SYNOPSIS

Name of Sponsor/Company: AstraZeneca Pharmaceuticals, LP	Individual Study Table Referring to Part of the Dossier Volume:	*(For National Authority Use Only)*
Name of Finished Product: R935788 Tablets	Page:	
Name of Active Ingredient: **R935788 sodium**		

Title of Study: A Phase II, Open-Label, Efficacy and Safety, Ascending Dose, Pilot Study of R935788 for the Treatment of Adult Refractory Immune Thrombocytopenic Purpura	
Investigators: Refer to Appendix 16.1.4 for the list of Investigators.	
Study Centers: 2 study centers in the United States	
Study Period (years): 4.5 years	Phase of Development: II
Objectives: The primary objective of this pilot study was to assess the preliminary efficacy of R788 in the treatment of chronic refractory immune thrombocytopenic purpura (ITP) as measured by platelet response. The secondary objective of this pilot study was to assess the safety of R788 in the treatment of chronic refractory ITP using standard safety tests.	
Study Design and Methodology: This study was designed to include patients with chronic refractory ITP who were eligible for a 6- to 12 week dose exploration therapeutic trial, and were eligible to continue on study if an investigator defined response was observed. In order to be eligible for study participation, patients had to have ITP defined as a platelet count <30,000/mm^3 consistently for 3 months. In some cases, the baseline platelet count could have been >30,000/mm^3 but the platelet count history 3 months prior to study entry met the ITP inclusion criterion. During the course of the study all patients were to visit the study site on as few as 9 occasions and as many as 39 occasions over a period of approximately 2 months to 25.5 months (with dosing from 6 weeks up to 2 years). After 24 months, patients who continued to demonstrate a sustained response, in the investigator's judgment, were to be offered the opportunity to receive continued ongoing therapy, provided that there were no contraindications. The investigator considered a patient to have had a response based on the protocol defined criteria of a baseline platelet count increase by at least 20,000/mm^3 to a total count of 30,000/mm^3 or more while being treated with R788 and the patient had not received a dose of intravenous immunoglobulin G (IVIg), or other concomitant therapy known to increase platelet counts, within 2 weeks of the increase in platelet count. Secondary endpoints included the percentage of patients who achieved a platelet count of 50,000/mm^3 or greater and the percentage of patients who achieved a platelet count of 150,000/mm^3 or greater. Up to 18 patients (in dose cohorts of 3 to 6 patients) were to be treated with R788 in this study, at doses from 75 mg orally (PO) twice daily (bid) up to a maximum of 225 mg PO bid. At least 3 patients must have been enrolled at a given dose cohort, and have completed 4 weeks of treatment, and the Independent Safety Reviewer (Dr. Doug Cines, University of Pennsylvania) must have provided consent, before any patient could be enrolled into the next higher dose cohort. If 2 or more patients demonstrated a sustained response at a given dose, an additional 3 patients may have been enrolled at that dose. If 4 or more patients demonstrated a sustained response at a given dose, an additional 6 patients could be enrolled to confirm the response and the tolerability.	

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For any given patient, the dose may have been increased by 25 mg PO bid after 2 weeks of treatment at a specific dose, provided that the previous dose had been without significant adverse effects (alanine aminotransferase [ALT] > 3 x upper limit of normal [ULN], polymorphonuclear neutrophils [PMN] <1000/mm^3, and/or other significant National Cancer Institute-Common Toxicity Criteria [NCI-CTC] AE Grade 2 toxicity). The dose may have been increased further in increments of 25 mg PO bid no more frequently than every 2 weeks; however, increases beyond Week 4 required the consent of the Independent Safety Reviewer.

Patients who did not experience a response to any dose by Week 6 were to be withdrawn from treatment. Patients who demonstrated a sustained response by Week 12 were eligible to continue therapy for up to an additional 9 to 21 months at the dose at which the patient sustained the response, provided that there were no contraindications.

Number of Patients (planned and analyzed): A total of 18 patients were planned and analyzed in this study.

Diagnosis and Main Criteria for Inclusion: Patients must have had a diagnosis of chronic refractory ITP for at least 3 months prior to enrollment.

Test and Reference Products, Dose and Mode of Administration, Lot or Batch Numbers:

R788 was supplied in 3 tablet strengths: 25 mg, 50 mg, and 100 mg. Batch numbers: C6B0184, C1145001, C7F0021, C6I0066, C8A00701, and C7K0010.

Duration of Treatment: At the time of data cutoff, 03 May 2010, the maximum duration of treatment received in this study was 1192 days.

