PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

GENERIC DRUG NAME / COMPOUND NUMBER: Prinaberel / PF-05230913 (ERB-041)

PROTOCOL NO.: 3142A1-202-WW (B2381010)

PROTOCOL TITLE: A Randomized, Parallel, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of 3 Oral Doses of ERB-041 in Subjects With Rheumatoid Arthritis on a Background of Methotrexate Therapy

Study Centers: A total of 47 centers took part in the study and randomized subjects: 21 in the United States (US), 6 in Canada, 5 in Hungary, 4 each in Argentina and Italy, 3 each in Chile and Mexico, and 1 in Spain.

Study Initiation Date and Final Completion Date: 25 July 2005 and 19 October 2006

Phase of Development: Phase 2

Study Objectives:

Primary Objective: To compare the efficacy and safety of 3 dose levels of oral prinaberel administered daily for 12 weeks versus placebo in subjects with active rheumatoid arthritis (RA) who have had a suboptimal response to therapy with stable doses of methotrexate (MTX).

Secondary Objectives:

- To assess health outcomes measures;
- To assess concentrations of prinaberel and explore the potential exposure-response relationship;
- To search for biomarkers that may correlate with severity of RA and/or clinical response to prinaberel using peripheral blood mononuclear cell gene expression and, possibly, protein expression profiling in a subset of subjects.

METHODS

Study Design: This was a randomized, double-blind, parallel-arm, placebo-controlled, multicenter, outpatient study to evaluate the efficacy and safety of 3 oral dose levels of prinaberel (5, 25, and 75 mg daily) versus placebo administered for in subjects with RA on stable doses of MTX who have had a suboptimal response. Subjects participated in the study

for approximately 18 weeks: a screening period not exceeding 4 weeks, a 12-week treatment period, and a 2-week follow-up period. The study flow chart is presented in Table 1.

Table 1. Study Flow Chart

Study Period	**Screening**	**Baseline**	**Treatment**					**Follow-Up**
Study Visit	**Screening**	**Baseline**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Early Withdrawal**	**Final Study Visit[a]**
Study Week	**-4 to -1[a]**	**Day 1**	**2[b]**	**4[b]**	**8[b]**	**12[b]**		**14[b]**
Informed consent	X							
Review eligibility criteria	X	X						
Medical history	X							
ACR functional classification	X							
Physical examination[c]	X	X	X	X	X	X	X	
Vital signs[d]	X	X	X	X	X	X	X	
Joint assessment (28-joint count)	X	X	X	X	X	X	X	
Hand and feet radiographs[e]	X							
Chest radiograph (PA and lateral)[f]	X							
ECG (12-lead)	X					X	X	
DMARD treatment history	→	X						
Corticosteroid / NSAIDs / MTX treatment history	→	X						
Prior medications / treatment for condition other than RA (past 30 days)	→	X						
Concomitant medications / treatments			X	X	X	X	X	X[g]
Randomization		X						
Clinical lab and endocrine evaluations[h]	X	X	X	X	X	X	X	
Women: Pap, gynecologic exam, mammogram[i]	X							
β-HCG[j]	X	X				X	X	
Rheumatoid factor	X					X	X	
CRP and ESR	X	X	X	X	X	X	X	
HBsAg & Hepatitis C Ab	X							
PK samples[k]		X		X	X	X	X	
PG samples (selected sites)[l]		X	X			X	X	
Physician global assessments		X	X	X	X	X	X	
Patient global assessments		X	X	X	X	X	X	
Morning stiffness duration	X	X	X	X	X	X	X	
Pain VAS		X	X	X	X	X	X	
Patient general health VAS thermometer like scale (EQ-5D)		X	X	X	X	X	X	
HAQ		X		X	X	X	X	
Fatigue VAS		X	X	X	X	X	X	

Table 1. Study Flow Chart

Study Period	Screening	Baseline	Treatment					Follow-Up
Study Visit	**Screening**	**Baseline**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Early Withdrawal**	**Final Study Visit[a]**
Study Week	**-4 to -1[a]**	**Day 1**	**2[b]**	**4[b]**	**8[b]**	**12[b]**		**14[b]**
Dispense TA recording worksheet[m]				X	X	X		
TA capsule count/calculate compliance		X	X	X	X	X	X	
TA administration		X	→	→	→	X		
AEs recording[n]	X	→	→	→	→	→	→	X[a]

