Sponsor

Novartis

Generic Drug Name

Pasireotide

Therapeutic Area of Trial

Cushing's disease

Protocol Number

CSOM230B2208E1

Title

Extension to a multicenter, open-label study to assess the safety and efficacy of 600 µg SOM230, administered subcutaneously, bid in patients with Cushing's disease

Study Phase

Phase II

Study Start/End Dates

13-Aug-2004 to 08-Jul-2013

Study Design/Methodology

This was an extension, open-label, single arm, multicenter study in patients with Cushing's disease who had already received 15 days of pasireotide treatment in the core study and had experienced significant clinical benefit from this therapy. Pasireotide was to be administered as a subcutaneous injection at a dose of 600 µg bid every 12 hours for as long as the Investigator believed it was in the best interest of the patient and there were no safety or tolerability concerns.

Centers

8 centers in 5 countries: GBR (1), Germany (2), France (1), Italy (1) and USA (3)

Test Product, Doses, and Mode of Administration

Pasireotide was supplied in boxes containing 1 mL ampoules of 900 µg pasireotide per 1 mL of solution. Patients were to self-administer pasireotide sc twice a day at a dose of 600 µg bid., or in case urinary free cortisol (UFC) normalization was not achieved or maintained at a dose of 900 µg bid or 600 µg tid each day. For the administration of 600 µg pasireotide, patients were instructed to use 0.67 mL from the 1 mL ampoules of pasireotide 900 µg.

Statistical Methods

Data from all centers participating in the study were combined. Summary statistics were provided for the primary and secondary endpoints. No formal statistical comparisons were performed for this study. All data were listed. If appropriate, data listings indicated the incident dose. A complete safety and efficacy profile of the subset of patients who entered the Extension Phase was presented.

The following analysis populations were defined for this study:

The Intent-to-Treat (ITT) Population consisted of patients who completed 15 days of treatment in the Core study, experienced significant clinical benefit without any unacceptable AEs, and received at least 1 dose in the extension period.

The Primary Efficacy Population consisted of those ITT patients whose mean UFC at core-baseline, based on at least 2 UFC samples, was >1.0x upper limit of normal (ULN) or for whom the one and only UFC sample available at baseline was >2.0xULN.

The Safety Population was identical to the ITT Population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Patients who have completed the 15 days of Pasireotide treatment in the CSOM230B2208 study and have achieved normalization of 24-hour urinary free cortisol. Patients who did not achieve normalization of 24 -hour urinary free cortisol may be enrolled if in the opinion of the investigator the patient is getting significant clinical benefits from treatment with Pasireotide .
- The patient did not experience any unacceptable adverse events of tolerability issues during the original 15 day treatment.
- Female patients of child bearing potential who have not undergone clinically documented total hysterectomy and/or ovariectomy, or tubal ligation must agree to use barrier contraception throughout the course of the extension study, and for one month after the study has ended

Exclusion Criteria:

- Patients who have developed poorly controlled diabetes mellitus as indicated by ketoacidosis or HgbA1C > 10 since starting [study CSOM230B2208]
- Patients with persistent ALT/AST or alkaline phosphatase levels more than 2.5X ULN, serum creatinine > 2.0 X ULN, serum bilirubin > 2 X ULN
- Patients with abnormal coagulation (PT and PTT elevated by 30% above normal limits), WBC <3.0x1'000'000'000/L; Hgb <12.0g/dL for females, Hgb <13.0g/dL for males; PLT <100x1'000'000'000/L

Participant Flow

Patient disposition by last incident dose group (ITT Population)

Disposition/Reason, n (%)	SOM230 1200 µg sc TDD N=9	SOM230 1800 µg sc TDD N=8	SOM230 sc Any Dose N=19
Completed	1 (11.1)	2 (25.0)	3 (15.8)
Discontinued	8 (88.9)	6 (75.0)	16 (84.2)

Disposition/Reason, n (%)	SOM230 1200 µg sc TDD N=9	SOM230 1800 µg sc TDD N=8	SOM230 sc Any Dose N=19
Reason for discontinuation			
AE(s)	0	1 (12.5)	1 (5.3)
Abnormal laboratory value(s)	1 (11.1)	1 (12.5)	2 (10.5)
Unsatisfactory therapeutic effect	1 (11.1)	2 (25.0)	3 (15.8)
Patient withdrew consent	3 (33.3)	0	3 (15.8)
New cancer therapy	3 (33.3)	0	5* (26.3)
Other	0	2 (25.0)	2 (10.5)

