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COMPOUND NUMBER: PF-00885706

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NATIONAL CLINICAL TRIAL NO.: NCT00730665

PROTOCOL NO.: A8311003

PROTOCOL TITLE: A Parallel-Group, Randomized, Double-Blind, Multi-Center Dose Response Study to Evaluate the Efficacy and Safety of PF-00885706, a 5-HT_4 Receptor Partial Agonist, as Add-On Therapy to Esomeprazole for the Relief of Symptoms in Subjects with Gastro-Esophageal Reflux Disease (GERD) Who Have a Poor Response to Proton Pump Inhibitor (PPI) Treatment

Study Centers: Belgium – 1 centre, Brazil – 4 centres, France – 9 centres, Germany - 13 centres, Korea – 5 centres, Slovakia – 4 centres, Spain – 2 centres

Study Initiation and Completion Dates: 24 January 2008 to 31 October 2008 (last subject last visit) - The study was terminated prematurely.

Phase of Development: Phase 2

Study Objectives:

Primary Objective

- To understand the dose-response characteristics of PF-00885706 for efficacy in terms of symptomatic relief when used as add-on treatment to 20 mg esomeprazole (standard PPI treatment), in subjects with GERD who have inadequate relief with PPIs.

Secondary Objectives

- To evaluate the safety of PF-00885706 in subjects with GERD who are poor responders to PPI treatment.
- To evaluate the population pharmacokinetics (POPPK) for PF-00885706 in a population of subjects with GERD in order to support the development of a pharmacokinetic pharmacodynamic (PKPD) model.
- To validate a modified patient reported outcome (PRO) instrument (modified version of the patient assessment of gastrointestinal symptoms [PAGI-SYM] instrument) in both paper and electronic formats.

METHODS

Study Design: This was a randomised, double-blind, placebo-controlled, parallel-group Phase II study using 4 dose levels of PF-00885706 (100 µg, 300 µg, 1 mg or 3 mg twice a day [BID]). The planned total duration of the study was 14 weeks.

The study comprised 4 phases:

1) 2-week Screening period.
2) 6-week run-in period with standard background PPI (20 mg esomeprazole).
3) 4-week randomised treatment period.
4) 2-week follow-up period.

Subjects were to be assessed for inclusion in the study and for baseline parameters at an initial Screening Visit 1 (Day -56) and return 7 to 14 days later for Visit 2 (Day -42) when they were to enter a run-in phase lasting 6 weeks (42 days), during which they were to take a standard background PPI (20 mg esomeprazole) once daily, 1 hour before breakfast. Subjects were to be seen in the clinic at Visit 3 (Day -21) and again on Visit 4 (Day 1). Subjects who met the randomisation criteria were to be randomised to 1 of the active treatment arms of PF-00885706 (100 µg, 300 µg, 1 mg or 3 mg BID) or matching placebo on Day 1. The first dose of PF-00885706 was to be administered in the clinic on Day 1 and the subject was to remain in the clinic for 3 hours. Supine and standing blood pressure (BP) were to be monitored hourly for 3 hours post-dose or if the subject became symptomatic. Subjects who developed orthostatic hypotension (symptomatic or asymptomatic) were to be excluded. Subjects were to take study treatment BID for 4 weeks (28 days) while continuing to take 20 mg esomeprazole once daily. Subjects were to attend the clinic at weekly (7 to 10 days) intervals until the end of treatment (Visit 5 [Day 8], Visit 6 [Day 15], Visit 7 [Day 22], Visit 8 [Day 29]) and attend for a follow-up visit 2 weeks later (Visit 9 [Day 43]). Visits 2, 3, 4 and 9 could have occurred within ±3 days of the scheduled date.

Subjects discontinuing study treatment after randomisation were not to be replaced. Any subject who discontinued at any time during the course of the study was to be followed up for safety assessments by returning 2 weeks later to complete the follow-up visit (Visit 9).

