1. ABSTRACT

Title

A Multi-country Prospective Observational Study to Describe Calcimimetic Use in Haemodialysis Patients

- **Keywords**

Etelcalcetide, Cinacalcet, Calcimimetic, Drug discontinuation, Secondary hyperparathyroidism

- **Rationale and Background**

In Europe, two calcimimetics, cinacalcet (Mimpara®) and etelcalcetide (Parsabiv®) are approved for the treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) receiving haemodialysis (HD) therapy. Cinacalcet was the first calcimimetic to be approved by the European Medicines Agency (EMA); marketing authorization was granted in October 2004, with posology of a starting dose of 30 mg daily, administered orally, titrating to a maximum of 180 mg daily to achieve the target intact parathyroid hormone (PTH) of 150-300 pg/mL, in SHPT patients. Etelcalcetide received marketing authorization from the EMA in November 2016, for intravenous (i.v.) administration of 5 mg three times weekly at the end of the HD session, adjusting dosage as necessary according to individual patient PTH and calcium (Ca) levels.

Data from clinical trials and real-life clinical practice have demonstrated the effectiveness of cinacalcet in reducing PTH levels (De Francisco et al, 2016; Peter et al, 2009). In a controlled clinical trial comparing etelcalcetide with cinacalcet, etelcalcetide was found to be at least as effective as cinacalcet in reducing PTH by more than 30% after a minimum of 20 weeks' treatment, and no difference in adherence was observed (Block et al, 2017). However, there is a lack of real-world data describing etelcalcetide medication persistence and consequently, achievement of PTH control. Increasingly, physicians and payers are requesting evidence of utilisation and effectiveness generated from real-world use of therapies which have received initial regulatory approval based on data obtained from strictly controlled and monitored randomised clinical trials (RCTs). To provide context, real world use of i.v. etelcalcetide as well as oral cinacalcet was observed. This observational study described utilization of both calcimimetics in a contemporary population of CKD HD patients in a real-world clinical setting to provide essential data to physicians and payers.

- **Research Question and Objectives**

The research question is how calcimimetics are used in routine practice in haemodialysis (HD) patients.

The primary objective is to describe the proportion of patients discontinuing calcimimetic treatment at 3-monthly intervals up to 18 months following treatment initiation.

The secondary objectives include:

1. To describe characteristics of haemodialysis (HD) patients at time of calcimimetic initiation (demographics, clinical history, dialysis treatment and laboratory parameters)
2. To describe clinical management of HD patients over time (calcimimetic use, secondary hyperparathyroidism (sHPT) medication use, and dialysis treatment)
3. To describe levels of parathyroid hormone (PTH), corrected calcium (cCa), phosphate (P) and other relevant laboratory parameters in HD patients over time
4. To describe the proportion of HD patients achieving KDIGO (Kidney Disease Improving Global Outcomes) target for PTH over time
5. To describe hypocalcemia incidence. Hypocalcemia is defined as total serum calcium $<$ 2.1 mmol/L.
6. To describe the frequency of events of interest (nausea, vomiting, hospitalisations, parathyroidectomy, kidney transplant after calcimimetic initiation, fractures, and cardiovascular events)

- **Study Design**
  This is a multi-country prospective observational study.
- **Setting**
  111 HD centres in European countries, Israel and Russia.
- **Subjects and Study Size, Including Dropouts**
  One thousand four hundred seventy five (1475) subjects were approached to be enrolled in this study. In total, 1446 subjects were enrolled, of which, 29 subjects were removed from the primary analyses set (PAS) due to ineligibility.
- **Data Source(s) and Methods**
  The data source for this study is patient medical chart notes, which includes a combination of paper and electronic records. Data were abstracted from patient medical charts and entered into the eCRF by site study staff.

Patients were enrolled through Interactive Voice Response System (IVRS) based on inclusion/exclusion criteria specified in protocol. This study used the Medidata RAVE database.

