1.0 Abstract

Title

Evaluation of treatment with Zemplar capsules in the therapy of secondary hyperparathyroidism (SHPT) in subjects with chronic kidney disease (CKD) stage 3 or 4 in the conditions of routine clinical practice.

A Multi-country, Multi-Center Post Marketing Observational Study in Routine Clinical Use in Eastern European Countries

Keywords

SHPT, CKD, iPTH, Ca×P

Rationale and Background

SHPT is an early and major complication of CKD and progresses as glomerular filtration rate (GFR) decreases.[1,2] In CKD, the diseased kidneys progressively lose their ability to hydroxylate the 1α position of 25 hydroxyvitamin D (25[OH]D_3), which inhibits production of the active vitamin D molecule 1,25 dihydroxyvitamin D (1,25$[OH]_2D_3$; calcitriol), the endogenous vitamin D receptor activator. The resultant suboptimal levels of 1,25 di-hydroxyvitamin D have a major role in the early development of SHPT by decreasing intestinal absorption of calcium and resulting in parathyroid hormone (PTH) production and hyperproliferation of parathyroid cells.[3] Decreased calcitriol levels and elevated PTH levels often occur early in the course of CKD (stages 2 to 3), although serum calcium and phosphorus levels remain within the normal range.[4,5]

Chronically high PTH levels cause increased bone remodeling, leading to high-turnover bone disease (osteitis fibrosa), as well as loss of bone density and structural integrity. The introduction of therapies that have the ability to suppress elevated PTH levels and correct a relative or absolute calcitriol deficiency with either minimal or no impact on serum calcium, phosphorus, and calcium-phosphorus product (Ca×P) and

no renal toxicity would enhance the overall treatment and management of SHPT in subjects with CKD [14, 15, 16, 17, 18, 19]. Zemplar is indicated for the prevention and treatment of SHPT associated with chronic renal insufficiency (CKD stages 3 and 4) subjects and chronic renal failure (CKD stage 5) subjects on hemodialysis or peritoneal dialysis.

Data concerning the epidemiology of CKD in Central and Eastern Europe are currently limited.

Research Question and Objectives

The primary objectives were to evaluate the time period needed for achievement of > 30% decrease of iPTH compared to the initial values and to describe the occurrence of subjects with clinically significantly higher Ca×P: Ca×P > 65 mg^2/dl^2 or 5.24 $mmol^2/l^2$). Secondary objectives were to evaluate the number of subjects who achieved the main treatment goal of > 30% decrease of iPTH compared to the initial value of each subject. Also to evaluate and describe the tolerability and compliance of treatment with Zemplar capsules in the therapy of SHPT in patients with CKD stage 3 or 4 in conditions of routine clinical practice.

Study Design

This was a non-interventional, observational, open-label, multi-country, multi-center post marketing study in which Zemplar was prescribed in the usual manner in accordance with the terms of the local market authorization with regards to dose, population and indication.

Setting

The sites were located in Bulgaria, Czech Republic and Romania.

Subjects and Study Size, Including Dropouts

A total of 994 subjects were enrolled and 737 subjects (74.1%) completed all study visits.

Variables and Data Sources

The primary variables were:

1. Time period needed for > 30% iPTH decrease compared with baseline values
2. Number of subjects with Ca×P > 65 mg^2/dl^2 (or 5.24 $mmol^2/l^2$)

The secondary variables were:

1. Number of subjects with > 30% iPTH decrease compared with baseline values
2. Weekly dose of Zemplar
3. Treatment-emergent adverse events (AEs) and clinically important changes in vital signs

Results

The results for the primary and secondary endpoints confirm a consistent reduction in iPTH and corresponding maintenance of circulating P levels. With regards to the primary endpoint, the mean time overall to reach > 30% decrease of iPTH compared with baseline, was 3.82 months (SD = 3.37 months) in the PP population. A clear majority of subjects (704 subjects, 75.3 %) in the ITT population achieved this goal. In the evaluation performed using the PP population, a similar majority was also observed (694 subjects, 75.5%).

