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COMPOUND NUMBER: PH-797804

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NCT NO.: NCT00383188

PROTOCOL NO.: A6631007

PROTOCOL TITLE: A 12-Week, Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Safety, Pharmacokinetics, and Efficacy of PH-797804, Administered Orally Once Daily in Subjects with Active Rheumatoid Arthritis

Study Centers: 43 centers: Brazil (3), Chile (5), Czech Republic (6), Estonia (2), India (6), Republic of Korea (4), Peru (3), Poland (4), Russian Federation (5), South Africa (4), and Spain (1)

Study Initiation and Completion Dates: 15 December 2006 to 16 July 2008

Phase of Development: Phase 2

Study Objectives:

Primary Objective

The primary objective of this study was to evaluate the safety and tolerability of PH-797804 monotherapy in subjects with active RA on their current treatment regimen and having failed in the past at least 1 disease-modifying antirheumatic drug (DMARD) regimen. This was accomplished in a 2-stage design, with an initial safety/pharmacokinetic evaluation stage (Stage 1) in the first 50 treated subjects. A successful Stage 1 launched the second stage (Stage 2) to complete the full enrollment of the study to evaluate the overall safety and tolerability of once daily (QD), oral PH-797804 versus placebo in all subjects through 12 weeks of treatment.

Secondary Objectives

1. To compare the efficacy of 4 dose levels of PH-797804 (0.5, 3, 6, and 10 mg QD) versus placebo, administered over 12 weeks for the treatment of the signs and symptoms of subjects with active rheumatoid arthritis (RA).

2. To evaluate the pharmacokinetic profiles of multiple doses of PH-797804 administered for 12 weeks to subjects with active RA.

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3. To evaluate the dose- and concentration-response of PH-797804 against measures of disease activity through 12 weeks of treatment.

METHODS

Study Design: This was a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week treatment study of a p38 inhibitor with oral delivery in subjects with active RA, on their current treatment regimen and having failed in the past at least 1 DMARD.

Subjects were randomized to receive 1 of 4 doses of PH-797804 (0.5, 3, 6, or 10 mg QD) or placebo. Approximately 290 subjects were to be randomized using a staged approach to initially confirm the safety and tolerability of PH-797804 (Stage 1, n=50) before initiating Stage 2 (n=240) for assessing longer-term safety and efficacy. Twelve-week data from Stage 1 were combined with 12-week data from Stage 2, for a complete analysis of the safety and efficacy of PH-797804. All subjects were followed for safety at 28 days after their last dose administration.

Subjects could continue treatment with stable background arthritis therapies such as non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 (COX-2) inhibitors, but parenteral opioid or intra-articular corticosteroid injections and other DMARDs or biologic response modifiers were not allowed during this study.

The study had a total of 3 interim analyses using un-blinded data: the first after 50 subjects had completed the Week 4 visit, the second after half of the subjects completed the Week 4 visit and the third after all subjects had completed the Week 16 visit. A DMC conducted the first 2 interim analyses which consisted of safety data only. The DMC's recommendation following the first interim analysis was continuation of the study as planned; the DMC also requested to review the safety data when approximately half of the subjects had completed 4 weeks of treatment. The DMC's recommendation following the second interim analysis was continuation of the study as planned. The third interim analysis, which consisted of safety and efficacy data, was performed by the Pfizer study team after all subjects had completed the Week 16 visit.

Number of Subjects (Planned and Analyzed): It was planned to include 290 subjects; 70 subjects per treatment group for placebo, PH-797894 0.5, and 3 mg treatment groups and 40 subjects per treatment group for the PH-797894 6 and 10 mg treatment groups. In total, 302 subjects were randomized as follows: PH-797804 0.5 mg (n=69), PH-797804 3 mg (n=74), PH-797804 6 mg (n=44), PH-797804 10 mg (n=40), placebo (n=75).