Ab = antibody; ACR = American College of Rheumatology; AEs = adverse events; BP = blood pressure; CRP = C-reactive protein; DMARD = disease-modifying anti-rheumatic drug; ECG = electrocardiogram; EQ-5D = EuroQOL 5 dimensions questionnaire; ESR = erythrocyte sedimentation rate; HAQ = health assessment questionnaire; HBsAg = hepatitis B surface antigen; β-HCG=beta-human chorionic gonadotropin; FSH = follicle-stimulating hormone; lab = laboratory; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; PA = postero-anterior; Pap=papanicolaou test; PG = pharmacogenomics; PK = pharmacokinetic; PR = pulse rate; PSA = prostate-specific antigen; RA = rheumatoid arthritis; SAE = serious adverse event; SHBG = sex hormone-binding globulin;
TA = test article; VAS = visual analog scale.

a. If approved by the Sponsor, the Screening period could have been extended up to an additional 4 weeks.
b. Study week Visits 2 to 12 and the final study visit were to occur within a window of ±3 days.
c. Height at Screening; body weight at Screening and Week 12 or early withdrawal visits.
d. Vital signs: BP and PR, after sitting for 5 minutes, and oral or tympanic temperature (°F or °C).
e. Hands and feet radiographs were to be performed at Screening, only if needed to diagnose RA.
f. Chest x-ray was to be performed at Screening, unless report of an x-ray performed within the previous 12 months was available.
g. Could be collected by telephone interview, if appropriate, 2 weeks after the end of treatment visit (Week 14), or 2 weeks after the early withdrawal visit.
h. Lab evaluations (ie, hematology, chemistry, urinalysis, coagulation tests). Hormonal safety monitoring: FSH at Screening, and Weeks 8 and 12 or early withdrawal (postmenopausal women only); PSA (men only) at Screening, and Week 12 or early withdrawal; and estradiol (postmenopausal women only), total and free testosterone (men), and SHBG were to be collected at Baseline, and at Week 8 and 12, or early withdrawal.
i. Breast and gynecologic (pelvic) exam, mammogram (age ≥40 years only) and Pap test were to be performed during Screening, unless performed in the previous 9 months and report available.
j. Serum β-HCG pregnancy test for women of childbearing potential at scheduled visits and at any time during the study if warranted for safety evaluation.
k. Trough blood samples (4 mL each) were to be obtained pre dose on Day 1, and within 2 hours of the usual time of the scheduled dose on the Week 4, 8, and 12 visit days. Therefore, subjects were not to take their dose of test article until after all study procedures for that visit were completed. A subset of subjects (approximately 130 subjects) at selected sites were to have an additional plasma PK sample drawn between 6 and 12 hours after TA administration at the Week 4, 8, and 12 visits.
l. Subjects had to sign and date a separate consent form for PG testing prior to any PG blood samples being collected. PG blood samples (whole blood, 8 mL each) were to be collected at Day 1 (prior to starting treatment), and at the Week 2 and 12 visits (or at early withdrawal visit in case of early withdrawal).
m. Subjects were to record the administration date and time for 2 daily doses prior to the day of the Weeks 4, 8, and 12 visits on the TA recording worksheets and bring them to study site at the respective visits.
n. From the signing of the informed consent until completion of final visit. If the AE or SAE continued, the Investigator was to follow-up the event until it had subsided, returned to baseline, or in case of permanent impairment, until the condition stabilized.

Number of Subjects (Planned and Analyzed): The study was planned to enroll a total of 260 subjects (65 subjects per group). A total of 291 subjects were randomized; 73 subjects to receive 5 mg prinaberel, 71 subjects to receive 25 mg prinaberel, 74 subjects to receive 75 mg prinaberel, and 73 subjects to receive placebo.

Diagnosis and Main Criteria for Inclusion: All subjects had to meet the American College of Rheumatology (ACR) criteria for RA, with ACR functional Class I-III, have a disease duration of ≥6 months, a disease onset at >16 years of age, aged 18 to 80 years, and have been treated with a stable, well-tolerated dose and route of administration of MTX (7.5 mg to 20 mg, oral, intramuscular or subcutaneous) weekly for at least 12 weeks before the baseline visit, and have been willing to remain on this fixed dose and route of administration for the duration of the study.

