NOVARTIS

Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

Pasireotide

Trial Indication(s)

Metastatic melanoma and/or metastatic Merkel cell carcinoma

Protocol Number

CSOM230X2404, EudraCT number: 2013-004573-27

Protocol Title

A Phase I, exploratory, intra-patient dose-escalation study to investigate the preliminary safety, pharmacokinetics, and anti-tumor activity of pasireotide (SOM230) sc followed by pasireotide LAR in patients with metastatic melanoma or metastatic Merkel cell carcinoma.

Clinical Trial Study Phase

Phase I

Study Start/End Dates

08-Nov-2012 to 21-Apr-2015

Reason for Termination (If applicable)

Due to slow enrolment into this trial and change in treatment landscape, Novartis decided to prematurely close the trial. Considering that there were ongoing patients in the study, Novartis decided to first stop recruitment and initiate trial closure activities. Patient recruitment was halted on 19-Dec-2014. The study was terminated early with the last patient last visit (LPLV) on 21-Apr-2015.

Study Design/Methodology

This was an open-label, single-arm, multi-center, Intra-patient dose-escalation, phase I study to evaluate the preliminary safety, pharmacokinetics, and anti-tumor activity of pasireotide (SOM230) sc (300, 600, 900 and 1200 μg tid) in patients with metastatic melanoma or metastatic Merkel cell carcinoma.

The present study was divided into three phases- Screening, Intra-patient dose-escalation and Follow-up phases. For patients with melanoma, BRAF and NRAS mutational status were to be assessed centrally at the start of the Screening phase. Patients entering Screening phase were informed of all aspects of the study and were then screened for study eligibility.

During the Intra-patient dose-escalation phase, 18 patients were planned to be treated with pasireotide sc 300 μg tid for 2 weeks (14 days). Patients were dose escalated to 600 μg tid for two more weeks followed by 900 μg tid for two weeks, and subsequently to 1200 μg tid for two weeks, provided there were no unacceptable adverse events (AEs), defined as drug-related clinically meaningful, uncontrolled grade 3 or any grade 4 toxicities. Each patient participated in the dose-escalation phase for a maximum of eight weeks.

At the end of the Intra-patient dose-escalation phase, patients entered the Follow-up phase. Patients were allowed to switch to 80 mg pasireotide LAR im q 28 d (intramuscularly every 28 days) (or a lower dose in case of toxicity) for an additional 6 months or until disease progression. In addition, all patients had to continue their pasireotide sc tid treatment (same dose as that at the end of the 8-week dose-escalation phase) during the first two weeks of the LAR Follow-up phase, except on the day receiving the first LAR dose because of an anticipated initial burst of drug release.

Centers

Three centers in two countries: Switzerland (2 centers) and Germany (1 center).

Publication

Not applicable.

Objectives:

Primary Objective

To assess the safety profile of pasireotide sc in patients with confirmed unresectable and/or metastatic melanoma (without BRAF and NRAS mutation) or confirmed unresectable and/or metastatic Merkel cell carcinoma during the first 8 weeks of treatment with pasireotide sc.

Secondary Objectives

- To assess the safety profile of pasireotide in patients with melanoma or Merkel cell carcinoma at study completion.
- To assess tumor response as measured by disease control rate (DCR).
- To assess the PK of pasireotide sc in patients with melanoma or Merkel cell carcinoma.
- To assess the effect of pasireotide, at each dose level, on melanoma response biomarkers (S100b) over time.
- To assess the effect of pasireotide on potential response and/or secretion biomarkers over time.

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

Study drug for this study was pasireotide sc and pasireotide LAR administered as an im depot injection.

Patients enrolled into the study received open-label pasireotide sc in the dose-escalation phase/Follow-up phase and two patients received pasireotide LAR in the Follow-up phase because this change was only introduced by Protocol Amendment 4 dated May 9th, 2014...

Statistical Methods

The study was terminated early without full enrollment of 18 patients according to the planned sample size. No patients with Merkel cell carcinoma were enrolled in the study and therefore this group of patients could not be included in the analysis.

The study protocol specified two time points for planned analyses

- A primary analysis when all patients completed Intra-patient dose-escalation phase (8-week) or have discontinued prior to completing the Intra-patient dose-escalation phase and
- A final analysis when all patients completed the Follow-up phase or have discontinued the study prior to completing the Follow-up phase.

