2.0 Synopsis

Name of sponsor: AbbVie
Name of Study Drug : Zemplar
Name of Active Ingredient: Paricalcitol
Protocol Title: A Prospective, Non-randomized, Single arm, Open-Label, Pilot Clinical Study Evaluating The Effect of PTH Lowering on Erythropoietin Consumption in Calcitriol-Resistant Patients
Objectives: Primary: To evaluate the effect of PTH lowering on erythropoietin consumption Secondary: • To evaluate the quality of life of patients by using the Short Form Health Survey 36 (SF-36) questionnaire in end-stage renal disease (ESRD) patients (stage 5) with secondary hyperparathyroidism (SHPT) • To observe the changes in commonly assessed biochemical parameters for bone and mineral metabolism (intact parathyroid hormone [iPTH], Calcium [Ca], Phosphorus [P], Alkaline Phosphatase [ALP]) • To observe the changes in hsCRP and FGF-23 values • To collect and evaluate data of all adverse events in order to establish the safety profile of paricalcitol in Turkish subjects.
Investigator: Multi-center study, Coordinating Investigator is Prof. Alaattin Yıldız, [redacted]
Study Site: 7 centers in Turkey
Study Population: Stage 5 chronic kidney disease (CKD) patients with persistent moderate to severe SHPT receiving hemodialysis.
Number of Subjects (Planned and Analyzed): 65 subjects were planned to be enrolled in the study, and 65 subjects were enrolled and 114 patients were screened. During the study 16 subjects discontinued for various reasons and 49 patients completed the study per protocol. Among these 49 patients, one patient was enrolled into the study according to protocol version 1.0 and this patient was not included in the analysis due to major protocol changes.
Methodology: Prospective, non-randomized, single-arm, open-label, multi-center clinical study.
Study Period (Years): First Subject First Visit: 10 May 2012 Last Subject Last Visit: 07April 2016

Development Phase: Phase IV
Diagnosis and Main Criteria for Inclusion/Exclusion:
Main Inclusion: 1. Patients > 18 years of age 2. Stage 5 CKD patients receiving hemodialysis and with moderate to severe secondary hyperparathyroidism (SHPT) 3. Patients with anemia due to renal insufficiency but who are iron replete; Transferrin saturation (TSAT) > 20% and Ferritin levels > 200 ng/mL and requiring treatment with erythropoietin (EPO) 4. Patients with Vitamin B levels > Lower Limit of Normal (LLN) and Folic acid levels > LLN 5. Patients treated with only intravenous calcitriol for at least 6 months 6. Patients with serum iPTH level > 500 pg/mL 7. Patients with Ca x PO4 product < 65 $mg^{2/dL2}$ 8. Patients willing to sign “written informed consents” before participating in any study related activity. 9. Patients with P levels <6.5 mg/dL and Ca levels <11.2 mg/dL

Main Exclusion:

1. Patients who have known hypersensitivity and/or toxicity to vitamin D metabolites and/or to paricalcitol and/or to other product ingredients.
2. Patients who have participated in a clinical study within the last month.
3. Patients whose previous concomitant medication and laboratory data for 6 months prior to the screening visit are not available.
4. Patients with known contraindication to selective Vitamin D receptor activators (VDRAs) according to the Summary of Product Characteristics (SmPC).
5. Pregnancy, breast-feeding or planning a pregnancy within next 6 months after enrolment. Sexually active female patients not accepting appropriate contraceptive methods during the course of the study will also be excluded.
6. Hypertensive and diabetic patients who are not on an optimal and steady medication regimen for more than 30 days.
7. Patients with microcytic (MCV < 80 fL) and macrocytic (MCV> 100 fL) anemia at screening that may be caused by diseases such as for microcytic anemias: Fe Deficiency, Thalassemias, Anemia of Chronic Disease, Copper Deficiency, Zn poisoning, Sideroblastic Anemia; for macrocytic anemias:ethanol abuse, myelodysplastic syndromes, acute myeloid leukemias, reticulocytosis, drug induced anemia, liver disease.

Investigational Product:	Paricalcitol (Zemplar® Ampoule)
Dose:	Dosing is based on iPTH, Ca and P levels. .
Mode of Administration:	Intravenous bolus
Reference Therapy:	Not applicable
Dose:	Not applicable
Mode of Administration:	Not applicable

Duration of Treatment: 8 months

Criteria for Evaluation:

Efficacy: Primary parameter will be the effect of PTH lowering on EPO consumption. Secondary parameters will be the change of quality of life scores (SF-36) and serum iPTH, Ca, P, Vitamin B12, Folic acid and ALP levels of the in patients with CKD and the change of CKD related inflammatory parameters from baseline, hsCRP and FGF-23.

Safety: The frequency of all adverse events (AEs), serious adverse events (SAEs) and deaths (all reasons).

Statistical Methods: Due to the exploratory nature of the study, no formal sample size calculation was made and a patient population of 65 evaluable patients was deemed satisfactory for reaching conclusions in the primary and secondary efficacy/safety parameters. Data will be appropriately summarized and analysed using tabulation and graphs with respect to demographic and baseline characteristics as well as efficacy and safety observations. Standard descriptive summary statistics (i.e., arithmetic mean, standard deviation, median, minimum/maximum values) will be calculated for continuous variables. Categorical data will be presented in frequency tables via counts and percentages. Summary tables will be displayed for the total sample set (full-analysis set) and per-protocol analysis set. Primary end-point in this study is the effect of PTH lowering use on the EPO consumption throughout the study compared to the baseline value. EPO use in units/mL (absolute values and changes from baseline) per scheduled study visits will be summarized by using descriptive statistics using tabulation and graphs including changes from the baseline. For all analyses, a P value < 0.05 will be considered statistically significant.
Conclusions: In this study it was demonstrated that paricalcitol treatment was effective in Stage 5 CKD patients. By the intravenous paricalcitol administration, EPO dosage was decreased and iPTH levels were reduced without occurrences of hyperphosphatemia and hypercalcemia.
Date of the report: February 09th, 2017