Number of Subjects (Planned and Analysed): It was planned to enroll approximately 450 subjects into the study to ensure a total of 250 evaluable subjects (50 subjects per treatment group). However, 1 subject died suddenly in this study on 29 September 2008 and notification to the sponsor followed on 30 September 2008. As a safety precaution, on 30 September 2008, the sponsor elected to put the study on immediate temporary hold. This was communicated to all health authorities in countries where the study was running by 01 October 2008. The Food and Drug Administration put the study on Full Clinical Hold on 02 October 2008. This was revised to a Partial Clinical Hold on 14 January 2009. At the time of death, 145 subjects had been screened and 67 subjects had been randomised to the study.

An autopsy was performed on 01 October 2008 and the full translated results were received by the sponsor on 21 November 2008. The autopsy described the cause of sudden death as "suspected cardiac arrhythmia due to high grade coronary artery sclerosis (high grade calcification) and old myocardial infarction". The autopsy also revealed conditions of chronic bronchitis, emphysema and pulmonary hypertension. The subject had several cardiac risk factors, but the findings of an old myocardial infarction on the left side and coronary heart disease were unknown until the autopsy. However, the sponsor could not exclude a possible contributory role of study treatment (PF-00885706) to the subject's death.

Based on the additional information received from the autopsy, the sponsor considered that the benefit/risk assessment for the product remained positive. However, in order to continue the study, modifications to the protocol may have been required and the sponsor considered that these potential modifications, combined with the complications of study re-initiation activities, made the study impractical to complete in a reasonable timeframe. Therefore, the sponsor decided to terminate study A8311003 on 26 November 2008.

As required for any terminated study, full safety results are reported. Key efficacy results are also reported.

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 18 to 65 years inclusive with a body mass index of 18 to 40 kg/m^2 and a diagnosis of GERD, who had symptoms for at least 6 months prior to enrollment, had daily treatment with a PPI at screening and had been on such treatment for at least 3 months, had symptoms that were persistent, troublesome and included heartburn and/or regurgitation as predominant symptoms despite treatment with a PPI and were seeking relief of persistent symptoms.

Study Treatment: Study treatment was formulated in capsules covering the dose ranges 100 µg, 300 µg, 1 mg, 3 mg and placebo. Run-in medication was supplied as 20 mg esomeprazole tablets. Rescue medication was supplied as 500 mg sodium alginate tablets.

In the 6-week (42 days) run-in period, subjects were to take 20 mg esomeprazole once daily, 1 hour before breakfast, with water, and the tablets were not to be chewed. Subjects received their first dose of PF-00885706 (100 µg, 300 µg, 1 mg or 3 mg) or matching placebo in the clinic on Day 1 of the 4-week (28 days) randomised treatment period. PF-00885706 or placebo capsules were to be taken every 12 hours, with water, and were not to be chewed. Subjects were to continue to take 20 mg esomeprazole once daily during the 4-week randomised treatment period. Rescue medication could be taken as required by the subject and in line with advice given by the investigator.

Efficacy Evaluations:

Unmodified PAGI-SYM

The unmodified PAGI-SYM paper-based instrument comprises 20 items that assess symptom severity on a 6-point Likert scale. This questionnaire has been fully validated in subjects with GERD and was to be administered at Visits 4, 6 and 8 (or at final visit for subjects who discontinued early). The subjects completed the questionnaire at the clinic visit for symptoms from the previous 2 weeks.

Modified PAGI-SYM

The unmodified PAGI-SYM was modified in 3 ways in order to assess the range, frequency and diurnal pattern of GERD symptoms in this clinical study population (GERD subjects who were poor responders to PPIs).

The modified PAGI-SYM was administered to subjects as an electronic diary.

Electronic Diary

The electronic symptom diary collected data on the following events:

1. The daily severity of daytime heartburn and regurgitation and of heartburn and regurgitation during the night (during sleep time), using a recall period of 'the past 24 hours'.
2. The severity of the remaining 24 symptoms of the modified PAGI-SYM at the end of each week using a recall period of 'the past week'.
3. The daily number of rescue medication tablets used.

