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Biostatistics & Statistical Programming /
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SOM230

CSOM230Y2201

A Multicenter, Placebo-Controlled, Single Dose Study in Acute Episodic and Chronic Cluster Headache to Evaluate the Safety and Efficacy of SOM230 subcutaneous (s.c.)

Statistical Analysis Plan (SAP)

Personal Data

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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 ***"CSOM230Y2201".***

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 v04 (incorporating Amendment 04) dated 14 March 2018.

1.3 Study objectives

1.3.1 Primary objective

The primary objective of this study is to assess headache response of single subcutaneous (s.c.) dose of SOM230 compared to placebo in managing cluster headache (CH) attack at 30 minutes post-dosing.

1.3.2 Secondary objectives

The secondary objectives of this study are:

- To assess pain free response of single s.c. dose of SOM230 compared to placebo in managing CH attack at 30 minutes post-dosing
- To assess the safety and tolerability of SOM230

1.4 Study design and treatment

This non-confirmatory study will be conducted in 2 cohorts using a one-sequence two-period design to compare SOM230 vs. Placebo. Following observed efficacy and safety signals in Cohort 1 with the 1.5 mg dose, Cohort 2 of the study assessing efficacy of a lower SOM230 dose (0.9 mg) may be considered.

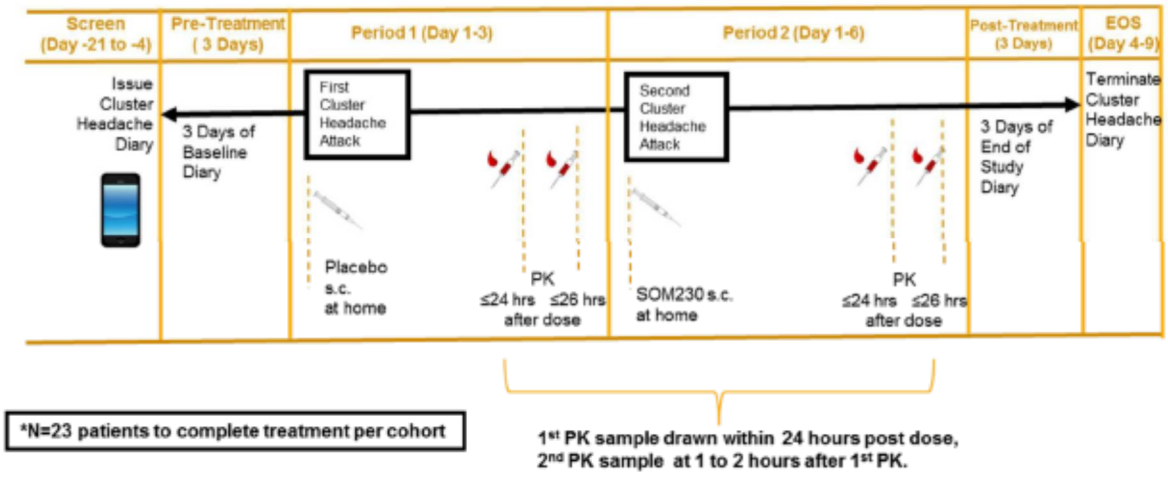
Two consecutive attacks will be treated: first attack will be treated with placebo (Period 1) and the following attack will be treated with SOM230 (Period 2). Approximately 30 subjects will be enrolled in Cohort 1 to receive Placebo s.c. single dose in Period 1 then SOM230 1.5 mg s.c., a single dose in Period 2. Each study cohort will consist of a 21 day screening period, a baseline

period of 3 days prior to the baseline visit, a treatment period (Period 1) lasting up to 3 days then a treatment period 2 of up to 3 days, followed by an end of study visit 3 days after study drug administration in Period 2. The subjects will have up to 5 visits. Similarly, in Cohort 2, approximately 30 subjects will receive placebo s.c. single dose in Period 1 and SOM230 0.9 mg s.c. as a single dose in Period 2.