Subjects had to have active RA consisting of ≥5 swollen and ≥5 painful joints (28-joint count) and have met at least 1 of the following 3 criteria:

- Erythrocyte sedimentation rate (Westergren) ≥28 mm/h;
- C-reactive protein ≥15 mg/L;
- Morning stiffness ≥45 minutes.

Subjects with clinically significant findings other than RA or a Papanicolau (Pap) test result with high-grade intraepithelial lesions or malignancy were excluded from the study.

Study Treatment: All subjects were randomized and assigned in a 1:1:1:1 ratio to 1 of the 4 treatment groups: prinaberel 5 mg; prinaberel 25 mg; prinaberel 75 mg; placebo. Capsules were administered once per day orally with food preferably in the morning, for 12 weeks.

Efficacy Endpoints:

Primary Efficacy Endpoint:

- ACR20 at Week 12.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints included but were not limited to the following:

- ACR50 and ACR70 at Week 12;
- Changes in the Disease Activity Score based on the 28-joint count at Week 12;
- ACR20, ACR50, and ACR70 at other time points and components of ACR response score;
- Changes of health outcomes measurements: Health Assessment Questionnaire, Patient General Health and Fatigue measured on a visual analog scale.

Safety Evaluations: Safety evaluations included the results of spontaneously reported signs and symptoms, scheduled physical examinations, elicited history reported by the subjects, vital sign measurements, 12-lead electrocardiograms (ECGs), postero-anterior and lateral chest radiographs, monitoring of all adverse events (AEs) and clinical and endocrine laboratory evaluations.

Statistical Methods: The modified intent-to-treat (mITT) population comprised all randomized subjects who received ≥1 dose of test article. The mITT population was the primary population for efficacy analysis.

Safety analysis was performed on the mITT population.

For the primary endpoint, ACR20 response, the comparisons of primary interest were each prinaberel dose level versus placebo at Week 12. A logistic regression model with treatment as a factor was used. All pairwise comparison p-values and an overall p-value were provided. The 95% confidence interval (CI) of ACR20 response proportion difference prinaberel dose vs placebo) was also provided.

ACR20 at Weeks 2, 4 and 8, and ACR50 and ACR70 at Weeks 2, 4, 8 and 12 were analyzed in the same way as ACR20 at Week 12.

For continuous efficacy endpoints comparison, the change from Baseline was analyzed using analysis of covariance, with treatment as a factor and baseline as a covariate, followed by all the pairwise comparisons of the groups. All pairwise comparison p-values, adjusted mean change from Baseline, 95% CI of adjusted mean change difference (prinaberel dose versus placebo) were provided.

For Baseline data, one-way analysis of variance (ANOVA) model with treatment group as a factor was used to compare groups for all variables, except nominal attributes (eg, sex, race), which were compared by the Fisher's exact test.

The incidence of AEs, treatment-emergent adverse events (TEAEs), and potentially clinically important laboratory measurements during the study was compared between treatment groups using Fisher's exact test procedure. Changes in the laboratory means, body weight and vital signs was compared between treatment groups by ANCOVA.

RESULTS

Subject Disposition and Demography: A total of 291 subjects (4 treatment groups) were enrolled in this study: 73 subjects were randomly assigned to receive 5 mg prinaberel; 71 subjects to receive 25 mg prinaberel; 74 subjects to receive 75 mg prinaberel; and 73 subjects to receive placebo; 247 subjects completed; 44 subjects discontinued.

A total of 34 subjects who received prinaberel and 10 subjects who received placebo were withdrawn from the study. There were no significant differences among treatment groups in the rate of discontinuation (p=0.165). A summary of subject participation is presented in Table 2.