"N" represents the number of ITT patients whose last non-zero TDD was the same as that identified by the particular dose group.
"n" represents the number of patients qualifying for inclusion in the identified row.
* One patient was evaluated for surgical intervention and 4 patients were to undergo pituitary surgery.
AE(s): adverse event(s); ITT: intent-to-treat; sc: subcutaneous; TDD: total daily dose.

Baseline Characteristics

Demographics (ITT Population)

Demographic Variable	SOM230 sc Any Dose (N=19)
Sex, n (%)	
Female	17 (89.5)
Male	2 (10.5)
Age, years	
n	19
Mean (SD)	43.0 (11.62)
Median	42.0
Min-Max	22-73
Race, n (%)	
Caucasian	19 (100.0)

"N" represents the number of patients in the ITT population who have ever received the total daily dose identified by the particular dose group.
ITT: intent-to-treat.

Outcome measures

Primary Outcome Result(s)

Summary of responders based on UFC (Primary Efficacy Population)

Responders, n (%)	SOM230 sc Any Dose N=18	Response rate 95% CI
Day 15 (Core)[1]		
Responder	3 (16.7%)	(3.6%, 41.4%)
Non-responder	15 (83.3%)	
Extension (Month 6)[2]		
Responder	4 (22.2%)	(6.4%, 47.6%)

Responders, n (%)	SOM230 sc Any Dose N=18	Response rate 95% CI
Non-responder	14 (77.8%)	

[1] A patient was a responder (Core), if the mean UFC levels from the 24-hour urine collections began on Days 14 and 15 was within normal limits.

[2] A patient was a responder (Extension), if the mean UFC levels from the 24-hour urine collections at Extension Month 6 were within normal limits. Patients who discontinued prior to Extension Month 6 or have missing mean UFC were classified as non-responders for the Extension.

"N" represents the number of patients in the primary efficacy population.

CI: confidence interval; UFC: urinary free cortisol.

Summary of responders, reducers and non-reducers based on UFC (Primary Efficacy Population)

Responder class, n (%)	SOM230 sc Any Dose N=18	Response rate 95% CI
Day 15 (Core)		
UFC Responder[1]	3 (16.7%)	(3.6%, 41.4%)
UFC Reducer[3]	11 (61.1%)	
UFC Non-Reducer[4]	4 (22.2%)	
Extension Month 6		
UFC Responder[2]	4 (22.2%)	(6.4%, 47.6%)
UFC Reducer[3]	6 (33.3%)	
UFC Non-Reducer[4]	8 (44.4%)	

[1] A patient is a UFC responder (Core), if the mean UFC levels from the 24-hour urine collections began on Days 14 and 15 is within normal limits.

[2] A patient was a responder (Extension), if the mean UFC levels from the 24-hour urine collections at Extension Month 6 were within normal limits.

[3] UFC Reducers have a mean UFC less than Core Phase Baseline but not within normal limits.

[4] UFC Non-reducers have a mean UFC that is higher than or equal to Core Phase Baseline.

"N" represents the number of patients in the primary efficacy population.

CI: confidence interval; UFC: urinary free cortisol.

Summary of mean UFC (nmol/24h) by visit (Primary Efficacy Population)

Visit	Statistic	SOM230 sc Any Dose (N=18)	
		Actual	Change from Core Baseline
Core Baseline	n	17	-
	Mean (SD)	1219.74 (752.9)	-
Day 14/Day 15	n	17	16
	Mean (SD)	521.97 (302.1)	-710.57 (740.6)
Month 6	n	11	10
	Mean (SD)	420.69 (339.7)	-801.85 (819.4)
Month 12	n	4	4
	Mean (SD)	398.38 (220.4)	-1202.1 (1084.1)
Month 24	n	4	4
	Mean (SD)	514.26 (455.7)	-1241.1 (925.6)

"n" (actual) represents the number of patients in the primary efficacy population whose mean UFC at the particular visit is associated with the particular incident dose group.

