NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Pasireotide LAR

Trial Indication(s)

Castration resistant prostate cancer

Protocol Number

CSOM230XDE04

Protocol Title

Phase 1 study to evaluate safety, and preliminary efficacy of pasireotide LAR in castration resistant prostate cancer

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase Ib

Study Start/End Dates

Study Start Date: March 2013 (Actual)
Primary Completion Date: November 2018 (Actual)
Study Completion Date: November 2018 (Actual)

Reason for Termination (If applicable)

Slow recruitment

Study Design/Methodology

This was a phase Ib, multicenter, open-label study that was planned to assess safety, tolerability, pharmacokinetics and preliminary efficacy of pasireotide LAR i.m. injection dosed every 28 days in patients with castration resistant prostate cancer. GnRH agonists or antagonists given prior to study start were continued as concomitant medication. This study was planned to consist of a dose escalation part and a dose expansion part. During the escalation part, dose limiting toxicities (DLT) observed within 56 days after start of study treatment were planned to be used to determine the maximum tolerated dose (MTD). During the expansion part, it was planned to evaluate preliminary efficacy data.

Dose escalation:

The study consisted of a time-lagged dose escalation design evaluating different doses of pasireotide LAR in cohorts of 3-6 patients. Each cohort consisted of newly enrolled patients. Planned doses of pasireotide LAR were 60, 80, 100, 120 and 140 mg. After each dose level, a Dose Decision Meeting (DDM) was planned to be conducted in order to determine the MTD.

The enrollment was terminated due to slow recruitment by protocol amendment 04 (protocol version 04, dated 09-Jul-2015), effective 08-Sep-2015. Patient enrollment was stopped after the 80mg dose cohort, the escalation phase was not completed and the MTD was not determined. Consequently, the expansion phase was not conducted at all.

Centers

Germany(4)

Objectives:

To assess preliminary efficacy of pasireotide LAR based on the rate of patients being progression free after 6 months of treatment.

Number of patients who experienced a dose limiting toxicity (DLT) in order to determine maximum tolerated dose (MTD)

To assess the safety profile of pasireotide LAR at different doses given.

Per Amendment 4, the study was terminated prematurely due to the unexpectedly low recruitment. Hence, the MTD as a primary objective could not be determined. Thus, all objectives were determined to be exploratory, including former secondary and exploratory objectives.

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

Pasireotide LAR for intramuscular injection (i.m.) was administered as a depot by an intragluteal injection once every 28 days by a study nurse or a study physician. The starting dose of pasireotide LAR for the study was 60mg. Subsequent doses were administered according to the dose-escalation schedule (80, 100, 120, 140mg).
Cohort sizes of at least 3 evaluable patients were treated at each dose level of pasireotide LAR. Evaluable patients are those who meet the minimum treatment and safety evaluation requirements of the study. Additional 3 patients have been enrolled, if one DLT was observed. If a second patient at the same dose level experienced a DLT or ≥ 2/6 patients experienced DLT, dose escalation should have been stopped and the previous dose level would be declared as the MTD once 6 patients have been treated at that dose and < 2/6 patients experienced a DLT.
As per amendment 4, the study was terminated prematurely due to the unexpectedly low recruitment. The enrollment to the study was stopped when dose level 2 (80mg) was finished.

Statistical Methods

Data was summarized with respect to demographic and baseline characteristics, preliminary efficacy observations and measurements, safety observations and measurements, pharmacokinetic measurements and biomarker measurements.

Patient sets for analysis had to be adapted according to amendment 4 of the amended protocol version 04. Since the maximum tolerated dose (MTD) - which was initially planned to be the primary endpoint - could not be reached, the definition of the ITT and per-protocol sets was not applicable. Hence, ITT and per-protocol sets and corresponding analyzes were omitted. The safety population set consisted of all patients who received at least one pasireotide LAR injection and had at least one post-baseline safety assessment. The safety analyses was performed for each dose group separately as well as for the safety set in whole.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
1. ECOG 0 - 2
2. Histologically proven adenocarcinoma of the prostate.
3. Patients with CRPC (castration resistant prostate cancer): advanced or metastatic adenocarcinoma of the prostate.

4. Prior treatment with a GnRH-agonist or GnRH-antagonist for at least 6 months. The medication must not have been changed for at least 3 months prior to start of study treatment.
5. Prior treatment with an anti-androgen (e.g. bicalutamide, flutamide, cyproteronacetate) is allowed but not necessary. Patients treated with anti-androgen must have discontinued anti-androgen for at least 6 weeks prior to start of study treatment.
a. Dose escalation part only: prior treatment with an anti-androgen and GnRH agonist or antagonist is allowed.
b. Dose expansion part only: prior concomitant treatment with an anti-androgen and GnRH agonist or GnRH antagonist for ≤6 weeks is allowed (in order to control flare up).
6. Serum testosterone within castration level (<50 ng/dl or < 1,7 nM)
7. Disease progression demonstrated by a rising PSA with or without metastases. PSA ≥2 ng/mL at study entry. Rising PSA is defined as two consecutive rises over a nadir value; the individual measurements are obtained at least 1 week apart.

