Protocol *B4541006*

AN OPEN-LABEL STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF PF-06412528 IN CHILDREN 7-17 YEARS FOR THE TREATMENT OF MODERATE-TO-SEVERE CHRONIC PAIN

Statistical Analysis Plan (SAP)

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[redacted]

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NOTE: Italicized text within this document has been taken verbatim from the Protocol.

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

PF-06412528 capsules consist of controlled-release pellets containing morphine sulfate and naltrexone hydrochloride. The pellets are designed to release morphine in an extended-release manner over time while retaining naltrexone, a mu-opioid antagonist, in the inner core unless the inner core is disrupted… The drug was developed with the potential to decrease the misuse, abuse, and diversion of prescription opioids, a public health problem among many age groups including adolescents.

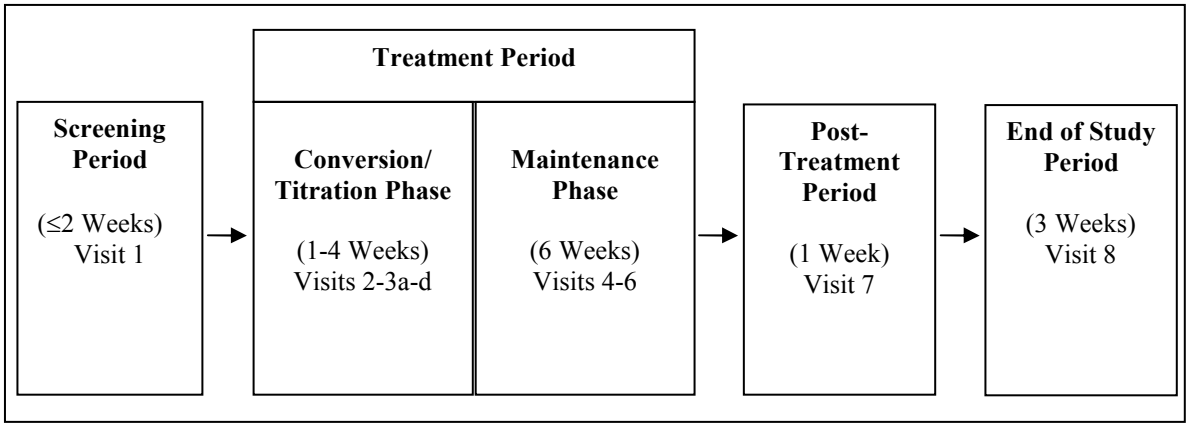
The use of morphine to treat pain in pediatric patients with cancer is well recognized. However, the increasing use of morphine in children to treat other forms of moderate to severe pain (eg, neurological pain) has become apparent only during the past decade… The present study is intended to establish safety and pharmacokinetic information on PF-06412528 in children with chronic moderate-to-severe pain.

2.1. Study Design

This is a multicenter, 6-week, open-label, single-arm study to demonstrate the safety and characterize the pharmacokinetics of PF-06412528 in children 7 to 17 years of age, with moderate-to-severe chronic pain requiring continuous around-the-clock therapy with an opioid analgesic for an extended period of time. The study consists of 4 study periods (Figure 1) including:

- *Screening Period (Visit 1) lasting up to 2 weeks.*
- *Treatment Period (Visits 2-6) lasting up to 10 weeks.*
- *Post-Treatment Period (Visit 7) lasting 1 week.*
- *End of Study Period (Visit 8) lasting 3 weeks.*

Figure 1. Overall Study Design



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The study will enroll approximately 140 children between the ages of 7 and 17 years with at least 100 subjects completing the Maintenance Phase. Plasma samples will be collected at 2 time points under steady-state conditions from each subject in the two age groups (7-11 years and 12-17 years) to characterize the pharmacokinetics of morphine and determine the systemic exposures of naltrexone and 6-β-naltrexol.

The Screening Period occurs up to 2 weeks. This period includes one scheduled study center visit.

The Treatment Period of the study will be conducted using an open-label, non-randomized, single-arm study design to demonstrate the safety and characterize the pharmacokinetics of PF-06412528 under multiple dose conditions. The Treatment Period occurs over 10 weeks and consists of two phases of variable lengths depending on when a subject achieves a stable dose of PF-06412528; a Conversion/Titration Phase lasting 1-4 weeks and a Maintenance Phase lasting 6 weeks. A stable dose is characterized as a dose that provides adequate analgesia and minimizes adverse reactions over a 5 to 7-day period. The purpose of the Conversion/Titration Phase is to convert subjects from their current opioid therapy to PF-06412528 using a standardized conversion guide…, and individualize subjects' pain management by titrating with PF-06412528. The purpose of the Maintenance Phase is to maintain the subject on a stable dose of PF-06412528 for an additional 6 weeks, such that a subject could potentially be exposed to up to 10 weeks of treatment with PF-06412528.