Table 2. Summary of Subject Participation

Conclusion Status Reason[a]	Overall p-Value[b]	Treatment Groups				
		Placebo (N=73)	5 mg Prinaberel (N=73)	25 mg Prinaberel (N=71)	75 mg Prinaberel (N=74)	Total (N=291)
Total		73 (100)	73 (100)	71 (100)	74 (100)	291 (100)
Completed	0.165	63 (86.3)	67 (91.8)	58 (81.7)	59 (79.7)	247 (84.9)
Discontinued	0.165	10 (13.7)	6 (8.2)	13 (18.3)	15 (20.3)	44 (15.1)
AE	0.100	4 (5.5)	1 (1.4)	5 (7.0)[c]	8 (10.8)	18 (6.2)
Discontinuation of study by Sponsor	0.244	0	0	1 (1.4)	0	1 (0.3)
Lost to follow-up	0.524	2 (2.7)	0	0	1 (1.4)	3 (1.0)
Other	0.058	0	0	3 (4.2)	1 (1.4)	4 (1.4)
Protocol violation	0.714	1 (1.4)	1 (1.4)	1 (1.4)	0	3 (1.0)
Subject request	0.247	0	0	0	2 (2.7)	2 (0.7)
Unsatisfactory response-efficacy	0.981	3 (4.1)	4 (5.5)	3 (4.2)	3 (4.1)	13 (4.5)

AE = adverse event; N = total number of subjects.

a. Total discontinued is the sum of individual reasons because they were mutually exclusive by subject.

b. Overall p-value: Fisher's exact test p-value (2-tail).

c. One (1) subject who discontinued because of an AE is included in this table as having discontinued for "Other" reason rather than "Adverse event."

Treatment groups were well balanced with respect to demographic and baseline disease characteristics. A summary of demographic characteristics is presented in Table 3.

Table 3. Summary of Demographic Characteristics

Characteristic	p-Value	Treatment Groups				
		Placebo (N=73)	Prinaberel 5 mg (N=73)	Prinaberel 25 mg (N=71)	Prinaberel 75 mg (N=74)	Total (N=291)
Age (years)	0.410[a]					
N		73	73	71	74	291
Mean		55.04	54.53	52.08	53.45	53.79
Standard deviation		11.97	12.02	10.18	10.94	11.31
Sex	0.069[b]					
Female		68 (93.15)	58 (79.45)	58 (81.69)	60 (81.08)	244 (83.85)
Male		5 (6.85)	15 (20.55)	13 (18.31)	14 (18.92)	47 (16.15)
Race	0.623[b]					
Black/African American		0	3 (4.11)	1 (1.41)	0	4 (1.37)
Other		24 (32.88)	24 (32.88)	23 (32.39)	24 (32.43)	95 (32.65)
White		49 (67.12)	46 (63.01)	47 (66.20)	50 (67.57)	192 (65.98)

N = number of subjects.

a. One-way analysis of variance with treatment as factor.

b. Fisher's exact test p-value (2-tail).

Efficacy Results:

Primary Efficacy Endpoint: The results from the last observation carried forward (LOCF) analysis of the primary efficacy endpoint, ACR20 at Week 12, for the mITT population are presented in Table 4. At Week 12, 27.4% of subjects in the placebo group, 35.6% of subjects in the 5 mg prinaberel group, 35.2% of subjects in the 25 mg prinaberel group, and 27.0% of subjects in the 75 mg prinaberel group achieved an ACR20 response (p=0.518).

Table 4. Number (%) of Subjects Achieving ACR20 Response (mITT Population, LOCF Data)

Week on Therapy	Treatment	N	n (%)	p-Value				95% CI of Proportion Difference With Placebo
				vs Placebo	vs Prinaberel 5mg	vs Prinaberel 25mg	Overall	
Week 2	Placebo	73	5 (6.8)				0.723	
	Prinaberel 5mg	73	9 (12.3)	0.267				(-4.0, 15.0)
	Prinaberel 25mg	71	8 (11.3)	0.360	0.844			(-4.9, 13.8)
	Prinaberel 75mg	74	8 (10.8)	0.401	0.774	0.930		(-5.2, 13.1)
Week 4	Placebo	73	16 (21.9)				0.937	
	Prinaberel 5mg	73	18 (24.7)	0.695				(-11.0, 16.4)
	Prinaberel 25mg	71	16 (22.5)	0.929	0.764			(-13.0, 14.2)
	Prinaberel 75mg	74	15 (20.3)	0.807	0.524	0.740		(-14.8, 11.5)
Week 8	Placebo	73	20 (27.4)				0.806	
	Prinaberel 5mg	73	23 (31.5)	0.586				(-10.7, 18.9)
	Prinaberel 25mg	71	19 (26.8)	0.932	0.531			(-15.2, 13.9)
	Prinaberel 75mg	74	18 (24.3)	0.671	0.333	0.737		(-17.2, 11.1)
Week 12	Placebo	73	20 (27.4)				0.518	
	Prinaberel 5mg	73	26 (35.6)	0.286				(-6.8, 23.2)
	Prinaberel 25mg	71	25 (35.2)	0.313	0.959			(-7.3, 22.9)
	Prinaberel 75mg	74	20 (27.0)	0.960	0.263	0.288		(-14.8, 14.0)