The electronic diary was to be distributed to subjects at Visit 2. At all subsequent visits, subjects were to return their diaries to investigators in order to facilitate the electronic download of the data contained in them.

Paper Diary

In order to safeguard the integrity of data collection on the co–primary endpoints of the study, subjects were asked to complete a daily paper diary on the days between Visits 3 and 4 and between Visits 7 and 8. This diary elicited data on the daily severity of daytime and night time heartburn and regurgitation.

Patient Global Impression of Change

The patient global impression of change is a subject-rated instrument that was designed to assess subject global satisfaction with treatments. It was to be administered at the end of Visits 6 and 8 (or at final visit for subjects who discontinued early) and completed by the subject at the clinic visit.

Patient Assessment of Gastrointestinal Quality Of Life

The patient assessment of gastrointestinal quality of life is a fully validated and culturally adapted paper instrument to assess health-related quality of life in GERD sufferers. The PAGI-QOL was to be administered at Visits 4, 6 and 8 (or at final visit for subjects who discontinued early) and completed by the subject during the clinic visit.

Pharmacokinetic and Other Evaluations:

Pharmacokinetic Sampling

Blood samples (5 mL) to provide approximately 2 mL of plasma were taken for analysis of PF-00885706 and its metabolite, CJ-038,422, to build a POPPK analysis in GERD patients.

For all subjects randomised to the double-blind treatment period (Visit 4), a sample was taken pre-dose and a second sample was taken between 30 minutes and 3 hours post-dose. Subjects had a single blood sample taken at Visits 5 to 8. The blood sample was taken at a

time dependent upon the time the subject arrived for each visit relative to when they took the study treatment. In all cases the time of the dose and the sample collection were recorded.

Blood Sampling for De-identified Genotyping

Subjects randomised to the double-blind treatment period (Visit 4) who provided the required informed consent, were requested to provide a 9 mL blood sample for de-identified genotyping analysis. Participation in this component of the study was voluntary and subject to regulatory Institutional Review Board/Independent Ethics Committee and subject consent.

Safety Evaluations: Safety evaluations included adverse events (AEs), vital signs (pulse rate and blood pressure), 12-lead electrocardiogram (ECG), physical examination, and safety laboratory tests.

Statistical Methods: Sample size determinations were made using the primary endpoint: the complete resolution of heartburn and regurgitation (responder/non-responder at Week 4). It was planned that 50 subjects per treatment group would be sufficient, requiring a total of 250 evaluable subjects across the whole study. As a result of study termination the sample size was greatly reduced from the number of subjects required for the planned analyses to be meaningful. For this reason no formal analyses were conducted.

Key efficacy summary tables were produced for:

- Number of subjects with complete resolution of heartburn and regurgitation, by visit.
- Summary of the average severity of daytime heartburn, by visit.
- Summary of the average severity of daytime regurgitation, by visit.
- Summary of the composite score of heartburn and regurgitation frequency and severity, by visit.

It was decided that the per protocol analysis set would not be used for reporting, as it was deemed to be of no benefit to subset the already small dataset and reduce the sample size further. The full analysis set was therefore used for all summary tables.

PK concentrations of PF-00885706 and its metabolite CJ-038,422 were listed

Safety parameters (AEs, vital signs, laboratory parameters, ECG and physical examination) were listed and summarised in accordance with sponsor data standards, where the resulting data presentations consisted of subjects from the safety analysis set.

RESULTS

Subject Disposition and Demography: Subject disposition and data sets analysed are summarised in Table S1.

Table S1. Subject Disposition and Data Sets Analysed

		PF-00885706 Dose (BID)			
Number of Subjects	Placebo	100 µg	300 µg	1 mg	3 mg
Screened	145				
Assigned to study treatment	67				
Treated	13	14	14	14	12
Completed	9	11	12	11	9
Discontinued	4	3	2	3	3
Subject died	0	0	0	0	1
Related to study treatment	0	2	0	0	0
Adverse event	0	2	0	0	0
Not related to study treatment	4	1	2	3	2
Adverse event	1	0	0	0	0
Other	1	1	2	3	2
Subject no longer willing to participate in the study	2	0	0	0	0
Analysed for safety					
Adverse events	13	14	14	14	12
Laboratory data	12	13	13	13	10

BID: twice a day.
Discontinuations occurring outside the lag period were attributed to the last study treatment received.

