Summary Table of Study Protocol

Title	A Multi-country Prospective Observational Study to Describe Calcimimetic Use in Haemodialysis Patients
Protocol version identifier	**Protocol Amendment 3, Version 4.0**
Date of last version of the protocol	**11 June 2019**
EU Post Authorization Study (PAS) Register No	EUPAS18923
Active Substance	Etelcalcetide Cinacalcet
Medicinal Product	Parsabiv® Mimpara®
Product Reference	EMEA/H/C/003995 EMEA/H/C/000570
Procedure Number	N/A
PASS	No

Research Question and Objectives	How are calcimimetics used in routine practice in haemodialysis (HD) patients? Primary objective - To describe the proportion of patients discontinuing calcimimetic treatment at 3-monthly intervals up to 18 months following treatment initiation Secondary objectives - To describe characteristics of haemodialysis (HD) patients at time of calcimimetic initiation (demographics, clinical history, dialysis treatment and laboratory parameters) - To describe clinical management of HD patients over time (calcimimetic use, secondary hyperparathyroidism (sHPT) medication use, and dialysis treatment) - To describe levels of parathyroid hormone (**PTH**), corrected calcium (cCa), phosphate (P) and other relevant laboratory parameters in HD patients over time - To describe the proportion of HD patients achieving KDIGO (Kidney Disease Improving Global Outcomes) target for **PTH** over time - To describe hypocalcemia incidence, risk factors and therapeutic responses - To describe the frequency of events of interest (nausea, vomiting, hospitalisations, parathyroidectomy, kidney transplant after calcimimetic initiation, fractures, and cardiovascular events)
Country(-ies) of Study	European countries, Israel, and Russia
Author	Amgen: PPD External: PPD

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Europe B.V. Minervum 7061 NL-4817 ZK Breda Netherlands
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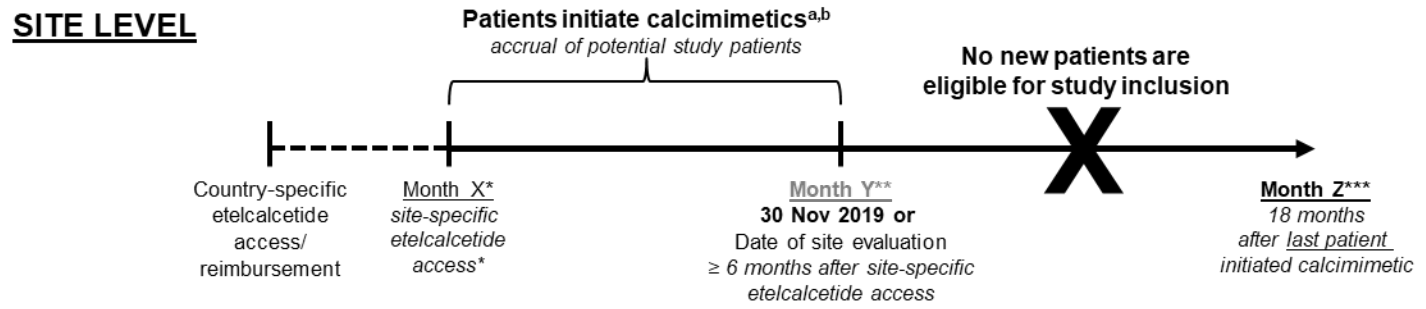
Investigator's Agreement

I have read the attached protocol entitled "A Multi-country Prospective Observational Study to Describe Calcimimetic Use in Haemodialysis Patients", dated **6 March 2020**, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

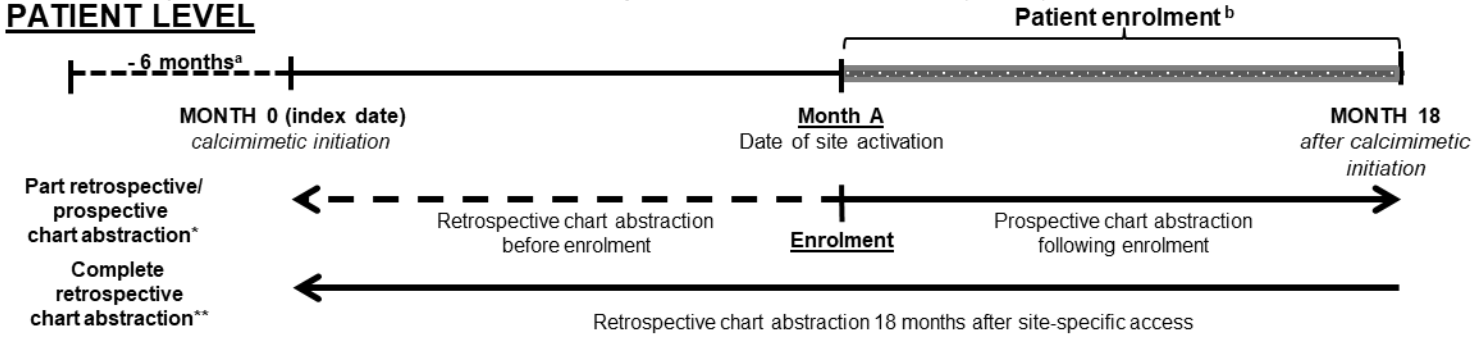
Signature	
Name of Investigator	Date (DD Month YYYY)

