Protocol *B4531015*

AN OPEN-LABEL STUDY TO EVALUATE THE PHARMACOKINETICS AND SAFETY OF ALO-02 (OXYCODONE HYDROCHLORIDE AND NALTREXONE HYDROCHLORIDE) EXTENDED-RELEASE CAPSULES IN CHILDREN AND ADOLESCENTS 7-17 YEARS OF AGE WHO REQUIRE OPIOID ANALGESIA

Statistical Analysis Plan (SAP)

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

TABLE OF CONTENTS

1. AMENDMENTS FROM PREVIOUS VERSION(S) 5
2. INTRODUCTION 5
2.1. Study Design 5
2.2. Study Objectives 6
2.2.1. Primary Objectives 6
2.2.2. Secondary Objectives 6
3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING 6
4. HYPOTHESES AND DECISION RULES 6
4.1. Statistical Hypotheses 6
4.2. Statistical Decision Rules 6
5. ANALYSIS SETS 6
5.1. Safety Analysis Set 6
5.2. Pharmacokinetic (PK) Analysis Set 6
5.3. Treatment Misallocations 7
5.4. Protocol Deviations 7
6. ENDPOINTS AND COVARIATES 7
6.1. Safety Endpoints 7
6.1.1. Primary 7
6.1.2. Secondary 7
6.2. Pharmacokinetics/Pharmacodynamics Endpoints 7
6.2.1. PK Endpoints 7
6.2.1.1. Primary 7
6.2.1.2. Secondary 8
6.2.2. PD Endpoints 8
6.3. Efficacy Endpoints 8
6.4. Covariates 8
7. HANDLING OF MISSING VALUES 8
7.1. Concentrations Below the Limit of Quantification 8
7.2. Deviations, Missing Concentrations and Anomalous Values 8
7.3. Pharmacokinetic Parameters 9
8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES 9
8.1. Safety Analysis 9

8.1.1. Treatment and Disposition of Subjects....9
8.1.2. Demographic and Clinical Examination Data....9
8.1.3. Discontinuation(s)....9
8.1.4. Adverse Events....9
8.1.5. Laboratory Data....9
8.1.6. Electrocardiogram....10
8.1.7. Vital Signs....10
8.1.8. Opiate Withdrawal....10
8.1.9. Columbia-Suicide Severity Rating Scale....10
8.1.10. Dosing and Compliance....10
8.1.11. Concomitant Treatments....10
8.1.12. Screening and Other Special Purpose Data....10
8.2. PK/PD Analysis....10
8.2.1. Pharmacodynamic Analysis....10
8.2.2. Pharmacokinetic Analysis....10
8.3. Efficacy Analysis....11
9. REFERENCES....11

1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

ALO-02 (PF-06412527) is a combination opioid agonist/opioid antagonist product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

ALO-02 capsules consist of controlled-release pellets containing oxycodone hydrochloride (HCl) and naltrexone HCl. The pellet formulation is designed to release oxycodone in an extended-release (ER) manner over time while retaining naltrexone HCl in the inner core unless the inner core is disrupted. Upon crushing or chewing the pellets, naltrexone is released along with the oxycodone, thereby, attenuating the liking and euphoric effects of the opioid. Naltrexone HCl is formulated in a 12% (w/w) ratio in combination with oxycodone HCl across all dosage strengths. ALO-02 was developed with the goal of decreasing misuse, abuse, and diversion of opioids; an increasing public health problem among many age groups, including adolescents.

One of the major challenges facing clinicians who wish to prescribe pain medications to children and adolescents is the paucity of information in the pediatric population about the proper choice of pain medication, dosage guidelines, and expectations with regard to efficacy and untoward effects. Efforts to address this challenge include the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). The study is being conducted as a Phase 4 post-marketing requirement to the Food and Drug Administration (FDA) consistent with ICH E11 guidelines for "Clinical Investigation of Medicinal Products in the Pediatric Population".

The proposed study is intended to characterize the pharmacokinetics (PK) of ALO-02 and evaluate the safety of ALO-02 in children and adolescents 7 to 17 years of age who require opioid analgesia for moderate-to-severe pain.

2.1. Study Design

This is a multicenter, open-label, single-arm study designed to characterize the PK and evaluate the safety of ALO-02 in opioid experienced children and adolescents with moderate-to-severe pain. The study will enroll approximately 140 children and adolescents to achieve at least 100 subjects exposed to at least 2 weeks of treatment with ALO-02 in the Maintenance Phase. Plasma samples will be collected during the Maintenance Phase under steady-state conditions to characterize the pharmacokinetics of oxycodone and determine the systemic exposures of oxymorphone, noroxycodone, naltrexone, and 6-β-naltrexol.

