NOVARTIS

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

AFQ056

CAFQ056X2201

A randomized, subject and investigator blinded, placebo-controlled, parallel group study to investigate whether AFQ056 reduces cocaine use in patients diagnosed with Cocaine Use Disorder (CUD)

Statistical Analysis Plan (SAP)

Author(s): Personal Protected Data

Document type: SAP Documentation – NIBR

Document status: Final Amendment 2

Release date: 07-Apr-2020

Number of pages: 18

Commercially Confidential Information

Table of contents

Commercially Confidential Information

Commercially Confidential Information

1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CAFQ056X2201".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

This SAP has been developed using Clinical Trial Protocol version v01 dated 15 November 2017.

1.3 Study objectives

1.3.1 Primary objective

To evaluate treatment effect of 98-day AFQ056 administration in reducing cocaine use.

1.3.2 Secondary objectives

- To assess the effects of 98-day AFQ056 administration versus placebo on:

a) other measures of cocaine use
b) alcohol use

- To assess the safety and tolerability of multiple bid oral doses of AFQ056.
- To evaluate the pharmacokinetics of AFQ056.

1.3.3 Exploratory objectives

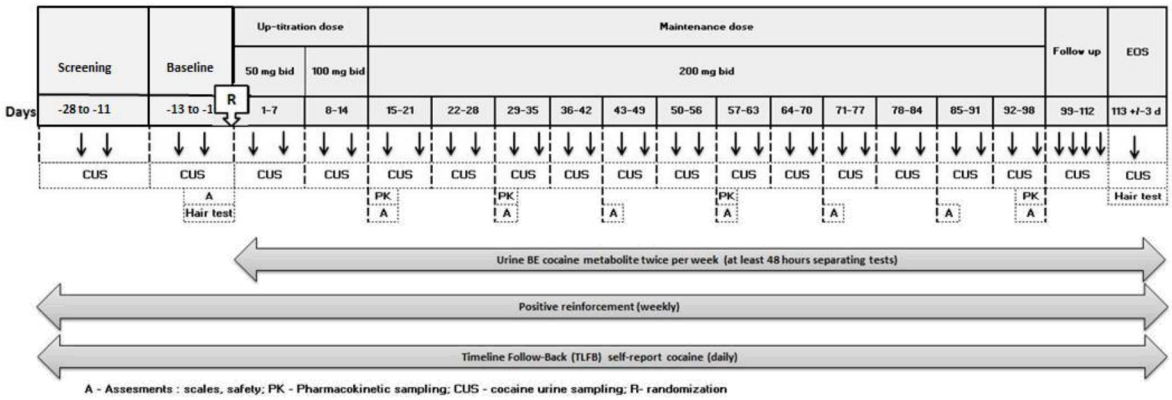
Commercially Confidential Information

1.4 Study design and treatment

This is a randomized, subject and investigator blinded, parallel group, placebo-controlled study in approximately 60 patients with cocaine use disorder. The study consists of: about 17-day screening period followed by a 12-day baseline; a 98-day out-patient treatment period (14-day up-titration dose regimen followed by 84-day maintenance dose) and finally an end of study visit evaluation approximately 14-days after the last study drug administration. The total

duration for each patient in the study is up to approximately 20-weeks including screening and baseline. The study design is summarized in Figure 1.4-1 below.

Figure 1.4-1 Overall study scheme



Following baseline, on Day 1, approximately 60 eligible patients will be randomly assigned in a 1:1 ratio to either AFQ056 or placebo.

- Group A – AFQ056: up-titration regimen for the first 2 weeks (14 days): 50 mg bid from Day 1 to Day 7, 100 mg bid from Day 8 to Day 14, followed by dosing at 200 mg bid for 84-days.
- Group B: matching placebo.

2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

Commercially Confidential Information

3 Interim analyses

Commercially Confidential Information

4 Statistical methods: Analysis sets

For subjects for which the actual treatment received does not match the randomized treatment the treatment actually received will be used for the analysis.

The randomized set will include all subjects randomized.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects with any available PD data, who received any study drug for at least 14 days in the treatment period and experienced no protocol deviations with relevant impact on PD data.

The Full analysis set (FAS) will include all subjects with any available PD data who received at least any study drug.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
TRT02	*Subject was randomized but did not take any dose of study treatment*	Subject will be counted in randomized set, but excluded from safety, PD and PK analysis sets
TRT05	*Bad compliance to study treatment*	Exclude subject from PD and PK analysis sets
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
TRT02	*Subject was randomized but did not take any dose of study treatment*	Subject will be counted in randomized set, but excluded from safety, PD and PK analysis sets
TRT05	*Bad compliance to study treatment*	Exclude subject from PD and PK analysis sets
Subjects are excluded from PK and PD analysis in case of these PDs:		Exclude subject from PK and PD analysis sets

Category Deviation code	Text description of deviation	Data exclusion
TRT02	*Subject was randomized but did not take any dose of study treatment*	Subject will be counted in randomized set, but excluded from safety, PD and PK analysis sets
TRT05	*Bad compliance to study treatment*	Exclude subject from PD and PK analysis sets
Subjects are excluded from Safety analysis in case of these PDs:		Exclude subject from Safety analysis set
TRT02	*Subject was randomized but did not take any dose of study treatment*	Subject will be counted in randomized set, but excluded from safety, PD and PK analysis sets
Subjects are analyzed according to treatment actually received		
TRT04	*Wrong treatment arm medication given to the subject by mistake of pharmacist – not according to treatment randomized.*	Subject will be analyzed according to treatment actually received (ie the other trt group than randomized)

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

5.1 Variables

Conventional PK parameters will not be calculated due to the limited sampling schedule.