Due to the early termination of the study there was no separation of these two analyses, i.e. the outlined analysis plan defined the final analysis of the study. Due to the associated low number of patients the following analyses stated in the protocol were not performed:

- For hematology, biochemistry, liver function tests and urinary laboratory tests: figures plotting (box plots) over time course and change from baseline over time
- All shift tables were limited to the dose-escalation phase
- For ECG parameter: change from baseline over time.
- For vital signs: change from baseline to the worst on-treatment result
- For Biomarker parameter: changes from baseline of each marker and its correlation with each dose.

Full analysis set

The Full Analysis Set (FAS) comprised of all patients who received at least one dose of study drug. The FAS was used for all efficacy analyses.

Safety set

The Safety Set included all patients who received at least one dose of study medication and had at least one post-baseline safety assessment. The safety set was used for all safety analyses, including the analysis of the primary objective.

Qualitative data (e.g. gender, race) were summarized using contingency tables (frequencies percentages); quantitative data (e.g. age, body weight) were summarized using appropriate descriptive statistics (mean, standard deviation, median, minimum, and maximum). Demographic data (such as age, sex, race, ethnicity, height, weight) were summarized by the full analysis set (FAS).

The primary objective of the study was to evaluate the safety profile of pasireotide sc in patients with melanoma during the first 8 weeks of treatment with pasireotide sc.

The primary safety variables were incidence of AEs, incidence of serious adverse events (SAEs) and laboratory, vital signs and electrocardiographic abnormalities during the first 8 weeks of treatment with pasireotide sc. It also included changes from baseline in laboratory and electrocardiograms assessment values and changes in the assessment values of physical examinations such as vital signs, during the first 8 weeks of treatment with pasireotide sc.

A secondary objective of this study was to assess the preliminary efficacy (anti-tumor activity) of pasireotide sc using the FAS. The efficacy endpoints analyzed were disease control rate as assessed by RECIST 1.0 at the end of the 8-week Intra-patient dose-escalation phase (Visit 10), Visits 12, 14 and EOT.

The best overall tumor response was assessed by RECIST criteria. Only overall tumor assessments reported by the investigator and performed before the start of any further anti-neoplastic therapies were considered in the assessment of best overall response.

Sample size and power calculation

Sample size of 18 patients was selected without regard for statistical power and was considered to be sufficient to assess the safety of pasireotide sc in this patient population. With 18 patients there was 85% probability of detecting an adverse event with 10% incidence rate. For the secondary biomarker objectives, a minimum of 12 patients with unresectable and/or metastatic melanoma needed to complete the Intra-patient dose escalation phase of the study to sufficiently examine the objectives of the study. Therefore, if after enrolling 18 patients if 12 patients with unresectable and/or metastatic melanoma did not complete the 8 -week Intra-patient dose escalation phase of the study, more patients were planned to be enrolled. As Merkel cell carcinoma is a very rare disease, there was no pre -defined patients number required to complete the 8-week Intra-patient dose escalation phase of the study.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Patients eligible for inclusion in this study had to meet all of the following criteria:

1. Adult male or female, age ≥ 18 years

2. Female patients of child bearing potential must have a negative pregnancy test at screening
3. Histologically or cytologically confirmed unresectable (stage III) and/or metastatic (stage IV) melanoma or unresectable and/or metastatic Merkel cell carcinoma
4. No mutation in BRAF and NRAS genes (for melanoma patients only)
5. Patients should have at least 1 (one) lesion suitable for standardized uptake value (SUV) measurements on ^{18}FDG-PET (e.g., ≥ 1.5 cm in longest diameter by CT/MRI and with a tumor-to-background ratio (TBR) ≥ 1.5), except where ^{18}FDG-PET scans are optional.
6. Patients must have lesions that can be biopsied
7. Presence of measurable or non-measurable disease according to RECIST 1.0
   a. In order to be considered measurable, skin or superficial lymph nodes must be ≥ 1 cm in longest diameter.
   b. Lesions in previously irradiated areas should not be considered measurable, unless they have clearly progressed since the radiotherapy
8. Assessable metastases (skin or superficial lymph nodes, minimal diameter 1 cm)
9. ECOG Performance Status of 0 or 1
10. Patients with a known history of impaired fasting blood glucose (glucose >100 and <126 mg/dL) may be included at the discretion of the PI. These patients should be monitored closely throughout the trial and treatment adjusted as necessary. Patients that are deemed ineligible due to elevated glucose may be re-screened again after adequate medical treatment
11. Adequate organ function
    - Adequate bone marrow function
    - WBC ≥ 2.5×10^9/L
    - ANC ≥ 1.5×10^9/L
    - Platelets ≥ 100×10^9/L
    - Hemoglobin ≥ 9 g/dL
    - Serum creatinine ≤ 1.5 mg/dL or estimated glomerular filtration rate (eGFR) > 40 ml/min/m^2
    - Serum lipase ≤ 1.5 ULN