One subject in the 3 mg PF-00885706 group died during the study. Two subjects in the 100 µg PF-00885706 group were discontinued due to AEs related to study treatment.

The majority of subjects who discontinued from the study were discontinued for "other" reasons not related to the study treatment. One subject (100 µg PF-00885706) was withdrawn on Day 1 because they had been inappropriately randomised; their GERD symptoms had improved during the run-in period to the extent that they did not fulfill the randomisation criteria. One subject (3 mg PF-00885706) was withdrawn for a protocol violation (Visit 5 did not occur on the scheduled date). For all other subjects, the "other" reason for discontinuation was that subjects were withdrawn at the request of the sponsor following the temporary hold on the study.

All subjects who received study treatment were analysed for AEs. Six subjects were not analysed for laboratory data as these subjects were discontinued from the study before post-dose laboratory assessments were performed.

All subjects in the study had been diagnosed with GERD and were between the ages of 18 and 65 years. The majority of subjects were white. The proportion of females vs males was higher in the placebo group and the 1 mg PF-00885706 group compared to the other treatment groups. There was no other notable difference in demographic characteristics between the treatment groups.

The mean duration since first diagnosis of GERD was variable (ranging from 4.1 years in the 3 mg PF-00885706 group to 8.2 years in the placebo group). The minimum duration since first diagnosis of GERD for any subject was 0.3 years (300 µg PF-00885706 group) and the maximum duration was 36.0 years (1 mg PF-00885706 group).

Efficacy Results: Due to study termination only key primary efficacy results are presented in this report.

The sponsor requested an audit at Centre 1050 as potential data issues were identified at this study centre during routine safety and other data review practices. The auditors confirmed there were issues with this study centre, documenting 4 critical findings and 1 major finding. During the audit, authenticity of the efficacy data from this study centre could not be fully verified and, as a result, it was decided before study unblinding that all efficacy data from this study centre should be excluded from the reporting outputs.

A maximum of 1 subject in any treatment group had complete resolution of heartburn and regurgitation at any time point measured. At Weeks 1, 3 and 4 only 1 subject overall had complete resolution of heartburn and regurgitation.

In general, the average severity of daytime heartburn and daytime regurgitation decreased from Weeks 0 to 4 in all treatment groups.

The mean composite score of heartburn and regurgitation frequency and severity decreased from Week 0 at each time point measured in all treatment groups.

In summary, there was no evidence of a treatment effect with any dose of PF-00885706 compared with placebo for any of the primary efficacy endpoints.

Pharmacokinetic Results: PK parameters were not reported as there was no evidence of study treatment efficacy.

Safety Results: During the study, 1 subject in the 3 mg PF-00885706 group died suddenly of a "suspected cardiac arrhythmia due to high grade coronary artery sclerosis (high grade calcification) and old myocardial infarction". However, the sponsor could not exclude a possible contributory role of PF-00885706 to the subject's death. Two subjects were permanently discontinued from the study due to treatment-emergent AEs (TEAEs) (ECG abnormal [placebo group] and abdominal pain upper [100 µg PF-00885706 group]) and 1 subject in the 100 µg PF-00885706 group was permanently discontinued from the study due to SAEs (atrial fibrillation and drug interaction). The events of abdominal pain upper and atrial fibrillation were considered to be treatment-related. There were no dose reductions or temporary discontinuations due to TEAEs.