"n" (change from Core Baseline) is the number of patients in the primary efficacy population who have a Core Baseline and whose mean UFC at the particular visit is associated with the particular incident dose group.

UFC: urinary free cortisol.

Summary and change from Baseline of mean UFC (nmol/24 h) by visit and UFC subgroups (Primary Efficacy Population)

Subgroup	Visit	Statistic	SOM230 sc Any Dose (N=18)	
			Actual	Change from Core Baseline
UFC Responders[1]	Core Baseline	n	3	-
		Mean (SD)	1516.05 (902.1)	-
	Month 6	n	4	3
		Mean (SD)	181.18 (28.2)	-1330.15 (922.2)
UFC Reducers[2]	Core Baseline	n	6	-
		Mean (SD)	1243.18 (951.9)	-
	Month 6	n	6	6
		Mean (SD)	566.10 (397.0)	-677.08 (736.4)
UFC Non-reducers[3]	Core Baseline	n	8	-
		Mean (SD)	1091.04 (599.0)	-
	Month 6	n	1	1
		Mean (SD)	506.30	34.50

"n" (actual) represents the number of patients in the subgroup whose mean UFC at the particular visit is associated with the particular incident dose group.

"n" (change from Core Baseline) represents the number of patients in the subgroup who have a Core Baseline and whose mean UFC at the particular visit is associated with the particular incident dose group.

[1] A patient was a responder (Extension), if the mean UFC levels from the 24-hour urine collections at Extension Month 6 were within normal limits. Patients who discontinued prior to Extension Month 6 were classified as non-responders.

[2] UFC Reducers had a mean UFC at Extension Month 6 no higher than Core Phase Baseline but not within normal limits.

[3] UFC Non-reducers had a mean UFC at Extension Month 6 that was higher than Core Phase Baseline.

UFC: urinary free cortisol.

Secondary Outcome Result(s)

Summary of serum cortisol (nmol/L) by visit (Primary Efficacy Population)

Visit (pre-dose)	Statistic	SOM230 sc Any Dose (N=18)	
		Actual	Change from Core Baseline
Core Baseline	n	18	-
	Mean (SD)	723.60 (221.5)	-
Day 15	n	18	18
	Mean (SD)	697.64 (160.6)	-25.96 (125.1)
Month 6	n	11	11
	Mean (SD)	559.37 (300.2)	-150.60 (308.9)
Month 12	n	5	5
	Mean (SD)	684.56 (78.9)	-66.06 (301.9)
Month 24	n	4	4
	Mean (SD)	628.00 (181.0)	-227.53 (283.1)

Core Baseline is considered as pre-dose on Day 1.

“n” (actual) represents the number of patients in the primary efficacy population whose serum cortisol at the particular visit was associated with the particular incident dose group.

“n” (change from Core Baseline) represents the number of patients in the primary efficacy population who had a Core Baseline and whose serum cortisol at the particular visit was associated with the particular incident dose group.

Summary of serum cortisol (nmol/L) by visit and UFC subgroups (Primary Efficacy Population)

Subgroup	Visit	Statistic	SOM230 sc Any Dose (N=18)	
			Actual	Change from Core Baseline
UFC Responders[1]	Core Baseline	n	4	-
		Mean (SD)	848.53 (203.1)	-
	Month 6	n	4	4
		Mean (SD)	655.40 (428.1)	-193.13 (317.8)
UFC Reducers[2]	Core Baseline	n	6	-
		Mean (SD)	653.17 (213.5)	-
	Month 6	n	6	6
		Mean (SD)	478.22 (230.0)	-174.95 (328.8)
UFC Non-reducers[3]	Core Baseline	n	8	-
		Mean (SD)	713.96 (235.9)	-
	Month 6	n	1	1
		Mean (SD)	662.20	165.60

Core Baseline was considered as pre-dose on Day 1.

"n" (actual) represents the number of patients in the subgroup whose serum cortisol at the particular visit is associated with the particular incident dose group.

"n" (Change from Core Baseline) represents the number of patients in the subgroup who had a Core Baseline and whose serum cortisol at the particular visit was associated with the particular incident dose group.

[1] A patient was a responder (Extension), if the mean UFC levels from the 24-hour urine collections at Extension Month 6 were within normal limits.

