EUROPEAN UNION RISK MANAGEMENT PLAN

Parsabiv® (Etelcalcetide)

Marketing Authorization Holder:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda Netherlands
Version:	4.0
Date:	21 February 2024
Supersedes:	Version 3.0, dated 28 September 2020

Risk Management Plan (RMP) version to be assessed as part of this application.

RMP version number:	4.0
Data lock point of this RMP:	10 November 2023
Date of final sign-off:	21 February 2024
Rationale for submitting an updated RMP:	• To remove the important potential risk of 'gastrointestinal hemorrhage' • To remove the completed category 3 Study 20170561

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
Part I: Product(s) Overview	Updated to show that etelcalcetide is not subject to additional monitoring in the European Union.	Version 4.0; 21 February 2024
Part II: Safety Specification		
SI: Epidemiology of the Indication(s) and Target Population(s)	Updated epidemiology data.	Version 4.0; 21 February 2024
SIII: Clinical Trial Exposure	Clinical trial exposure data updated to a data lock point of 10 November 2023.	Version 4.0; 21 February 2024
SIV: Populations Not Studied in Clinical Trials	Exposure of special populations updated to a data lock point of 10 November 2023.	Version 4.0; 21 February 2024
SV: Postauthorization Experience	Postauthorization exposure data updated to a data lock point of 10 November 2023.	Version 4.0; 21 February 2024
SVII: Identified and Potential Risks	Removed important potential risk of 'gastrointestinal hemorrhage.'	Version 4.0; 21 February 2024
SVIII: Summary of the Safety Concerns	Removed important potential risk of 'gastrointestinal hemorrhage.'	Version 4.0; 21 February 2024
Part III: Pharmacovigilance Plan (Including Postauthorization Safety Studies)	Removed completed category 3 Study 20170561.	Version 4.0; 21 February 2024
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	Removed important potential risk of 'gastrointestinal hemorrhage.'	Version 4.0; 21 February 2024
Part VI: Summary of the Risk Management Plan	Updated per changes listed above for Module SVII and Parts III and V.	Version 4.0; 21 February 2024
Part VII: Annexes		
Annex 2: Tabulated Summary of Planned, Ongoing, and Completed Pharmacovigilance Study Program	Updated category 3 Study 20170561 from ongoing to completed.	Version 4.0; 21 February 2024
Annex 3: Protocols for Proposed, Ongoing, and Completed Studies in the Pharmacovigilance Plan	Removed protocol for Study 20170561.	Version 4.0; 21 February 2024

Other RMP versions under evaluation:	
RMP version number:	None
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	3.0
Approved with procedure:	EMEA/H/C/PSUSA/00010533/202111
Date of approval (opinion date):	10 June 2021
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm, MSc Ind Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
ALT	alanine transaminase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CaSR	calcium-sensing receptor
CHF	congestive heart failure
CKD	chronic kidney disease
C_{max}	maximum plasma concentration
CRF	chronic renal failure
CYP	cytochrome P450
DOPPS	Dialysis Outcomes and Practice Patterns Study
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERA	European Renal Association
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association
ESA	erythropoietin-stimulating agent
EU	European Union
EVOLVE	evaluation of cinacalcet hydrochloride therapy to lower cardiovascular events
HCl	hydrochloride
HCP	healthcare professional(s)
hERG	human ether-à-go-go related gene
HPT	hyperparathyroidism
INN	International Nonproprietary Name
KAI	KAI Pharmaceuticals, Inc Effective 05 July 2012, KAI Pharmaceuticals, Inc. became a wholly owned subsidiary of Amgen Inc. In connection with Amgen's acquisition of KAI Pharmaceuticals, Amgen Inc. will be managing the etelcalcetide (formerly KAI-4169) development program.
MedDRA	Medical Dictionary for Regulatory Activities
NICE	National Institute for Health and Care Excellence
NYHAC	New York Heart Association Classification

Term/Abbreviation	Explanation
PI	Product Information
PL	Package Leaflet
pmp	per million population
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTH	parathyroid hormone
QPPV	Qualified Person for Pharmacovigilance
QTc	corrected QT interval
QTcF	corrected QT interval – Fridericia's correction formula
RMP	Risk Management Plan
RR	relative risk
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SHPT	secondary hyperparathyroidism
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
TdP	torsades de pointes
TIW	three times a week
UK	United Kingdom
ULN	upper limit of normal
US	United States
USRDS	United States Renal Data System

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Etelcalcetide
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	H05BX04
Marketing authorization holder	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	Etelcalcetide
Invented name(s) in the European Economic Area (EEA)	Parsabiv®
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Etelcalcetide (formerly KAI-4169) is a calcimimetic that functions as an allosteric activator of the calcium-sensing receptor (CaSR). Etelcalcetide is a synthetic peptide comprised of 7 D-amino acids linked to an L-cysteine via a disulfide bond.
Summary of mode of action	Etelcalcetide reduces parathyroid hormone (PTH) secretion through binding and activation of the calcium-sensing receptor. The reduction in PTH is associated with a concomitant decrease in serum calcium and phosphorus levels.
Important information about its composition	Etelcalcetide, the active pharmaceutical ingredient (API), is a synthetic peptide compound isolated in the hydrochloride (HCl) salt form by lyophilization from aqueous solution.
Hyperlink to the Product Information (PI)	Link to etelcalcetide PI on the European Medicines Agency (EMA) website: https://www.ema.europa.eu/documents/product-information/parsabiv-epar-product-information_en.pdf
Indication(s) in the EEA	
Current	Etelcalcetide is indicated for the treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on hemodialysis therapy.
Proposed (if applicable)	Not applicable.

Table 1. Product(s) Overview

Dosage in the EEA	
Current	The recommended initial dose of etelcalcetide is 5 mg administered by bolus injection 3 times per week. If a regularly scheduled hemodialysis treatment is missed, etelcalcetide should be administered at the next hemodialysis treatment at the same dose. Etelcalcetide should not be administered more frequently than 3 times per week. Etelcalcetide should be titrated so that doses are individualized between 2.5 mg and 15 mg. The dose may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks to a maximum dose of 15 mg 3 times per week to achieve the desired PTH target.
Proposed (if applicable):	Not applicable.
Pharmaceutical form(s) and strength(s)	
Current (if applicable):	Solution for injection: Clear colorless solution 2.5 mg, 5 mg, and 10 mg vials.
Proposed (if applicable):	Not applicable.
Is/will the product be subject to additional monitoring in the European Union (EU)?	No

PART II. SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Table 2. Summary of Epidemiology of Secondary HPT in Patients With CKD

Incidence	Secondary hyperparathyroidism (HPT) is a common and important complication among patients with chronic renal failure (CRF) on dialysis. The age and gender standardized incidence of kidney replacement therapy in all EU countries participating in the European Renal Association (ERA) Registry was 146.0 per million population (pmp) in 2008. It was stable until 2011, and slightly increased from 141.6 pmp in 2011 to 148.0 pmp in 2017 (Huijben et al, 2023).
Prevalence	The age and gender standardized prevalence of kidney replacement therapy across Europe increased from 990.0 pmp in 2008 to 1166.8 pmp in 2017 (annual percentage change: 1.82 [95% CI: 1.75; 1.89]) based on the ERA Registry study (Huijben et al, 2023). Across Europe and Australia, the prevalence of secondary HPT in adults within dialysis populations (PTH > 300 pg/mL) was estimated to be between 30% to 49%. The prevalence within dialysis populations in North America (United States [US], Canada) was estimated to be 54%. Within Asia, prevalence estimates for secondary HPT (intact PTH > 300 pg/mL) were only identified in India (28%) and Japan (11.5%) (Hedgeman et al, 2015).
Demographics of population in the authorized indication and risk factors for the disease	According to the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry, in 2018, among patients starting kidney replacement therapy, 62% were men, 51% were ≥ 65 years of age, and 20% had diabetes mellitus as cause of kidney failure. The median age of the patients starting kidney replacement therapy was 66.5 years, and differed by almost 20 years between Ukraine (55.0 years) and the Dutch-speaking part of Belgium (74.4 years) (Kramer et al, 2021). No data on race are available in the ERA-EDTA population; in the US, among prevalent end-stage renal disease patients in 2020, 42.7% of patients were non-Hispanic white, 29% were black, and 5.3% were Asian (United States Renal Data System [USRDS, 2020]). Other risk factors include: • Increased time on dialysis (Cunningham, 2005) • Vitamin D deficiency (Lee et al, 2008) • Demographic risk factors for a more severe manifestation are race (black), age (younger), and sex (female) (Gupta et al, 2000)
Main existing treatment options	In addition to surgical approach (eg, parathyroidectomy), current therapies for the biochemical abnormalities associated with secondary HPT include phosphate binders, which are used to reduce serum phosphorus levels, calcitriol, and other active vitamin D analogs, which are administered to reduce PTH (National Institute for Health and Care Excellence [NICE], 2021). Cinacalcet HCl (referred to as 'cinacalcet' in the remainder of this document) was the first calcimimetic approved for the treatment of secondary HPT in adult patients receiving dialysis.

