# 1.0 Abstract

**Title**

Prospective Postmarketing Multicenter Observational Program of Zemplar® in Patients with Stage 5 Chronic Kidney Disease and Hyperparathyroidism on Hemodialysis in Russian Federation.

**Keywords**

Chronic Kidney Disease, Secondary hyperparathyroidism, Selective vitamin D Receptor agonists

**Rationale and Background**

Renal osteodystrophy is an early complication of kidney disease, encompassing a host of metabolic and morphologic abnormalities of the bone. Secondary hyperparathyroidism is a major contributor to renal osteodystrophy. Paricalcitol (Zemplar®) is a vitamin D analog, which has been successful at suppressing iPTH levels and improving bone histology without limitations by hypercalcemia, hyperphosphatemia and elevated Ca × P product.

**Research Question and Objectives**

The purpose of current program is to describe demographics and clinical characteristics of stage 5 Chronic Kidney Disease (CKD) population receiving Zemplar® in the Russian Federation and also obtain additional local data on the effectiveness, and tolerability of long-term intravenous Zemplar® routine treatment in dialysis CKD patients with secondary hyperparathyroidism in the Russian Federation.

**Primary Objective:**

1. To assess proportion of patients with 5 stage CKD who reach the target level of iPTH (150 – 300 pg/mL) during the program period.

**Secondary Objectives:**

1. To assess proportion of patients who reach a KDIGO target level of iPTH (2 times to 9 times upper limit of normal) during the program period.
2. To identify incidence of elevated Ca × P (> 75 $mg^2/dL^2$).
3. To identify incidences of elevated normalized total calcium (> 11,2 mg/dL).
4. To evaluate incidence of hypercalcemia and hyperphosphatemia leading to termination of Zemplar® treatment (according to the doctors decision).
5. To evaluate the demographics and clinical characteristics of stage 5 ESRD population in the Russian Federation (age, sex, race, CKD cause, concomitant medications).

**Study Design**

This program was conducted in a prospective, multicenter non-interventional format. Only routine assessments were done, no additional information collected compared to the standard of care at the center. Only those subjects who receive Zemplar® iv injections as per local routine were enrolled in this program.

After screening into the program, patients returned to the site for visit assessments at a next routine visit scheduled by the doctor in accordance with clinical needs. Number of follow-up visits was not limited, and intervals between them varied according to clinical needs and local routine.

Follow-up visit were documented if the following new information obtained:

- New laboratory data (iPTH, normalized serum total calcium, phosphorous, Ca × P product);
- Dose/regimen was changed;
- Any events related to the safety occurred (SAE, AE, contraindication to paricalcitol treatment was diagnosed);

- Paricalcitol treatment withdrawn.

Duration of observation period for each patient was limited to 6 months and 30-day follow-up period.

**Setting**

The study took place in 13 clinical centres specialized in nephrology and haemodialysis and located in different regions of Russia. [redacted]

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**Subjects and Study Size, Including Dropouts**

A total of 86 patients were enrolled into the study. Patients had to meet all of the following criteria:

**Inclusion Criteria**

1. Age 18 – 65 years.
2. CKD stage 5 receiving hemodialysis.
3. Authorization (Consent) for Use/Disclosure of Data signed by the patient.
4. Planned prescription of Zemplar® treatment due to fair clinical need and irrespectively of the participation in the current program according to the local label within 2 weeks after screening into the program.
5. Screening iPTH level (measured not earlier than 1 month before first dose of Zemplar®) between 300 and 900 pg/mL.

**Exclusion Criteria**

1. Contraindications to Zemplar® as indicated in approved label, including but not limited to hypersensitivity, hypervitaminosis D (serum D3 level above 32 ng/mL), and concomitant use of vitamin D or phosphates, lactation period, pregnancy.
2. Any experimental drug within the period of 30 days before the inclusion into the program.
3. Screening Ca × P > 65 $mg^2/dL^2$.
4. Screening normalized serum total calcium > 10,2 mg/dL.
5. Necessity for calcitonin maintenance oral or intravenous glucocorticoids, or other drugs that could have affected calcium or bone metabolism, other than females on stable estrogen and/or progestin therapy.

**Variables and Data Sources**

All diagnostic procedures in the program were performed in the frames of routine clinical practice. The data obtained from the assessments were recorded in the patients' source documentation and CRF. The efficacy and safety assessment used in the study are standard for this indication and patient population.

**Results**

A total of 86 patients were enrolled into the study in 13 clinical sites located in the different regions of Russia.

Effectiveness: The efficacy endpoint was the proportion of patients who have reached target levels of iPTH (150 – 300 pg/mL) during the program period. Baseline was defined as the final value obtained before the start of Zemplar administration.

The primary efficacy endpoint was calculated in subjects in the Full analysis set population (FAS). Target level of iPTH was observed in 52 (60.5%) (CI 49.3% – 70.8%) patients enrolled in this study.

