3. Responsible Parties

Role	Contact Details
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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 (Parsibiv®) 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 2004, with posology of a starting dose of 30mg daily, administered orally, titrating to a maximum of 180mg daily to achieve the target iPTH of 150-300pg/mL, in SHPT patients. Etelcalcetide received marketing authorisation from the EMA in November 2016, for intravenous (i.v.) administration of 5mg three times weekly at the end of the HD session, adjusting dosage as necessary according to individual patient iPTH and Ca levels.

  Data from clinical trials and real-life clinical practice have demonstrated the effectiveness of cinacalcet in reducing iPTH 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 iPTH 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 achievement of iPTH control and medication persistence of etelcalcetide. Increasingly, physicians and payers are requesting evidence of utilisation and effectiveness generated from real-world use of therapies which have received regulatory approval based on data obtained from strictly controlled and monitored randomised clinical trials (RCTs). To provide context, real world use of cinacalcet as well as etelcalcetide will be observed; this allows utilization of either calcimimetic in a contemporary population of CKD HD patients to be described.

  This observational study will describe parameters of drug utilisation of both etelcalcetide and cinacalcet in a contemporary real world clinical setting, in order to provide essential data to physicians, prescribers and payers.

- **Research Question and Objectives**

How are calcimimetics used in routine practice in haemodialysis (HD) patients?

Primary objective

- To describe the proportion of HD subjects discontinuing calcimimetic treatment by 6,12 and 18 months following treatment initiation

Secondary objectives

- To describe the clinical characteristics of HD subjects at time of initiation of calcimimetic (demographics, clinical history, dialysis parameters)
- To describe clinical management of HD subjects over time (calcimimetic use, relevant concomitant medication use, dialysis, hospitalisation)
- To describe levels of iPTH, Ca, P and other relevant laboratory parameters in HD subjects over time
- To describe the proportion of HD subjects achieving KDIGO (Kidney Disease Improving Global Outcomes) target for iPTH over time
- **Hypotheses**

  Formal hypotheses will not be tested. The proportion of HD subjects discontinuing calcimimetics by 6, 12 and 18 months following treatment initiation will be described.

- **Study Design/Type**

  Multi-country prospective observational study.

- **Study Population**

  Adult patients receiving HD for end-stage renal disease (ESRD) for at least 6 months at time of initiating calcimimetic treatment with cinacalcet or etelcalcetide after February 2017, outside a clinical trial setting

- **Summary of Subject Eligibility Criteria**

Inclusion criteria

- Aged ≥18 years and receiving HD for ESRD
- Initiated calcimimetic treatment and received at least one administration of a calcimimetic following the granting of site-specific etelcalcetide access and prior to the site being evaluated to participate in the study
- Provided written informed consent or notified of participation, according to local requirements

Exclusion criteria

- Less than 6 months of HD at time of first dose of calcimimetic
- Participated in a clinical trial of calcimimetic within 90 days of initiation of cinacalcet or etelcalcetide following the granting of site-specific etelcalcetide access
- Previously participated in an expanded access program for etelcalcetide

- **Follow-up**

Individual subject follow-up is for 18 months after the date of initiation of calcimimetic. This follow-up may be part retrospective, part prospective, depending on timing of individual subject enrolment.

For countries where prospective follow-up is not possible, due for example to conditions of ethics approval, the entire 18-month follow-up will be retrospective.

Study variables will also be captured retrospectively for the 6-month period prior to calcimimetic initiation, and all relevant medical history prior to calcimimetic initiation will be reported.

The study period is anticipated to span August 2016 to November 2020.

- **Variables**

  Outcome Variables

  Primary outcome

  - Permanent discontinuation of calcimimetic (at 6, 12 and 18 months post-initiation)

  Secondary outcomes

  At initiation of calcimimetic:

  - Age
  - Gender
  - Country where HD is received
  - History of cardiovascular disease, musculoskeletal disease, parathyroidectomy, gastrointestinal bleeding,cirrhosis of the liver; diabetic status; BMI, blood pressure, smoking status,
  - Aetiology of ESRD
  - Kidney graft in situ; graft explanted; wait-listed for transplant
  - Dialysis vintage

Over observation period:

- Frequency and duration of HD sessions; dialysis modality, vascular access; dialysate calcium; actual blood flow
- Calcimimetic use over time: Type, date of first dose, dose, dosing frequency, dates of dose change(s), reason for interruption/permanent discontinuation
- Type, dose, dosing frequency of vitamin D, phosphate binders, calcium-supplements, antiemetics
- iPTH, Ca, P, Hb, ferritin, CRP, serum albumin, serum creatinine, alkaline phosphatase
- Incidence, date(s) and reason(s) for hospitalisation following initiation of calcimimetic

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; rather the expected levels of precision are presented for a range of rates of discontinuation following the initiation of calcimimetic treatment.