Table 2. Summary of Epidemiology of Secondary HPT in Patients With CKD

Main existing treatment options (continued)	Etelcalcetide was the second calcimimetic drug approved in the EU and the US, in 2016 and 2017 respectively, for the treatment of secondary HPT in patients undergoing hemodialysis (Zhang et al, 2022). Cinacalcet is an allosteric activator of the CaSR and is available in tablet form for oral administration once daily.
Natural history of the indicated condition in the untreated population, including mortality and morbidity	Secondary HPT is a clinical syndrome that results in adverse systemic effects associated with significant morbidity and mortality. Important consequences of secondary HPT and the accompanying metabolic disruptions include pathological changes in bone, reductions in bone mass, increased risk of skeletal fracture, soft-tissue and vascular calcification, left ventricular hypertrophy, and a greater risk for cardiovascular events (USRDS, 2009; Moe, 2001; Alem et al, 2000; Block and Port, 2000; Diaz-Corte and Cannata-Andia, 2000; Slatopolsky et al, 1980). Survival of patients starting renal replacement therapy improved between 1997 and 2008 in the United Kingdom (UK) (Castledine et al, 2011). For example, the unadjusted 1-year survival increased from 85.9% in 1997 to 91.9% in 2008 among incident patients aged 18 to 64, and from 64.2% in 1997 to 75.8% in 2008 for incident patients ≥ 65 years of age. The age-adjusted 1-year survival of prevalent dialysis patients in the UK rose from 85% in 2000 to 89% in 2009 (Castledine et al, 2011). Based on the ERA-EDTA 2010, the 5-year survival probability was 46.2% (95% CI: 46.0, 46.3) among secondary HPT patients in the EU (ERA-EDTA, 2012).
Important comorbidities	• Cardiovascular disease, including hypertension, coronary artery disease, congestive heart failure (CHF), and peripheral vascular disease (USRDS, 2013; Tentori et al, 2008; Bradbury et al, 2007; Meisinger et al, 2006; Collins et al, 2003; Drey et al, 2003; Levin, 2003; Jaradat and Molitoris, 2002; Culleton et al, 1999). • Ventricular arrhythmia (USRDS, 2015; Saragoca et al, 1991). • Diabetes (USRDS, 2014; Dialysis Outcomes and Practice Patterns Study [DOPPS] Annual Report, 2012). • Bone disease resulting in increased risk of bone fracture (Beaubrun et al, 2013; Danese et al, 2006; Jadoul et al, 2006; Ball et al, 2002; Alem et al, 2000). Additional medical therapies administered to patients undergoing hemodialysis may include erythropoietin-stimulating agents (ESAs), iron, phosphate binders, calcium supplements, and active vitamin D compounds such as paricalcitol, doxercalciferol, alfacalcidol, and calcitriol. In addition, patients with CRF are often prescribed therapies for comorbidities such as hypertension (eg, angiotensin-converting enzyme inhibitors, beta blockers, calcium channel blockers, diuretics), diabetes (eg, insulin), and coronary artery disease (statins, nitrates, aspirin, and antiarrhythmics).

Part II: Module SII - Nonclinical Part of the Safety Specification

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Nonclinical Toxicology Studies	In the toxicology studies in the rat and dog, all of the observed adverse effects associated with etelcalcetide were related directly or secondary to decreases in serum calcium due to pharmacological suppression of PTH. The observed hypocalcemia was reversible in nature.	The use of etelcalcetide may result in hypocalcemia. The clinical signs and symptoms of hypocalcemia may include paresthesias, myalgias, muscle spasms, and seizures. Cardiac effects of hypocalcemia may include a prolonged QT interval and, rarely, ventricular arrhythmia. The Summary of Product Characteristics (SmPC) includes a warning in Section 4.4 to instruct healthcare professionals (HCPs) to correct serum calcium before administration of etelcalcetide, a dose increase of etelcalcetide, or reinitiation of etelcalcetide after a dose stop, and to monitor for hypocalcemia during treatment with etelcalcetide. In clinical studies, most of the hypocalcemia events were mild and generally patients recovered when their hypocalcemia was treated and/or etelcalcetide was stopped.
Reproductive Toxicity	Reduced fetal growth in rats and rabbits, and a minimal increase in pup mortality, delay in parturition, and transient reductions in postnatal growth were observed at exposures associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. Studies in rats showed etelcalcetide crossed the placental barrier and is excreted into milk.	There are no or limited amounts of data from the use of etelcalcetide in pregnant women. As a precautionary measure, it is preferable to avoid the use of etelcalcetide during pregnancy. The effects of etelcalcetide in breast-fed infants have not been assessed. Because of the potential for etelcalcetide to cause adverse effects in infants, a decision should be made to discontinue etelcalcetide or to discontinue nursing.

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Cardiovascular Safety Pharmacology	A cardiovascular safety pharmacology study in dogs demonstrated corrected QT (QTc) interval prolongation associated with maximal decreases in serum calcium, and not plasma drug levels, indicating QTc prolongation is related to hypocalcemia. Similar prolongation of QTc interval was observed in repeat dose dog studies. Etelcalcetide had no effect on the human ether-à-go-go related gene (hERG) channel current in vitro at the highest concentration tested (10 µg/mL) which is approximately 40-fold greater than the estimated human maximum plasma concentration (C_{max}) at the maximum clinical dose of 15 mg.	Decreases in serum calcium can prolong QT interval, potentially resulting in ventricular arrhythmia. The SmPC includes a warning in Section 4.4 to instruct HCPs to correct serum calcium before administration of etelcalcetide, a dose increase of etelcalcetide, or reinitiation of etelcalcetide after a dose stop, and to monitor for hypocalcemia during treatment with etelcalcetide. Etelcalcetide should be used with caution in patients with congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT prolongation and ventricular arrhythmia.

Part II: Module SIII - Clinical Trial Exposure

Table 4. Total Subject Exposure to Etelcalcetide in Clinical Trials by Indication and Duration
Safety Analysis Set

	Exposure to Etelcalcetide by Duration								
Etelcalcetide	≤ 12 weeks n (subj-yrs)	> 12 weeks n (subj-yrs)	> 24 weeks n (subj-yrs)	> 36 weeks n (subj-yrs)	> 52 weeks n (subj-yrs)	> 64 weeks n (subj-yrs)	> 78 weeks n (subj-yrs)	> 96 weeks n (subj-yrs)	Total n (subj-yrs)
Healthy Volunteers	24 (0.20)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	24 (0.20)
sHPT - Pediatric	13 (0.34)	25 (11.53)	19 (9.34)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	38 (11.87)
sHPT - Adult	256 (21.95)	1772 (2578.90)	1658 (2538.83)	1175 (2289.72)	1025 (2156.34)	902 (2026.78)	795 (1874.81)	640 (1619.72)	2028 (2600.85)
sHPT - All	269 (22.29)	1797 (2590.43)	1677 (2548.17)	1175 (2289.72)	1025 (2156.34)	902 (2026.78)	795 (1874.81)	640 (1619.72)	2066 (2612.73)
Total	293 (22.49)	1797 (2590.43)	1677 (2548.17)	1175 (2289.72)	1025 (2156.34)	902 (2026.78)	795 (1874.81)	640 (1619.72)	2090 (2612.92)

n = number of subjects exposed to etelcalcetide; sHPT = secondary hyperparathyroidism; subj-yrs = total subject-years of exposure calculation on the subject level for Etelcalcetide as (the last exposure - first non-missing dose date + 1)/365.25.

Safety Analysis Set includes all subjects who received at least 1 dose of investigational product.

Includes 20130107 (Healthy Volunteers), 20130139 (sHPT), 20120330 (sHPT), 20130147 (sHPT), 20120331 (sHPT), 20120334 (sHPT), 20120229 (sHPT), 20120230 (sHPT), 20120359 (sHPT), 20120360 (sHPT), 20120231 (OLE1, sHPT), 20130213 (OLE2, sHPT), 20140336 (sHPT), 20140197 (sHPT), 20140315 (sHPT), 20150238 (sHPT), and 20170724 (sHPT).