Diagnosis and Main Criteria for Inclusion: Male and female subjects who were at least 18 years of age, and had had at least 1 DMARD regimen failure, were included in the study. Subjects had to have been diagnosed with RA in the last 6 months prior to the screening visit, based upon the American College of Rheumatology (ACR) 1987 Revised Criteria, and had to meet the ACR 1991 Revised Criteria for Global Functional Status in RA, Class I, II, or III. Subjects had to have a minimum current level of disease activity under their current

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treatment regimen. Subjects were excluded from the study if they had a diagnosis of any other inflammatory arthritis (eg, spondyloarthropathies) or fibromyalgia.

Study Treatment: PH-797804 capsules (0.5, 3, and 5 mg) and matching placebo were supplied by the sponsor, and were packaged in child resistant high density polyethylene bottles. After randomization, study treatment was dispensed for all treatment groups at the baseline and Weeks 4 and 8 visits. Each subject received his/her first oral dose of study treatment (0.5, 3, 6 or 10 mg of PH-797804, or placebo) in the clinic at the baseline visit. Thereafter, each subject self-administered a single dose of the same study treatment at the same time each day, without regard to food.

- **Efficacy Evaluations:** Assessment of current disease activity level (C-reactive protein and tender and swollen joint counts) at screening.

- ACR20/50/70 assessments performed at baseline and at Weeks 1, 2, 4, 8, 12 and 16:

  - Tender/painful joint count (28) and swollen joint count (28)

  - Physician's global assessment of arthritis (VAS)

  - Patient's global assessment of arthritis (VAS)

  - Patient's assessment of arthritis pain (VAS)

  - Health Assessment Questionnaire-Disability Index (HAQ-DI)

  - C-reactive protein (CRP).

- Disease Activity Score (DAS): calculated at Weeks 1, 2, 4, 8, 12 and 16 as follows: DAS 28-4 [CRP] = $0.56\sqrt{TJC28} + 0.28\sqrt{SJC28} + 0.36\ln(CRP + 1) + 0.014*PGA + 0.96$, where TJC(28) is the tender joint count, SJC(28) is the swollen joint count, ln is the natural logarithm, CRP is C-reactive protein, and PGA is the patient's global assessment of arthritis.

- Short Form-36 (SF-36) Health Survey: completed by the subject at baseline and at Weeks 4 and 12 or early withdrawal visit, prior to any procedures being performed at the visit, if possible.

- Modified Brief Pain Inventory-Short Form (mBPI-SF): completed at baseline and Weeks 1, 2, 4, 8 and 12 or early withdrawal visit.

Exploratory Evaluations: The primary objective of the laboratory exploratory assessments was to allow for the collection, storage, and use of samples to investigate possible associations between biomarker and genetic variation in relation to response to PH-797804 and in relation to characteristics of RA.

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Pharmacokinetic Evaluations: Blood samples (5 mL) were collected in blood collection tubes containing potassium EDTA at baseline and at Days 4, 7, 10, 14, 21, 28, 42, 56 and 84, for pharmacokinetic analysis of PH-797804.

Pharmacokinetic samples were analyzed using a validated analytical method in compliance with the sponsor's standard operating procedures.

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (blood pressure, pulse rate), 12-lead electrocardiograms (ECGs), adverse event (AE) monitoring and safety laboratory tests.

Statistical Methods: For the primary efficacy endpoint, ACR20 responder rate at Week 12, the treatment effect was assessed by the chi-square test. A logistic regression model was used to investigate dose-response relationship between ACR20 response rate at Week 12 on the logit scale and dose with adjustment of the country effect.

Repeated measures logistic regression model were used to investigate the dose-response relationship for ACRs (ACR20/50/70) at Weeks 1, 2, 4, 8, 12 and 16.

For the efficacy endpoints, tender/painful joint count, swollen joint count, physician's global assessment of arthritis (VAS), patient's global assessment of arthritis (VAS), patient's assessment of arthritis pain, HAQ-DI, CRP, SF-36, and mBPI-SF, the treatment effect was assessed using a repeated measures analysis of covariance (ANCOVA) model.

For the pharmacokinetic evaluation, plasma PH-797804 concentrations and corresponding dose and sample times were analyzed using nonlinear mixed effects modeling approaches. Evaluation of the samples collected for exploratory assessments was not within the scope of this study report.

