Sponsor
Novartis Pharmaceuticals

Generic Drug Name
SOM230

Trial Indication(s)
Cluster headache

Protocol Number
CSOM230Y2201

Protocol Title
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.)

Clinical Trial Phase
Phase II

Phase of Drug Development
Phase II

Study Start/End Dates
Study Start Date: October 2016 (Actual)
Primary Completion Date: September 2018 (Actual)
Study Completion Date: September 2018 (Actual)

Reason for Termination (If applicable)

Terminated (Non-efficacy in first Phase 2a cohort.)

Study Design/Methodology

This non-confirmatory study was planned to be conducted in 2 Cohorts using a one-sequence two-period design to compare SOM230 to placebo.
Two consecutive CH attacks were treated: the first attack was treated with placebo (Period 1) and the subsequent attack was treated with SOM230 (Period 2).

Centers

4 centers in 3 countries: United States(2), Germany(1), United Kingdom(1)

Objectives:

The primary objective of the study was to assess headache response of single s.c. dose of SOM230 compared to placebo in managing cluster headache (CH) attack at 30 minutes post-dosing.
The secondary objective of the study was to assess pain free response of single s.c. dose of SOM230 compared to placebo in managing CH attack at 30 minutes post-dosing.
Secondary endpoints also included assessment of the safety and tolerability of SOM230 in CH patients.
The study was terminated early. Based on results of Cohort 1, it was decided by Novartis not to recruit and enroll Cohort 2 of the study comparing 0.9 mg SOM230 to placebo.

Test Product (s), Dose(s), and Mode(s) of Administration

The investigational drug SOM230 (0.6 mg and 0.9 mg) and matching placebos were prepared and supplied by Novartis.

Statistical Methods

Efficacy Analysis: Percent of subjects with headache response defined as very severe, severe, or moderate pain before dosing that became mild or nil at 30 minutes post-dosing was the primary study endpoint.

A logistic regression analysis on the 30 minutes post-dosing data only with baseline headache severity (very severe, severe or moderate), CH type (episodic or chronic) and dose (0 for placebo, 1.5 mg for SOM230) as fixed effects was used to assess the effect of SOM230 on headache response. Dose was included as a categorical variable in the model. Placebo adjusted headache response rate was provided. Headache response measurements after 100% O2 therapy or sumatriptan was set to missing**,** which was considered as missing at random. The frequency and percentage of subjects with each response was displayed, along with the mean estimates, 90% confidence interval (CI) and p-value from the logistic regression analysis.

Supportive efficacy analysis

The McNemar's test with and without stratification by CH type was also used to compare headache response rates between treatments at the 30 minute post-dose.

The secondary efficacy endpoint Pain free response was analyzed using the same logistic regression model as used for the primary endpoint.

Safety analysis: AEs, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information were listed by treatment and subject. Summary statistics were provided by treatment.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Subject is male or female age 18-65 inclusive.
- Written informed consent must be obtained before any assessment is performed.
- 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.
- 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.
- Subject is able to self-inject medication subcutaneously or have the assistance of a partner on an out-patient basis.

Exclusion Criteria:

- Subjects that have a history of greater than 6 CH attacks per day within the last year.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the duration dosing of the study treatment. Or men who are sexually active with women of child bearing potential, unless the male subjects always use condoms during the study.
- History of multiple and recurring allergies or allergy to the investigational compound/compound class being used in this study.

• 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.
• 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:
o QTcF > 450 msec (males)
o QTcF > 460 msec (females)
• Uncontrolled diabetes as evidenced by screening HbA1c > 8.0%
• A positive Hepatitis B surface antigen or Hepatitis C test result.
• A positive pregnancy test or lactating mothers.
• 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.
• Significant acute illness which has not resolved within two (2) weeks prior to initial dosing.
• 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), γ-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
• γ-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]
• Acute cholecystitis or symptomatic cholelithiasis in subjects without H/O cholecystectomy

Participant Flow Table

Overall Study

	Placebo s.c. /1.5 mg SOM230 s.c.	Total
Arm/Group Description	A: single dose of placebo s.c. (Period 1) B: single dose of 1.5 mg s.c.	

	SOM230 (Period 2)	
Started	30	30
Completed	24	24
Not Completed	6	6
Physician Decision	5	5
Protocol Violation	1	1

Baseline Characteristics

	Placebo s.c. /1.5 mg SOM230 s.c.	**Total**
Arm/Group Description	A: single dose of placebo s.c. (Period 1) B: single dose of 1.5 mg s.c. SOM230 (Period 2)	
Number of Participants [units: participants]	28	28
Age Continuous (units: Years) Mean ± Standard Deviation		
	43.9±10.55	
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)		

Female	6	6
Male	22	22
Ethnicity (NIH/OMB) (units: Participants) Count of Participants (Not Applicable)		
Hispanic or Latino	3	3
Not Hispanic or Latino	3	3
Unknown or Not Reported	22	22

Summary of Efficacy

Primary Outcome Result(s)

Percent (%) of patients with headache response

(Time Frame: 30 minutes post dose)

	Placebo s.c.	SOM230 1.5 mg
Arm/Group Description	A single dose of placebo s.c.	single dose of 1.5 mg s.c. SOM230
Number of Participants Analyzed [units: participants]	20	20
Percent (%) of patients with headache response (units: Participants)		
	9	10