Each subject will be instructed to self-administer (or to be assisted by a helper, or health care provider) the study medications at the beginning of the CH attack (as early as possible; within 10 minutes of start of attack when pain is at least moderate). In case the subject experiences CH attacks prior to administering study treatment in Period 1 they can use 100% O_2 or their conventional treatment to manage their acute attacks experienced before Period 1. If the subject does not have a headache attack in 72 hours post-baseline, or 72 hours post Period 1 treatment the subject will be excluded from the study.

Subjects will be required to complete a patient diary to document the pain severity and pain relief before and after the administration of the study medication. In case the pain is not responding to the administered study drug after 30 minutes, subjects will be allowed to use only 100% oxygen or sumatriptan as a rescue management. If applicable and feasible, subjects in Period 1 may return to the study center for follow-up within 24 hour post treatment administration. The subjects will have a follow-up within 24 hours of the study drug administration in Period 2 where a PK sample will be collected, with a second PK sample collected to 1 to 2 hours after the 1st PK sample. In case the follow-up visit in Period 2 falls on a weekend, a window of up to 48 hours may be considered.

Figure 1.4-1 Study Design – Cohorts 1 and 2



2 First interpretable results (FIR)

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

4 Statistical methods: Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment received.

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

The PK analysis set will include all subjects with available PK data and no protocol deviations with relevant impact on PK data.

The efficacy/PD analysis set will include all subjects that received study drug in both periods and had no protocol deviations with relevant impact on efficacy/PD data.

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 all *(safety)* analysis in case of these PDs:		Exclude subject completely from all ***(safety)*** analysis sets
I2	*Written ICF not obtained*	
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set

TRTD01	*Study drug dosing error or incorrect treatment administered.*	
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
COMD01	*Used prohibited treatment within 24 hours before receipt of study drug and within the first 30 minutes post dose.*	
TRTD01	*Study drug dosing error or incorrect treatment administered.*	
	Predose severity of CH is not at least moderate at one of the periods (unless there was a diary entry error)	

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

5.2 Descriptive analyses

SOM230 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. Concentrations below LLOQ will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values. The PK parameters will be listed by treatment and subject.

5.2.1 Graphical presentation of results

Arithmetic mean (SD) and geometric mean (95% CI) plasma concentration data will be plotted across time.

Overlaying individual plasma concentration-time profiles will be generated along with concentration versus time profiles for individual subjects.

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary objective of this study is to assess headache response of single s.c. dose of SOM230 compared to placebo in managing CH attack at 30 minutes post-dosing.

6.1.1 Variables

Percent (%) of subjects with headache response defined as very severe, severe, or moderate pain before dosing that becomes mild or nil at 30 minutes post-dosing is the primary variable.

6.1.2 Descriptive analyses

If the second cohort (0.9 mg dose) is assessed then cohort will serve as a grouping factor for all relevant data listings.

The headache response will be defined at each post-dose timepoint separately and will be summarized by cohort, treatment and visit/timepoint using frequency tables. Percentage of subjects having received 100% oxygen therapy or sumatriptan at each time point will be tabulated by cohort and treatment.

6.1.3 Statistical model, assumptions and hypotheses

A logistic regression analysis on the 30 minutes post-dosing data only with baseline headache severity (very severe, severe or moderate), CH type (episodic or chronic) and dose (0 for placebo, 1.5 mg or 0.9 mg for SOM230) as fixed effects will be used to assess the effect of SOM230 on headache response. Dose will be included as a categorical variable in the model. Placebo adjusted headache response rate will be provided. Headache response measurements after 100% oxygen therapy or sumatriptan will be set to missing**,** which will be considered as missing at random. The frequency and percentage of subjects with each response shall be displayed, along with the mean estimates, 90% confidence interval and p-value from the logistic regression analysis.

The following approaches will be taken if the 0.9 mg dose is assessed in the second cohort:

Placebo adjusted headache response rate will be obtained for each of the two SOM230 doses. A linear dose-response trend test will be constructed within the logistic regression framework using a contrast with the first order orthogonal polynomial coefficients. Pairwise comparisons and further dose-response assessments will be performed as appropriate. If there is no difference between the two SOM230 doses then a comparison between the pooled SOM230 treatment and placebo will be conducted.