RESULTS

Subject Disposition and Demography: Of the 625 subjects screened, 302 subjects were randomized to 1 of 5 treatment groups (Table S1). The majority of subjects in all treatment groups completed the study; the percentage of subjects discontinuing from the study ranged from 14.9% in the PH-797804 3 mg group to 30.7% in the placebo group. In the PH-797804 0.5 mg group, the majority of discontinuations were due to lack of efficacy, whereas in the other treatment groups the most common reason for subject discontinuation was the occurrence of an AE. All subjects were analyzed for efficacy and safety. The Phase 2 concentration-time data from this study reflects 222 subjects with sparse pharmacokinetic sampling taken over a 12 week period (N=1469 observations). Amongst the 227 potential Phase 2 subjects, a total of 222 subjects had available pharmacokinetic data. Five subjects were not included in the analysis: 2 subjects had no response data and 3 had un-resolvable data issues; none of the data issues were considered systemic.

It should be noted that 5 subjects (3 in the PH-797804 6 mg group and 2 in the 10 mg group) who discontinued had the reason recorded as an AE in the AE Form but as 'protocol violation/no longer willing to participate' in the Subject Summary Form. In the clinical study report, the 5 subjects are considered as discontinued due to an AE.

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Table S1. Subject Evaluation Groups

Number (%) of Subjects	PH-797804 0.5 mg	PH-797804 3 mg	PH-797804 6 mg	PH-797804 10 mg	Placebo
Screened (N=625)					
Assigned study treatment (N=302)					
Treated	69	74	44	40	75
Completed	52 (75.4)	63 (85.1)	31 (70.5)	28 (70.0)	52 (69.3)
Discontinued	17 (24.6)	11 (14.9)	13 (29.5)	12 (30.0)	23 (30.7)
Adverse event	4 (5.8)	7 (9.5)	9 (20.5)[a]	8 (15.0)[b]	8 (10.7)
Lack of efficacy	9 (13.0)	3 (4.1)	3 (6.8)	2 (5.0)	6 (8.0)
Lost to follow-up	0	0	0	0	1 (1.3)
Other	3 (4.3)	1 (1.4)	0[a]	2 (5.0)[b]	6 (8.0)
Subject no longer willing to participate in the study	1 (1.4)	0	1 (2.3)	0[b]	2 (2.7)
Analyzed for efficacy (FAS)	69 (100.0)	74 (100.0)	44 (100.0)	40 (100.0)	75 (100.0)
Analyzed for safety (safety analysis set)					
Adverse events	69 (100.0)	74 (100.0)	44 (100.0)	40 (100.0)	75 (100.0)
Laboratory data	69 (100.0)	74 (100.0)	44 (100.0)	40 (100.0)	75 (100.0)

FAS = Full analysis set

[a] 3 subjects were recorded as discontinued due to 'other reason' (protocol violation) in the Subject Summary Form, but were actually discontinued due to AEs. They have been included in the 'AE' category in this table.

[b] 1 subject was recorded as discontinued due to 'other reason' (protocol violation) 1 subject was recorded as 'no longer willing to participate' in the Subject Summary Form. Both subjects were actually discontinued due to AEs and have been included in the AE category in this table.

Baseline subject characteristics were similar across treatment groups. The majority of subjects (85%) were female and approximately 55% were white. The mean age was 52.8 years. On average, subjects had had RA for 8.7 years (range 0.4 to 38.8 years).

At baseline subjects had active disease; the average mean number of tender/painful (28) joint counts was 16.6, the average mean number of swollen (28) joint counts was 13.5, and the average DAS28 was 6.27.

Efficacy Results: ACR Response Rates: The placebo-adjusted ACR20 responder rates at Week 12 were 8.1%, 10.8%, 9.8% and 8.9% for PH-797804 0.5 mg, 3 mg, 6 mg and 10 mg, respectively. There was no significant difference between the treatment groups in the percentage of subjects achieving an ACR20 response at Week 12 (Table S2).

The mean (±SE) ACR20 responder rates at Week 12 for each treatment group are presented graphically in Figure S1.