Exclusion criteria:
1. Dose expansion part only: Secondary hormonal manipulation of prostate cancer (other than GnRH agonist or antagonist) for more than 6 weeks, including concomitant anti-androgens.
2. Prior cytotoxic therapy e.g. with docetaxel, mitoxantrone.
3. Patients who have received radiotherapy of target lesions. Patients who have received local radiotherapy of non-target lesions for local symptom control within the last 4 weeks must have recovered from any adverse effects of radiotherapy before recording baseline symptoms. Lesions treated with locoregional therapies within the last 3 months before study inclusion do not qualify as target lesions.

Additional protocol-defined inclusion/exclusion criteria apply.

Participant Flow Table

Overall Study

	Pasireotide LAR 60mg	Pasireotide LAR 80mg	Total
Arm/Group Description	Pasireotide LAR 60mg	Pasireotide LAR 80mg	
Started	3	6	9
Completed	3	6	9
Not Completed	0	0	0

Baseline Characteristics

	Pasireotide LAR 60mg	Pasireotide LAR 80mg	Total
Arm/Group Description	Pasireotide LAR 60mg	Pasireotide LAR 80mg	
Number of Participants [units: participants]	3	6	9
Age, Customized (units: Participants) Count of Participants (Not Applicable)			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	1	2
From 65-84 years	2	5	7
85 years and over	0	0	0
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	0	0	0
Male	3	6	9

Age Continuous (units: years) Median (Full Range)		
	71.0 (61.0 to 73.0)	73.0 (62.0 to 78.0)

Summary of Efficacy

Primary Outcome Result(s)

Number of Patients experiencing a dose limiting toxicity (DLT)

(Time Frame: 8 weeks)

	Pasireotide LAR 60mg	**Pasireotide LAR 80mg**
Arm/Group Description	Pasireotide LAR 60mg	Pasireotide LAR 80mg
Number of Participants Analyzed [units: participants]	3	6
Number of Patients experiencing a dose limiting toxicity (DLT) (units: Patients) Count of Units (Not Applicable)		
Patient with Dose Limiting Toxicities	0	1

Number of Patients with PSA-progression after 24 weeks

(Time Frame: 24 weeks)

	Pasireotide LAR 60mg	Pasireotide LAR 80mg
Arm/Group Description	Pasireotide LAR 60mg	Pasireotide LAR 80mg
Number of Participants Analyzed [units: participants]	3	5
Number of Patients with PSA-progression after 24 weeks (units: Patients) Count of Units (Not Applicable)		
No PSA-Progression	0	1
PSA-Progression	3	2
Missing	0	2

Secondary Outcome Result(s)

Summary of Safety

Safety Results

All-Cause Mortality

	Pasireotide LAR@60 mg N = 3	Pasireotide LAR@80 mg N = 6	Total N = 9
Arm/Group Description	Pasireotide LAR@60 mg	Pasireotide LAR@80 mg	Total
Total participants affected	0 (0.00%)	1 (16.67%)	1 (11.11%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 56 days post treatment, ranging from 3 months up to maximum duration of 57 months.
Additional Description	AE additional description
Source Vocabulary for Table Default	MedDRA 21.1
Assessment Type for Table Default	Systematic Assessment

	Pasireotide LAR@60 mg N = 3	Pasireotide LAR@80 mg N = 6	Total N = 9

Arm/Group Description	Pasireotide LAR@60 mg	Pasireotide LAR@80 mg	Total
Total participants affected	0 (0.00%)	3 (50.00%)	3 (33.33%)
Gastrointestinal disorders			
Pancreatitis	0 (0.00%)	1 (16.67%)	1 (11.11%)
Papilla of Vater stenosis	0 (0.00%)	1 (16.67%)	1 (11.11%)
Hepatobiliary disorders			
Cholestasis	0 (0.00%)	1 (16.67%)	1 (11.11%)
Hepatotoxicity	0 (0.00%)	1 (16.67%)	1 (11.11%)
Infections and infestations			
Sepsis	0 (0.00%)	1 (16.67%)	1 (11.11%)
Metabolism and nutrition disorders			
Hyperglycaemia	0 (0.00%)	1 (16.67%)	1 (11.11%)