There was no dose-related trend in the number of subjects with TEAEs; however, the number of subjects who reported TEAEs and treatment-related TEAEs was higher in the 1 mg PF-00885706 group compared with the other treatment groups. The most commonly reported TEAE (all causality and treatment-related) was diarrhoea. This was reported only in subjects who received the 2 highest doses of PF-00885706 (5 subjects in the 1 mg group and 3 subjects in the 3 mg group). TEAEs of headache were reported in 2 subjects in the placebo group and 1 subject in the 1 mg PF-00885706 group and each event was considered to be treatment-related. TEAEs of urinary tract infection were reported in 2 subjects in the placebo group and were not considered to be treatment-related. No other TEAE was reported in >1 subject per treatment group. The majority of TEAEs were mild or moderate in severity. Five severe TEAEs were reported in 4 subjects. One severe TEAE was the sudden death and

2 of the severe TEAEs (atrial fibrillation and drug interaction) led to permanent discontinuation from the study. The other severe TEAEs of constipation (1 subject in the 100 µg PF-00885706 group) and arthropod bite (1 subject in the 3 mg PF-00885706 group) were not considered to be treatment-related.

The incidence of all causality and treatment-related TEAEs is summarised in Table S2.

Table S2. Incidence of Treatment-Emergent Adverse Events (All Causalities and Treatment-Related) by MedDRA Preferred Term in >1 Subject per Treatment Group

		PF-00885706 Dose (BID)			
MedDRA system organ class	Placebo (N=13)	100 µg (N=14)	300 µg (N=14)	1 mg (N=14)	3 mg (N=12)
Preferred term	n	n	n	n	n
Gastrointestinal disorders					
Diarrhoea	0	0	0	5[a]	3 (2[a])
Infections and infestations					
Urinary tract infection	2	0	0	0	0
Nervous system disorders					
Headache	2[a]	0	0	1[a]	0

MedDRA: Medical Dictionary for Regulatory Activities. BID: twice a day. N: number of evaluable subjects.
n: number of subjects with an observation.
If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once per treatment in each row. For the treatment-emergent signs and symptoms algorithm any missing severities were to be imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was to be summarised. Missing baseline severities were to be imputed as mild.
Includes data up to 7 days after the last dose of study treatment.
[a] Treatment-related adverse events.

There were no notable median changes from baseline or notable differences between the treatment groups in median changes from baseline for any laboratory parameter measured.

There were no notable mean changes from baseline or notable differences between the treatment groups in mean changes from baseline in weight, standing diastolic and systolic BP, or supine and standing pulse rate at any time point measured. There were notable mean changes from baseline in supine systolic BP in the 3 mg PF-00885706 group at some hourly time points compared with the other treatment groups, however these changes appeared to be due to an outlying subject and natural variability within the small sample size. There was a notable difference between the active treatments and placebo for the mean change from baseline in supine diastolic BP at the weekly time points, however due to the small sample size and variable data this may not reflect a true difference.

AEs of hypertension were reported in 1 subject each in the placebo group and the 1 mg and 3 mg PF-00885706 groups. This event was considered to be treatment-related for 1 subject (1 mg PF-00885706 group).

Mean changes from baseline in RR interval were variable between the treatment groups; however, there was no dose-related trend. There were no notable mean changes from

baseline or notable differences between the treatment groups in any other ECG parameter at any time point measured.

Two subjects in the placebo group and 1 subject each in the 100 µg and 1 mg PF-00885706 groups had a maximum QTcF interval of 450 to <480 msec. No subject had a QTcF interval of 480 to <500 msec. One subject each in the 100 µg and 300 µg PF-00885706 groups had a maximum QTcF interval ≥500 msec.

There was no dose-related trend in the number of subjects with a maximum increase from baseline of ≥30 to <60 msec in QTcF interval or a maximum increase from baseline of ≥60 msec in QTcF interval and no subject in the highest dose group (3 mg PF-00885706) had a QTcF interval increase from baseline of ≥30 msec.

CONCLUSIONS:

- There was no evidence of a treatment effect with 100 µg, 300 µg, 1 mg or 3 mg PF-00885706 compared with placebo for any of the primary efficacy endpoints.
- Doses of 100 µg, 300 µg, 1 mg and 3 mg PF-00885796 BID were generally well tolerated in subjects with GERD who were poor responders to PPI treatment.