive San Diego, CA 92121	Name of Finished Product TR701 FA Tablets, 200 mg	Name of Active Ingredient TR701 FA

Protocol Number: TR701-112

Title of Study: A Phase 3 Randomized, Double-Blind, Multicenter Study Comparing the Efficacy and Safety of 6-Day Oral TR-701 Free Acid and 10-Day Oral Linezolid for the Treatment of Acute Bacterial Skin and Skin Structure Infections

Study Period (years): 1 Date of First Enrollment: 23 August 2010 Date of Last Completed: 30 September 2011	**Phase of Development:** 3

Objectives:
The primary European Medicines Agency (EMA) analysis objective for the analysis to be presented to the EMA is to determine the noninferiority (NI) in the rate of the Investigator's assessment of clinical success of 6-day oral TR-701 FA compared with that of 10-day linezolid treatment at the Post-therapy Evaluation (PTE) Visit (7 to 14 days after the End of Therapy [EOT] Visit) in the Intent-to-Treat (ITT) and Clinically Evaluable at PTE (CE-PTE) Analysis Sets.

The secondary objectives include the following:

- To compare the per-patient favorable microbiological response rate at the PTE Visit in the microbiological ITT (MITT) and microbiologically evaluable (ME) Analysis Sets
- To compare the Investigator's assessment of clinical response at the 48-72 Hour, Day 7, and EOT Visits in the ITT and Clinically Evaluable at EOT (CE-EOT) Analysis Sets (for the EOT Visit only)
- To compare the per-pathogen favorable microbiological response rates at the PTE Visit in the MITT and ME Analysis Sets
- To compare the per-patient and per-pathogen favorable microbiological response rates at the EOT Visit in the MITT Analysis Set
- To evaluate the safety profile of TR-701 FA in comparison with that of linezolid
- To assess the population pharmacokinetic profile of TR-700

Methodology:
This was an NI randomized, double-blind, multicenter Phase 3 study of oral TR-701 FA 200 mg once daily for 6 days and oral linezolid 600 mg every 12 hours for 10 days in adults with acute bacterial skin and skin structure infection (ABSSSI), including cellulitis/erysipelas, major cutaneous abscess, and wound infections. The main TR701-112 clinical study report describes the full investigational plan.

Number of patients: A total of 667 patients were randomized; 332 to receive TR-701 FA and 335 to receive linezolid.

Statistical Methods: The Statistical Analysis Plan developed for the EMA was finalized on 23 March 2012.

The primary efficacy outcome is the percentage of patients with a clinical success based on the Investigator's assessment at the PTE Visit. The primary efficacy analyses were to be based on the ITT and CE-PTE Analysis Sets. The NI test was to be a 1-sided hypothesis test performed at the 2.5% level of significance. This NI test was to be based on the lower limit of the 2-sided 95% confidence interval (CI). The primary analysis was to be adjusted for the stratification factors of presence/absence of fever at baseline, geographic region, and clinical syndrome.

A stratified 2-sided 95% CI was to be constructed for the observed difference in per-patient favorable microbiological response rate between the TR-701 FA and linezolid groups using the stratified method of Miettinen and Nurminen. The number and percentage of patients determined by the Investigator to have clinical improvement at the 48-72 Hour Visit and at Day 7 in the ITT Analysis Set were to be

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Trius Therapeutics, Inc 6310 Nancy Ridge Drive San Diego, CA 92121	TR701 FA Tablets, 200 mg	TR701 FA

determined, as well as the Investigator's assessment of clinical response at EOT in the CE-EOT Analysis Set. Stratified (for presence/absence of fever at baseline, clinical syndrome, and geographic region) 2-sided 95% CIs were to be constructed for the observed difference in the success rates between treatment groups.

Analysis Sets

1. ITT: All randomized patients (N=667; 332 TR-701 FA, 335 linezolid)
2. Safety: All treated patients (N=666; 331, 335)
3. MITT: All randomized patients who have a baseline gram-positive bacterial pathogen known to cause ABSSSI (N=418; 209, 209)
4. CE-EOT: All randomized patients receiving at least 1 dose of study therapy, completed the Investigator's EOT assessments, no concomitant systemic antibiotic therapy through EOT, and no confounding events or factors (N=579; 287, 292)
5. CE-EOT for Sustained Response (CE-EOTSUS): All randomized patients receiving at least 1 dose of study therapy, completed the 48-72 Hour and EOT assessments, no concomitant systemic antibiotic therapy through EOT, and no confounding events or factors (N=559; 273, 286)
6. CE-PTE: All randomized patients receiving at least 1 dose of study therapy, completed Investigator's EOT and PTE assessments, no concomitant systemic antibiotic therapy through PTE, and no confounding events or factors (N=559; 279, 280)
7. ME: Patients in the MITT Analysis Set who are also in the CE-PTE Analysis Set (N=342; 171, 171)

Summary of Results
Efficacy:

TR-701 FA is statistically noninferior to linezolid for the primary efficacy analysis outcome of Investigator assessment of clinical success at the PTE Visit in the ITT and CE-PTE Analysis Sets. There were no meaningful differences between TR-701 FA- and linezolid-treated patients for Investigator assessment of clinical response rates at the PTE Visit by type of infection (cellulitis/erysipelas, major cutaneous abscess, and wound infection), geographic region (North America, Latin America, and Europe), baseline fever status, prior antibacterial use, baseline lesion size, and bacteremic patients.

In addition, a high clinical response rate was observed at the EOT and PTE Visits based on Investigator assessment. At these visits, the lower limit of the 95% CI was greater than -10%, which was the predefined requirement for NI. Based on these results, TR-701 FA administered once daily for 6 days is noninferior to linezolid administered twice daily for 10 days for the primary and secondary efficacy analyses of Investigator assessment of clinical response.

Results for the sensitivity analysis of the primary (Investigator assessment of clinical success at the PTE Visit) and key additional (clinical response at the EOT Visit) outcomes support the results seen for the primary analysis.

TR-701 FA is noninferior to linezolid for the per-patient microbiological response at the PTE and EOT Visits. There were no meaningful differences between TR-701 FA- and linezolid treated patients for microbial response by baseline pathogen from the primary ABSSSI site or blood culture, or by baseline monomicrobial and polymicrobial infection.

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Conclusions:

TR-701 FA administered once daily for 6 days was statistically noninferior to linezolid administered twice daily for 10 days as assessed by the Investigator assessment for all analysis sets and sensitivity analyses performed. Response rates for the early and late efficacy outcome measures were high and consistent across the varied definitions of the efficacy outcome measures.

TR-701 FA was also statistically noninferior to linezolid for the per-patient and per pathogen microbiological response at the PTE and EOT Visits.

Date of the Report: 05 December 2012