p-Values are based on logistic model response = treatment.
ACR = American College of Rheumatology; CI = confidence interval; LOCF = last observation carried forward; mITT = modified intent-to-treat; N = total number of subjects; n = number of subjects achieving ACR20 response; vs = versus.

Secondary Efficacy Endpoints: Data not available.

Safety Results:

Adverse Events: There was no statistically significant difference among treatment groups in the overall incidence of TEAEs (p=0.763). A summary of the incidence of common TEAEs (occurring in ≥5% of subjects in any treatment group) is presented in Table 5. Among all treatment groups, the most common TEAEs were: headache reported by 22 (7.6%) subjects, nausea reported by 18 (6.2%) subjects, infections reported by 14 (4.8%) subjects, and bronchitis reported by 12 (4.1%) subjects. There was a statistically significant difference among treatment groups in the incidence of serum glutamate pyruvate transaminase (SGPT) increased (p=0.034) and RA flare (p=0.021). Significantly more subjects in the 25 mg prinaberel group experienced increased SGPT compared with those in the 75 mg group (p=0.012). Significantly more subjects in the placebo group and the 25 mg prinaberel group experienced RA flare compared with those in the 5 mg group (p=0.028 and p=0.013, respectively).

Table 5. Number (%) of Subjects Reporting ≥5% TEAEs

Body System[a] Adverse Event	Sex[b]	Overall p-Value[c]	Placebo (N=73) n(F)=68	5 mg Prinaberel (N=73) n(F)=58	25 mg Prinaberel (N=71) n(F)=58	75 mg Prinaberel (N=74) n(F)=60	Total (N=291) n(F)=244
Any adverse event		0.763	46 (63.0)	43 (58.9)	48 (67.6)	47 (63.5)	184 (63.2)
Body as a whole		0.758	19 (26.0)	19 (26.0)	18 (25.4)	24 (32.4)	80 (27.5)
Abdominal pain		0.819	2 (2.7)	3 (4.1)	4 (5.6)	3 (4.1)	12 (4.1)
Headache		0.353	3 (4.1)	5 (6.8)	5 (7.0)	9 (12.2)	22 (7.6)
Infection		0.798	4 (5.5)	3 (4.1)	2 (2.8)	5 (6.8)	14 (4.8)
Cardiovascular system		0.273	7 (9.6)	4 (5.5)	4 (5.6)	10 (13.5)	25 (8.6)
Digestive system		0.069	13 (17.8)	10 (13.7)	9 (12.7)	21 (28.4)	53 (18.2)
Diarrhea		0.370	5 (6.8)	1 (1.4)	2 (2.8)	3 (4.1)	11 (3.8)
Liver function tests abnormal		0.165	1 (1.4)	0	1 (1.4)	4 (5.4)	6 (2.1)
Nausea		0.055	1 (1.4)	4 (5.5)	4 (5.6)	9 (12.2)	18 (6.2)
Hemic and lymphatic system		0.092	0	2 (2.7)	5 (7.0)	3 (4.1)	10 (3.4)
Metabolic and nutritional		0.305	6 (8.2)	5 (6.8)	9 (12.7)	3 (4.1)	23 (7.9)
SGPT increased		0.034*	2 (2.7)	2 (2.7)	6 (8.5)	0	10 (3.4)
Musculoskeletal system		0.064	9 (12.3)	2 (2.7)	10 (14.1)	6 (8.1)	27 (9.3)
Rheumatoid arthritis		0.021*	6 (8.2)	0	6 (8.5)	2 (2.7)	14 (4.8)
Nervous system		0.284	5 (6.8)	5 (6.8)	5 (7.0)	11 (14.9)	26 (8.9)
Respiratory system		0.831	10 (13.7)	9 (12.3)	11 (15.5)	13 (17.6)	43 (14.8)
Bronchitis		0.526	3 (4.1)	1 (1.4)	4 (5.6)	4 (5.4)	12 (4.1)
Skin and appendages		0.916	5 (6.8)	5 (6.8)	3 (4.2)	5 (6.8)	18 (6.2)
Special senses		0.729	2 (2.7)	2 (2.7)	4 (5.6)	4 (5.4)	12 (4.1)
Urogenital system		0.152	3 (4.1)	6 (8.2)	8 (11.3)	2 (2.7)	19 (6.5)
Urinary tract infection		0.509	1 (1.4)	2 (2.7)	4 (5.6)	2 (2.7)	9 (3.1)

