

Novartis Institutes for BioMedical Research

SOM230

Clinical Trial Protocol 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.)**

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## **Site Operations Manual (SOM)**

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

### **Notification of serious adverse events**

Refer to [Section 9.2](#) of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Chief Medical Office and Patient Safety (CMO&PS) (formerly known as Drug Safety and Epidemiology Department) and notify the Clinical Trial Leader.

Contact information is listed in the Site Operations Manual.

## Table of contents

Site Operations Manual (SOM).....	2
Notification of serious adverse events.....	2
Table of contents .....	3
List of tables .....	6
List of figures .....	6
List of abbreviations .....	7
Pharmacokinetic definitions and symbols .....	9
Corporate Confidential Information	
Protocol synopsis.....	18
1 Introduction .....	21
1.1 Background.....	21
Corporate Confidential Information	
1.2 Study purpose .....	26
2 Study objectives.....	26
2.1 Primary objective.....	26
2.2 Secondary objectives .....	26
Corporate Confidential Information	
3 Investigational plan .....	27
3.1 Study design.....	27
3.2 Rationale for study design .....	28
3.3 Rationale for dose/regimen, duration of treatment .....	29
3.4 Rationale for choice of comparator .....	29
3.5 Purpose and timing of interim analyses/design adaptations .....	30
3.6 Risks and benefits .....	30
4 Population.....	31
4.1 Inclusion criteria .....	31
4.2 Exclusion criteria .....	31
5 Restrictions for Study Subjects .....	32
5.1 Contraception requirements.....	32
5.2 Prohibited treatment.....	33
5.3 Dietary restrictions.....	33
5.4 General restrictions.....	33

6	Treatment.....	33
6.1	Study treatment.....	33
6.1.1	Investigational treatment.....	33
6.1.2	Additional study treatment.....	33
6.2	Treatment arms .....	34
6.3	Permitted dose adjustments and interruptions of study treatment .....	34
6.4	Treatment assignment.....	34
6.5	Treatment blinding.....	34
6.6	Emergency breaking of assigned treatment code .....	34
6.7	Treatment exposure and compliance .....	34
6.8	Recommended treatment of adverse events .....	34
6.9	Rescue medication .....	35
6.10	Concomitant treatment.....	35
7	Discontinuation and study completion .....	35
7.1	Discontinuation of study treatment.....	35
7.2	Study completion and post-study treatment .....	35
7.2.1	Lost to follow-up.....	36
7.3	Withdrawal of consent.....	36
7.4	Study Stopping rules.....	36
7.5	Early study termination.....	36
8	Procedures and assessments .....	37
8.1	Informed consent procedures.....	40
8.2	Subject demographics/other baseline characteristics.....	40
8.3	Efficacy / Pharmacodynamics .....	41
8.3.1	Cluster Headache History .....	41
8.3.2	Patient Diary.....	41
8.4	Safety .....	41
8.4.1	Physical examination .....	41
8.4.2	Vital signs.....	41
8.4.3	Height and weight .....	42
8.4.4	Laboratory evaluations.....	42
8.4.5	Electrocardiogram (ECG) .....	42
8.4.6	Pregnancy and assessments of fertility .....	42
8.5	Pharmacokinetics.....	43

9	Safety monitoring .....	44
9.1	Adverse events .....	44
9.2	Serious adverse event reporting .....	46
9.2.1	Definition of SAE .....	46
9.2.2	SAE reporting .....	47
9.3	Liver safety monitoring .....	48
9.4	Pregnancy reporting .....	49
9.5	Early phase safety monitoring .....	49
10	Data review and database management .....	49
10.1	Site monitoring .....	49
10.2	Data collection .....	50
10.3	Database management and quality control .....	50
10.4	Data Monitoring Committee .....	51
10.5	Adjudication Committee .....	51
11	Data analysis .....	51
11.1	Analysis sets .....	51
11.2	Subject demographics and other baseline characteristics .....	52
11.3	Treatments (study drug, rescue medication, other concomitant therapies, compliance) .....	52
11.4	Analysis of the primary variable(s) .....	52
11.4.1	Variable(s) .....	52
11.4.2	Statistical model, hypothesis, and method of analysis .....	52
11.4.3	Handling of missing values/censoring/discontinuations .....	52
11.4.4	Supportive analyses .....	53
11.5	Analysis of secondary and exploratory variables .....	53
11.5.1	Efficacy / Pharmacodynamics .....	53
11.5.2	Safety .....	53
11.5.3	Pharmacokinetics .....	54
11.5.4	Pharmacokinetic / pharmacodynamic interactions .....	54
11.5.5	Other assessments .....	54
11.6	Sample size calculation .....	55
Corporate Confidential Information		
12	Ethical considerations .....	56
12.1	Regulatory and ethical compliance .....	56
12.2	Responsibilities of the investigator and IRB/IEC .....	56

12.3	Publication of study protocol and results.....	56
13	Protocol adherence .....	57
13.1	Protocol Amendments .....	57
14	References .....	58
15	Appendix 1 Blinding levels .....	59
16	Appendix 2 Liver Safety Monitoring .....	60

### List of tables

Table 8-1	Assessment Schedule, (Cohorts 1 &2).....	37
Table 16-1	Liver Event and Laboratory Trigger Definitions .....	60
Table 16-2	Follow Up Requirements for Liver Events and Laboratory Triggers ...	60

### List of figures

Figure 3-1	Study Design Cohorts 1 and 2.....	28
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## List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
b.i.d.	twice a day
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
CGRP	Calcitonin Gene Related Peptide
CD	Cushing's Disease
CH	Cluster Headache
CK	creatinine kinase
cm	centimeter
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CV	coefficient of variation
DR	Data review
EC	Ethics Committee
ECG	electrocardiogram
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
$\gamma$ -GT	Gamma-glutamyl transferase
GCP	Good Clinical Practice
h	hour
HIV	human immunodeficiency virus
IA	Interim analysis
i.v.	intravenous
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
Kg	kilogram
LAR	long acting release
LDH	lactate dehydrogenase
LLN	lower limit of normal
LLQ	lower limit of quantification
mg	milligram(s)
ml	milliliter(s)
mSec	millisecond
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
RBC	red blood cell(s)
REB	Research Ethics Board
s.c.	subcutaneous
SAE	serious adverse event
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TBL	total bilirubin
ULN	upper limit of normal
ULQ	upper limit of quantification
vs.	versus
WBC	white blood cell(s)