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

A sample size of 1800 is planned to enable meaningful results to be provided to all countries participating in the study. There is uncertainty as to the final ratio of enrolment of subjects exposed to cinacalcetide and etelcaclcitide; three possible scenarios are presented:

- 50:50 split (900 per arm)
- 33:66 split (600 & 1200 per arm)
- 66:33 split (1200 & 600 per arm)

The latter is included as it is probable that cinacalcet subjects will be treatment naïve whereas etelcalcetide subjects may be either treatment naïve subjects prescribed etelcalcetide as their first calcimimetic or subjects who have been prescribed etelcalcetide after previously receiving cinacalcet (‘switchers’); this combination would

give the smallest estimated sample size per group. For simplicity; a 50:50 ratio of treatment-naïve:switchers is assumed for subjects receiving etelcalcetide.

The table below shows the level of precision that can be obtained for various discontinuation rates per arm, and groups within arm. Rates for cinacalcet are assumed to be 20-25% and for etelcalcetide 5-20%.

For example a sample size of 1800 with an enrolment ratio of 1:2 cincalcet:etelcalcetide subjects would ensure that the half-width of the 95% CI for an expected rate of discontinuation of 20-25% would be approximately 3%. A discontinuation rate of approximately 10-15% for etelcalcetide would give a half width of approximately 2-3% around the 95% CI within each of the groups receiving etelcalcetide.

Precision estimates calculated for a range of proposed ratios of cinacalcet:etelcalcetide recruitment all result in precision estimates which are relatively stable with the half width of the 95% falling within the 2-4% window.

Table 1. Level of Precision Achieved for Calcimimetic Treatment Groups Depending on the Rate of Calcimimetic Discontinuation

	cinacalcet		etelcalcetide				
	Trt Naive		Trt Naive		Switch		Total
Number of subjects (1:2)		600		600		600	1800
%, discontinuation of calcimimetic treatment	20%	(17%, 23%)	5%	(3%, 7%)	10%	(8%,12%)	
	25%	(22%, 28%)	10%	(8%, 12%)	15%	(12%, 18%)	
			15%	(12%, 18%)	20%	(16%, 24%)	
Number of subjects (1:1)		900		450		450	1800
%, discontinuation of calcimimetic treatment	20%	(18%, 22%)	5%	(3%, 7%)	10%	(7%, 13%)	
	25%	(22%, 28%)	10%	(7%, 13%)	15%	(12%, 18%)	
			15%	(12%, 18%)	20%	(16%, 24%)	
Number of subjects (2:1)		1200		300		300	1800
%, discontinuation of calcimimetic treatment	20%	(18%, 22%)	5%	(3%, 7%)	10%	(7%, 13%)	
	25%	(23%, 27%)	10%	(7%, 13%)	15%	(12%, 18%)	
			15%	(12%, 18%)	20%	(16%, 24%)	

95% CI using normal approximation

- **Data Analysis**

Analyses will be descriptive. For continuous variables, descriptive statistics, for example, mean, standard deviation (SD), standard error (SE), median, interquartile range (25^{th} and 75^{th} percentile), minimum, and maximum values will be presented. For categorical variables, the number and percentage of participants in each category will be reported

with 95% two-sided confidence intervals (CIs). Variables measured longitudinally (eg, iPTH, Ca and P prior to and after calcimimetic initiation) will also be summarised graphically by plotting the mean (+/- SE) against time.

5. Amendments and Updates

None

6. Milestones

Milestone	Planned date
Start of data collection	12 December 2017
Interim Analysis 1	Q2 2018
Interim Analysis 2	Q4 2018
End of data collection	9 November 2020
Final report of study results	21 April 2021

7. Rationale and Background

7.1 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 (iPTH) and thus to parathyroid gland hyperplasia which characterizes SHPT. Elevated levels of iPTH 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).