Non serious AEss and serious AEs are not separated out.
AEs = adverse events; F = female; N = number of subjects; n = number of subjects with specified criteria; SGPT = serum glutamic pyruvic transaminase; TEAEs = treatment-emergent adverse events.

a. Body system totals are not necessarily the sum of the individual adverse events because a subject may report 2 or more different adverse events in the same body system.
b. Sex: F, M, or blank indicates the calculation is based on subjects categorized by female only, male only, or both.
c. Overall p-value: Fisher's exact test p-value (2-tail). Statistical significance at the .05, .01, .001 levels is denoted by *, **, *** respectively.

Serious Adverse Events (SAEs): Five (5) subjects experienced SAEs during the study. The SAEs were considered treatment-related (definitely, probably, possibily or probably not related) for 4 of these subjects (SAEs of arthritis, arterial thrombosis, SGPT and serum glutamic oxaloacetic transaminase [SGOT] increased, and lab events not classified). In addition, 7 subjects experienced an overdose (6 subjects) or intentional overdose (1 subject). These cases of overdose were not associated with an AE, and, therefore, were not considered as SAEs, although they were reported in the same manner as an SAE. There was no significant difference among treatment groups in the incidence of SAEs. A summary of SAEs is presented in Table 6.

Table 6. Number (%) of Subjects Reporting Serious Adverse Events

Body System[a] Adverse Event	Overall p-Value[b]	Placebo (N=73)	5 mg Prinaberel (N=73)	25 mg Prinaberel (N=71)	75 mg Prinaberel (N=74)	Total (N=291)
Any adverse event	0.526	3 (4.1)	1 (1.4)	4 (5.6)	4 (5.4)	12 (4.1)
Body as a whole	0.578	2 (2.7)	1 (1.4)	3 (4.2)	1 (1.4)	7 (2.4)
Intentional overdose	1.000	0	0	0	1 (1.4)	1 (0.3)
Overdose	0.200	2 (2.7)	1 (1.4)	3 (4.2)	0	6 (2.1)
Cardiovascular system	1.000	0	0	0	1 (1.4)	1 (0.3)
Arterial thrombosis	1.000	0	0	0	1 (1.4)	1 (0.3)
Digestive system	1.000	0	0	0	1 (1.4)	1 (0.3)
Liver function tests abnormal	1.000	0	0	0	1 (1.4)	1 (0.3)
Metabolic and nutritional	0.244	0	0	1 (1.4)	0	1 (0.3)
SGOT increased	0.244	0	0	1 (1.4)	0	1 (0.3)
SGPT increased	0.244	0	0	1 (1.4)	0	1 (0.3)
Musculoskeletal system	1.000	0	0	0	1 (1.4)	1 (0.3)
Arthritis	1.000	0	0	0	1 (1.4)	1 (0.3)
Adverse event associated with miscellaneous factor	0.746	1 (1.4)	0	0	0	1 (0.3)
Laboratory events not classified	0.746	1 (1.4)	0	0	0	1 (0.3)

N = number of subjects; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

a. Body system totals are not necessarily the sum of the individual adverse events because a subject may report 2 or more different adverse events in the same body system.

b. Overall p-value: Fisher's exact test p-value (2-tail).

Deaths: No deaths were reported during the study.

Discontinuations due to Adverse Events: A total of 15 subjects who received prinaberel and 4 subjects who received placebo were withdrawn from the study because of an AE. A summary of subjects who were withdrawn because of AEs is presented in Table 7. There were no significant differences among the treatment groups in any AE that led to withdrawal from the study.