Patients who discontinued prior to Extension Month 6 were classified as non-responders.

[2] UFC Reducers had a mean UFC at Extension Month 6 less than Core Phase Baseline but not within normal limits.

[3] UFC Non-reducers had a mean UFC at Extension Month 6 that was higher than or equal to Core Phase Baseline.

Summary of plasma ACTH (pmol/L) by visit (Primary Efficacy Population)

Visit (pre-dose)	Statistic	SOM230 sc Any Dose (N=18)	
		Actual	Change from Core Baseline
Core Baseline	n	18	-
	Mean (SD)	13.72 (11.0)	-
Day 15	n	18	18
	Mean (SD)	12.44 (8.9)	-1.28 (7.1)
Month 6	n	11	11
	Mean (SD)	9.55 (4.9)	-3.36 (9.4)
Month 12	n	5	5
	Mean (SD)	9.80 (3.8)	-3.60 (15.2)
Month 24	n	4	4
	Mean (SD)	12.00 (6.3)	-4.50 (8.3)

Core Baseline was considered as pre-dose on Day 1.

“n” (actual) represents the number of patients in the primary efficacy population whose plasma ACTH at the particular visit was associated with the particular incident dose group.

“n” (change from Core Baseline) represents the number of patients in the primary efficacy population who had a Core Baseline and whose plasma ACTH at the particular visit was associated with the particular incident dose group.

ACTH: adrenocorticotropic hormone.

Summary of plasma ACTH (pmol/L) by visit and UFC subgroups (Primary Efficacy Population)

Subgroup	Visit	Statistic	SOM230 sc Any Dose (N=18)	
			Actual	Change from Core Baseline
UFC Responders[1]	Core Baseline	n	4	-
		Mean (SD)	9.75 (5.7)	-
	Month 6	n	4	4
		Mean (SD)	6.75 (4.2)	-3.00 (7.9)
UFC Reducers[2]	Core Baseline	n	6	-
		Mean (SD)	14.17 (10.7)	-
	Month 6	n	6	6
		Mean (SD)	10.17 (4.4)	-4.00 (11.8)
UFC Non-reducers[3]	Core Baseline	n	8	-
		Mean (SD)	15.38 (13.5)	-
	Month 6	n	1	1
		Mean (SD)	17.00	-1.00

Core Baseline was considered as pre-dose on Day 1. Only pre-dose samples were included.

"n" (actual) represents the number of patients in the subgroup whose plasma ATCH at the particular visit was associated with the particular incident dose group.

"n" (Change from Core Baseline) represents the number of patients in the subgroup who had a Core Baseline and whose plasma ATCH at the particular visit was associated with the particular incident dose group.

[1] A patient was a responder (Extension), if the mean UFC levels from the 24-hour urine collections at Extension Month 6 were within normal limits. Patients who discontinued prior to Extension Month 6 were classified as non-responders.

[2] UFC Reducers had a mean UFC at Extension Month 6 less than Core Phase Baseline but not within normal limits.

[3] UFC Non-reducers had a mean UFC at Extension Month 6 that was higher than or equal to Core Phase Baseline.

ACTH: adrenocorticotropic hormone; UFC: urinary free cortisol.

Plasma trough concentrations of pasireotide by UFC clinical response status on Month 6

PK parameter	UFC Responders n=4	UFC Reducers n=6	UFC Non-reducers n=1
Day 15	7.0 ± 4.3 (6.0)	4.4 ± 1.1 (4.7)	2.7
Month 6	17.4 ± 11.6 (17.3)	19.1 ± 10.9 (20.5)	5.2

The table displays the mean ± SD (median) and the concentration unit is ng/mL

Day 15 was study Day 15 in the core phase

PK: pharmacokinetics; UFC: urinary free cortisol.

