

## 1.0 Abstract

### Title

Postmarketing Observational Study to Evaluate the Effect of Zemplar (paricalcitol IV) on Cardiac Morbidity in Patients with Chronic Kidney Disease Stage 5 over 2 Years

### Keywords

Nephrology, paricalcitol, PTH, CKD

### Rationale and Background

As secondary hyperparathyroidism (SHPT) is a frequent complication in patients with chronic renal insufficiency who are receiving dialysis, increasing emphasis has been placed on treatment with Vitamin D metabolites and analogues to avoid this side effect. Here calcitriol is commonly used, but as a side effect can induce hypercalcemia and hyperphosphatemia, which is a factor that is correlated with the development or aggravation of cardiovascular impairment. However, it has been shown that paricalcitol IV and other Vitamin D-analogues have the ability to suppress PTH (Parathyroid Hormone) at noncalcemic doses. The purpose of this study was to ascertain the percentage of cardiac patients with chronic kidney disease (CKD) stage 5 and treated with paricalcitol IV achieving iPTH (intact Parathyroid hormone) target range of K/DOQI (Kidney Disease Quality Outcome Initiative) treatment guidelines (150 – 300 pg/mL) after 2 years and to evaluate cardiac events and hospitalization rates in this patient group.

### Research Question and Objectives

The primary objective of this study was to evaluate the percentage of patients achieving an iPTH level within the target range of K/DOQI treatment guidelines (150 – 300 pg/mL) in cardiac patients with chronic kidney disease (CKD) stage 5 over 2 years. Additionally secondary endpoints like hypercalcemia and

hyperphosphatemia, a 30%-reduction of iPTH-levels, and hospitalization rates were analyzed.

### **Study Design**

This was a multicenter, single-arm non-interventional, observational study.

### **Setting**

The study was conducted in Austria as a multicenter, single-arm non-interventional, observational study. The study population consisted of male and female patients aged at least 18 years, diagnosed with secondary hyperparathyroidism associated with CKD stage 5 receiving dialysis and cardiac disease as described by Medical Dictionary for Regulatory Activities (MedDRA) terms. These included cardiac arrhythmias, cardiac disorder signs and symptoms, cardiac neoplasm, cardiac valve disorder, congenital cardiac disorder, coronary artery disorder, endocardial disorder, heart failures, myocardial disorder, pericardial disorder.

### **Subjects and Study Size, Including Dropouts**

The total treatment period was for a maximum of 24 months for each patient and approximately 5 follow-up visits were expected over the 24 months period. The visit schedule was decided by the investigator according to the routine clinical practice.

Due to lack of eligible patients, only 67 of the intended 200 patients were enrolled, treated and analyzed.

### **Variables and Data Sources**

All enrolled patients with at least one dose of paricalcitol were analyzed according to the ITT principle. Data was inserted by study staff into an eDRF (electronic Data Report Form) and then analyzed. Demographic, Safety and Laboratory data sets were processed.

## Results

Sixty-seven (67) subjects enrolled in 12 centers in Austria. Forty (40) (59.7%) were male and 27 (40.3%) were female. Mean age was  $63.5 \pm 13.8$  years.

At study completion 26 patients finished all planned 6 study visits. Of the 41 patients who dropped out, 14 patients died during the study. Four patients died of cardiac failure, 3 of myocardial infarction, 2 of unknown reason, 2 of cerebral haemorrhage, and one each of cardiogenic shock, ileus and bronchopneumonia. Kidney transplant was done in 10 patients. Paricalcitol therapy was stopped in 8 patients as their iPTH levels were normal or low. Two patients experienced a serious adverse event (vertigo and panniculitis, respectively). The other patients who dropped out changed hospital or were lost to follow-up.

Forty-seven (47) patients (70.1% of 67 patients) had iPTH levels that were within the target range at least once, compared to 28.4% of 67 subjects at the first visit.

Forty-four (44) patients (65.7% of 67 patients) showed an at least 30% reduction of iPTH during the PMOS. Thirty-five (35) patients (52.2% of 67 patients) suffered from at least one episode of hyperphosphatemia and 2 patients (3% of 67 patients) experienced at least one episode of hypercalcemia during the study.

The total number of hospitalizations was 64. Ten (10) patients (14.9%) experienced at least one cardiac related hospitalization and 25 (37.3%) at least one non-cardiac related hospitalization. Cardiac disease progression occurred in 8 patients (11.9%) out of 67 subjects.

44 patients (65.7%) experienced at least one adverse event, and 19.4% of 67 subjects experienced at least one serious cardiovascular adverse event, but only 4 patients (6%) of 67 patients experienced a related adverse event according to the investigator.

## Discussion

Paricalcitol was well tolerated in this patient population who had multiple comorbidities. Hypercalcemia, a frequent problem when treating CKD patients with Vitamin D metabolites, was only seen in one patient after 2 years.

Hyperphosphatemia was frequently (52.2%) observed in this study; however, the frequency is comparable to that seen in another study of dialysis patients where paricalcitol and calcitriol induced hyperphosphatemia in 50.7% and 53.3% of patients respectively. Keeping patients in K/DOQI target ranges for iPTH was not easily achieved. 70.1% of 67 patients had at least one iPTH level that was within the target range.

The cardiac related hospitalization rate was 14.9% over the 24 months observation period. Additionally, 37.3% of patients had at least one non-cardiac related hospitalization. These rates are consistent with expectations for this patient population. Hospitalization rates increase with greater comorbidity. In the US according to Medicare data admission for Stage 4 – 5 CKD patients with both diabetes and cardiovascular disease reached 851 per 1.000 patient years in 2011, which was more than twice the rate among patients with neither diagnosis.

Only 4 patients (6%) experienced study related adverse events which were vertigo, hyperphosphatemia, dysgeusia and panniculitis. Cardiac disease progression occurred in 8 patients (11.9%) out of 67 subjects. In Austria prevalence of cardiovascular reasons for ESRD is 22%.

Fourteen patients (9.4%) died during the study. While mortality rates for patients aged 66 and older without CKD are about 54 per 1.000 patient years they are 109 per 1.000 patient years for CKD patients Stages 4 – 5. Prevalence of patients on hemodialysis in Austria lies at about 3.900 patients. The mortality rate, irrespective of the cause of death is 14.5% with cardio-vascular reasons being the leading cause of death (44%).

**Marketing Authorisation Holder(s)**

AbbVie GmbH

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**Names and Affiliations of Principal Investigators**

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