## Pharmacokinetic definitions and symbols

AUC <sub>0-t</sub>	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUC <sub>inf</sub>	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
CL/F	The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time]
C <sub>max</sub>	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
F	Bioavailability of a compound. F <sub>abs</sub> is the absolute bioavailability, i.e. the fraction (or percentage) of the administered extravascular dose systemically available. F <sub>rel</sub> is the relative bioavailability, i.e. the bioavailability relative to a reference
T <sub>1/2</sub>	The terminal elimination half-life [time]
T <sub>1/2,acc</sub>	The effective half-life based on drug accumulation at steady state [time]
T <sub>max</sub>	The time to reach the maximum concentration after drug administration [time]
V <sub>z</sub> /F	The apparent volume of distribution during the terminal elimination phase following extravascular administration [volume]

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## Protocol synopsis

<b>Protocol number</b>	CSOM230Y2201
<b>Title</b>	A Multicenter, Placebo-Controlled, Single Dose Study in Acute Episodic and Chronic Cluster Headache to Evaluate the Safety and Efficacy of SOM230 s.c.
<b>Brief title</b>	Safety and efficacy study of SOM230 s.c. in Cluster Headache
<b>Sponsor and Clinical Phase</b>	Novartis Phase II
<b>Intervention type</b>	Drug
<b>Study type</b>	Interventional
<b>Purpose and rationale</b>	The purpose of this non-confirmatory study is to determine if SOM230 has adequate efficacy and safety to warrant further clinical development in cluster headache (CH). This study will have 2 cohorts (2 doses). It will be a one sequence, 2 period design, SOM230 vs. Placebo, and following an observed signal in Cohort 1 at an interim analysis, Cohort 2 of the study may be considered to assess efficacy of a lower dose.
<b>Primary Objective(s)</b>	To assess headache response of single subcutaneous s.c. dose of SOM230 compared to placebo in managing cluster headache attack at 30 minutes post-dosing
<b>Secondary Objectives</b>	<ul style="list-style-type: none"> <li>To assess pain free response of single s.c. dose of SOM230 compared to placebo in managing cluster headache attack at 30 minutes post-dosing</li> <li>To assess the safety and tolerability of SOM230</li> </ul>
<b>Study design</b>	<p>This study will be conducted in 2 cohorts in 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 with the 0.9 mg dose may be considered.</p> <p>In a one sequence 2 period approach, two consecutive attacks will be treated: first attack will be treated with placebo (Period 1) and the next attack will be managed by SOM230 (Period 2). Each study cohort will consist of a 21 day screening period, baseline period of 3 days prior to dosing, first treatment period lasting up to 3 days followed by a second treatment period lasting up to 3 days followed by an end of study visit, 3 days after study drug administration in Period 2. The subjects will be blinded and will have up to 5 visits. Approximately 30 patients will be enrolled in Cohort 1 to receive a single dose of Placebo s.c. in Period 1 then a single dose of SOM230 1.5 mg s.c. in Period 2. In case the pain is not responding to the administered study drug after 30 minutes, subjects will be allowed to use only 100% oxygen as a rescue management. Similarly, in Cohort 2 approximately 30 subjects will receive a single dose of placebo s.c. in Period 1 and a single dose of SOM230 0.9 mg s.c. in Period 2. Each subject will be instructed to self-administer (or to be assisted by a helper) the study medication at the beginning of the CH attack (as early as possible; within 10 minutes of start of attack when pain is at least moderate). If the patient is domiciled, medical staff may assist with administration. In case patient experiences CH attacks PRIOR to administering study treatment in Period 1 they can use 100% O2 or their conventional treatment to manage their attacks experienced before Period 1. If the subject does not have a headache attack in <b>72 hours post-baseline</b> or 72 hours post Period 1 treatment the subject will be excluded from the study. If feasible, subjects in Period 1 may undergo follow-up</p>

	within 24 hour post treatment administration. Within <b>24</b> hours of the dose administration in Period 2, subjects will also go through follow-up procedures and pharmacokinetic sample (PK) collections.
<b>Population</b>	Approximately 60 male and female cluster headache patients between the ages of 18-65 inclusive.
<b>Key Inclusion criteria</b>	<ul style="list-style-type: none"> <li>• Subject is male or female age 18-65 inclusive.</li> <li>• Subjects must have established diagnosis of episodic cluster headaches (CH) or chronic CH, averaging 2-6 headache attacks per day each lasting at least 45 minutes without treatment, not to exceed 6 attacks per day within the last year.</li> <li>• Able to communicate well with the investigator, to understand and comply with the requirements of the study, as well as accepting NOT to share any study information through social media during their participation in the study.</li> <li>• Subject is able to self-inject medication subcutaneously or have the assistance of a helper if warranted.</li> </ul>
<b>Key Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Subjects that have a history of greater than 6 CH attacks per day within the last year.</li> <li>• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the duration of the study. Men who are sexually active with women of child bearing potential, unless the male subjects use condoms during the study as per local requirements.</li> <li>• History of multiple and recurring allergies or allergy to the investigational compound/compound class being used in this study.</li> <li>• Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations.</li> <li>• A history of clinically significant heart diseases, ECG abnormalities, continued use of drugs known to prolong QTc during the study conduct, or any of the following ECG abnormalities at screening or baseline: <ul style="list-style-type: none"> <li>○ QTcF &gt; 450 msec (males)</li> <li>○ QTcF &gt; 460 msec (females)</li> </ul> </li> <li>• Uncontrolled diabetes as evidenced by screening HbA1c &gt; 8.0%</li> <li>• A positive Hepatitis B surface antigen or Hepatitis C test result.</li> <li>• Acute cholecystitis or symptomatic cholelithiasis in subjects without H/O cholecystectomy</li> </ul>
<b>Investigational and reference therapy</b>	<ul style="list-style-type: none"> <li>• SOM230 (pasireotide)</li> <li>• Placebo</li> </ul>
<b>Efficacy/PD assessments</b>	

