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Novartis Clinical Trial Results

Sponsor

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Generic Drug Name

ZOL446/zoledronic acid

Trial Indication(s)

Paget's disease of bone

Protocol Number

CZOL446K2418

Protocol Title

An open label, Reclast®/Aclasta®, retreatment of relapsed patients with Paget's disease of bone who participated in the CZOL446K2304 and CZOL446K2305 core registration studies

Clinical Trial Phase

Phase IV

Phase of Drug Development

Phase IV

Study Start/End Dates

21-Oct-2008 to 14-Mar-2011

Reason for Termination

Not applicable.

Study Design/Methodology

This was a 6-month, open-label retreatment study of patients with Paget's disease of bone. Patients, who participated in and had met the definition of a responder at the completion of the core portion (6 month visit) of studies CZOL446K2304 and CZOL446K2305 but later relapsed during the extended observation period (EOP) of the core studies, were eligible for participation in this retreatment study. A responder was defined as a patient who had a ≥ 75% decrease from baseline in SAP excess (the difference between measured level and midpoint of normal range) or SAP within the normal range at 6 months.

Centers

5 centers in 4 countries: Canada (1), Spain (2), New Zealand (1), South Africa (1)

Objectives:

Primary objective(s)

The primary objective was to show that patients with Paget's disease of bone who had responded to zoledronic acid and later experienced a relapse can successfully have their total serum alkaline phosphatase normalized within 6 months after a single 5 mg retreatment dose of Reclast®/Aclasta®. This objective was demonstrated if at least 60% of patients had their total SAP normalized within 6 months.

Secondary objective(s)

- Determine the relative change in SAP levels at 3 months and 6 months following retreatment with Reclast®/Aclasta®.
- Collect information pertaining to the diagnosis of relapse used by practicing physicians that could define and support retreatment guidelines for Paget's disease of bone in patients who had previously responded to zoledronic acid treatment.
- Determine the adverse event profile of patients who received a retreatment dose of Reclast®/Aclasta®. A safety objective was demonstrated if the incidence of transient post-dose symptoms (PDS) was reduced by 20% relative to the incidence in the core study.

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

Reclast®/Aclasta® (zoledronic acid) 5 mg solution for infusion.

Statistical Methods

The primary efficacy variable was the proportion of patients with SAP within the normal range at Month 6. In this open-label trial, the aim was to show that the proportion of patients with SAP within the normal range at Month 6 after retreatment with Reclast®/Aclasta® is at least 60%. Number and proportion of patients with SAP level within the normal range at Month 6 were calculated for MITT patients who were randomized to zoledronic acid in the core studies. The 95% confidence interval for the proportion was calculated based on the “exact method,” due to the small number of patients. If a patient did not have an SAP value at Month 6 for any reason, the last post-baseline SAP value prior to Month 6 was used (Last Observation Carried Forward, LOCF).

Descriptive statistics (mean, median, standard deviation, Q1, Q3, IQR, minimum, and maximum) for SAP at baseline and each post-baseline visit and for percentage change at each post-baseline visit relative to baseline were presented. The number and proportion of patients with SAP within the normal range at Months 3 and 6 were presented. In addition, the 95% confidence intervals were obtained based on the “exact method.”

No interim analysis was performed.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Written Informed Consent
- Patients with Paget's disease randomized to the zoledronic acid arm from the CZOL446K2304 and CZOL446K2305 core studies and who were responders by 6 months
- Confirmed relapse of Paget's disease of bone (i.e. SAP above ULN, bone scan, worsening clinical symptoms)

Exclusion Criteria:

- A patient previously treated with zoledronic acid who relapsed and was retreated with anti-resorptive bisphosphonate or calcitonin therapy within the last 12 months
- Bisphosphonate Hypersensitivity
- Patients with suspected/proven metastases at re-treatment
- Calculated creatinine clearance <35 mL/min at screening
- Serum calcium level <2.07 mmol/L at screening
- Active primary hyperparathyroidism, hyperparathyroidism, hypoparathyroidism or hypothyroidism

Other protocol-defined inclusion/exclusion criteria may apply

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Participant Flow Table

Patient disposition (ITT population)

	Reclast/Aclasta (N=6) n (%)
Number (%) of patients completed	6 (100)
Primary reason for discontinuation	
None	0 (0.0)

Baseline Characteristics

Baseline demographics (ITT Population)