Study Design Schema



[a] Only patients initiating calcimimetic between date of site-specific etelcalcetide access (Month X) **to 30 November 2019 or** date of site evaluation (Month Y), **whichever occurs last,** are eligible for study enrolment.
[b] Eligible patients are:
- Calcimimetic naïve cinacalcet patients; or
- Etelcalcetide patients who initiate treatment and may or may not have a history of prior cinacalcet use

*Site-specific etelcalcetide access is defined as date of site availability of etelcalcetide (e.g. known date of first drug order or date of first drug administration).
**An interval of at least 6 months must elapse between etelcalcetide becoming accessible at the site to be eligible for evaluation for study participation.
***The end of study date at the site will be 18 months after the last subject initiated Calcimimetic [b] at the site (Month Z).



[a] 6 months of data (e.g. laboratory parameters) prior to date of calcimimetic initiation (Month 0) and 18 months of data following calcimimetic initiation will be collected. A total of 24 months of data will be collected for each patient.
[b] Individual patients may be enrolled at any time after date of site-activation (Month A; site activation occurs after site evaluation)

*Chart abstraction will be carried out part retrospectively (i.e. data prior enrolment) and part prospectively (i.e. data after enrolment).
**For countries where prospective chart abstraction is not possible (e.g. country-specific regulatory restrictions), patients will be enrolled ≥18 months after site-specific etelcalcetide access and data abstraction will be completely retrospective. In these countries, patients may have <24 months of data abstracted.

1. Table of Contents

List of Tables

List of Appendices

2. List of Abbreviations

AE	Adverse event
ALT	Alanine transaminase
ARO Study	Analysing Data, Recongising Excellence and Optimisng Outcomes Research Initiative, a retrospective cohort study
ASN	American Society of Nephrology
AST	Aspartate transaminase
BAP	Bone-specific alkaline phosphatase
BMI	Body Mass Index
Ca	Serum calcium
CaR	Calcium-sensing receptor
cCa	Corrected calcium
CI	Confidence interval
CKD	Chronic kidney disease
CKD-MBD	Chronic kidney disease-mineral and bone disorder
CRP	C-Reactive Protein
DCF	Data Clarification Form
DRG	Data Review Guidelines
DMP	Data Management Plan
eCRF	electronic Case Report Form
ECHO Study	Evaluation of the Clinical Use of Mimpara in Haemodialysis and Periotneal Dialysis Patients, an Observational Study
EDC	Electronic Data Capture
EMA	European Medicines Agency
ERBP	European Renal Best Practice
ESA	Erythropoiesis Stimulating Agent
ESRD	End-stage renal disease
ERA-EDTA	European Renal Association – European Dialysis and Transplant Association
EU	European Union
HD	Haemodialysis
HDL	High density lipoprotein
HgB	Haemoglobin
IA	Interim analysis
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
ICF	Informed Consent Form

i.v.	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
KM	Kaplan-Meier
LDL	Low density lipoprotein
NTx	N-telopeptide
P	Phosphorous
PTH	**Parathyroid hormone**
RCT	Randomised controlled trial
RRT	Renal replacement therapy
SAP	Statistical Anlaysis Plan
SHPT	Seconday hyperparathyrodism
TIW	Three times a week
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WBC	White blood cell

3. Responsible Parties

Role	Contact Details
Sponsor	Amgen Inc One Amgen Center Drive Thousand Oaks, CA 91320 United States
Principal Investigator	PPD Division of Nephrology and Immunology Uniklinik, Rheinisch-Westfälische Technische Hochschule Aachen Pauwelsstrasse 30 52074 Aachen, Germany

4. Abstract

- **Study Title:** A Multi-country Prospective Observational Study to Describe Calcimimetic Use in Haemodialysis (HD) Patients
- **Study Background and Rationale:** 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; St 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, 2017a). 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 will be observed. This observational study will describe 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**
  - How are calcimimetics used in routine practice in HD patients?