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<b>Safety assessments</b>	<ul style="list-style-type: none"><li>• Safety Labs (blood chemistry, hematology, urinalysis and urine pregnancy test)</li><li>• ECG</li></ul>
<b>Other assessments</b>	<ul style="list-style-type: none"><li>• Patient Diary</li></ul>
<b>Data analysis</b>	<p>A logistic regression analysis with baseline headache severity, CH type, dose, Corporate Confidential Information 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 over time. 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 will be set to missing, which will be considered as missing at random.</p> <p>Additionally 100% oxygen therapy will be included in the afore mentioned logistic regression model as a time dependent covariate so headache response measurements after 100% oxygen therapy can be included in the analysis.</p> <p>The following approaches will be taken if the 0.9 mg dose is assessed in the second cohort: The effect of cohort will be explored and cohort may be included as a covariate in the logistic regression model. Placebo adjusted headache response rate at each time point 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.</p>
<b>Key words</b>	Cluster Headache Attacks, Headache Response, Rescue Medication

## 1 Introduction

### 1.1 Background

Cluster headache (CH) is a painful, disorder characterized by severe unilateral pain lasting between 15-60 min with an annual prevalence of 180,000 in US and 160,000 in EU ([Fischera et al 2008](#)). Pain occurs around the eye in the region enervated by the trigeminal nerve. Attacks are metronomic often occurring at the same time of day or night and may show annual periodicity. These attacks are often accompanied by autonomic symptoms like lacrimation, blushing or pupil constriction. Most of these patients are disabled by the disorder and suffer from bouts of pain up to 8 bouts /day and from 2 to 20 times a week. Two common forms of cluster headache are recognized: a) Episodic clusters with at least two cluster phases lasting 7 days to 1 year separated by a cluster-free interval of 1 month or longer (80%); and b) Chronic form, in which the clusters occur more than once a year without remission or the cluster-free interval is less than 1 month (20%). Many patients have found no relief from the usual methods of treatment and are willing to submit to any operation which might bring relief.

A non-vasoconstrictor treatment for acute CH is not available ([Matharu et al 2004](#)). Causes underlying CH attacks are not fully known; Somatostatins believed to reduce pain by inhibiting pain mediators e.g. Substance P and CGRP ([Pinter et al 2006](#)). However natural somatostatin in CH has a very short half-life (<2 min). Somatostatin infusion (25 µg/min for 20 min i.v.) was superior to placebo, and comparable to intramuscular ergotamine (250 µg i.m), in relieving CH pain ([Sicuteri et al 1984](#)). Octreotide activates mainly SSTR2 and has relatively longer  $t_{1/2}$  (90 min). In a randomized controlled trial in patients with episodic cluster headache, ([Matharu et al 2004](#)) octreotide 100 µg s.c. was significantly superior to placebo with regard to headache response rates (52% vs 36%, with a mean response time of 18.3 min).

Currently, sumatriptan is the only approved therapy for cluster headaches in addition to 100% O<sub>2</sub> therapy. A significant number of patients are refractory to currently recommended acute vasoconstrictive therapies (s.c. sumatriptan), or have contraindications to its use.

Pasireotide (SOM230) is a cyclohexapeptide analog of the hormone somatostatin. Natural somatostatin is widely distributed in the neural, endocrine and immune system and has diverse physiological actions. Somatostatin is an important inhibitory regulator of endocrine and exocrine secretion of various organs, including the pituitary, pancreas, GI tract, thyroid, kidney, and adrenal glands. It modulates GI function (including bowel motility and absorption of nutrients), inhibits gallbladder contractility and bile flow, and stimulates GI water and electrolyte absorption. It also inhibits cell proliferation and promotes apoptosis ([Theodoropoulou and Stalla 2013](#)).

Pasireotide (SOM230) s.c. injection has been in clinical development since 2003 and is being developed for treatment of symptoms of metastatic carcinoid tumors, acromegaly, Cushing's disease (CD), and Dumping Syndrome with s.c. and long acting release (LAR) i.m. formulation. It was approved by the FDA under the name of Signifor (pasireotide) s.c. injection use for the treatment of Cushing's disease for whom pituitary surgery is not an option or has not been curative. In addition, the LAR formulation of pasireotide was recently approved by the FDA for the treatment of patients with acromegaly who have had an inadequate response to surgery or for whom surgery is not an option.

The current study will assess the safety and efficacy of pasireotide (SOM230) s.c. in cluster headache. This study will have two cohorts where cohort 1 will be a comparison of the 1.5 mg SOM230 vs. Placebo, and following observed efficacy and safety signals in Cohort 1 at the interim analysis, Cohort 2 of the study comparing the 0.9 mg SOM230 to Placebo may be considered.

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## 1.2 Study purpose

The purpose of this study is to determine if SOM230 has adequate efficacy and safety to warrant further clinical development in cluster headache (CH). This study will have two cohorts. Cohort 1 will be a comparison of 1.5 mg SOM230 vs. Placebo, and following observed efficacy and safety signals in cohort 1 at the interim analysis, cohort 2 of the study comparing 0.9 mg SOM230 to Placebo may be considered.

## 2 Study objectives

### 2.1 Primary objective

<i>Primary objective</i>	<i>Endpoints related to primary objective</i>
<ul style="list-style-type: none"><li>To assess headache response of single s.c. dose of SOM230 compared to placebo in managing cluster headache attack at 30 minutes post-dosing</li></ul>	<ul style="list-style-type: none"><li>Percent (%) of patients with headache response defined as very severe, severe, or moderate pain before dosing that becomes mild or nil at 30 minutes post-dosing</li></ul>

### 2.2 Secondary objectives

<i>Secondary objectives</i>	<i>Endpoints related to secondary objectives</i>
<ul style="list-style-type: none"><li>To assess pain free response of single s.c. dose of SOM230 compared to placebo in managing cluster headache attack at 30 minutes post-dosing</li></ul>	<ul style="list-style-type: none"><li>% of patients who are pain free at 30 minutes post dose.</li></ul>
<ul style="list-style-type: none"><li>To assess the safety and tolerability of SOM230</li></ul>	<ul style="list-style-type: none"><li>Physical exam, safety labs, ECG, and adverse experiences</li></ul>