Criteria for Evaluation:
Efficacy Assessments: The primary efficacy endpoint was the percentage of efficacy responders. A patient was considered an efficacy responder in the opinion of the investigator, if the platelet count increased by at least 20,000/mm^3 from baseline and to a total count of 30,000/mm^3 or more The baseline platelet count was the closest measurement prior to first dosing time. The secondary efficacy endpoints were the percentage of patients who achieved a platelet count of 50,000/mm^3 or greater and the percentage of patients who achieved a platelet count of 150,000/mm^3 or greater.

Safety Assessments: Safety measurements included clinical laboratory tests (hematology including white blood cell count [WBC] differential counts, chemistry including liver function tests, urinalysis, etc.), physical examinations, vital sign, 12-lead electrocardiograms (ECGs), AEs, and concomitant medications.

Pharmacokinetic and Pharmacodynamic Assessments: Six mL whole blood were collected into a dipotassium ethylenediaminetetraacetic acid vacutainer. Samples were centrifuged at 2750 rpm (1500 g) for 10 minutes at 4°C, within 30 minutes of sampling. Two equal aliquots of plasma were collected into pre-labeled polypropylene sample tubes (Series A and B). Within 30 minutes of centrifugation, all samples were placed in a freezer at -70°C until shipment. Series A were shipped to Quest Pharmaceutical Services and Series B samples were kept at the site. Pharmacokinetic samples were not collected for patients continuing on the study after 24 months of treatment.

Samples were collected for flow cytometry of surface protein markers; no formal analysis of this data was

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performed due to limited sample size.

Statistical Methods: All data collected in this study were to be documented with the help of patient data listings, summary tables, and graphical displays. Descriptive statistics were to be provided by observation time (visit) of interest and treatment group. The statistics for continuous variables were to include the sample size, mean, standard deviation, median (where applicable), and range. The mean and median statistics were to be presented with 1 decimal beyond the accuracy of collection. The standard deviation was to be presented with 2 decimals beyond the accuracy of collection. The range was to be presented using the same accuracy of collection.

Results:
Disposition, Demographics, and Baseline Characteristics: This study was conducted at 2 clinical research centers in the United States.

A total of 18 patients were enrolled; 4 (22.2%) discontinued the study due to 'other' (2 patients failed to respond, 1 patient was withdrawn at Week 20 due to failure to respond, and 1 patient withdrew from the study on his own), 3 (16.7%) due to AEs (however, 2 additional patients are reported in AE tables as having withdrawn due to an AE including 1 patient that died and 1 patient that withdrew consent, below), 2 (11.1%) discontinued at the investigators discretion, 1 patient died, 1 patient discontinued due to being a non-responder at Week 12, and 1 patient withdrew consent.

The mean age of patients was 61.9 years (range: 30 to 81 years), the majority of patients were female (55.6%), and 77.8% of patients were Caucasian. All patients reported using an acceptable method of contraception. All subjects tested negative for HIV, HBV, and HCV. A total of 5 (27.8%) patients had an ITP bleeding history that was severe or life-threatening, 7 (38.9%) patients had been previously hospitalized due to a bleeding event, and 14 (77.8%) patients had a blood or platelet transfusion due to a bleeding event. Medical history included splenectomy for 9 (50.0%) patients) and 11 (61.1%) of patients were classified as hypertensive at study entry by either having hypertension recorded on medical history or by having a supine blood pressure greater than or equal to 140/90 mmHg recorded at screening or the baseline visit. Mean platelet count at baseline was 42,222/mm^3 (range: 6,000 to 155,000/mm^3).

Efficacy: The investigator assessed efficacy response rate for the primary analysis was 50% (5 out of 10 patients) at Week 12 and 57.1% (4 out of 7 patients) at Week 24. Definitive conclusions cannot be drawn due the limited sample size included in this study.

Safety: In this relatively small study of R788 in ITP patients, AEs reported with previous studies of R788 (gastrointestinal effects, transaminase elevations, and hypertension) were among the AEs observed in this study. The frequency and distribution of AEs did not differ greatly from the initial treatment period to the extension period or >25 months into the extension period.

Pharmacokinetic and Pharmacodynamic: Three patients had pharmacokinetic blood samples drawn during treatment with 75 mg bid R788, 5 patients during treatment with 100 mg bid R788, 6 patients during

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treatment with 125 mg bid R788, and 4 patients during treatment with 150 mg bid R788. Due to limitations of sample collection, no formal calculations were performed. Flow cytometry samples were collected; however, no analysis of these data was performed due to limited sample size.		
Date of Report: 11 January 2011		