12. Life expectancy of at least 12 weeks
13. Written informed consent obtained prior to any screening procedures

Exclusion criteria

Patients eligible for this study must not meet any of the following criteria:

1. Patients with unknown BRAF or NRAS mutational status (for melanoma patients only)
2. Primary uveal melanoma
3. Patients with symptomatic CNS metastases who are neurologically unstable or requiring increasing doses of steroids to control their CNS disease
4. Prior treatment with somatostatin analogue or radiolabeled somatostatin analogs
5. Patients with a known hypersensitivity to somatostatin analogs or any component of the pasireotide sc and im formulations or their excipients
6. Patients for whom standard treatment is available and indicated due to rapidly progressive or aggressive disease
7. Patients who received more than 3 prior lines of systemic therapy for the treatment of the disease (the wash out period has to be 4 weeks prior to baseline).
8. Patients receiving any anti-neoplastic therapy within the 4 weeks prior to baseline
9. Patients receiving an investigational drug within 1 month prior to baseline
10. Patients who have undergone major surgery/surgical therapy for any cause within 1 month prior to baseline. Patients must have recovered from the treatment and have a stable clinical condition before entering this study
11. Patients who have received prior radiation therapy $\leq$ 4 weeks, or limited field radiation $\leq$ 2 weeks, prior to baseline or the side effects of such therapy have not resolved to $\leq$ grade 1.
12. Patients unwilling to perform repeated biopsies
13. Patients with known gallbladder or bile duct disease, acute or chronic pancreatitis (patients with asymptomatic cholelithiasis and asymptomatic bile duct dilation can be included)
14. Patients with abnormal coagulation (PT or PTT elevated by 30% above normal limits)

15. Patients on continuous anticoagulation therapy. Patients who were on anticoagulant therapy must complete a washout period of at least 10 days prior to baseline and have confirmed normal coagulation parameters before study inclusion
16. Patients who are not biochemically euthyroid
    - Patients with known history of hypothyroidism are eligible if they are on adequate and stable replacement thyroid hormone therapy for at least 3 months prior to baseline
17. QT-related exclusion criteria
    - Baseline QTcF >450 ms
    - History of syncope or family history of idiopathic sudden death
    - Known history of prolonged QT syndrome
    - Sustained or clinically significant cardiac arrhythmias
    - Patients with risk factors for torsades de pointes such as uncorrected hypokalemia, uncorrected hypomagnesemia, clinically relevant cardiac failure (NYHA class III or IV), clinically significant/symptomatic bradycardia or high-grade AV block
    - Concomitant medications known to prolong the QT interval
    - Known concomitant disease(s) that could prolong QT such as autonomic neuropathy (caused by diabetes mellitus or Parkinson's disease), HIV, liver cirrhosis, uncontrolled hypothyroidism or cardiac failure
    - Patients with unstable angina, sustained ventricular tachycardia, ventricular fibrillation, high grade (NOT advanced!) heart block or history of acute myocardial infarction less than one year prior to baseline
18. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    - Uncontrolled diabetes as defined by HbA1c > 8% despite adequate therapy
    - Patients with the presence of active or suspected acute or chronic uncontrolled infection or with a history of immunodeficiency, including a positive HIV test result (ELISA and Western blot). A HIV test will not be required; however, previous medical history will be reviewed

- Non-malignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with this study treatment
- Liver disease or history of liver disease such as cirrhosis, decompensated liver disease, or chronic active hepatitis B and C or chronic persistent hepatitis
- Life-threatening autoimmune and ischemic disorders