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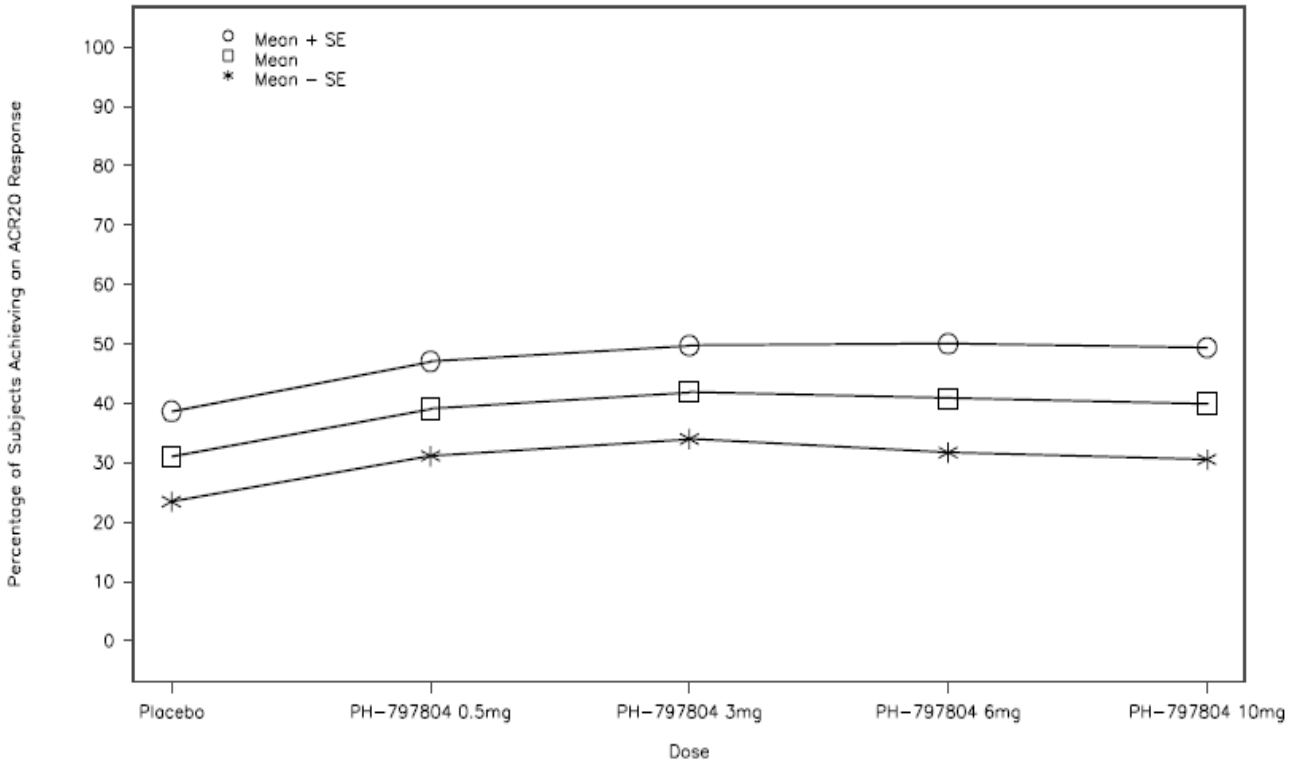
Table S2. ACR20 Response Rate at Week 12 (LOCF) – FAS

					Difference from Placebo			
	N	n	Percent	SE	Difference	SE of Difference	95% CI	p-value
PH-797804 0.5 mg	69	27	39.1	5.88	8.05	7.97	-7.565, 23.664	0.3131
PH-797804 3 mg	74	31	41.9	5.74	10.81	7.86	-4.602, 26.224	0.1719
PH-797804 6 mg	44	18	40.9	7.41	9.83	9.16	-8.123, 27.779	0.2783
PH-797804 10 mg	40	16	40.0	7.75	8.92	9.43	-9.566, 27.404	0.3381
Placebo	74	23	31.1	5.38	-	-	-	-

N = number of subjects, n = number of responders, SE = Standard error, CI = Confidence interval
p-value based on Chi-square test

Figure S1. ACR20 Responder Rate (%) by Dose at Week 12 (LOCF) - FAS



A linear logistic regression was used to model the ACR20 response rate at Week 12 on the logit scale, with dose as the predictor variable. The effect of dose was not significant, and there was no evidence of a linear trend between the logit of ACR20 response and the dose. A similar conclusion can be drawn with non-linear E_{max} model, in which a 3-parameter E_{max} model was used to model the dose response between logit of ACR20 response rate at Week 12 and dose.

