Use of ETElcacitide for pReserving vitamin K-dependent proteInactivitY ITAlian Study (ETERNITY-ITA Study)

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Background and Aims: Vascular calcifications (VCs) are prevalent in chronic kidney disease (CKD) and mineral disorders, associated with aortic calcification and increased bone fracture risk. The complex pathogenesis involves factors like calcium overload, phosphate imbalance, and secondary hyperparathyroidism. Key inhibitors, vitamin K-dependent proteins (VKDPs) like matrix Gla protein (MGP) and osteocalcin (BGP), play pivotal roles in VC development. Traditional VC risk reduction focuses on lowering parathyroid hormone, calcium and phosphorus levels. Etelcalcetide, a synthetic peptide activating the calcium-sensing receptor, demonstrates promise in clinical trials. Studies on Vitamin K Italian (VIKI) show that calcimimetic treated hemodialysis patients exhibit higher levels of total BGP and MGP, suggesting a protective effect. These findings underscore the multifactorial nature of VC in CKD, informing refined treatment strategies and targeted pathways for improved outcomes. The proposed study will investigate real world evidence of the effect of Etelcalcetide in preserving active forms of VKDPs among total MGP and total BGP with a resulting reduction of those inactive such as dephosphorylated-undercarboxylated MGP or dp-uc MGP, undercarboxylated BGP or uc-BGP, thus contributing to bone and vascular health in hemodialysis patients (Table 1).

Method: This is a multi-center comparative effectiveness observational longitudinal study with no predefined interference on drug dosing on the part of the investigators. The study will enroll 160 hemodialysis patients: 80 patients considered in the exposed group (treated with Etelcalcitide) and 80 age and sex matched patients considered in the unexposed group (treated with Calcitriol or vitamin D analogs). The treating nephrologist will base their target dose of Etelcalcitide on an individual-level patient basis in order to achieve the KDIGO PTH target level. In the Etelcalcitide-treated group, the addition of calcitriol is allowed when required by normal clinical practice (for correction of hypocalcemia) (Fig. 1).

The primary endpoint is the comparison of the levels of active and non-active forms of VKDP between patients treated with Etelcalcitide and those treated with vitamin D or vitamin D analogues.

The two groups will be compared for longitudinal changes in the following biomarkers, measured at baseline and after 3, 9, and 18 months of treatment: total MGP, dephosphorylated-undercarboxylated MGP, total BGP, and undercarboxylated BGP. As secondary outcomes will be evaluated bone vascular markers levels, serum calcification propensity TcT test, anemia markers levels, dialysis routine biomarkers, changes from baseline prevalence VCs (Aorta and Iliac arteries) and vertebral fractures by lateral Dorsal Lumbar spine x-Ray and Bone Mass Density (BMD) by Dual-energy X-ray absorptiometry (DEXA).

Results:

Conclusion:
**Table 1: Inclusion and Exclusion Criteria.**

<table>
<thead>
<tr>
<th>Condition or disease</th>
<th>Intervention/treatment</th>
<th>Phase</th>
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<tr>
<td>Chronic Kidney Disease, Mineral and Bone Disorder, Renal Osteodystrophy, Vascular Calcification, Hyperparathyroidism; Secondary, Renal</td>
<td>Drug: Etercalcitide</td>
<td>This is prospective observational study of comparative effectiveness.</td>
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**Inclusion criteria:**

1. Patient has provided informed consent.
2. Patient is 18 years of age or older of both gender
3. Patients receiving maintenance HD three times per week (Kt/V >1.2)
4. Parathyroid hormone concentrations >500 mg/dl at screening, or if parathyroidectomy is planned or expected, Ca >8.3 mg/dl
5. Will be considered patients in the exposed group:
   a. Patients who have started Etercalcitide within 1-month before the study enrolment
   b. Patients naïve to intravenous calcimimetics use
   c. Patients who have suspended oral calcimimetics from at least 1-month,
   d. Patients who are not responder or not compliant to the treatment with calcitriol
6. In the unexposed group, patients on treatment with calcitriol or vitamin D analogs and who are age (> 2 years) and sex comparable (matching) to those in the exposed group will be considered.
7. Native vitamin D can be used in both groups and should be administered to target a 25(OH)D level >30 ng/ml
8. Dialysate calcium concentration must be stable for at least 4 weeks prior to screening laboratory assessments.
9. Patient must have severe HPT as defined by two laboratory screening pre-dialysis serum PTH values > 500 pg/ml, measured on two consecutive lab checks prior to entering the study.
10. Total alkaline phosphatase greater than the normal range, or even within the normal range but if greater than the tertile of the reference range for the assay.
11. Patients will be eligible only if they will show at least a/moderate Aorta VCs (16) and/or iliac arteries VCs and at least a mild VF (17,18).

**Exclusion Criteria:**

1. Previous treatment with oral calcimimetics (cinacalcet) must have been suspended for at least 30 days. Recent start of calcimimetics (Etercalcitide) is acceptable, but patients are excluded if treatment lasts for more than 1 month.
2. Patients has received a bisphosphonate, denosumab or teriparatide during the 12 months prior to screening.
3. The patient underwent parathyroidectomy in the 6 months before the start of the study or if scheduled soon.
4. Scheduled kidney transplant during the study period or anticipated living donor evaluation within three months of recruitment.
5. Patient has an unstable medical condition based on medical history, physical examination, and routine laboratory tests, or is otherwise unstable in the judgment of the investigator.
6. Metabolic bone diseases not related to the kidney (i.e., Pagets, Osteogeansis Imperfecta)
7. Severe untreated hyperthyroidism
8. Malnourishment within the last 3 years (except non-melanoma skin cancers or cervical carcinoma in situ).
9. Patient is pregnant or nursing.
10. Patients with Long QT Syndrome
11. Patient likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the patient and Investigator’s knowledge.

**Figure 1:** Trial design of ETERNITY Study.