Safety Results

Number (%) of patients with AEs, regardless of study drug relationship, by primary SOC and by incident dose group (Safety Population)

Primary SOC, n (%) MedDRA v.16.0	SOM230 1200 µg sc TDD N=19	SOM230 1800 µg sc TDD N=8	SOM230 sc Any Dose N=19
Any primary system organ class	19 (100.0)	8 (100.0)	19 (100.0)
Gastrointestinal disorders	18 (94.7)	4 (50.0)	18 (94.7)
General disorders and administration site conditions	14 (73.7)	1 (12.5)	14 (73.7)
Metabolism and nutrition disorders	12 (63.2)	3 (37.5)	12 (63.2)
Investigations	9 (47.4)	3 (37.5)	10 (52.6)
Nervous system disorders	9 (47.4)	1 (12.5)	10 (52.6)
Skin and subcutaneous tissue disorders	9 (47.4)	2 (25.0)	10 (52.6)
Infections and infestations	6 (31.6)	4 (50.0)	8 (42.1)
Musculoskeletal and connective tissue disorders	6 (31.6)	3 (37.5)	8 (42.1)
Vascular disorders	5 (26.3)	2 (25.0)	7 (36.8)
Injury, poisoning and procedural complications	5 (26.3)	2 (25.0)	6 (31.6)
Blood and lymphatic system disorders	4 (21.1)	0	5 (26.3)
Hepatobiliary disorders	1 (5.3)	3 (37.5)	4 (21.1)
Reproductive system and breast disorders	3 (15.8)	1 (12.5)	4 (21.1)
Respiratory, thoracic and mediastinal disorders	4 (21.1)	0	4 (21.1)
Eye disorders	3 (15.8)	0	3 (15.8)
Psychiatric disorders	2 (10.5)	2 (25.0)	3 (15.8)
Renal and urinary disorders	3 (15.8)	0	3 (15.8)
Ear and labyrinth disorders	2 (10.5)	0	2 (10.5)
Cardiac disorders	0	1 (12.5)	1 (5.3)
Congenital, familial and genetic disorders	1 (5.3)	0	1 (5.3)
Endocrine disorders	1 (5.3)	0	1 (5.3)

“N” represents the number of patients in the safety population who received the TDD identified by the particular dose group.

“n” represents the number of patients who had an AE (belonging to the specific system organ class) associated with the particular incident dose group.

AEs: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; SOC: system organ class; TDD: total daily dose.

Most frequent AEs (>10% overall) regardless of study drug relationship by preferred term and incident dose group (Safety Population)

Preferred term, n (%) MedDRA v.16.0	SOM230 1200 µg sc TDD N=19	SOM230 1800 µg sc TDD N=8	SOM230 sc Any Dose N=19
Diarrhoea	12 (63.2)	2 (25.0)	13 (68.4)
Nausea	12 (63.2)	1 (12.5)	12 (63.2)
Hyperglycaemia	11 (57.9)	3 (37.5)	11 (57.9)

Abdominal pain	8 (42.1)	2 (25.0)	9 (47.4)
Headache	7 (36.8)	0	7 (36.8)
Injection site pain	6 (31.6)	0	6 (31.6)
Asthenia	4 (21.1)	1 (12.5)	5 (26.3)
Dizziness	4 (21.1)	1 (12.5)	5 (26.3)
Fatigue	5 (26.3)	0	5 (26.3)
Injection site pruritus	5 (26.3)	0	5 (26.3)
Alopecia	4 (21.1)	0	4 (21.1)
Constipation	4 (21.1)	0	4 (21.1)
Flatulence	4 (21.1)	0	4 (21.1)
Hyperhidrosis	3 (15.8)	0	4 (21.1)
Hypertension	2 (10.5)	2 (25.0)	4 (21.1)
Hypotension	4 (21.1)	0	4 (21.1)
Alanine aminotransferase increased	2 (10.5)	1 (12.5)	3 (15.8)
Arthralgia	3 (15.8)	0	3 (15.8)
Back pain	2 (10.5)	1 (12.5)	3 (15.8)
Cholelithiasis	0	3 (37.5)	3 (15.8)
γ-glutamyltransferase increased	3 (15.8)	1 (12.5)	3 (15.8)
Iron deficiency anaemia	2 (10.5)	0	3 (15.8)
Oedema peripheral	3 (15.8)	0	3 (15.8)
Pruritus	2 (10.5)	1 (12.5)	3 (15.8)
Abdominal pain upper	1 (5.3)	1 (12.5)	2 (10.5)
Amenorrhoea	2 (10.5)	0	2 (10.5)
Depression	1 (5.3)	1 (12.5)	2 (10.5)
Dry skin	1 (5.3)	0	2 (10.5)
Erythema	2 (10.5)	0	2 (10.5)
Foot fracture	2 (10.5)	0	2 (10.5)
Fungal skin infection	2 (10.5)	0	2 (10.5)
Glycosylated haemoglobin increased	1 (5.3)	1 (12.5)	2 (10.5)
Hypercholesterolaemia	2 (10.5)	0	2 (10.5)
Hypertriglyceridaemia	2 (10.5)	0	2 (10.5)
Influenza	1 (5.3)	1 (12.5)	2 (10.5)
Influenza like illness	2 (10.5)	0	2 (10.5)
Infusion related reaction	2 (10.5)	0	2 (10.5)
Injection site erythema	2 (10.5)	0	2 (10.5)
Injection site oedema	2 (10.5)	0	2 (10.5)
Nephrolithiasis	2 (10.5)	0	2 (10.5)
Oedema	2 (10.5)	0	2 (10.5)
Procedural nausea	2 (10.5)	0	2 (10.5)
Rash	2 (10.5)	0	2 (10.5)
Tendonitis	0	1 (12.5)	2 (10.5)
Upper respiratory tract infection	0	2 (25.0)	2 (10.5)
Vertigo	2 (10.5)	0	2 (10.5)