For completed studies, final data snapshot was used. Data snapshots for ongoing Studies 20140315 and 20170724 were on 10Nov2023.

Source: Program: /userdata/stat/amg416/safety/rmp/analysis/202311/tables/t-rmp-exp-ind-dur.sas

Output: t-01-004-rmp-exp-ind-dur.rtf (Date generated: 11JAN2024:00:11) Source data: d202311.dsur_exp

Table 5. Total Subject Exposure to Etelcalcetide in Clinical Trials by Age Group and Gender
Safety Analysis Set

	Number of Subjects			Subject-years of Exposure		
Age Group	Male	Female	Total	Male	Female	Total
Healthy Volunteers						
2 - 11 years	0	0	0	0.00	0.00	0.00
12 - 17 years	0	0	0	0.00	0.00	0.00
18 - 64 years	24	0	24	0.20	0.00	0.20
65 - 74 years	0	0	0	0.00	0.00	0.00
75 - 84 years	0	0	0	0.00	0.00	0.00
Over 85 years	0	0	0	0.00	0.00	0.00
Total	24	0	24	0.20	0.00	0.20
sHPT - Pediatric						
2 - 11 years	5	7	12	1.51	1.43	2.93
12 - 17 years	12	14	26	3.56	5.38	8.94
Total	17	21	38	5.07	6.81	11.87
sHPT - Adult						
18 - 64 years	856	595	1451	1087.45	711.88	1799.33
65 - 74 years	215	162	377	290.81	213.91	504.71
75 - 84 years	96	76	172	148.90	116.28	265.17
Over 85 years	16	12	28	19.52	12.12	31.63
Total	1183	845	2028	1546.67	1054.18	2600.85

Footnotes are defined on the next page.

Table 5. Total Subject Exposure to Etelcalcetide in Clinical Trials by Age Group and Gender
Safety Analysis Set

	Number of Subjects			Subject-years of Exposure		
Age Group	Male	Female	Total	Male	Female	Total
sHPT - All						
2 - 11 years	5	7	12	1.51	1.43	2.93
12 - 17 years	12	14	26	3.56	5.38	8.94
18 - 64 years	856	595	1451	1087.45	711.88	1799.33
65 - 74 years	215	162	377	290.81	213.91	504.71
75 - 84 years	96	76	172	148.90	116.28	265.17
Over 85 years	16	12	28	19.52	12.12	31.63
Total	1200	866	2066	1551.73	1060.99	2612.73
Total						
2 - 11 years	5	7	12	1.51	1.43	2.93
12 - 17 years	12	14	26	3.56	5.38	8.94
18 - 64 years	880	595	1475	1087.65	711.88	1799.53
65 - 74 years	215	162	377	290.81	213.91	504.71
75 - 84 years	96	76	172	148.90	116.28	265.17
Over 85 years	16	12	28	19.52	12.12	31.63
Total	1224	866	2090	1551.93	1060.99	2612.92

sHPT = secondary hyperparathyroidism
Safety Analysis Set includes all subjects who received at least 1 dose of investigational product.
Includes 20130107 (Healthy Volunteers), 20130139 (sHPT), 20120330 (sHPT), 20130147 (sHPT), 20120331 (sHPT), 20120334 (sHPT), 20120229 (sHPT), 20120230 (sHPT), 20120359 (sHPT), 20120360 (sHPT), 20120231 (OLE1, sHPT), 20130213 (OLE2, sHPT), 20140336 (sHPT), 20140197 (sHPT), 20140315 (sHPT), 20150238 (sHPT), and 20170724 (sHPT).
Subject-years of exposure = (the last exposure - first non-missing dose date + 1)/365.25.
Subjects with missing age/sex are not counted.
For completed studies, final data snapshot was used. Data snapshots for ongoing Studies 20140315 and 20170724 were on 10Nov2023.
Source: Program: /userdata/stat/amg416/safety/rmp/analysis/202311/tables/t-rmp-exp-ind-age-sex.sas
Output: t-01-005-rmp-exp-ind-age-sex.rtf (Date generated: 11JAN2024:00:12) Source data: d202311.dsur_exp

Table 6. Total Subject Exposure to Etelcalcetide in Clinical Trials by Indication and Race
Safety Analysis Set

Treatment	Number of Subjects	Subject-years of Exposure
Healthy Volunteers		
White	17	0.14
Black	0	0.00
Asian	6	0.05
American Indian or Alaska Native	0	0.00
Unknown	0	0.00
Other	1	0.01
Total	24	0.20
sHPT - Pediatric		
White	25	7.30
Black	6	1.88
Asian	6	2.65
American Indian or Alaska Native	0	0.00
Unknown	0	0.00
Other	1	0.03
Total	38	11.87
sHPT - Adult		
White	1121	1695.19
Black	466	634.97
Asian	392	205.68
American Indian or Alaska Native	0	0.00
Unknown	1	0.50
Other	48	64.52
Total	2028	2600.85

Footnotes are defined on the next page.

Table 6. Total Subject Exposure to Etelcalcetide in Clinical Trials by Indication and Race
Safety Analysis Set

Treatment	Number of Subjects	Subject-years of Exposure
sHPT - All		
White	1146	1702.49
Black	472	636.85
Asian	398	208.33
American Indian or Alaska Native	0	0.00
Unknown	1	0.50
Other	49	64.55
Total	2066	2612.73
Total		
White	1163	1702.63
Black	472	636.85
Asian	404	208.38
American Indian or Alaska Native	0	0.00
Unknown	1	0.50
Other	50	64.56
Total	2090	2612.92

sHPT = secondary hyperparathyroidism
Safety Analysis Set includes all subjects who received at least 1 dose of investigational product.
Includes 20130107 (Healthy Volunteers), 20130139 (sHPT), 20120330 (sHPT), 20130147 (sHPT), 20120331 (sHPT), 20120334 (sHPT), 20120229 (sHPT), 20120230 (sHPT), 20120359 (sHPT), 20120360 (sHPT), 20120231 (OLE1, sHPT), 20130213 (OLE2, sHPT), 20140336 (sHPT), 20140197 (sHPT), 20140315 (sHPT), 20150238 (sHPT), and 20170724 (sHPT).
Subject-years of exposure = (the last exposure - first non-missing dose date + 1)/365.25.
Subjects with missing race are not counted.
For completed studies, final data snapshot was used. Data snapshots for ongoing Studies 20140315 and 20170724 were on 10Nov2023.
Source: Program: /userdata/stat/amg416/safety/rmp/analysis/202311/tables/t-rmp-exp-ind-race.sas
Output: t-01-006-rmp-exp-ind-race.rtf (Date generated: 11JAN2024:00:10) Source data: d202311.dsur_exp