Longitudinal logistic regression analysis of ACR20 response at Weeks 1, 2, 4, 8, 12 and 16 using a linear link function suggested that there was an early treatment effect attenuated with

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time. This corresponded with the ACR20 weekly response rates, where the separation between each dose and placebo was reduced over time.

Consistent with the indication of early treatment effect which was not sustained, significant differences compared to placebo ($p < 0.05$; Chi square test) were observed only for the ACR50 responses at Week 2 (PH-797804 3, 6 and 10 mg treatment groups) and Week 4 (PH-797804 6 and 10 mg groups). There were no significant differences between treatment groups in ACR70 response rates at any time point.

Tender/Painful Joint Count and Swollen Joint Count: There were no statistically significant differences for PH-797804 versus placebo in swollen joint count at any time point. For tender/painful joint count, statistically significant improvements compared to placebo were observed at Week 12 for PH-797804 0.5 mg ($p = 0.0410$), at Weeks 8 and 12 for PH-797804 3 mg ($p = 0.0434$ and 0.0255, respectively), and at Weeks 2, 4 and 12 for PH-797804 6 mg ($p = 0.0187$, $p = 0.0394$, and $p = 0.0410$, respectively). There were no statistically significant differences for PH-797804 10 mg versus placebo in tender joint count at any time point.

C-Reactive Protein: C-reactive protein showed an initial reduction from baseline with PH-797804 treatment (mean value change of up to 40%) at Week 1, but by Week 2 values started to return to baseline values. Statistically significant differences compared to placebo were observed at Week 1 for all PH-797804 treatment groups (0.5 mg $p = 0.0447$; 3 mg $p = 0.0005$; 6 mg $p = 0.0006$; 10 mg $p = 0.0019$), and at Week 2 for PH-797804 3 mg and 6 mg ($p = 0.0276$ and $p = 0.0093$, respectively).

VAS assessments: Results from the physician's global assessment of arthritis, patient's global assessment of arthritis and patient's assessment of arthritis pain showed significant differences from placebo for the PH-797804 3 mg dose group at Week 12. The PH-797804 3 mg and 6 mg dose groups were also statistically significantly different from placebo at many of the earlier timepoints for these measures.

HAQ-DI: Mean HAQ-DI score was decreased from baseline at Weeks 1, 2, 4, 8, 12 and 16 with all treatments, but to a greater extent with PH-797804 3 and 6 mg doses; often with a statistically significant difference compared to placebo. No statistically significant treatment differences compared to placebo were observed for the PH-797804 0.5 or 10 mg treatment groups.

DAS28-4(CRP): Mean DAS28-4(CRP) was decreased from baseline at Weeks 1, 2, 4, 8, 12 and 16 with all treatments, but to a greater extent with PH-797804 3 and 6 mg doses. Statistically significant decreases from baseline compared to placebo were observed at Weeks 1, 2, 4, 8, and 12 for the PH-797804 3 and 6 mg doses and at Weeks 1 and 2 only for the PH-797804 10 mg dose. No statistically significant treatment differences compared to placebo were observed for the PH-797804 0.5 mg dose.

SF36: The physical component score of the SF-36 health survey was statistically significantly increased from baseline at Weeks 4 and 12 with PH-797804 3 and 6 mg doses. The mental component score of the SF-36 health survey was increased from baseline at

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Weeks 4 and 12 with all treatment groups; however, there were no statistically significant differences compared to placebo.

mBPI-SF: Results were generally consistent with the other secondary endpoints. For the 'pain at it's worst' data, statistically significant decreases from baseline compared to placebo were observed at Weeks 1, 2, 4, 8, and 12 for the PH-797804 3 mg dose and at Weeks 1, 2 and 8 only for the 6 mg dose. No statistically significant treatment differences compared to placebo were observed for the PH-797804 0.5 or 10 mg doses.