5.2 Descriptive analyses

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary objective is to evaluate the effect of AFQ056 in reducing cocaine use.

6.1.1 Variables

The primary variable is the proportion of cocaine use days during the treatment period (day 1 to last day of treatment).

For each subject, the proportion of cocaine use days will be calculated by dividing the number of days of cocaine use by the number of days during the treatment period, i.e. 98 days for completers and number of days between Day 1 and day of last dose in case of premature discontinuation of study treatment. For the weekly proportions, the full 7 days of data should be available for a subject. For monthly proportions, at least 7 days of data should be available. It is considered as a continuous variable with a normal distribution. The cocaine consumption will be recorded daily (Yes/No) using the timeline follow-back during the entire study.

The timeline follow-back cocaine is a cocaine assessment method that obtains estimates of daily cocaine intake and has been evaluated with clinical and nonclinical populations. Using a calendar, people provide retrospective estimates of their daily cocaine use over a specified time period that can vary up to 12 months from the interview data.

6.1.2 Descriptive analyses

The cocaine daily consumption (Yes/No) will be listed by treatment, subject, and day. The overall proportion of cocaine use days, along with the monthly and weekly proportions will be listed by treatment and subject.

A descriptive summary table of the proportion of cocaine use days will be provided by treatment and week. A similar table shall also be provided to summarize the proportion of cocaine use days by treatment and month (28 days was selected as a nominal length month, rather than actual calendar month). The overall proportion of cocaine use days will also be summarized.

6.1.3 Statistical model, assumptions and hypotheses

A Bayesian analysis will be conducted on the proportion of cocaine use days

Commercially Confidential Information

6.1.3.1 Model checking procedures

Commercially Confidential Information

6.1.3.2 Sensitivity analyses

Commercially Confidential Information

6.1.3.3 Supportive analyses

Commercially Confidential Information

6.1.3.4 Graphical presentation of results

Commercially Confidential Information

6.2 Secondary objectives

The secondary objectives are to assess the effect of AFQ056 on other measures of cocaine use and on measures of alcohol use, to assess the safety and tolerability and to evaluate the pharmacokinetics of AFQ056.

6.2.1 Variables

Two urine samples per week will provide a quantitative measure of cocaine's metabolite Benzoylecgonine.

Alcohol consumption will be recorded by the subjects using timeline follow-back. The number of drinks will be recorded daily. For the weekly consumption, the full 7 days of data should be available for a subject. For monthly consumptions, the full 28 days of data should be available.

The timeline follow-back alcohol is a drinking assessment method that obtains estimates of daily drinking and has been evaluated with clinical and nonclinical populations. Using a calendar, people provide retrospective estimates of their daily drinking over a specified time period that can vary up to 12 months from the interview data.

Abstinence last x weeks at end of treatment

Binary response variables based on abstinence will be calculated as follows:

A subject is considered abstinent the last x weeks of treatment if they completed the 14 weeks treatment period and were abstinent the last x weeks (with x=1 , 2, 3...., 14).

If a subject didn't complete 14 weeks they will be considered as not abstinent.

6.2.2 Descriptive analyses

The log-transformed quantitative urine measurements of Benzoylecgonine will be summarized by treatment and visit / time and weekly. To obtain the weekly profiles, the BE measurements obtained by a subject during each week (aligned with the weekly profiles of TLFB) will be averaged. These data shall also be listed by subject, and time point.

Descriptive summary tables shall be provided to summarize the alcohol consumption by treatment and week, and by treatment and month. The alcohol daily consumption, weekly consumption and monthly consumption will be listed by subject and time point. If country is a significant effect in the model stated in section 6.2.3 then summary statistics will also be provided by country.

The amount spent on cocaine will be summarized by treatment and listed by subject and time point. The amount spent will be converted inEuros for the summary statistics, using the exchange rates recorded on 7th August 2019 from XE currency converter website (https://www.xe.com/currencyconverter/convert). The exchange rates are:

US Dollar to Euro – 0.891

Swiss Franc to Euro – 0.916

Argentine Peso to Euro – 0.019

The number and % of subjects abstinent the last x weeks will be described both on the PD analysis set and FAS.

6.2.3 Statistical model, assumptions and hypotheses

Commercially Confidential Information

6.2.3.1 Model checking procedures

Commercially Confidential Information

6.2.3.2 Graphical presentation of results

Commercially Confidential Information

6.3 Exploratory objectives

6.3.1 Variables

Commercially Confidential Information

Commercially Confidential Information

6.3.2 Descriptive analyses

Commercially Confidential Information

6.3.3 Statistical model, assumptions and hypotheses

Commercially Confidential Information

6.3.4 Graphical presentation of results

Commercially Confidential Information

7 Statistical methods for safety and tolerability data

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and patient.

Treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and patient.

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time. Newly occurring liver enzyme abnormalities will be listed by treatment, subject and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> adverse events which are not serious adverse events with an incidence greater than X% and on <on-treatment/treatment emergent> serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same subject, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Other safety evaluations

The Columbia Suicide Severity Rating Scale data will be listed by treatment group, subject and visit.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

Commercially Confidential Information