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Hypersensitivity to the active substance or to any of the excipients	Patients who are hypersensitive to etelcalcetide or to any of the excipients listed in Section 6.1 of the SmPC should not receive etelcalcetide.	No	Included in the SmPC as a contraindication and as an undesirable effect in Section 4.3 and Section 4.8, respectively.
Serum calcium less than the lower limit of the normal range	Etelcalcetide should not be initiated if the corrected serum calcium is less than the lower limit of the normal range. Potential manifestations of hypocalcemia include paresthesias, myalgias, muscle spasm and seizures.	No	Included as a contraindication in Section 4.3 of the SmPC. Hypocalcemia is included in the RMP (Section SVII.3.1) as an important identified risk.
Pregnant or breastfeeding women	No studies of etelcalcetide have been conducted in pregnant women. There have been a small number of pregnancies reported in the etelcalcetide clinical program. None of the pregnancies resulted in known live births and no fetal abnormalities were reported. There were no effects on embryo-fetal development in rats and rabbits when exposed to etelcalcetide during organogenesis at exposures 1.8 to 4.3 times human exposures at the clinical dose of 15 mg three times a week (TIW). At higher exposures in rats and rabbits (2.7- and 7-fold exposures, respectively, compared with subjects), there was reduced fetal growth associated with maternal toxicity.	Yes	Not applicable.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Pregnant or breastfeeding women (continued)	In a pre- and postnatal development study in rats, there were no effects on sexual maturation, neurobehavioral, or reproductive function in the offspring at exposures 1.8 times human exposures at the clinical dose of 15 mg TIW. At the same exposures, there was a minimal increase in pup mortality and delay in parturition, and transient reductions in postnatal growth associated with maternal toxicity. Studies in rat showed etelcalcetide crossed the placental barrier and was excreted into milk. It is not known whether etelcalcetide is excreted in human breast milk. The effects of etelcalcetide in breast-fed infants have not been assessed.		
Subject has received a parathyroidectomy within 3 months prior to dosing.	Subjects with recent parathyroidectomy are less likely to have secondary HPT requiring treatment.	No	There is currently no potential safety concern in this patient group.
Anticipated or scheduled parathyroidectomy during the study period.	Subjects scheduled for parathyroidectomy are unlikely to remain on study and may confound results.	No	There is currently no potential safety concern in this patient group.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Anticipated or scheduled kidney transplant during the study period.	Subjects scheduled for transplant are unlikely to remain on study and therefore were excluded.	No	There is currently no potential safety concern in this patient group.
Subject received cinacalcet within the 4 weeks prior to screening laboratory tests.	Subjects were excluded to ensure a stable PTH value prior to randomization. Patients receiving etelcalcetide should not be given cinacalcet, as concurrent administration may result in severe hypocalcemia.	No	Hypocalcemia has occurred during co-administration of etelcalcetide with other medicinal products, including cinacalcet, that are known to lower serum calcium. The SmPC includes a warning in Section 4.4 that patients receiving etelcalcetide should not be given cinacalcet, as concurrent administration may result in severe hypocalcemia. Hypocalcemia as a result of co-administration of etelcalcetide with other medicinal products known to lower serum calcium is included in Section 4.8 (Undesirable effects) of the SmPC.
Abnormal laboratory values: serum albumin $\leq$ 3.0 g/dL; serum magnesium $<$ 1.5 mg/dL; serum transaminase (alanine transaminase [ALT] or serum glutamic pyruvic transaminase [SGPT], aspartate aminotransferase [AST] or serum glutamic oxaloacetic transaminase [SGOT]) $>$ 2.5 times the upper limit of normal (ULN) at screening.	These laboratory abnormalities are indicative of having clinically significant acute or subacute serious disease which limit study participation and may confound results.	No	Analysis presented in the clinical summary of safety demonstrates that etelcalcetide is not hepatotoxic and had no effect on serum albumin or magnesium. In vitro studies demonstrate that etelcalcetide is not a substrate, inhibitor, or an inducer of the hepatic cytochrome P450 (CYP) enzymes. Also, etelcalcetide is not a substrate or inhibitor of common hepatic transporters (eg, bile salt export pump transporter).

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Treatment for a seizure disorder or has a history of a seizure within the last 12 months prior to screening.	Seizures are an uncommon diagnosis and unequal randomization may skew safety results confounding assessment of risk. Additionally, it was felt to be unwise to treat subjects with a recent history of a seizure disorder within 12 months prior to dosing with etelcalcetide until a more comprehensive understanding of the safety of etelcalcetide could be assessed given that the threshold for seizure may be lowered by significant reductions in serum calcium levels. Serum calcium levels should be closely monitored in patients with a history of a convulsion disorder while being treated with etelcalcetide.	No	Adjudicated events of seizure in the etelcalcetide pivotal studies (20120229 and 20120230) were balanced between placebo and etelcalcetide (1.0% in each treatment arm). The SmPC includes a warning in Section 4.4 to closely monitor serum calcium levels in patients with a history of a convulsion disorder while being treated with etelcalcetide. Convulsions is also included Section 4.8 (Undesirable effects) of the SmPC.
History of myocardial infarction, percutaneous coronary angioplasty, or coronary arterial bypass grafting within the past 6 months prior to screening.	Subjects with these cardiac disorders are at high risk for secondary events which may limit study participation and confound results.	No	Adjudicated events of myocardial infarction in the etelcalcetide pivotal studies (20120229 and 20120230) were balanced between placebo and etelcalcetide (1.6%).

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
History within the past 6 months of either angina pectoris with symptoms that occur at rest or minimal activity, or CHF (New York Heart Association Classification [NYHAC] III or IV).	Subjects with these cardiac disorders are at high risk for secondary events which may limit study participation and confound results.	No	Based on clinical data to date, etelcalcetide has not been associated with an increased incidence of angina. A difference was noted in the subject incidence of adjudicated CHF requiring hospitalization in the placebo-controlled studies (2.2% etelcalcetide; 1.2% placebo). The rate of events in the Cardiac Failure Standardized MedDRA (Medical Dictionary for Regulatory Activities) Query (SMQ) (3.2% etelcalcetide; 2.5% placebo) was consistent with the background rate of 3.3% in the placebo arm of the EVOLVE (evaluation of cinacalcet hydrochloride therapy to lower cardiovascular events) study, a large cardiovascular outcomes study conducted in subjects with CKD on dialysis comparing cinacalcet versus placebo. Approximately 24% and 23% of subjects in the etelcalcetide treatment group and placebo group, respectively, had past medical history of CHF (NYHAC I and II). The SmPC includes a warning in Section 4.4 to monitor serum calcium in patients with CHF. Worsening heart failure is included in the RMP (Section SVII.3.1) as an important identified risk.
Poorly controlled hypertension.	Subjects with uncontrolled hypertension are at high risk for cardiac events and/or neurological events which may limit study participation and confound results.	No	Analysis of blood pressure on study did not reveal any differences between placebo and etelcalcetide.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Ventricular arrhythmia or other cardiac abnormality.	Subjects with ventricular arrhythmias may limit participation and confound results. Cardiac changes following dosing of etelcalcetide could arise indirectly from drug-related decreases in serum calcium. This, in turn, may increase the risk of QT prolongation, and/or life-threatening cardiac ventricular arrhythmias.	No	QT prolongation, if observed, is associated with decreases in serum calcium (as no direct effect of etelcalcetide on hERG has been observed), therefore measures to prevent and manage hypocalcemia in association with etelcalcetide use should be effective in preventing or reducing the risk of QT prolongation and ventricular arrhythmias. The SmPC includes a warning in Section 4.4 that serum calcium levels should be closely monitored in patients with congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT prolongation and ventricular arrhythmia whilst being treated with etelcalcetide. QT prolongation secondary to hypocalcemia is included in the RMP (Section SVII.3.1) as an important identified risk. Ventricular arrhythmia is included in the RMP (Section SVII.3.1) as an important potential risk.
Symptomatic ventricular dysrhythmias or torsades de pointes (TdP).	Subjects with symptomatic ventricular dysrhythmias or TdP may limit participation and confound results. Cardiac changes following dosing of etelcalcetide could arise indirectly from drug related decreases in serum calcium.	No	Measures to prevent and manage hypocalcemia in association with etelcalcetide use should be effective in preventing or reducing the risk of TdP.

Table 7. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Symptomatic ventricular dysrhythmias or torsades de pointes (TdP) (continued)	This, in turn, may increase the risk of QT prolongation, and/or life threatening cardiac ventricular arrhythmias.		The SmPC includes a warning in Section 4.4 that serum calcium levels should be closely monitored in patients with congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT prolongation and ventricular arrhythmia whilst being treated with etelcalcetide. There was no imbalance of ventricular dysrhythmias between the etelcalcetide and placebo treatment groups in the placebo-controlled studies.
Serious concurrent medical condition likely to result in death during the next 12 months.	Subjects with serious concurrent medical conditions likely to result in death during the next 12 months may limit study participation and confound results.	No	There is currently no potential safety concern in this patient group.
History of malignancy within the last 5 years (except non-melanoma skin cancers, or cervical carcinoma in situ).	Subjects with these malignant conditions may limit study participation and confound results.	No	Etelcalcetide was mutagenic in the Ames (bacterial) assay; however, it was nongenotoxic in mammalian cells in vitro and in vivo and was not carcinogenic in the mouse and rat. There was no imbalance in new onset malignancy between the etelcalcetide and placebo treatment groups in the placebo-controlled studies.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as very rare adverse reactions (frequency $< 0.01\%$).

