1. ABSTRACT

- **Title**

Calcimimetics Adherence and Preference in the Management of Secondary Hyperparathyroidism in Europe – CAP Study

- **Keywords**

Etelcalcetide, Cinacalcet, Adherence, Preference, Secondary Hyperparathyroidism

- **Rationale and Background**

Oral cinacalcet and IV-administered etelcalcetide are calcimimetics available for the management of secondary hyperparathyroidism (SHPT) in hemodialysis (HD) patients. Evidence from a randomized controlled trial shows etelcalcetide to be more effective than cinacalcet in reducing parathyroid hormone (PTH) concentrations in HD patients with SHPT. However, physicians and payers are requesting data on the real-world use of therapies that received initial regulatory approval and conditional reimbursement based on data obtained solely from randomised controlled trials (RCTs). For instance, there is a lack of of real-world evidence describing calcimimetic adherence and preference following the marketing authorization of Etelcalcetide in Europe. The goal of this study is to provide relevant patient-reported outcome (PRO) data on calcimimetic adherence and calcimimetic preference from the perspectives of nephrologists and dialysis nurses.

- **Research Question and Objectives**

i. What is the self-reported adherence to calcimimetic treatment in patients with SHPT on maintenance hemodialysis (HD)?

ii. What is the level of nephrologist/nurse preference for intravenous (IV) Etelcalcetide versus oral Cinacalcet for managing patients with SHPT on maintenance HD?

The primary objectives are:

i. To describe the self-reported adherence to calcimimetic therapy in patients with SHPT on maintenance HD.

ii. To evaluate perceptions of IV Etelcalcetide or oral Cinacalcet in patients with SHPT on maintenance HD

iii. To describe the level of nephrologist/nurse preference for intravenous (IV) Etelcalcetide versus oral Cinacalcet for managing patients with SHPT on maintenance HD.

The secondary objectives are:

iv. To describe the characteristics of patients with SHPT on maintenance HD in the study.

v. To describe the persistence with Cinacalcet compared to Etelcalcetide in a subset of surveys from patients who participate in both the 20170519 and EU DOPPS 7 studies.

vi. To describe how patient-level factors and dialysis facility-level approaches for managing SHPT relate to calcimimetic persistence in a subset of surveys from patients who participate in both the 20170519 and EU DOPPS 7 studies.

vii. To describe the associations between nephrologist or nurse calcimimetic preference and dialysis facility-level SHPT management practices (e.g., rate of parathyroidectomy, laboratory targets, and concomitant medication use).

- **Study Design**

A multi-country prospective observational panel survey of patients (i.e. repeat cross-sectional survey of the same participants), and a cross-sectional survey of nephrologists and dialysis nurses.

- **Setting**

HD centres in Belgium, France, Germany, Italy, Spain, Sweden and the United Kingdom

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

Patients aged ≥18 years receiving maintenance HD and calcimimetic treatment (oral cinacalcet or IV Etelcalcetide) at the time of recruitment were eligible for the study. Nephrologists and dialysis nurses with experience of prescribing and/or administering calcimimetics were also eligible for the study. We aimed to recruit 400 patients to complete the patient surveys at two data collection timepoints (visit 1 and 2). We also aimed to recruit between 100 – 120 nephrologists and 100 – 120 nurses to complete the healthcare professional (HCP) surveys.

- **Data Source(s) and Methods**

Patient questionnaires were adapted from the Medication Adherence Report Scale (MARS), the Beliefs about Medicines Questionnaires (BMQ-specific Necessity and

Concern Scales), and Treatment Intrusiveness Scale (TIS) to understand patterns of adherence and perceptions of medications; questions about gastrointestinal (GI) symptoms were included. Questionnaires for nephrologists and nurses were adapted from the Health Professional Preference Scale (HPPS) to understand calcimimetic preference. These questionnaires were initially validated in a pilot study, and subsequently administered in the larger main study. To address the secondary objectives, patient and nephrologist questionnaires were linked to data collected from the EU DOPPS 7 dataset.

- **Results**

Pilot study: 60 HD patients (33 Cinacalcet and 27 Etelcalcetide), 16 nephrologists and 18 dialysis nurses participated in the pilot study. Patient-reported adherence to Cinacalcet was high (mean MARS = 4.7±0.7). There were no significant differences in perceptions of Calcimimetic Necessity (mean BMQ-Necessity = Cinacalcet: 2.4±0.6 and Etelcalcetide: 2.3±0.4) or Calcimimetic Concerns (mean BMQ-Concerns = Cinacalcet: 3.1±0.6 and Etelcalcetide: 3.5±0.7). Neither Etelcalcetide nor Cinacalcet patients reported that their treatment regimen ─ excluding dietary/fluid restrictions (DFR) and dialysis ─ was intrusive (mean TIS: 1.5±0.5 vs. 1.6±1.6). Overall, patient questionnaires showed good internal consistency for MARS (Cronbach's α=0.99), BMQ-Necessity (Cronbach's α: Etelcalcetide = 0.94 and Cinacalcet =0.92) and BMQ-Concerns (Cronbach's α: Etelcalcetide = 0.94 and Cinacalcet =0.92), and TIS scales (Cronbach's α: Etelcalcetide = 0.99 and Cinacalcet = 0.99). HCPs preferred Etelcalcetide (%) to Cinacalcet for encouraging patient adherence (Nephrologist 93%, Nurses 88%); minimizing patient burden (Nephrologist 87%, Nurses 94%); minimizing GI side-effects (Nephrologist 80%, Nurses 76%).