“N” represents the number of patients in safety population who received the TDD identified by the particular dose group.

"n" represents the number of patients who had an AE (identified by the preferred term) associated with the particular incident dose group.
AEs: adverse events; MedDRA: Medical Dictionary for Regulatory Activities; TDD: total daily dose.

Number (%) of patients who died, had other serious AEs, discontinued, experienced study drug interruption, or required additional therapy by treatment class and overall (Safety Population)

Event, n (%)	**SOM230 1200 µg sc TDD N=19**	**SOM230 1800 µg sc TDD N=8**	**SOM230 sc Any Dose N=19**
Deaths	0	0	0
Serious or significant events	16 (84.2)	7 (87.5)	18 (94.7)
SAEs	2 (10.5)	2 (25.0)	4 (21.1)
Discontinued due to AEs	0	1 (12.5)	1 (5.3)
AEs requiring dose adjustment or study-drug interruption	1 (5.3)	1 (12.5)	2 (10.5)
AEs requiring additional therapy	16 (84.2)	7 (87.5)	18 (94.7)

"N" represents the number of patients in the safety population who received the TDD identified by the particular dose group.
"n" represents the number of patients who had an AE (of the particular type) on the incident dose specified by the dose group.
AEs: adverse events. SAEs: serious adverse events, TDD: total daily dose.

Serious adverse events, excluding deaths, regardless of study drug relationship, by primary system organ class and preferred term (Safety population)

Primary system organ class **MedDRA v.16.0** Preferred term, n (%)	**SOM230** **1200µg sc TDD** **N=19**	**SOM230** **1800µg sc TDD** **N=8**	**SOM230 sc** **Any Dose** **N=19**
Any primary system organ class			
Total	2 (10.53)	2 (25.00)	4 (21.05)
Infections and infestations			
Total	0	1 (12.50)	1 (5.26)
Urinary tract infection	0	1 (12.50)	1 (5.26)
Injury, poisoning and procedural complications			
Total	0	1 (12.50)	1 (5.26)
Skin injury	0	1 (12.50)	1 (5.26)
Metabolism and nutrition disorders			
Total	0	1 (12.50)	1 (5.26)
Type 2 diabetes mellitus	0	1 (12.50)	1 (5.26)
Nervous system disorders			
Total	1 (5.26)	0	1 (5.26)
Convulsion	1 (5.26)	0	1 (5.26)
Respiratory, thoracic and mediastinal disorders			
Total	1 (5.26)	0	1 (5.26)
Pneumothorax	1 (5.26)	0	1 (5.26)

“N” represents number of patients in Safety population who have ever received the total daily dose identified by the particular dose group.

“n” represents number of patients who had an adverse event (of the particular type) on the incident dose specified by the dose group.

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically. A patient with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment. A patient with multiple adverse events within a primary system organ class was counted only once in the maximum rating.

Date of Clinical Trial Report

18-Dec-2013