Blood samples will be collected for pharmacokinetic analysis at Visit 4 only for those subjects that achieve a stable dose between Visits 3a-d. Two blood samples will be taken two-hours apart at Visit 4. Subjects will be assigned 1:1 with respect to beginning the pharmacokinetic sampling within either 0-to-5 hours or >5 to ≤9 hours after the morning dose of PF-06412528. Only the first of the two pharmacokinetic samples must be collected within the designated time window; the other sample should be collected approximately two hours after the first sample.

The purpose of the Post-Treatment Period (Visit 7) is to perform safety assessments 7 ±2 days after the last dose of PF-06412528. All treated subjects will be required to attend Visit 7, including those who discontinued early.

The purpose of the End of Study Period (Visit 8) is to perform final safety assessments 28 ±2 days after the last dose of PF-06412528 for all treated subjects. This visit may be performed as an in-clinic visit or by telephone.

2.2. Study Objectives

2.2.1. Primary Objectives

- *To demonstrate the safety of PF-06412528 in children 7 to 17 years of age treated with PF-06412528 for chronic, moderate-to-severe pain.*

- *To characterize the pharmacokinetics of morphine in children 7 to 17 years of age treated with PF-06412528 for chronic, moderate-to-severe pain.*

[redacted]

2.2.2. Secondary Objectives

- *To determine the exposures of naltrexone and 6-β-naltrexol in children 7 to 17 years of age treated with PF-06412528 for chronic, moderate-to-severe pain.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analysis is planned. Final analysis will follow the official database release. Since this is an open label single-arm study, unblinding is not applicable.

With respect to pharmacokinetics, it is estimated that a sample size of N=50 per treatment group would provide adequate (>80%) power to estimate CL/F and Vd/F, taking into consideration the sample size estimates for various levels of PK variability as described by Wang, et al. However, since the study is expected to enroll slowly over time, modeling and simulation will be performed - beginning with adult population PK model and adding pediatric data from each age group as it becomes available – to verify that the sample size and the sampling scheme proposed for the present study are adequate to estimate CL/F and Vd/F with 80% power to establish the 95% CI within 60 to 140% of the geometric mean value for each PK parameter.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

Since this is open label single arm study, no statistical hypothesis is proposed.

4.2. Statistical Decision Rules

Not Applicable.

5. ANALYSIS SETS

5.1. Safety Analysis Set

One safety population is planned consisting of all subjects who participate in the Treatment Period and receive at least one dose of PF-06412528.

5.2. Pharmacokinetic (PK) Analysis Set

The pharmacokinetic concentration population will be defined as all subjects who have undergone at least 1 plasma concentration measurement in this study. The pharmacokinetic analysis population will be defined as all pediatric subjects who have usable pharmacokinetic data (ie, data for which the relationship between the time of dose time of sampling can be determined) and are included in the estimates of the primary pharmacokinetic parameters of interest.

5.3. Treatment Misallocations

All analyses will be performed on an “as-treated” basis. Subjects receiving a treatment that is not consistent with the treatment they are intended to receive will be reported under the treatment that they actually received for all safety and PK analyses, where applicable.

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5.4. Protocol Deviations

Subjects who experience events that may affect their PK profile (eg, lack of compliance with dosing) may be excluded from the PK analysis. At the discretion of the pharmacokineticist/clinical pharmacologist, a concentration value may also be excluded if the last dose time prior to PK sampling is not recorded or if the concentration is anomalous for any other reason.

A full list of protocol deviations will be compiled and reviewed to identify major and minor deviations prior to database closure.

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

6.1.1. Primary

Incidence, intensity, relationship, and seriousness of adverse events (including symptoms of opioid toxicity or withdrawal) during treatment with PF-06412528.

6.1.2. Secondary

Changes in vital signs (pulse rate, blood pressure, respiratory rate), clinical chemistry, and hematology laboratory values.

Additional safety data includes:

- Electrocardiogram
- Clinical opiate withdrawal scale (COWS)
- Physical examination
- Urine drug test
- Columbia- Suicide Severity Rating Scale (C-SSRS)

6.2. Pharmacokinetics/Pharmacodynamics Endpoints

6.2.1. PK Endpoints

6.2.1.1. Primary

population pharmacokinetic estimates of morphine apparent clearance (CL/F) and volume of distribution (Vd/F) following treatment with PF-06412528

6.2.1.2. Secondary

exposure levels of the metabolites of morphine (morphine-3-glucuronide [M3G] and morphine-6-glucuronide [M6G]), naltrexone, and 6-β-naltrexol following multiple-dose treatment with PF-06412528.

[redacted]

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6.2.2. PD Endpoints

Not applicable

6.3. Efficacy Endpoints

- *Pain intensity scores*
- *Rescue medication or additional analgesic medication use*

6.4. Covariates

Covariate testing will be done by adding continuous (age, body weight) and categorical (gender) variables to the structural PK *model to improve fit and reduce variability.*

7. HANDLING OF MISSING VALUES

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

7.1. Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.)