KDIGO target level of iPTH, defined as achievement of iPTH value 2 times to 9 times upper limit of normal during the program period, was observed in 75 (87.2%) (CI 78.3% – 93.4%) patients (FAS). Among patients completed the study (55 patients) KDIGO target level of iPTH was reached in 52 (94.5%) (CI 84.9% – 98.9%) patients.

Elevated Ca × P product was found in 33 (38.4%) (CI 28.1% – 49.5%) patients mostly at Visits 1 – 3. Elevated total calcium (> 11,2 mg/dL) was observed in 9 (10.5%) (CI 4.9% – 18.9%) patients (FAS).

There were no cases of hypercalcemia leading to termination of Zemplar® treatment. Hyperphosphatemia defined as phosphate level greater than 6.5 mg/dL for two consecutive post-baseline measurements was observed in 39 (45.3%) (CI 34.6% – 56.5%) patients. In 6 (7.0%) (CI 2.6% – 14.6%) patients duration of hyperphosphatemia was over 8 weeks, study treatment was prematurely discontinued in these patients (FAS).

Mean age of study population was 45.4 (± 12.6) years. There were 38 male (44.2%) and 48 female (55.8%). The majority of patients were White (90.7%); while 8 patients (9.3%) were Asian.

The most often cause of chronic kidney disease was chronic glomerulonephritis, observed in 40 of 86 patients (46.5%). Congenital, familiar and genetic disorders were found in 20 (23.3%) patients, among them most frequent diagnosis was congenital cystic kidney disease, observed in 13 patients. Diabetes mellitus and diabetic nephropathy was found in 10 (11.6%) patients.

Assessment of previous Vitamin D therapy was conducted in 65 (75%) patients. Most patients (65.1%) had previously been treated with alphacalcidol, 10.5% patients had

previously been treated with calcitriol (10.5%), 5 (5.8%) patients received combined therapy containing calcium and vitamin D before enrollment into the study. Previous SHPT therapy with non-vitamin D anti-parathyroid agents was provided to 31 (36.0%) patients, all these patients were treated with Cinacalcet. Both types of previous therapy were discontinued before patients' enrollment into the study or at screening visit. Cinacalcet was administered as SHPT therapy in all cases.
Forty-eight (48) (55.8%) patients were treated with Calcium containing drugs during the study.

Safety: The statistical safety summary was based on the incidence rates of adverse events, and the change from baseline in laboratory assessments and vital signs.

Adverse events were summarized by counts and percents using the most severe episode (severity) and also using the relationship to study drug (as indicated by the Investigator). An overall summary of adverse events was generated to show the numbers of subjects reporting adverse events, as well as an overall display of adverse events in descending order of incidence.

Overall, 9 (10.5%) patients experienced at least one adverse event. There were no adverse events that exceeded 5% frequency threshold. The most common adverse event by MedDRA preferred term (Restless Legs Syndrome) was observed in 2 (2.3 %) patients. The majority of the adverse events reported (5 out of 9) was moderate in severity.

Three (3) patients experienced SAE while participating in this study. Two cases of Vascular Disorders (Circulatory Collapse and Hypertension), one case of Post Procedural Hematoma and one case of Dyspnoea were registered. The cases were assessed as probably or possibly related to Zemplar®.

No patient died during the study.

Discontinuation of Zemplar® due to adverse events occurred in 7 (8.1%) patients. Two (2) patients discontinued the treatment due to Restless Legs Syndrome (PT). Other reasons of Zemplar® discontinuation were observed in 1 patient each.

The results on normalized serum total Calcium have shown that Zemplar® had only small impact on serum calcium during the treatment.

**Discussion**

The study had been proposed to assess proportion of patients with 5 stage CKD who reach the KDOQI target level of iPTH (150 – 300 pg/mL) during the program period, to assess the proportion of patients who reach a KDIGO target level of iPTH (2 to 9 times the upper limit of normal), to identify the incidence of elevated Ca × P and elevated normalized total calcium, to evaluate the incidence of hypercalcemia and hyperphosphatemia leading to termination of Zemplar® treatment during the program period and to study the demographics and clinical characteristics of stage 5 CKD population in the Russian Federation.

No hypothesis was tested in this observational study.

**Interpretation of Results:**

The study met its primary and secondary objectives:

The proportion of patients with 5 stage CKD who reach the target level of iPTH during the program period was assessed.

The proportion of patients who reach a KDIGO target level of iPTH during the program period was assessed.

The incidences of elevated Ca × P, elevated normalized total calcium, as well as hypercalcemia and hyperphosphatemia leading to termination of Zemplar® treatment were evaluated.

The demographics and clinical characteristics of stage 5 CKD population in the Russian Federation were evaluated.

**Conclusion:**

Zemplar® is safe and well tolerated for the treatment of stage 5 Chronic Kidney Disease subjects.

**Marketing Authorisation Holder(s)**

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AbbVie LLC

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