		Reclast/Aclasta N = 6
Sex - n (%)	Male	4 (66.7)
	Female	2 (33.3)
Predominant race - n (%)	Caucasian	5 (83.3)
	Other	1 (16.7)
Age (years)	n	6
	Mean (SD)	75.2 (6.08)
	Median	75.0
	Min, Max	66.0, 85.0
Age group (years) - n (%)	65 – 74	3 (50.0)
	>= 75	3 (50.0)
Weight (kg)	n	6
	Mean (SD)	67.8 (10.44)
	Median	70.4
	Min, Max	47.8, 76.0
Height (cm)	n	6
	Mean (SD)	163.7 (5.24)
	Median	163.5
	Min, Max	155.0, 170.0
BMI (kg/m**2)	n	6
	Mean (SD)	25.4 (3.99)
	Median	26.2
	Min, Max	17.8, 29.7
BMI group (kg/m**2) - n (%)	<19	1 (16.7)
	> 25	5 (83.3)
Core study - n (%)	K2304	3 (50.0)
	K2305	3 (50.0)

N = the number of patients in the analysis population
n = the number of patients meeting the criterion (for categorical variables) or the number of patients with a measurement (for continuous variables)
% = 100*n/N

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Primary Outcome Result(s)

Proportion of patients with SAP within the normal range at Month 6-LOCF (MITT population)

		Reclast/Aclasta N = 6		
Visit	**Total**	**n**	**%**	**95% CI**
Month 6-LOCF	6	5	83.3	(35.9, 99.6)

If a patient did not have an SAP assessment at Month 6, the last post-baseline SAP value was used in the analysis. (LOCF).
The 95% confidence interval is calculated based on the exact method.

SAP (U/L) level by patient and visit (ITT Population)

Country/center/patient	Visit	SAP (U/L)	Reference range
Patient 1	Baseline	222	35, 115
	Month 3	86	35, 115
	Month 6	80	35, 115
Patient 2	Baseline	117	35, 115
	Month 3	93	35, 115
	Month 6	110	35, 115
Patient 3	Baseline	172	35, 115
	Month 3	62	35, 115
	Month 6	66	35, 115
Patient 4	Baseline	177	35, 115
	Month 3	104	35, 115
	Month 6	117	35, 115
Patient 5	Baseline	221	35, 115
	Month 3	83	35, 115
	Month 6	84	35, 115
Patient 6	Baseline	293	35, 115
	Month 3	90	35, 115
	Month 6	89	35, 115

Secondary Outcome Result(s)

Proportion of patients with SAP within normal range by visit (MITT Population)

	Reclast/Aclasta N = 6			
Visit	**Total**	**n**	**%**	**95% CI**
Month 3	6	6	100.0	(54.1, 100.0)
Month 6	6	5	83.3	(35.9, 99.6)

The 95% confidence interval is calculated based on the exact method.

Summary statistics for SAP (U/L) by visit (MITT Population)

Visit	Statistic	Reclast/Aclasta
Baseline	n	6
	Mean (SE)	200.3 (24.34)
	Median	199.0
	Min, Max	117, 293
Month 3	n	6
	Mean (SE)	86.3 (5.70)
	Median	88.0
	Min, Max	62, 104
Percentage change from baseline at Month 3	n	6
	Mean (SE)	-53.12 (7.607)
	Median	-61.85
	Min, Max	-69.3, -20.5
Month 6	n	6
	Mean (SE)	91.0 (7.82)
	Median	86.5
	Min, Max	66, 117
Percentage change from baseline at Month 6	n	6
	Mean (SE)	-49.51 (10.090)
	Median	-61.81
	Min, Max	-69.6, -6.0

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Safety Results

Most frequent adverse events (at least 5%) by preferred term (Safety population)

Preferred term	Reclast/Aclasta (N=6) n (%)
-Any preferred term	1 (16.7)
Influenza	1 (16.7)

Serious Adverse Events and Deaths

No patients died during the study. No serious or other significant adverse events were reported during the study.

Conclusion:

A single infusion of zoledronic acid 5 mg for the treatment of Paget's patients produces a persistent effect on disease suppression. Even though the study objectives were not met due to the small number of patients enrolled, the data provide valuable information with respect to the effectiveness of retreatment with zoledronic acid in relapsed patients.

Date of Clinical Trial Report

14-Oct-2011