### 3 Investigational plan

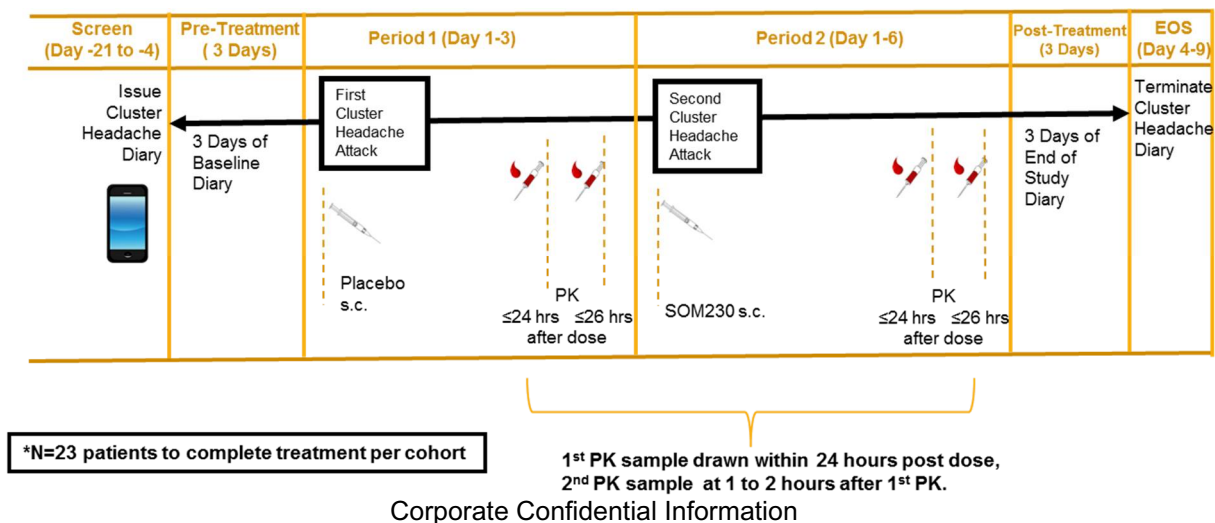
#### 3.1 Study design

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 patients 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 assisted by a helper, or by medical staff if domiciled at a clinic) 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 patient experiences CH attacks PRIOR to administering study treatment in Period 1 they can use 100% O<sub>2</sub> 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 ([Figure 3-1](#)). In case the pain is not responding to the administered study drug after 30 minutes, subjects will be allowed to use only 100% oxygen 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 visit within 24 hours of the study drug administration in Period 2 where a pharmacokinetic (PK) sample will be collected, with a second PK sample collected 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 3-1 Study Design Cohorts 1 and 2**



### 3.2 Rationale for study design

Based on the nature of the studied disease and PK characteristics of SOM230, a single s.c. dose will provide an assessment of effect of SOM230 in managing cluster headache attack as well as the time to next attack. It is expected that a single dose of SOM230 will relieve the cluster headache attack and will delay the time to next attack resulting in reduced number of attacks per day. Given the nature of the disease (repeated attacks up to 8 attacks/day for up to 2 months), the relatively long half-life of SOM230, and to ensure consistency between attacks, treating 2 consecutive attacks in a one-sequence two-period design with a placebo treatment in Period 1 will be appropriate to cluster headache patients and will increase the statistical power by taking advantage of a within-patient comparison in the absence of carryover effects. The treatment effect will be confounded with the period effect in this one-sequence 2 period study. However, this is not a major concern considering the 2 periods are  $\leq 3$  days apart and we are looking for a substantial treatment effect. Subjects will be blinded to the sequence of treatment to minimize any potential bias. The Investigator input in this study will not have any influence on study outcome being solely entered by the subjects in the e-diary, thus the Investigators don't need to be blinded. Considering the severe pain associated with CH, patients benefiting from sumatriptan are expected to continue their conventional management that successfully relieves their pain. Accordingly, enrolled population in the study is expected to be mainly composed of non-sumatriptan users. To avoid confounding AE evaluation in

case of concomitant use of sumatriptan, and the relatively longer study period, patients will be allowed to only use 100% oxygen as rescue-medication, and a conventional randomized cross-over design seemed unsuitable. The use of placebo will allow unbiased assessment of the benefit of SOM230 using subjective endpoints. Consecutive assessment of the 1.5mg dose followed by assessment of low dose (0.9 mg s.c.) will provide cluster headache patients with a better chance of getting efficacious doses with a potential for earlier relief of pain and possibly a longer interval till the next attack. Inclusion of the two SOM230 dose levels in cohort 1 and cohort 2 will provide the opportunity to determine the dose response relationship and obtain initial estimates of the treatment differences in efficacy parameters.

Due to the medical condition, it is not possible to collect PK samples during an attack. Samples will therefore be collected during the visit following an attack after drug administration in each period.

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### **3.3 Rationale for dose/regimen, duration of treatment**

SOM230 is approved and marketed under the name of Signifor® for Cushing's disease and acromegaly. For Cushing's disease the recommended s.c. pasireotide initial dose is either 0.6 mg or 0.9 mg bid. For acromegaly, the recommended initial dose of long-acting depot formulation (LAR) of pasireotide is 40 mg administered by deep intramuscular injection every 4 weeks.

Two SOM230 dose levels, 0.9 mg and 1.5 mg are considered. This approach will provide an early signal about any potential difference between the selected 2 dose levels starting assessment of the high dose followed by the low one if applicable.

For the single dose of 0.9 mg s.c., this is based on the study of octreotide in cluster headache patients ([Matharu et al 2004](#)). In this study, a single s.c. dose of 0.1 mg octreotide resulted in headache response of 52% with a placebo response of 36%. Both octreotide and SOM230 have comparable binding affinity to SSTR2; however SOM230 has additionally a higher affinity and functional activity at the SSTR 1, 3 & 5 than octreotide. Therefore, a 9 fold higher comparable dose of SOM230 is expected to yield meaningful efficacy response in the same disease entity.

For the single dose of 1.5 mg s.c., The MTD for SOM230 single s.c. dose was established at 1.95 mg. This MTD was demonstrated and proved to be tolerated in previous studies conducted as part of the SOM230 program. For this PoC study in order to maximize the chance of detecting efficacy signal, a single s.c. dose of 1.5 mg will be used to evaluate the efficacy of SOM230 in managing acute attack of cluster headache. In addition, use of this relatively high single dose of 1.5 mg may allow for earlier relief of cluster headache and possibly longer interval till next attack based on its PK profile as compared to the 0.9 mg dose.

### **3.4 Rationale for choice of comparator**

The study will compare the SOM230 2 dose levels (0.9 and 1.5 mg) against placebo since the targeted patients are those who are non-sumatriptan users.