Objectives	Endpoints
Primary	
• To describe the proportion of HD patients discontinuing calcimimetic treatment at 3-monthly intervals up to 18 months following treatment initiation	• Proportion of patients discontinuing treatment at 3-monthly intervals up to 18 months following calcimimetic initiation.
Secondary	
• To describe the characteristics of HD patients at time of calcimimetic initiation (demographics, clinical history, dialysis treatment and laboratory parameters)	• Summary statistics of demographics, clinical history, dialysis treatment and laboratory parameters
• To describe clinical management of HD patients over time (calcimimetic use, sHPT medication use, and dialysis treatment	• Summary statistics of calcimimetic use, sHPT medication use, and dialysis treatment
• To describe levels of **PTH**, cCa, P and other relevant laboratory parameters in HD patients over time	• Median and 25th and 75th percentile values will be described
• To describe the proportion of HD patients achieving KDIGO (Kidney Disease Improving Global Outcomes) target for **PTH** over time	• Proportion of HD patients achieving KDIGO target for **PTH**
• To describe hypocalcemia incidence, risk factors and therapeutic responses	• Hypocalcemia incidence, and summary of risk factors (ie, hazard ratios) and therapeutic responses
• To describe the frequency of events of interest (nausea, vomiting, hospitalisations, parathyroidectomy, kidney transplant, fractures after calcimimetic initiation, and cardiovascular events)	• Number of events of interest

  - **Hypotheses**

    Formal hypotheses will not be tested. The proportion of HD patients discontinuing calcimimetics at 3-monthly intervals up to 18 months following treatment initiation will be described.

- **Study Design/Type**

  Multi-country prospective observational study

- **Study Population**

  Adult patients with CKD on HD therapy initiating calcimimetic treatment (ie, calcimimetic naïve cinacalcet patients or etelcalcetide patients with or without a history of prior cinacalcet use) after site-specific etelcalcetide access (**eg,** known date of first drug order or date of first drug administration of etelcalcetide at study site).

- **Summary of Patient Eligibility Criteria**

  Inclusion criteria

  - Aged ≥ 18 years and receiving HD for end-stage renal disease (ESRD) at time of calcimimetic initiation
  - Patients initiating calcimimetic between date of site-specific etelcalcetide access (eg, known date of first drug order or date of first drug administration at site) **to 30 November 2019 or** date of site evaluation (ie, evaluation of site for study participation)**, whichever occurs last,** are eligible, specifically:
    - Calcimimetic naïve cinacalcet patients with at least one prescription for cinacalcet; or
    - Etelcalcetide patients with or without a history of prior cinacalcet use and received at least one dose administration of etelcalcetide
  - Provided informed consent or notified of participation, according to local **laws and regulations** requirements

  Exclusion criteria

  - No **PTH** measurement within 90 days prior to calcimimetic initiation
  - Participated in a clinical trial of calcimimetic ≤ 90 days of initiating calcimimetic treatment
  - Previously participated in an expanded access program for etelcalcetide

- **Follow-up**

Data will be abstracted from charts. Patient chart abstraction will include 18 months of data after calcimimetic initiation and 6 months of data (eg, laboratory parameters) prior to date of calcimimetic initiation. A total of 24 months of data will be collected for each patient.

Data abstraction will be carried out either:

- part retrospective (ie data prior to patient enrolment) and part prospective (ie, data after site patient enrolment); or
- completely retrospective, specifically in countries where prospective chart abstraction is not possible (eg country-specific regulatory restrictions). Patients will be enrolled ≥ 18 months after site-specific etelcalcetide access and patients may have < 24 months of data abstracted.

- **Variables**
  - Outcome Variables

Primary outcome

- Discontinuation of calcimimetic treatment at 3-monthly intervals up to 18 months

Secondary outcomes

Baseline

- Demographics: age, gender, country
- Smoking history
- Clinical history: diabetes, hypertension, cardiovascular events, cardiac arrhythmia, other cardiac disease, revascularization, gastrointestinal bleed, fracture, calciphylaxis, tumoral calcinosis, cancer, parathyroidectomy, kidney transplant before calcimimetic initiation

Observation Period

- Dialysis treatment: dialysis vintage, modality, access, dose, frequency, duration, dialysate calcium, ionized calcium before dialysis, net ultrafiltration, weight after dialysis, sitting heart rate before dialysis, pre-dialysis systolic and pre-dialysis diastolic blood pressure)
- Laboratory parameters: **PTH**, total serum Ca, albumin, cCa, ionized Ca, P, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, bicarbonate, bone-specific alkaline phosphatase (BAP), creatinine, C-reactive protein (CRP), ferritin, glucose, haemoglobin (Hgb), high-density lipoprotein (HDL), low-density lipoprotein (LDL), N-telopeptide (NTx), platelets, potassium, sodium, total cholesterol, total protein, white blood cell (WBC), 25OH Vitamin-D3
- Calcimimetic use: type at initiation (etelcalcetide or cinacalcet), start and end date, dose, frequency, length of prescription (for cinacalcet use only), type of prescription/administration change (dose change, drug withheld, drug discontinuation), reason for prescription change (dose titration, noncompliance, adverse event, nausea, vomiting, PTH-Low, PTH-High, PTH within target, hypocalcemia, hypercalcemia, hemodialysis discontinued, switch-to-etelcalcetide, switch-to-cinacalcet, parathyroidectomy, kidney transplant, patient refusal, safety finding, product complaint, other)
- SHPT medication use (vitamin D supplement, active vitamin D, calcium supplements, phosphate binders): medication, dose, frequency, route, date first taken and date last taken
- Achieving KDIGO target for **PTH** (ie, 2-9 times upper limit of normal (ULN) of assay)
- Incidence of hypocalcemia will be summarized in two ways: occurrence of laboratory value reporting cCa< 2.1 mmol/L; or reported adverse event due to hypocalcemia