19. Patients who have a history of another primary malignancy, with the exception of locally excised non-melanoma skin cancer and carcinoma in situ of uterine cervix. Patients who had no evidence of disease from another primary cancer for 3 or more years are allowed to participate in the study
20. Patients who have any current or prior medical condition that may interfere with the conduct of the study or the evaluation of its results in the opinion of the Investigator or the Sponsor's Medical Monitor
21. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study
22. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL)
23. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, UNLESS they are
    - Women whose sexual orientation precludes intercourse with a male partner
    - Women whose partners have been sterilized by vasectomy or other means
    - Using a highly effective method of birth control (i.e. one that results in a less than 1% per year failure rate when used consistently and correctly, such as implants, injectables, combined oral contraceptives, and some intrauterine devices (IUDs); periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) is not acceptable
24. Baseline ALT or AST > 3 × ULN
25. Baseline total bilirubin > 1.5 × ULN
26. Presence of Hepatitis B surface antigen (HbsAg)
27. Presence of Hepatitis C antibody test (anti-HCV)
28. History of, or current alcohol misuse/abuse within the past 12 months prior to visit 1 (baseline)

Participant Flow Table

Patient disposition (FAS)

Disposition Reason	All Patients N=10 n (%)
Dose-escalation phase	
Completed dose-escalation phase	5 (50.0)
Discontinued Study treatment prematurely	5 (50.0)
Subject withdrew consent	1 (10.0)
Disease progression	4 (40.0)
Follow-up phase	
Completed study	3 (30.0)
Discontinued Study prematurely	2 (20.0)
Disease progression	2 (20.0)

Baseline Characteristics

Demographic Variable	All patients N=10
Age (years)	
n	10
Mean (SD)	69.8 (5.94)
Median	71.5
Minimum – Maximim	60 – 77
Age category (years) - n(%)	
<65	3 (30.0)

Demographic Variable	All patients N=10
≥ 65	7 (70.0)
Sex - n(%)	
Male	8 (80.0)
Female	2 (20.0)
Race - n(%)	
Caucasian	10 (100.0)
Ethnicity - n(%)	
Other	10 (100.0)
Baseline weight (kg)	
n	10
Mean (SD)	77.04 (13.416)
Median	79.00
Minimum – Maximim	51.6 - 98.0
Height (cm)	
n	10
Mean (SD)	170.6 (8.69)
Median	174.0
Minimum – Maximim	150 – 180

Summary of Efficacy

This study was terminated due to low enrolment only safety data will be disclosed.

Summary of Safety

Safety Results

Adverse events regardless of study drug relationship, by primary system organ class (SOC), and severity (Safety set) - Overall

Primary system organ class	Grade 3/4 n (%)	All grades n (%)
Any primary system organ class	**6 (60.0)**	**10 (100.0)**
Gastrointestinal disorders	1 (10.0)	9 (90.0)
General disorders and administration site conditions	2 (20.0)	7 (70.0)
Metabolism and nutrition disorders	2 (20.0)	5 (50.0)
Infections and infestations	0	4 (40.0)
Investigations	0	4 (40.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (20.0)	3 (30.0)
Musculoskeletal and connective tissue disorders	0	2 (20.0)
Nervous system disorders	0	2 (20.0)
Blood and lymphatic system disorders	0	1 (10.0)
Ear and labyrinth disorders	0	1 (10.0)
Injury, poisoning and procedural complications	0	1 (10.0)
Respiratory, thoracic and mediastinal disorders	1 (10.0)	1 (10.0)
Skin and subcutaneous tissue disorders	0	1 (10.0)
Vascular disorders	0	1 (10.0)

Primary system organ class	Grade 3/4 n (%)	All grades n (%)
A patient with multiple AEs within a primary system organ class is counted only once in the All grades column.		
Primary system organ classes sorted in descending frequency of All grades column.		
AEs with onset after last day with study medication + 28 days are not included here.		
AEs with onset before first day with study medication are not included here.		