### 3.6 Risks and benefits

There is no benefit expected for subjects participating in this study.

Based on the knowledge of the somatostatin (SSA) drug class and experience gained during the clinical development of pasireotide, potential risks identified included QT-prolongation, bradycardia, hyperglycemia, cholelithiasis, hematological abnormalities, abnormal liver functions, injection site reactions, gastrointestinal disorders, pancreatitis, and hypothyroidism.

The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, and a single dose study.

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In patients with cluster headache attacks, because of their severe pain condition hyperactivity of sympathetic system results in tachycardia making the chance of relevant QT prolongation unlikely. Based on the interpretation of the central tendency results of the TQT study the prolonging effect on QT interval associated with pasireotide treatment does not translate into increased pro-arrhythmic risk. The impact of GI AEs on the study outcome is minimal as the endpoint is being determined shortly post-dosing (at 30 minutes), i.e. prior to experiencing this set of AEs. For the LFT elevation, this risk is minimal because of the single dose used in this study. Furthermore, cholethiasis risk is minimal given the single dose administration and applying the exclusion criteria.

A maximum of 75 mL of blood is planned to be collected over a period of approximately a month, from each subject as part of the study. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population. However, injection site reactions and infections at injection site are additional related risks.

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study and have a negative pregnancy test at the beginning of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

There may be unknown risks of SOM230 which may be serious and unforeseen. Subjects will be notified in case any of these unknown risks become identified.

## 4 Population

Subjects that have a history of episodic or chronic cluster headaches (chronic cluster headache subjects not to exceed 50% of total study population) will be included in this study. Subjects enrolled in Cohort 1 will not be allowed to participate in Cohort 2.

### 4.1 Inclusion criteria

1. Subject is male or female age 18-65 inclusive.
2. Written informed consent must be obtained before any assessment is performed.
3. Subjects must have established diagnosis of episodic cluster headaches (CH) or chronic CH, averaging 2-6 headache attacks per day each lasting at least 45 minutes without treatment, not to exceed 6 attacks per day within the last year.
4. Able to communicate well with the investigator, to understand and comply with the requirements of the study, as well as accepting NOT to share any study information through social media during their participation in the study.
5. Subject is able to self-inject medication subcutaneously or have the assistance of a helper on an out-patient basis, if subject is not domiciled in a clinic for the study.

### 4.2 Exclusion criteria

1. Subjects that have a history of greater than 6 CH attacks per day within the last year.
2. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment;  
Men who are sexually active with women of child bearing potential, unless they use contraception as specified in [Section 5.1](#) during the study.  
Contraception specific details are listed in [Section 5.1](#).
3. History of multiple and recurring allergies or allergy to the investigational compound/compound class being used in this study.
4. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations.
5. A history of clinically significant heart diseases, ECG abnormalities, continued use of drugs known to prolong QTc during the study conduct, or any of the following ECG abnormalities at screening or baseline:
  - QTcF > 450 msec (males)
  - QTcF > 460 msec (females)
6. Uncontrolled diabetes as evidenced by screening HbA1c > 8.0%
7. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
8. A positive Hepatitis B surface antigen or Hepatitis C test result.
9. A positive pregnancy test or lactating mothers.
10. History of drug or alcohol abuse within the 12 months prior to dosing other than prescription medications to manage their CH attacks, or evidence of such abuse as

indicated by the laboratory assays conducted during screening and in the judgment of the Investigator.

11. Significant acute illness which has not resolved within two (2) weeks prior to initial dosing.
12. Any surgical or medical condition which might significantly jeopardize the subject's safety in case of participation in the study. The Investigator should make this determination in consideration of the subject's medical history and/or clinical or laboratory evidence of any of the following:
  - Liver disease or liver injury as indicated by abnormal liver function tests. ALT (SGPT), AST (SGOT),  $\gamma$ -GT, alkaline phosphatase and serum bilirubin will be tested.
    - ALT must be within the normal range
    - Serum bilirubin must not exceed 1.2 x ULN
    - $\gamma$ -GT, AST and alkaline phosphatase must not exceed 2 x ULN

[If necessary, laboratory testing may be repeated on one occasion (as soon as possible) prior to treatment, to rule out any laboratory error]
13. Acute cholecystitis or symptomatic cholelithiasis in subjects without H/O cholecystectomy

## 5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the following restrictions:

### 5.1 Contraception requirements

Female subjects of child-bearing potential must use highly effective methods of contraception during dosing of study treatment. Highly Effective contraception methods include:

- Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.



Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Male contraception is aligned with the local Health Authority requirements i.e. no male contraception in the UK. In the US and Germany, condom contraception for a male subject starts at the Baseline Visit, and until at least 3 days after the last administration of study drug. (3 days equals 5 half-lives of SOM230)

## **5.2 Prohibited treatment**

Subjects will not be allowed to take the following at least 24 hours before Baseline Visit through study completion:

- Use of steroids
- Use of ergot compounds, or other prophylactic therapies for cluster headache such as verapamil, or any drug known to cause QTc prolongation or Preventive care for at least 3 half-lives prior to study drug administration
- Use of NSAIDS

## **5.3 Dietary restrictions**

- No alcohol from 24 hours before Baseline Visit until after Study Completion evaluation.

## **5.4 General restrictions**

- No strenuous physical exercise (e.g. weight training, aerobics, football) from 24 hours before Baseline Visit until after Study Completion evaluation (End of Study visit).

# **6 Treatment**

## **6.1 Study treatment**

Details on the storage and management of study medication, treatment and instructions for prescribing and taking study treatment are outlined in Section 3 of the Site Operations Manual.

### **6.1.1 Investigational treatment**

The investigational drug, SOM230 0.6mg, 0.9mg and placebo. will be supplied by Novartis as single blind patient kits. Patients will be instructed on home based administration of study drug, or assisted by a helper/medical staff. Further details will be included in the Site Operations Manual.

### **6.1.2 Additional study treatment**

N/A

## 6.2 Treatment arms

The number of patients with chronic cluster headache is not to exceed 50% of patients in each cohort. Subjects enrolled in Cohort 1 will not be allowed to participate in Cohort 2.