Statistical Analysis

Groups	Placebo s.c., SOM230 1.5 mg	
Non-Inferiority/Equivalence Test	Other	1.5mg SOM230 s.c. vs. Placebo s.c.
P Value	0.698	
Method	Regression, Logistic P-value vs. Placebo	
Odds Ratio (OR)	1.308	
90 % Confidence Interval 2-Sided	0.419 to 4.082	

Secondary Outcome Result(s)

Percent of patients who are pain free at 30 minutes post dose

(Time Frame: 30 mins post dose)

	Placebo s.c.	SOM230 1.5 mg
Arm/Group Description	A single dose of placebo s.c.	single dose of 1.5 mg s.c. SOM230
Number of Participants Analyzed [units: participants]	20	20
Percent of patients who are pain free at 30 minutes post dose (units: Participants)		
	5	7

Statistical Analysis

Groups	Placebo s.c., SOM230 1.5 mg	
Non-Inferiority/Equivalence Test	Other	1.5mg SOM230 s.c. vs. Placebo s.c.
P Value	0.385	
Method	Regression, Logistic P-value vs. Placebo	
Odds Ratio (OR)	2.033	
90 % Confidence Interval 2-Sided	0.530 to 7.790	

Hemoglobin

(Time Frame: throughout study, up up 9 days after treatment)

	Placebo s.c. /1.5 mg SOM230 s.c.
Arm/Group Description	A: single dose of placebo s.c. B: single dose of 1.5 mg s.c. SOM230
Number of Participants Analyzed [units: participants]	28
Hemoglobin (units: g/L) Mean ± Standard Deviation	
Screening	153.4 ± 12.93
End of Study	149.5 ± 15.13

Pulse Rate

(Time Frame: throughout study, up up 9 days after treatment)

	Placebo s.c. /1.5 mg SOM230 s.c.
Arm/Group Description	A: single dose of placebo s.c. B: single dose of 1.5 mg s.c. SOM230
Number of Participants Analyzed [units: participants]	28
Pulse Rate (units: Beats/min) Mean ± Standard Deviation	
Screening	77.2 ± 15.02
Baseline	78.1 ± 11.99
Period 1	76.9 ± 12.77
Period 2	74.0 ± 10.86
End of Study	81.1 ± 13.50

Summary of Safety

Safety Results

All-Cause Mortality

	1.5 mg SOM230 s.c. N = 26	Placebo s.c. N = 28
Arm/Group Description	single dose of 1.5 mg s.c. SOM230	A single dose of placebo s.c.
Total participants affected	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 30 days post treatment, up to maximum duration of 26 months.
Source Vocabulary for Table Default	MedDRA (21.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

	1.5 mg SOM230 s.c. N = 26	Placebo s.c. N = 28

Arm/Group Description	single dose of 1.5 mg s.c. SOM230	A single dose of placebo s.c.
Total participants affected	23 (88.46%)	5 (17.86%)
Cardiac disorders		
Palpitations	1 (3.85%)	0 (0.00%)
Gastrointestinal disorders		
Abdominal distension	1 (3.85%)	0 (0.00%)
Abdominal pain	3 (11.54%)	0 (0.00%)
Diarrhoea	7 (26.92%)	0 (0.00%)
Flatulence	1 (3.85%)	0 (0.00%)
Nausea	12 (46.15%)	0 (0.00%)
Vomiting	7 (26.92%)	1 (3.57%)
General disorders and administration site conditions		
Fatigue	6 (23.08%)	1 (3.57%)
Injection site bruising	0 (0.00%)	1 (3.57%)
Injection site erythema	4 (15.38%)	1 (3.57%)
Injection site pain	5 (19.23%)	1 (3.57%)
Injection site reaction	1 (3.85%)	1 (3.57%)
Injection site warmth	1 (3.85%)	0 (0.00%)
Malaise	1 (3.85%)	0 (0.00%)
Vessel puncture site bruise	0 (0.00%)	1 (3.57%)

Injury, poisoning and procedural complications		
Contusion	1 (3.85%)	0 (0.00%)
Ligament sprain	1 (3.85%)	0 (0.00%)
Investigations		
Haematocrit decreased	1 (3.85%)	0 (0.00%)
Red blood cell count decreased	1 (3.85%)	0 (0.00%)
Metabolism and nutrition disorders		
Decreased appetite	2 (7.69%)	0 (0.00%)
Nervous system disorders		
Dizziness	1 (3.85%)	0 (0.00%)
Headache	2 (7.69%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders		
Pleuritic pain	1 (3.85%)	0 (0.00%)
Skin and subcutaneous tissue disorders		
Pruritus	1 (3.85%)	0 (0.00%)
Vascular disorders		
Flushing	1 (3.85%)	1 (3.57%)

Other Relevant Findings

Conclusion:

- This study did not demonstrate any effect of 1.5 mg SOM230 in managing a CH attack in comparison to placebo at 30 minutes post-dosing.
- There was also no difference in the pain-free response at 30 minutes post dose of 1.5 mg SOM230 over placebo in headache response.
- SOM230 appeared to be safe and well tolerated as the AEs were manageable and of similar type and frequency to those reported in prior studies. There were no deaths or SAEs reported during the study.

Date of Clinical Trial Report

08 August 2019