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 8. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Three pregnancies (of which 1 was paternal exposure) were reported in the clinical study development program.
Breastfeeding women	There were no reports of infants receiving breast milk from mothers who were being treated with etelcalcetide.
Patients with relevant comorbidities	
Patients with hepatic impairment	No dedicated studies in subjects with hepatic impairment were done, although the clinical development program included subjects with a reported medical history of hepatic impairment.
Patients with renal impairment	As all subjects in the phase 2 and phase 3 clinical studies were receiving hemodialysis for the indication of secondary HPT in subjects with CKD, no exposure by renal impairment is provided.
Patients with cardiovascular impairment	Patients with end-stage renal disease generally have a number of cardiovascular comorbidities. In the pivotal phase 3 placebo-controlled studies, 24.2% of subjects receiving etelcalcetide had a baseline cardiovascular history of CHF. Additionally, 14.9% had a family history of coronary artery disease. In a pivotal head to head study (etelcalcetide versus cinacalcet), 18.4% of subjects receiving etelcalcetide had a baseline cardiovascular history of CHF. Additionally, 10.8% of subjects receiving etelcalcetide had a family history of coronary artery disease.
Immunocompromised patients	End-stage renal disease patients are generally considered immunocompromised.
Patients with a disease severity different from inclusion criteria in clinical trials	Patients with a broad severity of disease were enrolled in etelcalcetide clinical studies.
Population with relevant different ethnic origin	A total of 1163 subjects (1702.63 subject-years), 472 subjects (636.85 subject-years), 404 subjects (208.38 subject-years), 1 subject (0.50 subject-years), and 50 subjects (64.56 subject-years) of White, Black, Asian, Unknown, or Other race were exposed to etelcalcetide, respectively.

Table 8. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other	
Pediatric patients	A total of 38 pediatric subjects (11.87 subject-years) received etelcalcetide in clinical studies. Of these, 12 subjects (2.93 subject-years) were 2 to 11 years of age and 26 subjects (8.94 subject-years) were 12 to 17 years of age.
Elderly patients	A total of 577 elderly subjects (801.51 subject-years) received etelcalcetide in clinical studies. Of these, 377 subjects (504.71 subject-years) were 65 to 74 years of age, 172 subjects (265.17 subject-years) were 75 to 84 years of age, and 28 subjects (31.63 subject-years) were 85 years of age or over.

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

The cumulative number of patient-years of exposure to etelcalcetide through commercial distribution is shown in Table 9 below.

Estimates of postmarketing patient exposure by age and sex are not yet available for etelcalcetide.

SV.1.2 Exposure

Table 9. Estimated Number of Patient-years of Exposure to Etelcalcetide, by Region, in the Postmarketing Setting

EUR	US	Other	Total
163 517	162 508	47 448	373 473

EUR = Europe (European Union, European Economic Area, Switzerland, and the United Kingdom);
Other = countries, otherwise not specified, where Amgen is the marketing authorization holder;
US = United States
Note: Numbers may not add to the total due to rounding.
Cumulative through 10 November 2023.

Postauthorization Use From Business Partners

Cumulatively, an estimated 305 058 patient-years of exposure to etelcalcetide was accrued in the business partner ONO Pharmaceutical Co., Ltd. (Japan) territory from launch through 10 November 2023.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

No evidence to suggest a potential for drug abuse or misuse has been observed.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Table 10. New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Removal of Safety Concerns from the RMP		
Important Potential Risks		
Gastrointestinal hemorrhage	Gastrointestinal hemorrhage, previously classified as an important potential risk, has been removed from the list of safety concerns in the EU RMP.	The findings from Study 20170561 (an observational study to evaluate the potential association between Parsabiv [etelcalcetide] and gastrointestinal bleeding) do not suggest an elevated risk of gastrointestinal bleeding for hemodialysis patients exposed to etelcalcetide. The EMA requested to *"remove from the RMP the category 3 PASS study 20170561 as additional pharmacovigilance activity and the risk of "Gastrointestinal haemorrhage" as important potential risk, at the first regulatory opportunity. In consideration of the limitations of study results (e.g. scarce sample size), the MAH is requested to maintain "Gastrointestinal haemorrhage" as important potential risk for the scope of the PSURs, and provide cumulative reviews in the context of the PSURs submitted in the future."*

EMA = European Medicines Agency; EU = European Union; MAH = marketing authorization holder; PASS = post authorization safety study; PSUR = Periodic Safety Update Report; RMP = Risk Management Plan

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 11. Important Identified Risk: Hypocalcemia

Potential mechanisms	Parathyroid hormone is a principal regulator of calcium metabolism. Control of calcium homeostasis is achieved through several distinct mechanisms, which include activation of bone resorption, stimulation of renal hydroxylation of vitamin D3, and increased renal reabsorption of calcium. The pharmacologic action of etelcalcetide reduces PTH secretion by the chief cell of the parathyroid gland; a reduction in PTH could lead to decrease in serum calcium concentrations.
Evidence source(s) and strength of evidence	This risk was identified in the clinical study setting; both asymptomatic and symptomatic events of low calcium (hypocalcemia) were reported more frequently in etelcalcetide-treated subjects compared with placebo-treated subjects in the phase 3 placebo-controlled studies. Additionally, other products in the same pharmacological class have shown an increased incidence of hypocalcemia.
Characterization of the risk	

Frequency

	6-month Placebo-Controlled Pool[a]		
Preferred term	Placebo (N = 513) n (%)	Etelcalcetide (N = 503) n (%)	RR[b] (95% CI)
Hypocalcemia[c]	1 (0.2)	35 (7.0)	35.7 (4.91, 259.56)
Blood Calcium Decreased[c]	52 (10.1)	321 (63.8)	6.3 (4.83, 8.21)
Subjects with ≥ 1 post-baseline serum corrected Ca (cCa) value - N1	511	499	
cCa < 7.5 mg/dL[d]	28 (5.5)	135 (27.1)	4.94 (3.35, 7.28)
cCa < 8.3 mg/dL[d]	99 (19.4)	392 (78.6)	4.05 (3.38, 4.87)

[a] This pool includes data from the two placebo-controlled studies 20120229 and 20120230. Safety analysis set includes subjects who received at least 1 dose of investigational product.
[b] RR (relative risk) is the relative risk of the event for etelcalcetide vs. placebo.
[c] During clinical development of etelcalcetide, asymptomatic reductions in calcium below 7.5 mg/dL or asymptomatic reductions in cCa between 7.5 and < 8.3 mg/dL that required medical management or that the investigator deemed clinically significant were reported as adverse events of "blood calcium decreased". Symptomatic reductions in cCa < 8.3 mg/dL were reported as adverse event of "hypocalcemia", and the associated signs and symptoms were also captured.
[d] Percentage is based on N1.
Program:/userdata/stat/amg416/meta/nda_2015shpt/analysis/eurmp/tables/tfrq-rr-hypoca.sas. Output: t1-05-frq-rr-hypoca.rtf (Date generated: 03JUN2015:03:09) Source data: adamiss.adae, adamiss.adlb.
Program:/userdata/stat/amg416/meta/nda_2015shpt/analysis/eurmp/tables/tfrqrr-pbcca.sas. Output: t1-11-frq-rr-pbcca.rtf (Date generated: 04JUN2015:02:01) Source data: adamiss.adlb

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 11. Important Identified Risk: Hypocalcemia

Characterization of the risk (continued)		
	Frequency (continued)	A higher proportion of subjects in the etelcalcetide treatment group had asymptomatic blood calcium decreased (68.9% in the etelcalcetide treatment group; 59.8% in the cinacalcet group) and symptomatic hypocalcemia (5.0% in the etelcalcetide group; 2.3% of subjects in the cinacalcet group), compared with cinacalcet in an active-controlled study (Study 20120360).
	Severity	Most hypocalcemia events in the pooled placebo-controlled studies were mild or moderate in severity. There were no life-threatening or fatal hypocalcemia events.
	Reversibility	Most of the hypocalcemia events were mild and generally patients recover when their hypocalcemia is treated and etelcalcetide is stopped (and dose reduced when etelcalcetide is resumed).
	Long-term outcomes	No long-term effects are expected when calcium levels have been corrected.
	Impact on quality of life	For severe hypocalcemia, patients may be hospitalized for treatment. Potential manifestations of hypocalcemia may include paresthesia, myalgias, muscle cramping, and in severe cases, tetany, also convulsion, QT prolongation (Table 13), and ventricular arrhythmia (Table 14). Generally, patients recover when their hypocalcemia is treated and etelcalcetide is stopped (and dose reduced when etelcalcetide is resumed).
Risk factors and risk groups		Patients with CKD who have low serum calcium due to concurrent medical conditions such as hyperphosphatemia, vitamin D deficiency, acute pancreatitis, calcitonin-producing tumors, low serum magnesium or who are treated with medications that lower the serum calcium.
Preventability		Etelcalcetide is contraindicated in subjects with a corrected serum calcium less than the lower limit of the normal range. Corrected serum calcium should be above the lower limit of the normal range before administration of first dose of etelcalcetide, a dose increase, or reinitiation of etelcalcetide after a dose stop. Etelcalcetide should not be administered more frequently than 3 times per week. Since etelcalcetide lowers serum calcium, patients should be monitored carefully during treatment for the occurrence of hypocalcemia. The SmPC notes that events of hypocalcemia can be managed with adjustments to calcium supplements, calcium-containing phosphate binders, vitamin D sterols, or adjustments in etelcalcetide dose. Dialysate calcium concentration can also be increased, if clinically indicated.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 11. Important Identified Risk: Hypocalcemia

Impact on the risk-benefit balance of the product	The risk of hypocalcemia has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. Routine risk minimization measures for hypocalcemia and adverse events secondary to hypocalcemia are considered appropriate.
Public health impact	Because hypocalcemia is treatable with no long-term effects expected, the public health impact is considered low.