Levels of serum phosphorous remained essentially unchanged during the study (1.3 mmol/l at Visit 1 and 1.32 mmol/l at Visit 6, p-value: 0.1067). Circulating levels of serum calcium increased from 2.23 mmol/l at Visit 1 to 2.69 mmol/l at Visit 6 (p-value: < 0.0001). However, an indicator of bone loss, Ca×P > 65 mg^2/dl^2 or

5.24 $mmol^2/l^2$, was observed in few subjects over the course of the study (68 subjects, 7.4%; PP population). The average weekly dose of Zemplar at the beginning of the study was 6.29 mcg (minimum of 3 mcg and maximum of 28 mcg), which had decreased to 5.77 by Visit 6. It is not clear if this decrease in dosage correlates with therapeutic benefit.

Overall, 141 subjects (14.2%) reported a total of 331 AEs. The most frequently reported events were related to CKD: chronic renal failure (2.3%), haemodialysis (1.6%), hypertension (1.4%) and nausea (1.1%). All other AEs were reported by < 1% of all subjects. SAEs were reported for 27 subjects; all were related to the subjects' underlying CKD with the exception of 1 subject with renal failure, metabolic acidosis, haemodialysis, hypertension and oedema for which the investigator considered there might be a possible relationship to treatment. A total of 14 subjects died; all were due to CKD and none were considered related to treatment.

Discussion

SHPT, which manifests as a high PTH, is an early and major complication of CKD and progresses as GFR decreases. Chronically high PTH levels cause increased bone remodeling, leading to high-turnover bone disease (osteitis fibrosa), as well as loss of bone density and structural integrity. This results in loss of bone mineral, increased release of calcium and phosphorus from bone, and increased risk for vascular and visceral calcification. Thus, interventions to treat and/or prevent SHPT should be initiated early in patients with mild to moderate CKD.

Zemplar reduces PTH levels by inhibiting parathyroid proliferation and decreasing PTH synthesis and secretion, with minimal impact on calcium and phosphorus levels, and can act directly on bone cells to maintain bone volume and improve mineralization surfaces. Correcting abnormal PTH levels, with normalization of calcium and phosphorus homeostasis, may prevent or treat the metabolic bone disease associated with CKD.

In the population of subjects evaluated in this study, all of whom had stage 3 or 4 CKD, levels of iPTH decreased significantly over the course of the study (p-value: < 0.0001), as would be expected based on the activity of Zemplar. Levels of phosphorous remained essentially unchanged during the study, while serum calcium was observed to increase. However, another indicator of impact on PTH-induced loss of bone mineral is the calcium-phosphorous product (Ca×P). Therefore, analysis of the number of subjects who had reached a clinically important threshold of > 65 mg^2/dl^2 or 5.24 $mmol^2/l^2$ during the whole study period was performed. Very few subjects (68 subjects, 7.4%; in the PP population) had values of this magnitude at any time during the course of the study. This indicates that any effect of the increase in circulating calcium was somewhat mitigated by the lack of impact on the release of phosphorous levels.

The treatment goal of > 30% decrease of iPTH compared with baseline was achieved for a total of 694 subjects (75.5%) in the PP population. Although the mean time overall to reach this goal was 3.82 months, it is interesting to note that 39.7% of subjects in the ITT population achieved this main treatment goal as early as Visit 2 (Month 1).

The average weekly dose of Zemplar decreased slightly over the course of the study; however, it is not clear if this decrease in dosage correlates with the therapeutic benefit.

With regards to safety, Zemplar was well tolerated with a low incidence of AEs (141 subjects; 14.2% of all subjects who received at least 1 dose). Considering the severity of the chronic illness of this population, the rates of SAEs and deaths were also low and almost entirely attributed to the subjects' underlying condition. No clinically meaningful changes in vital signs were observed over the course of the study.

Marketing Authorisation Holder(s)

Names and Affiliations of Principal Investigators