# ABRIDGED CSR

**Title of the Study:** FINAL REPORT (Protocol 3165A1-1108-EU, CSR-75523), A Double-Blind, Placebo-Controlled, Randomized, Single-Dose, 2-Period Crossover Study of the Pharmacodynamics of Orally Administered PSI-697 in Healthy Subjects Who Smoke

**Investigator and Study Centers:**
The study was conducted at a single investigational site. The name and address of the principal investigator is [redacted]

**Study Period:** April 2008 to August 2008

**Clinical Phase:**

| 1 | 2 | 3 | 4 | Other |
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| X | | | | |

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## Introduction

PSI-697 is a novel, orally active inhibitor of the cellular adhesion molecule P-selectin, which offers a unique first-in-class mechanism for preventing the vascular atherothrombotic disease state that is driven by the accumulation of leukocytes and platelets in the vascular wall. PSI-697 may inhibit atherothrombosis by reducing the accumulation of platelets and leukocytes at the sites of atherosclerotic plaques.

This study was conducted to assess the effect of PSI-697 on circulating platelet-monocyte aggregates (PMA) following administration of a single oral dose of 600 mg to healthy subjects.

## Objectives

The primary objective of the study was to assess the pharmacodynamics (PD) of a single oral dose of PSI-697 in healthy subjects who smoke.

The secondary objective of the study was to obtain additional safety and pharmacokinetics (PK) data concerning PSI-697 in healthy subjects who smoke.

## Methodology

This was a single-dose, randomized, double-blind, 2-period, 2-sequence crossover, inpatient and outpatient study of PSI-697 in healthy subjects who smoke. Each subject received single oral doses of 600 mg of PSI-697 and placebo in the fasting state after an overnight fast of at least 10 hours. Each single dose was separated by an interval of at least 7 days. Subjects were randomly assigned to 1 of 2 treatment sequences, A/B or B/A in which A was administration of a single dose of PSI-697 and B was administration of a single dose of placebo.

For details, refer to the appendix: Protocol and Amendments.

## Number of Subjects

Twenty-five (25) healthy men who smoked, aged 19 to 49 years (mean, 30.40 years), were enrolled in this study. All subjects completed the study. A summary of subject demographic and

baseline characteristics is presented in Supportive Table 1.1. A summary of reasons for conclusion of subject participation is presented in Supportive Table 1.2.

**Diagnosis and Main Criteria for Inclusion**

The main inclusion criteria that were used to render a subject eligible for the study included: Men aged 18 to 55 years inclusive at screening, with a body mass index (BMI) in the range of 18.0 to 30.0 kg/m$^2$ and body weight ≥50 kg, and deemed healthy by the investigator. Sexually active men were included if they agreed to use a medically acceptable form of contraception during the study and to continue it for 12 weeks after test article administration. Subjects were smokers of at least 1 pack of cigarettes per day (20 ± 3 cigarettes) for ≥1 year. Subjects had to have a high probability for compliance with and completion of the study, and had to be willing to sign an informed consent form (ICF).

Refer to the appendix, Protocol and Amendments, for a complete list of study inclusion and exclusion criteria.

**Test Product, Dose and Mode of Administration, Batch Number**

PSI-697 was provided as 100 mg capsules. Each subject received a single oral dose of 600 mg PSI-697 (6 x 100 mg capsules) on day 1 (of either period 1 or 2) after an overnight fast of at least 10 hours. Test article was administered with 240 mL of room-temperature water. A summary of test article information is presented in Supportive Table 1.3.

**Duration of Treatment**

Each subject participated in the study for approximately 6 weeks. This included a screening evaluation within 3 weeks before test article administration, two 1-day 1-night inpatient visits, and two 1-day outpatient visits. A minimum of at least 7 days occurred between doses of test article. A follow-up telephone contact occurred approximately 15 days after the administration of the last dose of test article. The total duration of the study was 6 months.

**Reference Therapy, Dose and Mode of Administration, Batch Number**

Placebo capsules were supplied by Wyeth. Each subject received a single oral dose of placebo (6 x placebo capsules) on day 1 (of either period 1 or 2) after an overnight fast of at least 10 hours. Test article was administered with 240 mL of room-temperature water. A summary of test article information is presented in Supportive Table 1.3.

**Criteria for Evaluation**

Assessments were performed according to the schedule described in the appendix, Protocol and Amendments.

**Safety**

Safety results were evaluated from reported symptoms and signs, scheduled physical examinations, vital sign measurements, 12-lead electrocardiogram (ECG) readings, and the results of clinical laboratory tests.

All adverse events (AEs) were recorded from the time subjects signed the ICF.

**Safety Results**

Fifteen (15, 60.0%) subjects experienced AEs; 8 (61.5%) of those subjects received the treatment sequence PSI-697/placebo and 7 (58.3%) subjects received placebo/PSI-697. The listing of AEs and the number and percentage of subjects reporting AEs are presented in Supportive Tables 1.4 and 1.5, respectively.

Ten (10, 40.0%) subjects experienced treatment-emergent adverse events (TEAEs); 4 (30.8%) of those subjects received the treatment sequence PSI-697/placebo and 6 (50.0%) subjects received placebo/PSI-697. The most common TEAE was nasopharyngitis, experienced by 2 (8.0%) subjects in the treatment sequence placebo/PSI-697. The number and percentage of subjects reporting TEAEs are presented in Supportive Table 1.6.

Two (2, 8.0%) subjects, 1 from each treatment sequence, experienced TEAEs that were considered by the investigator as drug related. All TEAEs were considered mild, except skin

laceration (1 subject, 4.0%) which was considered as moderate and as not related to test article. The number and percentage of subjects reporting TEAEs by severity and drug relationship are presented in Supportive Table 1.7.

The medical monitor reviewed all the ECG findings, vital sign measurements, and laboratory test results for potential clinical importance (PCI) and concluded that none were of clinical relevance.

No subject discontinued from the study because of AEs. No subject died and no serious adverse events (SAEs) occurred during the study.

**Summary and Conclusions**

Twenty-five (25) subjects were enrolled in the study. No SAEs or deaths occurred during the study and no subjects withdrew from the study.

PSI-697 was safe and well tolerated when administered as a single oral dose of 600 mg to healthy subjects who smoke.

The PSI-697 program was terminated by the sponsor and therefore this abridged clinical study report has been prepared.