Study treatments are defined as:

Cohort 1:

- A: single dose of placebo s.c. (Cohort 1-Period 1)
- B: single dose of 1.5 mg s.c. SOM230 (Cohort 1-Period 2)

Subjects will receive both treatments starting with placebo

Cohort 2

- A: single dose of placebo s.c (Cohort 2 – Period 1)
- B: single dose of. 0.9 mg s.c. SOM230 (Cohort 2- Period 2)

Subjects will receive both treatments starting with placebo

## 6.3 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments and/or interruptions are not permitted.

## 6.4 Treatment assignment

This study is a non-randomized study.

## 6.5 Treatment blinding

This study is a non-randomized and subject blinded study: subjects will remain blinded to the identity of study treatments during the study.

Corporate Confidential Information

## 6.6 Emergency breaking of assigned treatment code

The investigator will be unblinded, however the subject will remain blinded. There will not be a need for emergency breaking codes at the site for this study.

## 6.7 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with [SOM230], as detailed in [Section 8.5](#).

## 6.8 Recommended treatment of adverse events

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

## **6.9 Rescue medication**

Subjects will be allowed to use 100% oxygen as rescue medication during the study as described in [Section 7.1](#). If subjects require use of other rescue medication, they must contact the site immediately to be discontinued from the study. Every effort must be made to obtain study data for at least 24 hours after study medication has been administered. Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF after start of study drug.

## **6.10 Concomitant treatment**

Subjects are not to take any other medication to treat cluster headaches other than study medication. Concomitant treatment will be limited to only treat adverse experiences not associated with cluster headaches. Patients will be allowed to take 100% oxygen as rescue medication during the study starting 30 minutes after study drug administration.

In case patient experiences CH attacks PRIOR to administering study treatment in Period 1 they can use 100% O<sub>2</sub> or their conventional treatment to manage their headache attacks experienced before Period 1.

# **7 Discontinuation and study completion**

## **7.1 Discontinuation of study treatment**

Subjects will be discontinued from the study if the subject receives additional treatment for the CH pain other than 100% oxygen after subject has had no relief of pain for at least 30 minutes following study medication administration. However data collected up to this point will be included in the assessment.

## **7.2 Study completion and post-study treatment**

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. Study completion is defined as when the last subject completes their End of Study visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

At a minimum, subjects will be contacted for safety evaluations during the 30 days following the Study Completion visit, including a final post-study safety contact at the 30-day point. Documentation of attempts to contact the subject should be recorded in the source documentation.

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

### **7.2.1 Lost to follow-up**

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

### **7.3 Withdrawal of consent**

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject does not want to participate in the study anymore **and** does not want any further visits or assessments **and** does not want any further study related contact **and** does not allow analysis of already obtained biologic material.

If a subject withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

### **7.4 Study Stopping rules**

Under any of the following conditions, the current study may be placed on temporary hold, or consider initiation of lower dose (Cohort #2) pending a review of applicable safety data by the investigator and Sponsor:

- Three or more incidents of the same serious adverse event in a single cohort of the study that, in the opinion of the investigator, are related to the study drug
- The principal investigator (or his/her designee) and the sponsor consider that the number and/or severity of adverse events justify discontinuation of the study.
- The Sponsor requests it
- Cohort 1 will be stopped and Cohort 2 may be initiated if a safety signal is observed

Corporate Confidential Information

### **7.5 Early study termination**

The study can be terminated at any time for any reason by Novartis. Should this be necessary, subjects should be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests.

The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

## 8 Procedures and assessments

**Table 8-1 Assessment Schedule, (Cohorts 1 &2)**

Epoch <sup>1</sup>	Baseline		Treatment 1			Treatment 2			
Study Visit	Screening	Baseline	Period 1			Period 2			End of Study
Visit Numbers <sup>1</sup>	V1	V2	V101 <sup>2</sup>			V201 <sup>2</sup>			V299 <sup>10</sup>
Study Day(s)	-21 to -4	-1	1 to 3			1 to 6			4 to 9
Time (post-dose)	-	-	0h <sup>3</sup>	≤24h <sup>4</sup>	≤26h <sup>5</sup>	0h <sup>3</sup>	≤24h <sup>4-a</sup>	≤26h <sup>5</sup>	-
Informed consent	X								
Corporate Confidential Information		X							
Medical history/current medical conditions	X								
Patient History for Cluster Headache	X								
Physical examination	X	X							X
Study drug dispensation <sup>6</sup>		X							
Study drug administration <sup>7</sup>			X			X			
Body temperature	X	X		X			X		X
Patient Diary (pain assessment) <sup>8</sup>	X	X	X	X		X	X		
Diary review <sup>8</sup>		X		X			X		X
Blood Pressure and Pulse Rate	X	X		X			X		X
Demography	X								
Body height	X								
Body weight	X								
ECG evaluation	X <sup>11</sup>	X					X		X
Hepatitis screen	X								

[illegible]

<sup>1</sup> Visit structure given for internal programming purpose only.

<sup>2</sup> In the event the subject requires SOC treatment for CH or a recurrent CH attack, the subject must contact the site, every effort must be made to discontinue the subject after 24 hours of taking the study medication, all EOS evaluations should be performed if a subject is discontinued.

<sup>3</sup> If subject is not domiciled in a clinic for the study, study drug will be administered at home, before study visits.

<sup>4</sup> If possible in Period 1, the subject may have a follow-up visit as soon as possible within 24 hours of the dose. The collected PK sample must be obtained as soon as the patient arrives to the clinic. The date, time and the time the subject took the study medication must be collected on the eCRF. If logistically not possible the sample may be collected by a visiting nurse or equivalent.

<sup>4-a</sup> In Period 2, the subject must have a follow up visit as soon as possible within 24 hours of the dose for ECG & to collect PK samples. The sample must be collected as soon as the patient arrives to the clinic. If logistically not possible the sample may be collected by a visiting nurse or equivalent. The date, time and the time the subject took the study medication must be collected on the eCRF. In case the follow-up visit in Period 2 falls on a weekend, a window of up to 48 hours may be considered.

<sup>5</sup> A second PK sample will be collected 1-2 hours after the 1st sample was collected; the collection time of PK samples must be entered in eCRF. The second PK can be optional if not logistically possible.

<sup>6</sup> If subject is not domiciled in a clinic for the study, the study drug and instructions for use will be dispensed to the subject to be used as out-patient.