Withdrawal due to lack of efficacy was most prevalent in the PH-797804 0.5 mg (13% of subjects) and placebo (8.0% of subjects) treatment groups. The time to withdrawal due to lack of efficacy was typically between 30 and 50 days, which was consistent with the attenuation of the early treatment effect

Pharmacokinetic Results: PH-797804 exposures in this study were substantially higher than those expected at equivalent doses based on Phase 1 data. This was due to the lower estimated mean CL/F values for a typical male subject in this study (4.20, 4.25, 5.05, and 5.74 L/hr, respectively, at 0.5, 3, 6, and 10 mg PH-797804), compared to equivalent predictions based on the Phase 1 model (6.75, 10.5, 12.4, and 14.1 L/hr, respectively, at 0.5, 3, 6, and 10 mg PH-797804). In addition, gender was a predictor of CL/F in this study, with females having approximately 82% the clearance of males. Since the majority of subjects in the current study were female, mean estimated PH-797804 exposures were further increased compared to predictions from Phase 1 data.

Safety Results: Treatment emergent AEs were experienced most commonly by subjects in the PH-797804 10 mg treatment group (82.5%) and by a similar percentage of subjects in the PH-797804 0.5 mg and placebo groups (55.1% and 56.0%, respectively).

Adverse events which were reported by >5% of subjects in any treatment group (all causalities) are listed in Table S3. The most commonly reported all causality AEs across all treatment groups were diarrhea, rash (including rash, rash macular, rash maculo-papular, rash papular and rash pruritic), and pharyngitis. The most commonly reported treatment-related AEs in the PH-797804 treatment groups were rash (multi-term event), diarrhea and dizziness. The most commonly reported treatment-related AEs in the placebo group were rheumatoid arthritis and constipation. The majority of AEs were considered mild or moderate in intensity.

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Table S3. Incidence of Most Commonly Reported[a] Treatment Emergent Adverse Events

Number (%) of subjects with MedDRA (v11.0) preferred term:	PH-797804 0.5 mg N=69		PH-797804 3 mg N=74		PH-797804 6 mg N=44		PH-797804 10 mg N=40		Placebo N=75	
	A/C	T/R	A/C	T/R	A/C	T/R	A/C	T/R	A/C	T/R
Any AE	38 (55.1)	15 (21.7)	47 (63.5)	23 (31.1)	31 (70.5)	21 (47.7)	33 (82.5)	26 (65.0)	42 (56.0)	20 (26.7)
Diarrhoea	4 (5.8)	0	4 (5.4)	2 (2.7)	4 (9.1)	2 (4.5)	7 (17.5)	2 (5.0)	5 (6.7)	1 (1.3)
Rash[b]	0	0	6 (8.1)	3 (4.1)	3 (6.8)	3 (6.8)	4 (10.0)	3 (7.5)	2 (2.7)	1 (1.3)
Pharyngitis	3 (4.3)	1 (1.4)	7 (9.5)	0	1 (2.3)	1 (2.3)	2 (5.0)	0	1 (1.3)	0
Rheumatoid arthritis	1 (1.4)	0	1 (1.4)	1 (1.4)	3 (6.8)	2 (4.5)	3 (7.5)	1 (2.5)	6 (8.0)	2 (2.7)
Nasopharyngitis	4 (5.8)	0	1 (1.4)	0	1 (2.3)	0	5 (12.5)	1 (2.5)	2 (2.7)	0
Urinary tract infection	1 (1.4)	0	4 (5.4)	2 (2.7)	2 (4.5)	1 (2.3)	3 (7.5)	0	2 (2.7)	0
Bronchitis	1 (1.4)	0	3 (4.1)	0	0	0	3 (7.5)	0	5 (6.7)	1 (1.3)
Dizziness	2 (2.9)	1 (1.4)	2 (2.7)	1 (1.4)	1 (2.3)	1 (2.3)	5 (12.5)	3 (7.5)	1 (1.3)	0
Hypertension	0	0	2 (2.7)	1 (1.4)	3 (6.8)	0	4 (10.0)	2 (5.0)	2 (2.7)	1 (1.3)
Headache	4 (5.8)	2 (2.9)	2 (2.7)	1 (1.4)	2 (4.5)	1 (2.3)	0	0	2 (2.7)	0
Constipation	3 (4.3)	3 (4.3)	1 (1.4)	0	0	0	3 (7.5)	2 (5.0)	3 (4.0)	2 (2.7)
Back pain	1 (1.4)	0	0	0	2 (4.5)	0	4 (10.0)	0	3 (4.0)	0
Oedema peripheral	4 (5.8)	0	1 (1.4)	0	0	0	1 (2.5)	1 (2.5)	2 (2.7)	0
Vomiting	0	0	4 (5.4)	3 (4.1)	1 (2.3)	0	2 (5.0)	1 (2.5)	0	0
Gastritis	0	0	2 (2.7)	0	0	0	3 (7.5)	3 (7.5)	1 (1.3)	0
Upper respiratory tract infection	1 (1.4)	0	4 (5.4)	1 (1.4)	0	0	0	0	0	0