The study consists of 4 study periods including occurring over a period of up to 9 weeks:

- *Screening Period (Visit 1) lasting up to 2 weeks.*
- *Treatment Period (Visits 2-5) lasting up to 6-8 weeks.*

- *Post-Treatment Period (Visit 6) lasting 1 week.*

All subjects will be treated with ALO-02 capsules for oral use for up to 8 weeks in this single-arm, open-label study. Subjects must be taking opioids prior to entry into the study. Initial ALO-02 dose will be determined by the subject's pre-study opioid treatment prior to the Conversion/Titration Period. The Treatment Period duration is 6 to 8 weeks and consists of two phases of variable lengths depending on when a subject achieves a stable dose of ALO-02 and how long opioid analgesia is required.

2.2. Study Objectives

2.2.1. Primary Objectives

- *To characterize the PK of oxycodone in children and adolescents 7 to 17 years of age treated with ALO-02.*

- *To evaluate the safety of ALO-02 in children and adolescents 7 to 17 years of age.*

2.2.2. Secondary Objectives

- *To determine the systemic exposures of naltrexone and 6-β-naltrexol in children and adolescents 7 to 17 years of age treated with ALO-02.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

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

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

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 ALO-02.

5.2. Pharmacokinetic (PK) Analysis Set

The PK concentration population is defined as all subjects with at least 1 plasma concentration measurement in this study. The PK analysis population will be defined as all subjects who have usable PK data (ie, concentration data can be associated with the dose level, time of dosing, and time of PK sampling) and are included in the estimates of the primary PK 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.

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 withdrawal or overdose) during treatment with ALO-02.

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

Estimates of oxycodone average steady-state concentration ($C_{ss,av}$) and apparent oral clearance (CL/F).

6.2.1.2. Secondary

Apparent volume of distribution (V_z/F) of oxycodone (data permitting); and exposure levels of the metabolites of oxycodone (oxymorphone and noroxycodone), naltrexone, and 6-β-naltrexol. Graphical representations and regression analyses may be used to characterize the dose-exposure relationships for oxycodone, naltrexone, and 6-β-naltrexol (data permitting).

6.2.2. PD Endpoints

Not applicable.

6.3. Efficacy Endpoints

- *Pain intensity scores* (Numerical Rating Scale) *(actual* scores *and % change from baseline).*
- *Rescue medication or additional analgesic medication use over time.*

6.4. Covariates

Covariates of interest (ALO-02 dosage, age, body weight, gender, concomitant medications etc.) will be evaluated in order to explain the observed between-subject variability in oxycodone $C_{ss,av}$.

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 calculation of the PK parameters.

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.

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 ALO-02 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 listed.

8.1.7. Vital Signs

Vital signs data including changes from Baseline will be summarized descriptively by study visit, as applicable. Baseline will be the in-clinic assessments at Visit 2.

8.1.8. Opiate Withdrawal

COWS scores will be summarized descriptively by study visit, as applicable. Additionally, for COWS, the proportion of subjects with no withdrawal (COWS Score <5), *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 by study visit and by age group (as well as both age groups combined).

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), urine drug screen, serum or urine 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

Given the expected low fluctuation in steady-state oxycodone concentrations following ALO-02 BID dosing in children and adolescents based on the ALO-02 study B4531006 in adults, the concentrations observed during the Maintenance Phase will be used as an estimate of $C_{ss,av}$ of oxycodone and its metabolites (data permitting) in subjects. The CL/F of oxycodone will be estimated using a ratio of the daily dosing rate of ALO-02 and the estimates of oxycodone $C_{ss,av}$ in the Maintenance Phase. The concentration-time dataset will

be analyzed to obtain estimates for V_z/F of oxycodone in subjects, data permitting. Covariates of interest (ALO-02 dosage, age, body weight, gender, concomitant medications etc.) will be evaluated in order to explain the observed between-subject variability in oxycodone $C_{ss,av}$.

The observational data will be summarized using descriptive statistics (mean, standard deviation, median, minimum, and maximum) for the study group as a whole. Graphical representations and regression analyses may be used to characterize the dose-exposure relationships for oxycodone, naltrexone, and 6-β-naltrexol (data permitting).

8.3. Efficacy Analysis

Analgesic effect analyses will be performed using all available in-clinic pain intensity data (NRS pain scale) *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

None.