Table 7. Number (%) of Subjects Reporting AEs That Caused Withdrawal From the Study

Body System[a] AE	Overall p-Value[b]	Placebo (N=73)	5 mg Prinaberel (N=73)	25 mg Prinaberel (N=71)	75 mg Prinaberel (N=74)	Total (N=291)
Any AE	0.083	4 (5.5)	1 (1.4)	6 (8.5)	8 (10.8)	19 (6.5)
Body as a whole	0.247	0	0	0	2 (2.7)	2 (0.7)
Abdominal pain	1.000	0	0	0	1 (1.4)	1 (0.3)
Headache	1.000	0	0	0	1 (1.4)	1 (0.3)
Cardiovascular system	1.000	1 (1.4)	0	0	1 (1.4)	2 (0.7)
Arterial thrombosis	1.000	0	0	0	1 (1.4)	1 (0.3)
Thrombophlebitis superficial	0.746	1 (1.4)	0	0	0	1 (0.3)
Digestive system	0.166	0	0	1 (1.4)	3 (4.1)	4 (1.4)
Liver function tests abnormal	0.334	0	0	1 (1.4)	2 (2.7)	3 (1.0)
Nausea	1.000	0	0	0	1 (1.4)	1 (0.3)
Metabolic and nutritional	0.335	1 (1.4)	1 (1.4)	4 (5.6)	1 (1.4)	7 (2.4)
Alkaline phosphatase increased	0.746	1 (1.4)	0	0	0	1 (0.3)
Peripheral edema	1.000	0	0	0	1 (1.4)	1 (0.3)
SGOT increased	0.192	1 (1.4)	1 (1.4)	3 (4.2)	0	5 (1.7)
SGPT increased	0.094	1 (1.4)	1 (1.4)	4 (5.6)	0	6 (2.1)
Musculoskeletal system	0.493	1 (1.4)	0	1 (1.4)	0	2 (0.7)
Arthralgia	0.244	0	0	1 (1.4)	0	1 (0.3)
Rheumatoid arthritis	0.746	1 (1.4)	0	0	0	1 (0.3)
Respiratory system	0.247	0	0	0	2 (2.7)	2 (0.7)
Dyspnea	1.000	0	0	0	1 (1.4)	1 (0.3)
Lung disorder	1.000	0	0	0	1 (1.4)	1 (0.3)
Pharyngitis	1.000	0	0	0	1 (1.4)	1 (0.3)
Pulmonary physical finding	1.000	0	0	0	1 (1.4)	1 (0.3)
Skin and appendages	1.000	0	0	0	1 (1.4)	1 (0.3)
Rash	1.000	0	0	0	1 (1.4)	1 (0.3)
Special senses	1.000	0	0	0	1 (1.4)	1 (0.3)
Blindness transient	1.000	0	0	0	1 (1.4)	1 (0.3)
AE associated with miscellaneous factors	1.000	1 (1.4)	0	0	1 (1.4)	2 (0.7)
Laboratory events not classified	1.000	1 (1.4)	0	0	1 (1.4)	2 (0.7)

AEs = adverse events; N = number of subjects; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

a. Body system totals are not necessarily the sum of the individual AEs because a subject may report 2 or more different AEs in the same body system.

b. Overall p-value: Fisher's exact test p-value (2-tail).

Laboratory Evaluations: The majority of the laboratory test results were National Cancer Institute Grade 0, 1, or 2. Seven (7) Grade 4 laboratory abnormalities were reported during therapy: 1 subject with a serum glutamic oxaloacetic transaminase (SGOT) abnormality, 4 subjects with white blood cell abnormalities, and 2 subjects with neutrophil abnormalities. Of the Grade 3 and 4 laboratory abnormalities reported, those reported in 1 subject were considered to be clinically significant: a subject who received the 25 mg dose of prinaberel experienced elevated liver functions tests (Grade 3 SGPT and Grade 4 SGOT) that were approximately 4 and 6 times the upper limit of normal, respectively, and reported as SAEs. The subject was withdrawn from the study as a result of these clinically significant elevated liver function tests. The subject was asymptomatic. The subject continued use of MTX and diclofenac. The subject's SGPT returned to within normal limits and SGOT returned to 1.5 times the upper limit of normal in 7 days.

CONCLUSION: Prinaberel was generally well tolerated and there were no unexpected safety findings in this subject population. Prinaberel did not demonstrate efficacy in the treatment of RA.