<sup>7</sup> Subjects will take 2 injections (in Cohort 1) / 1 injection (in cohort 2) of SOM230 or placebo s.c. in each study Period (1 &2) as instructed. These injections must be administered at the same time one after the other. The date and time of dose must be recorded on the patient diary.

<sup>8</sup> Diary: issued at screening visit; baseline information should be collected only for last 3 days prior to the baseline visit. Diary will be reviewed at the clinic visits.

<sup>9</sup> Blood chemistry should be repeated if Baseline Visit is greater than 10 days from Screening Visit.

<sup>10</sup> The EOS visit will occur 3 days after Period 2, post study drug administration.

<sup>11</sup> At the Investigator's discretion, optional screening ECG may be performed. The baseline ECG is optional, if screening ECG is done within not more than 7 days, and there is no change in medications. All subjects must have one ECG performed, either at screening or baseline, prior to the treatment phase.

## **8.1 Informed consent procedures**

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

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In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

## **8.2 Subject demographics/other baseline characteristics**

Subject demographic and baseline characteristic data will be collected on all subjects.

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses, not symptoms will be recorded.

Investigators have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.



### **8.3.1 Cluster Headache History**

Patients will be asked to provide a history of their cluster headache episodes. The questions will be initiated by the site (the frequency of cluster headaches per week, duration, severity, treatment used & response to treatment, history of any sumatriptan usage) and history will be recorded.

### **8.3.2 Patient Diary**

A patient diary will be administered to assess cluster headache (severity of pain, associated symptoms, time to resolve or becoming minimal, any use of rescue medication and time of its use post dose administration) during the times indicated on the [Assessment Schedule](#). A validated diary will be provided to the patients in their local language. The subject will complete the diary as instructed by the site staff. The Study coordinators will review the diary information for completeness at the study visits. Further details on completing the diary will be provided in the SOM.

## **8.4 Safety**

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the [Assessment Schedule](#) detailing when each assessment is to be performed.

### **8.4.1 Physical examination**

A physical examination will be obtained at time points indicated on the [Assessment Schedule](#) and maintained as source at the site. Any adverse event findings during a physical examination must be recorded on the appropriate adverse experience eCRF.

### **8.4.2 Vital signs**

Vital signs i.e. temperature, heart rate and blood pressure will be obtained at time points indicated on the [Assessment Schedule](#). These vital signs will be recorded on the eCRF.

### **8.4.3 Height and weight**

Height in centimeters (cm) and body weight in kilograms (Kg) (in indoor clothing without shoes) will be measured at screening visits according to the [Assessment Schedule](#). These recordings will be maintained at the site as source documentation except body weight will be collected on eCRF.

### **8.4.4 Laboratory evaluations**

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

#### **Hematology**

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count will be measured.

#### **Clinical chemistry**

Sodium, potassium, magnesium, creatinine, urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, lipase, CK, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

#### **Urinalysis**

A urinalysis sample will be collected at the time points specified in the [Assessment Schedule](#).

#### **Special clinical laboratory evaluations**

- Urine pregnancy test will be performed for female patients.

### **8.4.5 Electrocardiogram (ECG)**

PR interval, QRS duration, heart rate, RR, QT, QTc

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

### **8.4.6 Pregnancy and assessments of fertility**

All pre-menopausal women who are not surgically sterile will have regular urine pregnancy tests at screening and at end of the study. A positive urine pregnancy test requires exclusion of patient from the study unless serum  $\beta$ -hCG is performed and found to be negative.

## **8.5 Pharmacokinetics**

PK samples will be collected at the time points defined in the [Assessment Schedule](#).

Further details on sample collection, numbering, processing and shipment can be found in the Site Operations Manual.

Pharmacokinetic (PK) samples will be obtained and evaluated in all subjects at all dose levels.

SOM230 will be determined by a validated method.

Untreated samples (placebo) will not be analyzed.

Concentrations will be expressed in mass per volume units. Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

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## **8.6 Other assessments**

No additional tests will be performed on subjects entered into this study.

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## **9 Safety monitoring**

### **9.1 Adverse events**

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver related events are included in [Section 9.3](#).

Adverse events must be recorded on the Adverse Events CRF for subjects that pass screening and enter into the study. The adverse events should be reported according to the signs, symptoms or diagnosis associated with them, and accompanied by the following information: the severity grade using CTC-AE grading. In case CTC-AE grading does not exist for an adverse event, use:

- 1=mild,
  - 2=moderate,
  - 3=severe
  - 4=life threatening (qualifying as an SAE).
1. its relationship to the study treatment (no/yes),
  2. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
  3. whether it constitutes a serious adverse event (SAE) See [Section 9.2](#) for definition of SAE
  4. action taken regarding study treatment.
  5. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- no action taken (i.e. further observation only)
- study treatment dosage adjusted/temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- subject hospitalized/subject's hospitalization prolonged

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or Core Data Sheet (for marketed drugs) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

The investigator should also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

If required by a local regulatory authority, the investigator will identify and declare a consulting endocrinologist to review relevant Adverse Events.

## 9.2 Serious adverse event reporting

### 9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition of cluster headache elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

All malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per [Section 9.2.2](#).

### **9.2.2 SAE reporting**

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit, must be reported to Novartis within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to each specific component of study treatment (if study treatment consists of several drugs) complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department, notifying the Clinical Trial Leader. Contact information is listed in the Site Operations Manual.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the source documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

SAEs (initial and follow-up) that are recorded electronically in the Electronic Data Capture system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first. Study site personnel must also inform the Clinical Trial Leader.

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

### 9.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to [Appendix 2-Table 16-1](#) and [Appendix 2-Table 16-2](#) for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in [Appendix 2-Table 16-2](#).

#### For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

#### For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug (refer to [Section 7.1](#), if appropriate)
- Hospitalization of the subject if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded as appropriate in the CRF, including the liver event overview CRF pages.



## **9.4 Pregnancy reporting**

To ensure patient safety, each pregnancy in a subject on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments. Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on an SAE Report Form.

## **9.5 Early phase safety monitoring**

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

## **10 Data review and database management**

### **10.1 Site monitoring**

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

## **10.2 Data collection**

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and [Assessment schedule](#) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

## **10.3 Database management and quality control**

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

The CRO working on behalf of Novartis review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to the CRO working on behalf of Novartis who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

This will be a non-randomized study the investigator and site will be unblinded while the patient will remain blinded. The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the COAR Analytics and TM-TA Head.