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cCa = corrected serum calcium; CKD = chronic kidney disease; HPT = hyperparathyroidism; n = number of subjects; PTH = parathyroid hormone; RR = relative risk; SmPC = Summary of Product Characteristics

Table 12. Important Identified Risk: Worsening Heart Failure

Potential mechanisms	It is possible that an etelcalcetide-mediated reduction in calcium levels may trigger hemodynamic instability and that rapid or prolonged hypocalcemia may potentially reduce myocardial contractility particularly in patients with impaired heart function; however, the role of low serum calcium in the development of CHF has not been established.
Evidence source(s) and strength of evidence	This risk was originally identified from postmarketing data with another calcimimetic therapy. Thus, it was investigated in clinical trials for etelcalcetide. Some numerical differences were noted in the subject incidence of adjudicated CHF requiring hospitalization in the clinical trial setting. The subject incidence of cardiac failure (SMQ) in the etelcalcetide treatment group of Study 20120360 (3.0%) was similar to that reported in the etelcalcetide treatment groups of the placebo-controlled studies (3.2%).
Characterization of the risk	
Frequency	

	6-month Placebo-Controlled Pool[a]		
Events	Placebo (N = 513) n (%)	Etelcalcetide (N = 503) n (%)	RR[b] (95% CI)
Confirmed CHF requiring hospitalization[c]	6 (1.2)	11 (2.2)	1.87 (0.70, 5.02)
Cardiac failure (SMQ)[d]	13 (2.5)	16 (3.2)	1.26 (0.61, 2.58)

[a] This pool includes data from the two pivotal placebo-controlled studies 20120229 and 20120230. Safety analysis set includes subjects who received at least 1 dose of investigational product.
[b] RR is the relative risk of the event for etelcalcetide vs. Placebo.
[C] Adjudicated events of congestive heart failure requiring hospitalization
[d] MedDRA version 17.1
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In the integrated data from Study 20120229 and Study 20120230, the subject incidence of adjudicated events of CHF requiring hospitalization was 2.2% and 1.2% in the etelcalcetide and placebo group, respectively.

Severity	In the clinical trial setting, cardiac failure events ranged from mild to fatal, with most events reported as moderate or severe.
Reversibility	It is unknown if worsening of pre-existing CHF is reversible even with proper monitoring/correction of calcium levels.
Long-term outcomes	For severe disease, patients may be hospitalized for treatment and disability may occur.
Impact on quality of life	For severe disease, patients may be hospitalized for treatment and disability may occur.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 12. Important Identified Risk: Worsening Heart Failure

Risk factors and risk groups	Pre-existing cardiomyopathy or CHF, coronary artery disease, hypertension, and valvular heart disease appear to be risk factors for the development of heart failure (Kenchaiah et al, 2004; Levy et al, 1996).
Preventability	Monitoring of PTH levels, and monitoring and management of calcium and phosphorus levels. The SmPC instructs that serum calcium levels should be monitored in patients with a history of CHF while being treated with etelcalcetide, which may be associated with reductions in serum calcium levels.
Impact on the risk-benefit balance of the product	The risk of worsening heart failure has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. Routine risk minimization measures for hypocalcemia and adverse events secondary to hypocalcemia are considered appropriate.
Public health impact	Recommendations are provided to monitor and manage hypocalcemia. Thus, there would be few patients per year that would experience the event and the public health impact is considered low.

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CHF = chronic heart failure; MedDRA = Medical Dictionary for Regulatory Activities; PTH = parathyroid hormone; RR = relative risk; SmPC = Summary of Product Characteristics; SMQ = Standardised MedDRA Query

Table 13. Important Identified Risk: QT Prolongation Secondary to Hypocalcemia

Potential mechanisms	As a consequence of etelcalcetide-mediated reductions in circulating PTH levels, serum calcium levels may decrease. Decreases in serum calcium below the normal range may cause prolongation of myocardial repolarization and increase the QT interval.
Evidence source(s) and strength of evidence	This risk was identified in the nonclinical setting on the basis of the pharmacologic action of etelcalcetide to lower serum calcium. Nonclinical studies in the dog indicate that etelcalcetide causes QT prolongation in association with maximal decreases in serum calcium, but not in association with maximal plasma drug levels, suggesting that etelcalcetide does not directly affect cardiac repolarization. Administration of etelcalcetide is associated with QTc interval prolongation secondary to reductions in serum calcium in both etelcalcetide nonclinical and clinical studies.
Characterization of the risk	

Frequency

	6-month Placebo-Controlled Pool[a]		
Pre-HD QTcF (msec)	Placebo (N = 513) n (%)	Etelcalcetide (N = 503) n (%)	RR[b] (95% CI)
Maximum post baseline			
>450	134 (26.1)	203 (40.4)	1.55 (1.29, 1.85)
>480	38 (7.4)	60 (11.9)	1.61 (1.09, 2.37)
>500	10 (1.9)	24 (4.8)	2.45 (1.18, 5.07)
Maximum Increase from Baseline			
>30	29 (5.7)	105 (20.9)	3.69 (2.49, 5.47)
>60	0 (0.0)	6 (1.2)	NE

[a] This pool includes data from the two pivotal placebo-controlled studies 20120229 and 20120230. Safety analysis set includes subjects who received at least 1 dose of investigational product.
[b] RR (relative risk) is the relative risk of the event for etelcalcetide vs. placebo.
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Footnotes, including abbreviations, are defined on the last page of the table.

Table 13. Important Identified Risk: QT Prolongation Secondary to Hypocalcemia

Characterization of the risk (continued)

Frequency (continued)

SMQ Preferred Term[b]	6-month Placebo-Controlled Pool[a] Placebo (N = 513) n (%)	Etelcalcetide (N = 503) n (%)	RR[c] (95% CI)
Torsade de pointes-QT prolongation (SMQ)	3 (0.6)	6 (1.2)	2.04 (0.51, 8.11)
Electrocardiogram QT prolonged	3 (0.6)	4 (0.8)	1.36 (0.31, 6.05)
Ventricular tachycardia	0 (0.0)	2 (0.4)	NE

[a] This pool includes data from the two pivotal placebo-controlled studies 20120229 and 20120230. Safety analysis set includes subjects who received at least 1 dose of investigational product.
[b] MedDRA version 17.1
[c] RR (Relative Risk) is the relative risk of the event for etelcalcetide vs. Placebo.
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Severity	Most events in the pooled placebo-controlled studies were mild or moderate in severity. There were no life-threatening or fatal QT prolongation events reported.
Reversibility	Adequate calcium supplementation and antiarrhythmic treatment (if necessary) are required in the event of QT prolongation/ventricular arrhythmias due to hypocalcemia. Generally, patients recover when their hypocalcemia and arrhythmia are treated.
Long-term outcomes	Patients may be hospitalized for treatment and disability may occur. Improved outcomes are anticipated in patients who undergo consistent serum calcium monitoring.
Impact on quality of life	Clinical symptoms of QT prolongation may vary in severity. Patients may be hospitalized for treatment and disability may occur.
Risk factors and risk groups	Subjects with a congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT prolongation and ventricular arrhythmia.
Preventability	Prevention and management of hypocalcemia in association with etelcalcetide use should be effective in preventing or reducing the risk of QT prolongation. The SmPC instructs that serum calcium levels should be closely monitored in patients with congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT prolongation and ventricular arrhythmia while being treated with etelcalcetide.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 13. Important Identified Risk: QT Prolongation Secondary to Hypocalcemia

Impact on the risk-benefit balance of the product	The risk of QT prolongation secondary to hypocalcemia has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive. Routine risk minimization measures for hypocalcemia and adverse events secondary to hypocalcemia are considered appropriate.
Public health impact	Recommendations are provided to monitor and manage hypocalcemia in order to prevent this event. Thus, the overall impact on public health is considered to be low.