A/C = All causality, T/R = Treatment-related
[a] Reported by >5% of subjects in any treatment group
[b] Rash includes the MedDRA terms of rash, rash macular, rash maculo-papular, rash papular and rash pruritic
Note: Listed in descending order of total events reported across all treatment groups

Treatment-emergent AEs which led to discontinuation were experienced by 36 subjects as summarized in Table S4 and Table S5.

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Table S4. Discontinuations Due to Treatment-Emergent Adverse Events (PH-797804)

Age (years)	Sex	Adverse Event	Severity	Treatment-Related	Outcome
PH-797804 0.5 mg					
72	M	Atrial fibrillation[a]	Severe	No	Resolved
48	F	Rheumatoid arthritis	Severe	No	Still present
38	F	Arthralgia	Severe	No	Resolved
55	M	Dermatitis acneiform, Pruritus	Moderate	Yes	Resolved
PH-797804 3 mg					
40	F	Viral infection[a]	Severe	No	Resolved
65	F	Electrocardiogram QT prolonged	Mild	Yes	Resolved
55	F	Pruritus	Severe	Yes	Resolved
56	F	Ventricular extrasystoles	Moderate	Yes	Resolved
66	F	Palpitations, Diarrhoea, Chills	Mild	Yes	Resolved
		Asthenia, Dizziness	Moderate	Yes	Resolved
51	F	Pyrexia	Mild	No	Resolved
49	F	Gastroenteritis	Moderate	Yes	Resolved
PH-797804 6 mg					
60	F	Rheumatoid arthritis	Severe	Yes	Resolved
45	F	Cyclitis[a]	Moderate	No	Still present
46	F	Transaminases increased	Mild	Yes	Resolved
45	F	Pruritus	Severe	Yes	Resolved
56	F	Rash maculo-papular	Moderate	Yes	Resolved
55	F	Joint swelling	Severe	No	Still present
64	M	Myocardial infarction[a]	Severe	No	Resolved
60	F	Vomiting[a], Pyrexia[a]	Moderate	No	Resolved
47	M	Limb injury[a]	Mild	No	Resolved
PH-797804 10 mg					
58	F	Enterocolitis	Moderate	No	Resolved
		Gastritis	Moderate	Yes	Still present
61	F	Anaemia[a]	Severe	Yes	Resolved
		Myocardial infarction[a], Gastrointestinal haemorrhage[a]	Severe	Yes	Resolved
		Colitis[a], Gastritis[a]	Severe	Yes	Still present
		Vomiting	Moderate	Yes	Resolved
		Urinary tract infection[a]	Moderate	No	Resolved
36	F	Diarrhoea	Moderate	Yes	Resolved
62	F	Back pain	Moderate	No	Resolved
61	F	Oedema peripheral[a]	Moderate	Yes	Still present
		Herpes simplex[a]	Moderate	Yes	Resolved
35	F	Aphthous stomatitis	Severe	Yes	Still present
24	M	Rash	Moderate	Yes	Resolved
		Diarrhoea	Severe	Yes	Resolved
60	F	Dermatitis allergic	Moderate	Yes	Resolved