Main study: 414 HD patients (204 Cinacalcet and 210 Etelcalcetide) during the first visit and 394 HD patients (190 Cinacalcet and 204 Etelcalcetide) during the second visit participated in the main study. Generally, patient characteristics were similar between Cinacalcet and Etelcalcetide users during both visits: mean age = 65y vs. 64y (visits 1 & 2); men = 57% vs. 61% (visits 1 & 2); mean number of current medications = 9 vs. 8 (visits 1 & 2); mean duration of hospitalization in the last 6 months = 3 vs. 3 days (visit 1) and 2 vs. 2.5 days (visit 2); and hypertension 26% vs. 27% (visit 1) and 21% vs. 24% (visit 2). Patient-reported adherence to Cinacalcet was high (mean MARS: 4.8) with 78% of patients reporting that they used all Cinalcet prescribed in the month prior to enrolment. There were no significant differences in perceptions of Calcimimetic

Necessity (mean BMQ-Necessity: Etelcalcetide = 3.6±0.5 vs. Cinacalcet = 3.5±0.7, p = 0.49) or Calcimimetic Concerns (mean BMQ-Concerns: Etelcalcetide = 2.3±0.9 vs. Cinacalcet = 2.3±0.6; p = 0.17). Routine medications (mean TIS: Etelcalcetide = 1.8±0.9 and Cinacalcet = 1.6±0.7) were considered less intrusive than DFR (mean TIS: Etelcalcetide = 2.4±1.1 and Cinacalcet = 2.4±1.1) and dialysis (mean TIS: Etelcalcetide = 2.7±1.2 and Cinacalcet = 2.8±1.3). Patient questionnaires showed good internal consistency for MARS (Cronbach's α=0.7), BMQ-Necessity (Cronbach's α: Cinacalcet = 0.7 and Etelcalcetide = 0.6), BMQ-Concerns (Cronbach's α: Cinacalcet = 0.8 and Etelcalcetide = 0.8), and TIS (Cronbach's α: Cinacalcet = 0.9 and Etelcalcetide = 0.9 each for medications, DFR and dialysis). Etelcalcetide patients were more likely than Cinacalcet patients to experience GI symptoms in the prior month: nausea (31% vs. 24% visit 1 and 24% vs. 21% visit 2), vomiting (18% vs. 8% visit 1 and 17% vs. 8% visit 2), and diarrhoea (25% vs. 16% visit 1 and 20% vs. 15% visit 2).

224 HCPs (111 nephrologists and 113 dialysis nurses) participated in the survey. Nephrologists had been practising for a mean duration of 15 yrs, and nurses for a mean of 14 years. HCPs preferred Etelcalcetide (*Etelcalcetide vs. Cinacalcet vs. No preference*) for encouraging patient adherence (Nephrologist 89% vs. 4% vs. 7%; Nurses 78% vs. 9% vs. 12%); minimizing patient burden (Nephrologist 87% vs. 5% vs. 9%; Nurses 86% vs. 5% vs. 8%); minimizing side-effects (Nephrologist 78% vs. 3% vs. 20%; Nurses 66% vs. 9% vs. 25%); improving quality of life (Nephrologist 72% vs. 4% vs. 24%; Nurses 75% vs. 5% vs. 19%); reducing the need for parathyroidectomy (Nephrologist 47% vs. 5% vs. 48%; Nurses 55% vs. 8% vs. 36%); and general efficacy (Nephrologist 60% vs. 16% vs. 24%; Nurses 74% vs. 5% vs. 20%).

Only 12 patients in the 20170519 study were eligible for the linked analysis with the EU DOPPS 7 dataset. None of these 12 patients discontinued calcimimetic treatment during the DOPPS follow-up, and no further insights could be gained from addressing the other secondary objectives.

- **Discussion**

The questionnaires were acceptable to recipients with adequate psychometric properties.The responses to the patient questionnaires were consistent between visit 1 and visit 2. Self-reported adherence to Cinacalcet was high, and neither Cinacalcet nor Etelcalcetide was perceived by patients to be concerning. Neither Cinacalcet patients nor Etelcalcetide patients perceived their routine treatment regimen to be intrusive; however, medicines were considered to be less intrusive than DFR and dialysis.

Nephrologists and nurses overwhelmingly preferred Etelcalcetide to Cinacalcet across all treatment attributes, including encouraging patient adherence, minimizing patient burden, minimizing side-effects, improving quality of life, reducing the need for parathyroidectomy, and general efficacy.

- **Marketing Authorization Holder(s)**

  Amgen Europe B.V.
  Minervum 7061
  NL – 4817 ZK Breda
  The Netherlands

- **Names and Affiliations of Principal Investigators**

  [redacted]
  Amgen, United Kingdom

  [redacted]
  Amgen, GmBH

  [redacted]
  Arbor Research Collaborative for Health