Sponsor

Novartis

Generic Drug Name

Zoledronic Acid

Therapeutic Area of Trial

Paget's Disease of Bone

Approved Indication

Reclast is a bisphosphonate indicated for:

- Treatment and prevention of postmenopausal osteoporosis
- Treatment to increase bone mass in men with osteoporosis
- Treatment and prevention of glucocorticoid-induced osteoporosis
- Treatment of Paget's disease of bone in men and women

Protocol Number

CZOL446K2418

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

Phase of Development

Phase IV

Study Start/End Dates

21-Oct-2008 (first patient first visit)
14-Mar-2011 (last patient last visit)

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 $\geq$ 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

It was planned to re-treat a total of approximately 30 patients from the above studies at approximately 15 to 25 centers worldwide. A total of 6 patients were enrolled, all of whom were included in the ITT, MITT, and safety populations.

Publication

Outcome measures

Primary outcome measures(s)

Title: Total serum alkaline phosphatase normalization within 6 months after a single re-treatment dose of Zoledronic acid 5 mg

Timeframe: 6 months

Outcome Measure Description:

This objective will be demonstrated if at least 60% of patients have their total SAP normalized within 6 months.

Secondary outcome measures(s)

The specific key measure(s) or observation(s) that will be used to determine the effect of the intervention(s).

1. Title: To determine the relative change from baseline in SAP levels at 3 months and 6 months following retreatment with zoledronic acid 5 mg

Timeframe:

3 and 6 months

Outcome Measure Description:

Same as title

2. Title: To determine the adverse event profile of patients who receive a re-treatment dose of zoledronic acid 5 mg.

Timeframe:

6 months

Outcome Measure Description:

A safety objective was to be demonstrated if the incidence of transient

Post-dose symptoms (PDS) is 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: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

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

1. Patients had to give written informed consent to participate in the study

2. Male or female patients who were randomized to receive zoledronic acid in the

CZOL446K2304 or CZOL446K2305 pivotal studies and met the definition of responder at

the 6 month post-dose visit

3. Confirmed relapse of Paget's disease of the bone based on Investigator's assessment

through one or more of the following:

• SAP that was above the ULN

• Bone scan consistent with relapse of Paget's disease of bone, and/or

• Worsening of clinical symptoms (e.g., bone pain or compression symptoms)

Exclusion criteria

Patients were excluded from this study if they met any of the following criteria:

1. A patient treated with Reclast®/Aclasta® who relapsed during the EOP and was treated with anti-resorptive bisphosphonate or calcitonin therapy within the past 12 months
2. Hypersensitivity to any drug within the class of bisphosphonates
3. Patients with a new diagnosis or active treatment for any malignancy (other than basal cell or squamous cell skin cancer) less than or equal to 12 months prior to study entry
4. Patients with suspected or proven metastases at time of retreatment
5. Patients who were unlikely to be able to complete the study or to comply with the visit schedule and who required assessments due to cancer, non-skeletal metastases or paraneoplastic syndrome or their ongoing/planned treatments

   Specific exceptions to the cancer exclusion (within 12 months prior to retreatment):

6. Patients may be included if they had:
7. Basal cell or squamous cell carcinoma of the skin, colonic polyps with non-invasive

malignancy had been removed

a. Ductal carcinoma in-situ (DCIS) had been surgically removed or

b. Carcinoma in-situ (CIS) of the uterine cervix had been surgically removed

8. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, as confirmed by a positive urine test Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precluded intercourse with a male partner and women whose partners had been sterilized by vasectomy or other means, unless they were using two birth control methods. The two methods can be a double barrier method or a barrier method plus a hormonal method:
    - Adequate barrier methods of contraception include: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide
    - Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progestational agent
9. Reliable contraception had to be maintained throughout the study and for 60 days after study drug discontinuation
10. Woman were considered post-menopausal and not of child bearing potential if they had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 20 pg/mL or had surgical bilateral oophorectomy (with or without hysterectomy) at least 6 weeks prior to Visit 2. In the case of oophorectomy alone, classification of a woman as post-menopausal could only occur when her reproductive status was confirmed by follow up hormone level assessment.
11. Any disease or therapy which could interfere with the procedures or data collection of this trial
12. Patients with active (symptomatic or asymptomatic) iritis, uveitis or episcleritis
13. Calculated creatinine clearance < 35 ml/min at Screening visit
14. Serum calcium level < 2.07 mmol/L
15. Active primary hyperparathyroidism, hyperthyroidism, hypoparathyroidism or hypothyroidism

- No additional exclusions could be applied by the Investigator, in order to ensure that the study population was representative of all eligible patients.

Diagnosis and main criteria for inclusion: Male or female patients who were randomized to receive zoledronic acid in the CZOL446K2304 or CZOL446K2305 pivotal studies and met the definition of responder at the 6 month post-dose visit who presented with confirmed relapse of Paget's disease of the bone based on Investigator's assessment through one or more of the following:

• SAP that was above the ULN

• Bone scan consistent with relapse of Paget's disease of bone, and/or

• Worsening of clinical symptoms (e.g., bone pain or compression symptoms)

Participant Flow

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)

Outcome measures

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 levels for all six patients are provided for each visit in table below. The SAP value (117 U/L) for one patient with abnormal SAP at Month 6 was only 2 unit above the ULN (115 U/L).

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

Center/patient	Visit	SAP (U/L)	Reference range
One patient	Baseline	222	35, 115
	Month 3	86	35, 115
	Month 6	80	35, 115
One patient	Baseline	117	35, 115
	Month 3	93	35, 115
	Month 6	110	35, 115
One patient	Baseline	172	35, 115
	Month 3	62	35, 115
	Month 6	66	35, 115
One patient	Baseline	177	35, 115
	Month 3	104	35, 115
	Month 6	117	35, 115
One patient	Baseline	221	35, 115
	Month 3	83	35, 115
	Month 6	84	35, 115
One patient	Baseline	293	35, 115
	Month 3	90	35, 115
	Month 6	89	35, 115

The proportion of patients with SAP within the normal range by visit is presented in the following table. Although 100% of the patients had SAP normalized at Month 3, the lower limit of the 95 % CI was less than 60% due to the small number of patients.

Center and Subject Number removed from table to protect personal data. Replaced with “One patient”.

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

Safety Results

Adverse Event (Non-Serious)

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)

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

Other Relevant Findings

None

Date of Clinical Trial Report

24 Nov 2011

Date Inclusion on Novartis Clinical Trial Results Database

12 March 2012

Date of Latest Update