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HD = hemodialysis; MedDRA = Medical Dictionary for Regulatory Activities; NE = not estimable; PTH = parathyroid hormone; QTc = corrected QT; QTcF = corrected QT interval – Fridericia's correction formula; RR = relative risk; SmPC = Summary of Product Characteristics; SMQ = Standardised MedDRA Query

Table 14. Important Potential Risk: Ventricular Arrhythmias

Potential mechanisms

Etelcalcetide administration may be associated with cardiac events, including arrhythmias, because it lowers serum calcium.

In preclinical studies with telemetrized dogs receiving etelcalcetide, changes in QTc interval were temporally associated with maximum decreases in serum calcium concentrations and not with maximum etelcalcetide concentrations. In addition, no effects of etelcalcetide on hERG channel currents were observed in vitro at concentrations approximately 40 times higher than the maximum plasma free drug concentrations achieved in subjects. No evidence of an increased subject incidence in adverse events potentially associated with QTc interval prolongation was observed among subjects receiving etelcalcetide in the placebo-controlled pivotal studies.

Evidence source(s) and strength of evidence

Data to evaluate this safety concern derives from the nonclinical setting on the basis of the pharmacological action of etelcalcetide to lower serum calcium (see potential mechanisms above).

Characterization of the risk

Frequency

SMQ Preferred Term[b]	6-month Placebo-Controlled Pool[a] Placebo (N = 513) n (%)	Etelcalcetide (N = 503) n (%)	RR[c] (95% CI)
Ventricular tachyarrhythmias (SMQ)	4 (0.8)	2 (0.4)[d]	0.51 (0.09, 2.77)
Ventricular tachycardia	0 (0.0)	2 (0.4)	NE
Ventricular extrasystoles	2 (0.4)	0 (0.0)	NE
Ventricular fibrillation	1 (0.2)	0 (0.0)	NE
Ventricular tachyarrhythmia	1 (0.2)	0 (0.0)	NE

[a] This pool includes data from the two pivotal placebo-controlled studies 20120229 and 20120230. Safety analysis set includes subjects who received at least 1 dose of investigational product.
[b] MedDRA version 17.1
[c] RR (relative risk) is the relative risk of the event for etelcalcetide vs. placebo.
[d] These 2 cases are also presented in Table 13 (QT Prolongation Secondary to Hypocalcemia)
Program: /userdata/stat/amg416/meta/nda_2015shpt/analysis/eurmp/tables/t-frq-rr-smq.sas. Output: t1-08-frq-rr-smq.rtf (Date generated: 06MAY2015:00:18)
Source data: adamiss.adae

No subjects in either treatment group of the comparison study with cinacalcet (Study 20120360) had events from the Ventricular Tachyarrhythmia SMQ.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 14. Important Potential Risk: Ventricular Arrhythmias

Characterization of the risk (continued)	
Severity	Ventricular arrhythmia events reported in the placebo-controlled clinical studies ranged from mild to fatal in severity. There were no life-threatening or fatal ventricular arrhythmia events reported in the etelcalcetide-treatment group.
Reversibility	Adequate calcium supplementation and antiarrhythmic treatment (if necessary) are required in the event of ventricular arrhythmias due to hypocalcemia. Generally, patients recover when their hypocalcemia and arrhythmia are treated.
Long-term outcomes	Patients may be hospitalized for treatment and disability may occur. Improved outcomes are anticipated in patients who undergo consistent serum calcium monitoring.
Impact on quality of life	Clinical symptoms of ventricular arrhythmias may vary in severity. Patients may be hospitalized for treatment and disability may occur.
Risk factors and risk groups	Subjects with a congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT prolongation and ventricular arrhythmia.
Preventability	Prevention and management of hypocalcemia in association with etelcalcetide use should be effective in preventing or reducing the risk of ventricular arrhythmias. The SmPC instructs that serum calcium levels should be closely monitored in patients with congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT prolongation and ventricular arrhythmia while being treated with etelcalcetide.
Impact on the risk-benefit balance of the product	The potential risk of ventricular arrhythmias secondary to hypocalcemia has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive.
Public health impact	Prevention and management of hypocalcemia in association with etelcalcetide use should be effective in preventing or reducing the risk of ventricular arrhythmias. Thus, the overall impact on public health is considered to be low.

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hERG = human ether-à-go-go related gene; MedDRA = Medical Dictionary for Regulatory Activities; NE = Not estimable; QTc = corrected QT; RR = relative risk; SmPC = Summary of Product Characteristics; SMQ = Standardised MedDRA Query

Table 15. Important Potential Risk: Fractures

Potential mechanisms	The target range for PTH recommended by the National Kidney Foundation's Clinical Practice Guidelines for Bone Metabolism and Disease in CKD differs according to level of kidney function (National Kidney Foundation, 2003). The target PTH range is relatively higher for patients with relatively lower levels of kidney function due to an increase in skeletal resistance to PTH that occurs as kidney function declines. Chronic oversuppression of PTH to levels below the lower limit of the target range for a given patient can result in the histomorphometric features of low bone turnover, or adynamic bone. Therapy of hyperparathyroid bone disease may result in oversuppression of PTH, increasing further the prevalence of adynamic bone disease. Controversy exists, however, as to whether or not adynamic bone is associated with microfractures that do not heal and can eventually result in clinical fracture (Parfitt, 2003; Hruska and Teitelbaum, 1995). Because etelcalcetide is very effective in reducing PTH concentrations, the theoretical possibility exists that etelcalcetide could lead to oversuppression of PTH and subsequently adynamic bone.
Evidence source(s) and strength of evidence	Data to evaluate this safety concern derives from the documented association in the literature between oversuppression of PTH and adynamic bone. In rat models of established secondary HPT, etelcalcetide effectively reduced the high bone turnover and was effective in preventing reductions in cortical porosity and preserving bone strength (Studies 20130074 and 20130075). These results are consistent with the effects of cinacalcet and related phenylalkylamine calcimimetics in the prevention of trabecular bone defects in rodent models of secondary HPT (Henley et al, 2009; Wada et al, 1998). In the toxicology studies, marked reductions in PTH were observed in rats and dogs (up to lifetime exposure in rats, 9 months in dogs), but there was no evidence of adverse effects on bone health as measured by clinical examination and histological evaluation of long bones, sternebrae, and cartilage. In addition, a mouse model bearing a gain–of-function mutation in the CaSR did not reveal any gross or histological abnormalities indicative of effects on bone (Hough et al, 2004).

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 15. Important Potential Risk: Fractures

Characterization of the risk

Frequency

Events of Interest Preferred Term	6-month Placebo-Controlled Pool[a] Placebo (N = 513) n (%)	AMG 416 (N = 503) n (%)	RR[b] (95% CI)
Fractures (EOI)	15 (2.9)	8 (1.6)	0.54 (0.23, 1.27)
Femur fracture	3 (0.6)	2 (0.4)	NE
Tibia fracture	1 (0.2)	2 (0.4)	NE
Hip fracture	1 (0.2)	1 (0.2)	NE
Lower limb fracture	0 (0.0)	1 (0.2)	NE
Rib fracture	3 (0.6)	1 (0.2)	NE
Scapula fracture	0 (0.0)	1 (0.2)	NE
Spinal fracture	0 (0.0)	1 (0.2)	NE
Ankle fracture	2 (0.4)	0 (0.0)	NE
Avulsion fracture	1 (0.2)	0 (0.0)	NE
Clavicle fracture	2 (0.4)	0 (0.0)	NE
Facial bones fracture	1 (0.2)	0 (0.0)	NE
Foot fracture	1 (0.2)	0 (0.0)	NE
Fracture nonunion	1 (0.2)	0 (0.0)	NE
Hand fracture	1 (0.2)	0 (0.0)	NE
Pelvic fracture	1 (0.2)	0 (0.0)	NE

[a] This pool includes data from the two placebo-controlled studies 20120229 and 20120230. Safety analysis set includes subjects who received at least one dose of investigational product

[b] RR (relative risk) is the relative risk of the event for AMG 416 vs. placebo.