- **Results**

  A total of 1475 subjects were approached to be enrolled in this study, and 29 subjects were removed from the primary analyses set (PAS) due to ineligibility. A total of 1446 subjects were treated with either cinacalcet (n=274) or etelcalcetide (n=1172). Among the 1172 subjects treated with etelcalcetide, 772 were calcimimetic-naïve etelcalcetide subjects and 450 were subjects who switched from cinacalcet to etelcalcetide. These subjects were enrolled in 111 sites across 16 countries (15 European countries and Israel) from 07 June 2018 up to 30 September 2021 and followed up to data cut-off on 03 November 2021, with sites in Greece, Spain, and Italy enrolling the most subjects (24.0%, 12.9%, and 12.7%, respectively).

  Most clinical and demographic characteristics were similar across the three groups of subjects. The group switching from cinacalcet to etelcalcetide had the highest proportion of subjects who underwent parathyroidectomy (7.3%) and kidney transplant (17.6%) before the initiation of calcimimetic among three groups. The average (SD) baseline PTH of the calcimimetic-naïve cinacalcet group was 735.26 (404.17) pg/mL, which was slightly lower compared with that of the other two groups (calcimimetic-naïve etelcalcetide group: 775.94 [479.75 pg/mL]; cinacalcet-switching etelcalcetide subjects: 772.10 [586.69 pg/mL]).

  The proportion of subjects discontinuing calcimimetics across all time intervals was highest in the cinacalcet group (31.4%), compared with 19.5% among calcimimetic-naïve etelcalcetide group and 17.8% among cinacalcet-switching etelcalcetide group.

  The average (SD) time to first discontinuation was 8.4 (5.1) months among cinacalcet group, 8.8 (5.2) months among the cinacalcet-switching etelcalcetide group, and 9.1 (5.3) months among the calcimimetic-naïve etelcalcetide group.

  The average (SD) time to first calcimimetic treatment discontinuation following first hypocalcemia was 6.2 (4.0) months for the cinacalcet-switching etelcalcetide group, 7.1 (4.3) months for calcimimetic-naïve cinacalcet group, and 7.4 (5.0) months for the calcimimetic-naïve etelcalcetide group.

  The average (SD) time to calcimimetic re-initiation after first hypocalcemia was 8.2 (4.4) months for the group switching from cinacalcet to etelcalcetide, 8.5 (3.6)

months for calcimimetic-naïve etelcalcetide group, and 9.6 (4.3) months for calcimimetic-naïve cinacalcet group.

A higher proportion of subjects in the calcimimetic-naïve etelcalcetide group achieved >30% reduction and > 50% in PTH from baseline up to 18 months (82.7% and 71.6%, respectively) than that in the other two groups (calcimimetic-naïve cinacalcet group 71.5% and 62.0%; etelcalcetide switcher group: 69.8% and 53.8%). The proportion of subjects achieving KDIGO Target for PTH up to 18 months was slightly higher in the cinacalcet group compared with that in other two groups (calcimimetic-naïve cinacalcet group: 40.1%, calcimimetic-naïve etelcalcetide group: 33.0%, etelcalcetide switcher group: 38.4%).

Subjects in the calcimimetic-naïve etelcalcetide group had the highest proportion of subjects experiencing hypocalcemia (78.1%). The proportion was 71.2% among subjects in the calcimimetic-naïve cinacalcet group and 72.0% among subjects in the group switching from cinacalcet to etelcalcetide. The median time to hypocalcemia was longest among the calcimimetic-switching etelcalcetide group (3.5 months) compared with calcimimetic-naïve cinacalcet subjects (1.8 months) and calcimimetic-naïve etelcalcetide subjects (2.0 months).

Only a few subjects experienced events of interest including nausea, vomiting, hospitalisations, parathyroidectomy, kidney transplant after calcimimetic initiation, fractures, and cardiovascular events. The proportion of subjects having the events of interest was similar across groups.

- **Discussion**

  This was an observational, non-comparative, prospective study. We found that etelcalcetide and cinacalcet subjects achieved the target PTH range to a similar degree at 18 months. However, etelcalcetide subjects had lower PTH values over time than that of cinacalcet subjects. The calcimimetic persistence was higher among etelcalcetide users than that in cinacalcet users.

  This study showed the real-world persistence of calcimimetics and the PTH of calcimimetic users in a 18-month follow-up period across 16 countries. As an observational study, it has some inherent limitations such as potential confounding due to the lack of randomization, and the results may not be used to demonstrate causality.

- **Marketing Authorization Holder(s)**

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