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 56 days post treatment, ranging from 3 months up to maximum duration of 57 months.
Additional Description	AE additional description
Source Vocabulary for Table Default	MedDRA 21.1
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Pasireotide LAR@60 mg N = 3	Pasireotide LAR@80 mg N = 6	Total N = 9
Arm/Group Description	Pasireotide LAR@60 mg	Pasireotide LAR@80 mg	Total
Total participants affected	3 (100.00%)	5 (83.33%)	8 (88.89%)
Blood and lymphatic system disorders			
Anaemia	0 (0.00%)	1 (16.67%)	1 (11.11%)
Cardiac disorders			
Atrioventricular block	1 (33.33%)	0 (0.00%)	1 (11.11%)
Gastrointestinal disorders			
Anal haemorrhage	0 (0.00%)	1 (16.67%)	1 (11.11%)
Diarrhoea	1 (33.33%)	0 (0.00%)	1 (11.11%)
Dyspepsia	1 (33.33%)	0 (0.00%)	1 (11.11%)
Nausea	2 (66.67%)	0 (0.00%)	2 (22.22%)
Pancreatitis	0 (0.00%)	1 (16.67%)	1 (11.11%)
Toothache	0 (0.00%)	1 (16.67%)	1 (11.11%)
Vomiting	2 (66.67%)	0 (0.00%)	2 (22.22%)
General disorders and administration site conditions			
Fatigue	1 (33.33%)	0 (0.00%)	1 (11.11%)
General physical health deterioration	1 (33.33%)	0 (0.00%)	1 (11.11%)
Hepatobiliary disorders			
Hepatotoxicity	0 (0.00%)	1 (16.67%)	1 (11.11%)

Infections and infestations			
Pneumonia	0 (0.00%)	1 (16.67%)	1 (11.11%)
Injury, poisoning and procedural complications			
Animal bite	0 (0.00%)	1 (16.67%)	1 (11.11%)
Investigations			
Alanine aminotransferase increased	1 (33.33%)	1 (16.67%)	2 (22.22%)
Aspartate aminotransferase increased	0 (0.00%)	1 (16.67%)	1 (11.11%)
Blood lactate dehydrogenase increased	0 (0.00%)	1 (16.67%)	1 (11.11%)
Gamma-glutamyltransferase increased	1 (33.33%)	2 (33.33%)	3 (33.33%)
Glycosylated haemoglobin increased	0 (0.00%)	1 (16.67%)	1 (11.11%)
Liver function test increased	1 (33.33%)	0 (0.00%)	1 (11.11%)
Residual urine volume	1 (33.33%)	0 (0.00%)	1 (11.11%)
Metabolism and nutrition disorders			
Diabetes mellitus	1 (33.33%)	1 (16.67%)	2 (22.22%)
Hyperglycaemia	2 (66.67%)	2 (33.33%)	4 (44.44%)
Type 2 diabetes mellitus	0 (0.00%)	1 (16.67%)	1 (11.11%)

Musculoskeletal and connective tissue disorders			
Arthralgia	0 (0.00%)	1 (16.67%)	1 (11.11%)
Back pain	1 (33.33%)	0 (0.00%)	1 (11.11%)
Osteoporosis	0 (0.00%)	1 (16.67%)	1 (11.11%)
Nervous system disorders			
Restless legs syndrome	1 (33.33%)	0 (0.00%)	1 (11.11%)
Syncope	0 (0.00%)	1 (16.67%)	1 (11.11%)
Renal and urinary disorders			
Leukocyturia	1 (33.33%)	0 (0.00%)	1 (11.11%)
Urinary tract obstruction	2 (66.67%)	0 (0.00%)	2 (22.22%)
Respiratory, thoracic and mediastinal disorders			
Cough	0 (0.00%)	1 (16.67%)	1 (11.11%)
Surgical and medical procedures			
Tooth extraction	0 (0.00%)	1 (16.67%)	1 (11.11%)
Vascular disorders			
Hypertension	0 (0.00%)	1 (16.67%)	1 (11.11%)

Other Relevant Findings

None.

Conclusion:

The study was terminated prematurely due to low recruitment. 9 patients had been treated in the escalation phase: 3 patients received 60mg pasireotide LAR, 6 patients received 80 mg. Patient enrollment was stopped after the 80mg dose level by Amendment 4 which became effective 08-Sep-2015. Due to this premature termination of the study, only limited data for the efficacy variables and pharmacokinetics are available. PSA-progression at month 6, PCWG2-progression at month 6, disease control rate (RECIST1.1) at month 6 and pharmacokinetics of Pasireotide LAR were evaluated but statistical significant conclusions could not be drawn due to low sample size. No clue regarding correlation of PSA-values and IFG-1 level was observed.

Date of Clinical Trial Report

September 25, 2019