7.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie not done) or NS (ie no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

7.3. Pharmacokinetic parameters

Actual PK sampling times will be used in the population PK analysis.

If an individual subject has a known biased estimate in PK concentrations (due for example to an unexpected event such as vomiting before all the drug is absorbed in the body), this will be footnoted in summary tables and will not be included in population PK analyses.

[redacted]

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Safety Analysis

For the analysis of safety endpoints, the sponsor data standard rules for reporting will be applied.

8.1.1. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics and safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by phase.

8.1.2. Demographic and Clinical Examination Data

A breakdown of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by sex at birth and 'All Subjects' in accordance with the sponsor reporting standards.

8.1.3. Discontinuation(s)

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized.

8.1.4. Adverse Events

All AEs will be coded to System Organ Class and Preferred Term (using MedDRA®). Treatment-emergent AEs will be defined as AEs that commence on or after the start of PF-06412528 administration. Subjects who have multiple events in the same System Organ Class and Preferred Term in a period will be counted only once at each level of summation (overall, by System Organ Class, and by Preferred Term).

Treatment-emergent AEs will be summarized separately for the Conversion/Titration Phase and the Maintenance Phase (including up to End of Study) by System Organ Class, Preferred Term, maximum intensity, and highest relationship to study drug.

Serious AEs and those leading to study discontinuation will be summarized.

8.1.5. Laboratory Data

Clinical laboratory data (hematology, chemistry and urinalysis) including changes from Screening will be summarized descriptively by study visit, as applicable.

8.1.6. Electrocardiogram

Electrocardiogram data including changes from Screening will be summarized descriptively by study visit, as applicable.

8.1.7. Vital Signs

Vital signs data including changes from Baseline will be summarized descriptively by study visit, as applicable.

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8.1.8. Opiate Withdrawal

COWS scores will be summarized descriptively by study visit, as applicable. Additionally, for COWS, the proportion of subjects with mild (COWS Score 5-12), moderate (COWS Score 13-24), moderately severe (COWS Score 25-36), or severe withdrawal (COWS Score >36) will be presented.

8.1.9. Columbia-Suicide Severity Rating Scale

Responses to the C-SSRS will be summarized descriptively.

8.1.10. Dosing and Compliance

Study drug administration will be summarized descriptively by each subject's mean and median total daily dose and duration of exposure, separately for the Conversion/Titration Phase and Maintenance Phase.

8.1.11. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

8.1.12. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s), serum FSH concentrations, urine drug screen, serum or urine B-hCG for all females of childbearing potential will be obtained at Screening.

These data will be provided in the listings.

8.2. PK/PD Analysis

8.2.1. Pharmacodynamic Analysis

Not applicable.

8.2.2. Pharmacokinetic Analysis

The pharmacokinetics of morphine and its metabolites (data permitting) will be characterized using nonlinear mixed-effects modeling with the population pharmacokinetic software program (NONMEM). For modeling building purposes, a one-compartment model with first-order absorption and elimination will be evaluated as the initial structural model. During model building, the sparse concentration data from the PK analysis population in this study may be enriched with full concentration data from previously conducted PF-06412528 studies in adults, or the PK absorption parameters (ka and T_{lag}) may be fixed based on modeling with full concentration data.

Covariate testing will be done by adding continuous (age, body weight) and categorical (gender) variables to the structural model to improve fit and reduce variability. Goodness of fit will be evaluated based on the minimization of the objective function, precision of PK parameter estimates, randomness of scatter in appropriate plots, and reduction in the intersubject variability and residual error.

[redacted]

CCI [redacted].

An analysis describing the details of model building, covariate assessment, and model validated will be provided in a separate document.

In addition to population pharmacokinetic modeling, the highest exposure level and observed exposure levels over time will be reported from the Maintenance Treatment Phase for morphine, naltrexone, and 6-β-naltrexol. The observational data will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum) for the study group as a whole. Data permitting, graphical representations and regression analyses may be used to characterize the dose-exposure relationships for morphine, naltrexone, and 6-β-naltrexol.

8.3. Efficacy Analysis

Analgesic effect analyses will be performed using all available in-clinic pain intensity data from the safety population… The baseline pain intensity score will be the score from the in-clinic assessment at Visit 2.

Pain intensity scores will be summarized descriptively by study week and phase of the Treatment Period (Conversion/Titration Phase and Maintenance Phase). Actual scores and the change and percentage change from baseline will be calculated.

Rescue medication or additional analgesic medication use over time will be summarized descriptively.

9. REFERENCES

"Modern Robust Statistical Methods," David M Erceg-Hurn, Vikki M. Mirosevich, *American Psychologist*, October 2008, Vol. 63, No. 7, 591-601.

Wang Y, Jadhav PR, Mallika L, and Gobburu JV. Clarification on Precision Criteria to Derive Sample Size When Designing Pediatric Pharmacokinetic Studies. J Clin Pharmacol. 2012;52:1601-1606.

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