[a] Adverse event was a serious adverse event

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Table S5. Discontinuations Due to Treatment-Emergent Adverse Events (Placebo)

Age (years)	Sex	Adverse Event	Severity	Treatment-Related	Outcome
Placebo					
61	M	Rheumatoid arthritis	Severe	Yes	Resolved
54	F	Rheumatoid arthritis	Moderate	No	Still present
45	F	Fibromyalgia	Moderate	No	Resolved
		Polyarthritis	Moderate	No	Resolved
54	F	Diarrhoea[a], Sensory disturbance[a], Hypovolaemic shock[a]	Severe	Yes	Resolved
48	M	Rheumatoid arthritis	Moderate	No	Resolved
50	F	Herpes zoster	Moderate	Yes	Still present
60	F	Electrocardiogram Q wave abnormal	Mild	No	Resolved
55	F	Arthralgia	Severe	No	Resolved

[a] Adverse event was a serious adverse event

One subject died of respiratory failure in the context of pneumonia, 47 days after last dose of PH-797804 0.5 mg. This death was considered not related to study treatment by the investigator.

Treatment-emergent SAEs were experienced by 15 subjects as detailed in Table S6. This includes the subject who died. Five subjects experienced SAEs which were considered by the investigator to be related to study treatment. The majority of the SAEs were resolved at the end of the study.

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Table S6. Treatment Emergent Serious Adverse Events

Age (years)	Sex	Adverse Event	Severity	Treatment-Related	Outcome
PH-797804 0.5 mg					
72	M	Atrial fibrillation[a]	Severe	No	Resolved
		Pneumonia, Respiratory failure[b]	Severe	No	Still present
69	F	Pre-syncope	Severe	No	Resolved
PH-797804 3 mg					
40	F	Viral infection[a]	Severe	No	Resolved
62	F	Arthralgia	Moderate	No	Resolved
62	F	Acute coronary syndrome	Severe	Yes	Resolved
PH-797804 6 mg					
64	M	Myocardial infarction[a]	Severe	No	Resolved
60	F	Vomiting, Pyrexia[a]	Moderate	No	Resolved
47	M	Limb injury[a]	Mild	No	Resolved
45	F	Cyclitis[a]	Moderate	No	Still present
PH-797804 10 mg					
61	F	Anaemia[a]	Severe	Yes	Resolved
		Myocardial infarction[a], Gastrointestinal haemorrhage[a]	Severe	Yes	Resolved
		Colitis[a], Gastritis[a]	Severe	Yes	Still present
		Urinary tract infection[a]	Moderate	No	Resolved
57	F	Electrocardiogram change	Mild	No	Resolved
57	F	Gastroenteritis, Dehydration	Moderate	Yes	Resolved
61	F	Oedema peripheral[a]	Moderate	Yes	Still present
		Herpes simplex[a]	Moderate	Yes	Resolved
		Apthous stomatitis	Mild	No	Resolved
35	F	Abdominal pain	Mild	No	Resolved
Placebo					
54	F	Diarrhoea[a]	Severe	Yes	Resolved
		Sensory disturbance[a], Hypovolaemic shock[a]	Severe	Yes	Resolved

[a] Adverse event led to subject discontinuation from the study
[b] Eventual fatal outcome

There were no clinically significant changes in laboratory parameters or vital signs parameters during the study.

CONCLUSIONS: PH-797804 administered QD for 12 weeks in doses of 0.5, 3, 6, and 10 mg was generally safe and well-tolerated in this population of subjects with active RA.

No doses of PH-797804 were significantly different from placebo with respect to the primary endpoint ACR20 response at Week 12. PH-797804 showed transient moderate efficacy that was not maintained over time.

PH-797804 exposures achieved at all 4 dose levels in this study were higher than originally targeted for the purpose of establishing proof-of-concept.

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