Adverse events regardless of study drug relationship, by preferred term and maximum grade (Safety set) - Overall

Preferred term	Grade 3/4 n (%)	All grades n (%)
Any preferred term	6 (60.0)	10 (100.0)
Diarrhoea	1 (10.0)	5 (50.0)
Nausea	1 (10.0)	5 (50.0)
Fatigue	0	3 (30.0)
Hyperglycaemia	0	3 (30.0)
Hypophosphataemia	2 (20.0)	3 (30.0)
Chills	0	2 (20.0)
Tumour pain	2 (20.0)	2 (20.0)
Weight decreased	0	2 (20.0)
Abdominal pain upper	0	1 (10.0)
Anaemia	0	1 (10.0)
Arthralgia	0	1 (10.0)
Ascites	0	1 (10.0)
Asthenia	1 (10.0)	1 (10.0)
Basal cell carcinoma	0	1 (10.0)

Preferred term	Grade 3/4 n (%)	All grades n (%)
Basophil count increased	0	1 (10.0)
Blood creatinine increased	0	1 (10.0)
Blood lactate dehydrogenase increased	0	1 (10.0)
Blood urea increased	0	1 (10.0)
Cystitis	0	1 (10.0)
Decreased appetite	0	1 (10.0)
Diabetes mellitus	0	1 (10.0)
Eosinophil count increased	0	1 (10.0)
Facial bones fracture	0	1 (10.0)
Flatulence	0	1 (10.0)
Gamma-glutamyltransferase increased	0	1 (10.0)
General physical health deterioration	1 (10.0)	1 (10.0)
Hyperkalaemia	0	1 (10.0)
Hyperuricaemia	0	1 (10.0)
Hypocalcaemia	0	1 (10.0)
Hypogeusia	0	1 (10.0)
Influenza	0	1 (10.0)
Melaena	0	1 (10.0)
Musculoskeletal pain	0	1 (10.0)
Nasopharyngitis	0	1 (10.0)
Neoplasm progression	1 (10.0)	1 (10.0)
Pain	0	1 (10.0)
Paraesthesia	0	1 (10.0)
Pruritus	0	1 (10.0)

Preferred term	Grade 3/4 n (%)	All grades n (%)
Pulmonary thrombosis	1 (10.0)	1 (10.0)
Thrombosis	0	1 (10.0)
Tongue discolouration	0	1 (10.0)
Vertigo	0	1 (10.0)
Vomiting	0	1 (10.0)
Wound infection	0	1 (10.0)

Preferred terms are sorted in descending frequency, as reported in All grades column.

A patient with multiple occurrences of an AE preferred term is counted only once for that preferred term.

AEs with onset after last day with study medication + 28 days are not included here. AEs with onset before first day with study medication are not included here.

Other Relevant Findings

Not applicable

Conclusion:

This was a Phase I exploratory study with primary objective to assess the safety profile of pasireotide sc in patients with confirmed unresectable and/or metastatic melanoma (without BRAF and NRAS mutation) or confirmed unresectable and/or metastatic Merkel cell carcinoma during the first 8 weeks of treatment with pasireotide sc. Patients with metastatic Merkel cell carcinoma could not be recruited and the study was terminated due to the slow recruitment of patients.

Most of the recruited patients were terminally ill and only five patients completed the dose-escalation study. Therefore, study drug exposure was possibly insufficient with patients dropping out due to disease progression. Three patients reached high dosing (one patient 3600 µg in the dose-escalation phase and Follow-up phase and two patients 3600 µg in the dose-escalation phase and 80 mg in the Follow-up phase) and were stable for more than five months. All the patients reported at least one AE during the study, and six (60%) patients reported grade

3-4 AEs. AEs suspected to be study drug related were reported in eight (80%) patients. Patients discontinued mainly due to disease progression. Overall, the safety profile of the drug is consistent with established safety profile of pasireotide in other indications but cannot be confirmed in this small patient population. The AEs were well managed with concomitant medications.

This study also intended to assess tumor response as measured by the DCR. By tumor assessment using CT or MRI, and also by using FDG-PET, DCR was 20.0%, reflecting limited efficacy, however, the sample size was very low (n=10).

All patients participated in the dose-escalation phase and had PK assessments, following the Intra-patient dose-escalation, each dose (300 µg tid, 600 µg tid, 900 µg tid, and 1200 µg tid) was given to the patients for 2 weeks, the mean plasma concentration of pasireotide versus time profiles on Day 8 suggested that the AUC0_2hr, Cmax and Cmin increased with increasing dose.

The patient population size in this terminated trial was very limited (n=10), all results related to the PD, biomarker, PK, and safety of the treatment need to be interpreted with caution due to the limited amount of data.

Date of Clinical Trial Report

08-Mar-2016