- Number of events of interest (nausea, vomiting, hospitalisations, parathyroidectomy, kidney transplant after calcimimetic initiation, fractures, and cardiovascular events).

  – Exposure Variables

- Etelcalcetide
- Cinacalcet

- **Study Sample Size**

The analyses will be descriptive in nature. Therefore the sample size has not been assessed in terms of statistical power but rather the expected levels of precision (ie, half-width) of the 95% confidence interval (CI) for a range of rates of discontinuation following calcimimetic treatment initiation.

Based on previous studies in similar populations, the rate of cinacalcet discontinuation at 12 months is expected to be around 25% (ECHO study 24% (Urena et al, 2009 and Vervloet et al, 2010); ARO study 23.3% (de Francisco et al, 2016)). Rates of discontinuation for etelcalcetide are expected to be lower. For the purposes of estimating precision, it is assumed that rates of discontinuation will be constant throughout the study.

A sample size of 1600 is planned Data based on an interim analysis showed that the distribution of patients enrolled who were exposed to cinacalcet and etelcalcetide was observed to be 20% and 80%. The observed discontinuation rate at 12 months for cinacalcet, etelcalcetide cinacalcet-naïve and etelcalcetide switchers were 30%, 10% and 17%, respectively. A sample size of 1600 with an enrolment ratio of 1:4 cinacalcet:etelcalcetide patients would ensure that the half-width of the 95% CI for a discontinuation rate of 25-35% would result in a half-width of approximately 5% for cinacalcet. A discontinuation rate of approximately 5-20% for etelcalcetide would result in a half-width of approximately 3% (see Section 8.5).

- **Data Analysis**

There are no formal hypotheses for the study. Descriptive analyses will be performed. The proportion of patients discontinuing treatment will be described. Treatment characteristics (calcimimetic, sHPT medications and dialysis treatment) will be summarised prior to calcimimetic initiation and after hypocalcemia event. PTH, cCa, P and other relevant laboratory values over time will be summarised. The proportion of

patients achieving KDIGO target will be described. To describe time-to-event of calcimimetic discontinuation, calcimimetic interruption, hypocalcemia and calcimimetic re-initiation, Kaplan-Meier (KM) curves will be plotted and KM estimates will be calculated.

5. Amendments and Updates

Amendment or Update Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	09 August 2017	See summary of changes in Appendix		
2	11 June 2019	See summary of changes in Appendix		
3	**6 March 2020**	**See summary of changes in Appendix**		

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Secondary hyperparathyroidism (SHPT) is a common complication of chronic kidney disease (CKD) (Goodman, 2004). As kidney function declines this causes disturbances in the balance of calcium (Ca), phosphorous (P) and vitamin D and, consequently, CKD-related mineral and bone disorders (CKD-MBD). These biochemical imbalances lead to the overproduction of intact parathyroid hormone (**PTH**) and thus to parathyroid gland hyperplasia which characterizes SHPT. Elevated levels of **PTH** can develop at early stages of CKD even when Ca and P are within normal range limits (Martinez *et al*, 1997). The impact of SHPT in progressive CKD results in bone mass reduction and an impaired rate of bone remodelling. Inadequate control of SHPT can consequently lead to increased risk of vascular calcification, fracture and cardiovascular morbidity and mortality (Horl, 2004).

Worldwide it is estimated that 2.6 million people with end stage renal disease (ESRD) receive renal replacement therapy (RRT), of whom approximately 80% receive dialysis and the remainder receive a kidney transplant (Liyanage *et al*, 2015). The European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) registry reports that there are approximately 69,000 incident and 450,000 prevalent ESRD patients receiving renal replacement therapy (RRT) in Europe (Pippias *et al*, 2015), of whom up to 90% receive haemodialysis (HD). It is estimated that 30-47% of dialysis patients in Europe are affected by SHPT (Hedgeman *et al*, 2015).

Prevention and treatment of SHPT remains a challenge although successful management can be partially achieved with dietary phosphate restriction, administration