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#### **10.4 Data Monitoring Committee**

Not required.

#### **10.5 Adjudication Committee**

Not required

### **11 Data analysis**

If the 0.9 mg dose is assessed then cohort will serve as a grouping factor for all relevant data listings. Additionally the effects of cohort on different endpoints will be explored and cohort may be included as a covariate in the corresponding analysis models as needed. A separate analysis may be performed for each cohort.

#### **11.1 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 any study drug and had no protocol deviations with relevant impact on efficacy/PD data.

## **11.2 Subject demographics and other baseline characteristics**

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

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

## **11.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)**

Data for study drug administration (rescue medication) and concomitant therapies will be listed by Cohort, treatment and subject as appropriate.

## **11.4 Analysis of the primary variable(s)**

### **11.4.1 Variable(s)**

Percent (%) of patients 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.

### **11.4.2 Statistical model, hypothesis, and method of analysis**

A logistic regression analysis with baseline headache severity, CH type, dose, 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 over time. 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 will be set to missing, which will be considered as missing at random.

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

Placebo adjusted headache response rate at each time point 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.

A subgroup analysis for non-sumatriptan users may be conducted as needed.

### **11.4.3 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.

#### **11.4.4 Supportive analyses**

Additionally 100% oxygen therapy will be included in the logistic regression model described above as a time dependent covariate so headache response measurements after 100% oxygen therapy can be included in the analysis.

The McNemar test with or without stratification by CH type may also be used to compare headache response rates between treatments at each time point.

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. A random subject effect will be included in the model as well to account for the correlation among measurements from the same subject. Percentage of subjects receiving 100% oxygen therapy at each time point will be tabulated by treatment.

Joint modelling of the headache response and time to 100% oxygen therapy data may be attempted as appropriate.

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.

### **11.5 Analysis of secondary and exploratory variables**

#### **11.5.1 Efficacy / Pharmacodynamics**

Pain free data will be analyzed using the same approach described for the primary variable.

A generalized linear model with CH type and dose as fixed effects and subject as a random effect will be used to compare the number of headache attacks following SOM230 treatment to baseline assuming the underlying data distribution is Poisson. Over dispersion, if any, will be accounted for as appropriate.

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#### **11.5.2 Safety**

##### **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. Summary statistics will be provided by 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 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.

### **11.5.3 Pharmacokinetics**

SOM230 plasma concentration data will be listed by treatment, subject, and visit/sampling time point.

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### **11.5.4 Pharmacokinetic / pharmacodynamic interactions**

The relationship between reconstructed individual PK profiles and/or the derived PK parameters with various efficacy/PD variables will be explored as appropriate.

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## **11.6 Sample size calculation**

Data from 23 subjects in each cohort will provide approximately 80% power to detect a drug effect (headache response rate at 30 minutes) that is both clinically significant (defined as the estimated treatment difference  $\geq 30\%$ ) and statistically significant (defined as  $\geq 90\%$  probability of a  $>0\%$  net drug effect) if the true placebo adjusted drug effect is 42%. The power calculation was performed using simulations assuming a correlation of 0.25 and the headache response rate for placebo treatment and 0.9 mg or 1.5 mg SOM230 dose is 30% and 72%, respectively. To account for a potential 20% drop-out rate approximately 30 patients will be enrolled in a cohort.

## **11.7 Power for analysis of key exploratory variables**

Data from 23 subjects will provide 86% power to detect a mean difference of 0.5 headache attack a day using a 1-sided paired t-test at the 0.05 significance level assuming an SD of 0.84 ([Leone et al 2000](#)) and a correlation of 0.5.

## **12 Ethical considerations**

### **12.1 Regulatory and ethical compliance**

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

### **12.2 Responsibilities of the investigator and IRB/IEC**

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

### **12.3 Publication of study protocol and results**

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as [clinicaltrials.gov](http://clinicaltrials.gov). In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.



## **13 Protocol adherence**

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators must apply due diligence to avoid protocol deviations. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

### **13.1 Protocol Amendments**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented, provided the Health Authorities and the reviewing IRB/IEC are subsequently notified by protocol amendment.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the CTL should be informed and (serious) adverse event reporting requirements ([Section 9](#)) followed as appropriate.

## 14 References

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## **15      Appendix 1 Blinding levels**

Not applicable, being a subject only blinded.

## 16 Appendix 2 Liver Safety Monitoring

**Table 16-1 Liver Event and Laboratory Trigger Definitions**

	Definition/ threshold
Liver laboratory triggers	$3 \times \text{ULN} < \text{ALT} / \text{AST} \leq 5 \times \text{ULN}$ $1.5 \times \text{ULN} < \text{TBL} \leq 2 \times \text{ULN}$
Liver events	ALT or AST $> 5 \times \text{ULN}$ ALP $> 2 \times \text{ULN}$ (in the absence of known bone pathology) TBL $> 2 \times \text{ULN}$ (in the absence of known Gilbert syndrome) ALT or AST $> 3 \times \text{ULN}$ and INR $> 1.5$ Potential Hy's Law cases (defined as ALT or AST $> 3 \times \text{ULN}$ and TBL $> 2 \times \text{ULN}$ [mainly conjugated fraction] without notable increase in ALP to $> 2 \times \text{ULN}$ ) Any clinical event of jaundice (or equivalent term) ALT or AST $> 3 \times \text{ULN}$ accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia Any adverse event potentially indicative of a liver toxicity *

**Table 16-2 Follow Up Requirements for Liver Events and Laboratory Triggers**

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case <sup>a</sup>	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion)
ALT or AST		
$> 8 \times \text{ULN}$	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion)
$> 3 \times \text{ULN}$ and INR $> 1.5$	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion)
$> 5$ to $\leq 8 \times \text{ULN}$	Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for <i>more than 2 weeks</i> , discontinue the study drug Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms <sup>b</sup>	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	Repeat LFT within 48 hours If elevation persists, establish causality Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study drug immediately Hospitalize the patient Establish causality Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	Consider study drug interruption or discontinuation Hospitalization if clinically appropriate Establish causality Complete liver CRF	Investigator discretion

\*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

<sup>a</sup>Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

<sup>b</sup> (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

<sup>c</sup> Resolution is defined as an outcome of one of the followings: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.