6.1.3.1 Sensitivity analyses

Subjects are able to take a rescue medication at least 30 minutes following study medication administration. As a sensitivity analysis, the logistic regression analysis shall be repeated on all timepoints, where only the timepoints with at least 50% of non-missing data will be kept.

The logistic regression analysis with baseline headache severity (very severe, severe or moderate), CH type (episodic or chronic), dose (0 for placebo, 1.5 mg or 0.9 mg for SOM230), time and dose by time interaction as fixed effects and subject as a random effect will be used to assess the effect of SOM230 on headache response. Dose and time will be included as categorical variables in the model. Placebo adjusted headache response rate at each time point will be provided. Headache response measurements after 100% oxygen therapy or sumatriptan will be set to missing**,** which will be considered as missing at random. The frequency and percentage of subjects with each response shall be displayed, along with the mean estimates, 90% confidence interval and p-value from the logistic regression analysis.

The sensitivity logistic regression will only be performed if the primary analysis indicates a significant result.

6.1.3.2 Handling of missing values/censoring/discontinuations

Assuming missing at random, a subject with missing value at a time point will still contribute to the estimation of the treatment effect at that particular time point as the likelihood-based repeated measures analysis borrows information from non-missing values of this subject and other subjects.

6.1.3.3 Graphical presentation of results

If there are sufficient data to analyze, then the time to headache response, time to pain free response and time to recurrence curves, using Kaplan-Meier estimates will be constructed by dose. A clustered log-rank test for correlated survival data will be performed to compare the time to event curves between treatments while hazard ratios will be estimated by the Cox proportional hazard frailty model with CH type and baseline headache severity or frequency included as covariates as appropriate. If subjects do not have an event, they will be censored at their last available visit. These analyses will only be conducted if the primary analysis indicates a significant result and if there is sufficient data.

6.1.4 Supportive analyses

The McNemar test with or without stratification by CH type may also be used to compare headache response rates between treatments at 30 minutes post-dosing only.

If there are sufficient data to analyze, a Cox proportional hazard model with dose and CH type as classification factors and headache severity as a time dependent covariate will be used to analyze time to 100% oxygen therapy or sumatriptan. A random subject effect will be included in the model as well to account for the correlation among measurements from the same subject. This model will only be performed if the primary analysis indicates a significant result and there is sufficient data.

Joint modelling of the headache response and time to 100% oxygen therapy or sumatriptan data may be attempted as appropriate. This analysis will only be performed if a good response rate at 30 minutes versus placebo is detected.

Finally to avoid reducing statistical efficiency due to analyzing the dichotomized data, the headache severity measurements over time may be analyzed using a proportional-odds model similar to the aforementioned logistic regression model.

6.2 Secondary and exploratory objectives

6.2.1 Efficacy/Pharmacodynamics

6.2.1.1 Variables

The percentage of subjects who are pain free at 30 minutes pose dose is one of the secondary endpoints.

6.2.1.2 Descriptive analyses

Number and percentage of subjects pain free and of subjects reporting improvement of associated autonomic symptoms (for example, lacrimation, blushing, pupil constriction, etc.) over time will be tabulated by dose.

Number and percentage of subjects receiving rescue medication at or after 30 minutes.

6.2.1.3 Statistical model, assumptions and hypotheses

Pain free data will be analyzed using the same approach described for the primary variable. Pain free response measurements after 100% oxygen therapy or sumatriptan will be set to missing**,** which will be considered as missing at random.

6.2.2 Pharmacokinetic/pharmacodynamic interactions

The relationship between reconstructed individual PK profiles with various efficacy/PD variables will be explored as appropriate and the results reported in a separate report.

7 Statistical methods for safety and tolerability data

7.1.1 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.

7.1.2 Descriptive analyses

Subject demographics and other baseline characteristics

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

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

Treatment

Data for study drug administration, rescue medications and concomitant therapies will be listed by cohort, treatment and subject as appropriate.

Vital signs

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

ECG evaluations

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

Clinical laboratory evaluations

All laboratory data will be listed by cohort, 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 cohort, treatment 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 cohort and treatment. An adverse event starting in one period and continuing into the next period is counted only in the onset period. A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment.

7.1.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals) will be created.