Program: /userdata/stat/amg416/meta/nda_2015shpt/analysis/eurmp/tables/t-frq-rr-eoi-frac-pc.sas

Output: t2-01-frq-rr-eoi-frac-pc.rtf (Date generated: 21JUN2016:21:27) Source data: adamiss.adae

Severity

Fracture events reported in the placebo-controlled clinical studies ranged from mild to severe. There were no life-threatening or fatal fracture events reported.

Footnotes, including abbreviations, are defined on the last page of the table.

Table 15. Important Potential Risk: Fractures

Characterization of the risk (continued)	
Reversibility	Appropriate management of PTH levels should both prevent and reverse events of adynamic bone.
Long-term outcomes	Adynamic bone may predispose patients to fractures. Fractures cause short-term or long-term disability. Surgery may be required.
Impact on quality of life	Fractures cause short-term or long-term disability. Surgery may be required.
Risk factors and risk groups	Older age, women, prior kidney transplant, low serum albumin, selective serotonin reuptake inhibitors, combination narcotic medications, and PTH > 900 pg/mL (versus PTH 150 to 300 pg/mL) were associated with an increased risk of new fractures (Jadoul et al, 2006). In a study of the elderly (≥ 75 years of age in the UK), an estimated glomerular filtration rate < 45 mL/min/1.73 m^2 was associated with an almost 2-fold increase in hip-fracture-related mortality (Nitsch et al, 2009). Risks for hip and vertebral fracture had a U-shaped relationship with PTH concentration, with the lowest risk observed with a PTH concentration of approximately 300 pg/mL.
Preventability	Based on clinical data to date, etelcalcetide has not been associated with an increased incidence of fracture; therefore, no preventive measures are defined.
Impact on the risk-benefit balance of the product	The potential risk of fractures has been incorporated in the benefit-risk assessment with the overall benefit-risk balance remaining positive.
Public health impact	The recommended dosing regimen for etelcalcetide is designed to avoid oversuppression of PTH. As a result the overall impact on public health is considered to be low.

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CaSR = calcium-sensing receptor; CKD = chronic kidney disease; EOI = event of interest; HPT = hyperparathyroidism ; NE = Not estimable; PTH = parathyroid hormone; RR = relative risk; UK = United Kingdom

SVII.3.2 Presentation of the Missing Information

Table 16. Missing Information: Use in Pregnancy and Lactation

Evidence source	There were no effects on embryo-fetal development in rats and rabbits when exposed to etelcalcetide during organogenesis at exposures 1.8 to 4.3 times human exposures at the clinical dose of 15 mg TIW. At higher exposures in rats and rabbits (2.7- and 7-fold exposures, respectively, compared with subjects), there was reduced fetal growth associated with maternal toxicity. In a pre- and postnatal development study in rats, there were no effects on sexual maturation, neurobehavioral, or reproductive function in the offspring at exposures 1.8 times human exposures at the clinical dose of 15 mg TIW. At the same exposures, there was a minimal increase in pup mortality and delay in parturition, and transient reductions in postnatal growth associated with maternal toxicity. Studies in rat showed etelcalcetide crossed the placental barrier and was excreted into milk.
Population in need of further characterization	No studies of etelcalcetide have been conducted in pregnant women. Pregnant women and women planning to become pregnant were not eligible to participate in clinical trials with etelcalcetide. There have been a small number of pregnancies reported in the etelcalcetide clinical program. None of the pregnancies resulted in known live births and no fetal abnormalities were reported. It is not known whether etelcalcetide is excreted in human breast milk. The effects of etelcalcetide in breast-fed infants have not been assessed.

TIW = three times a week

Part II: Module SVIII - Summary of the Safety Concerns

Table 17. Summary of Safety Concerns

Important identified risks	Hypocalcemia Worsening heart failure QT prolongation secondary to hypocalcemia
Important potential risks	Ventricular arrhythmias Fractures
Missing information	Use in pregnancy and lactation

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 18.

Table 18. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Etelcalcetide hypocalcemia questionnaire	Hypocalcemia	To better characterize serious adverse event reports of hypocalcemia in patients treated with etelcalcetide in the clinical trial and postmarketing setting. The questionnaire is used as a supplemental form to the postmarketing adverse event form.

III.2 Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance activities.

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance activities.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 19. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Hypocalcemia	Routine risk communication: • SmPC Sections 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 4.9, 5.1, and 5.3 • Package Leaflet (PL) Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation that corrected serum calcium should be at or above the lower limit of normal prior to administration of etelcalcetide, and to monitor corrected serum calcium, is included in SmPC Section 4.2. • Recommendation that etelcalcetide should not be initiated in patients if the corrected serum calcium is less than the lower limit of normal, for patients to seek medical attention if they experience symptoms of hypocalcemia, and to monitor corrected serum calcium, is included in SmPC Section 4.4. • Recommendation to check serum calcium and to monitor for symptoms of hypocalcemia in the event of etelcalcetide overdose is included in SmPC Section 4.9. • Recommendation for the monitoring of blood calcium levels and for patients to tell their doctor if they have symptoms of low calcium levels is included in PL Section 2. • Recommendation for patients to tell their doctor if they have symptoms of low calcium levels is included in PL Section 4.
Worsening heart failure	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation that serum calcium levels should be monitored in patients with a history of CHF while being treated with etelcalcetide is included in SmPC Section 4.4. • Recommendation for patients to tell their doctor if they have a history of heart problems such as heart failure or experience heart failure while receiving etelcalcetide is included in PL Section 2.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 19. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks (continued)	
QT prolongation secondary to hypocalcemia	Routine risk communication: • SmPC Sections 4.4 and 4.8 • PL Sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation that serum calcium levels should be closely monitored in patients with congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death and other conditions that predispose to QT prolongation and ventricular arrhythmia while being treated with etelcalcetide is included in SmPC Section 4.4. • Recommendation for patients to tell their doctor if they have a history of heart problems, such as arrhythmias, or experience an unusually fast or pounding heartbeat or have heart rhythm problems while receiving etelcalcetide, is included in PL Section 2.
Important Potential Risks	
Ventricular arrhythmias	Routine risk communication: • SmPC Section 4.4 • PL Section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation that serum calcium levels should be closely monitored in patients with congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death and other conditions that predispose to QT prolongation and ventricular arrhythmia while being treated with etelcalcetide is included in SmPC Section 4.4. • Recommendation for patients to tell their doctor if they have a history of heart problems, such as arrhythmias, or experience an unusually fast or pounding heartbeat or have heart rhythm problems while receiving etelcalcetide, is included in PL Section 2.

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 19. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks (continued)	
Fractures	Routine risk communication: • SmPC Section 4.4 • PL Sections 1 and 2 Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation that if PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or etelcalcetide should be reduced or therapy discontinued, is included in SmPC Section 4.4. • Recommendation for the monitoring of PTH levels and that the dose of etelcalcetide may need to be reduced if PTH levels become very low is included in PL Section 2.
Missing Information	
Use in pregnancy and lactation	Routine risk communication: • SmPC Sections 4.6 and 5.3 • PL Section 2

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PL = Package Leaflet; PTH = parathyroid hormone; SmPC = Summary of Product Characteristics

V.2 Additional Risk Minimization Measures

Routine risk minimization measures as described in Part V.1 are sufficient to manage the safety concerns of etelcalcetide.

V.3 Summary of Risk Minimization Measures

Table 20. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Hypocalcemia	Routine risk minimization measures: • SmPC Section 4.2 where advice on serum calcium level and administration of etelcalcetide, and monitoring of serum calcium is included • SmPC Section 4.4 where advice on serum calcium level and administration of etelcalcetide, seeking medical attention for symptoms of hypocalcemia, and monitoring of serum calcium is included • SmPC Section 4.9 where advice on monitoring serum calcium and symptoms of hypocalcemia in the event of etelcalcetide overdose is included • SmPC Sections 4.3, 4.5, 4.7, 4.8, 5.1, and 5.3 • PL Section 2 where advice on monitoring blood calcium levels and for patients to tell their doctor if they have symptoms of low calcium levels is included • PL Section 4 where advice for patients to tell their doctor if they have symptoms of low calcium levels is included Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Adverse event follow-up form for adverse reaction (Etelcalcetide hypocalcemia questionnaire) Additional pharmacovigilance activities: • None

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 20. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks (continued)		
Worsening heart failure	Routine risk minimization measures: • SmPC Section 4.4 where advice on monitoring serum calcium levels in patients with a history of CHF is included • SmPC Section 4.8 • PL Section 2 where advice for patients to tell their doctor if they have a history of heart problems such as heart failure or experience heart failure while receiving etelcalcetide is included • PL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
QT prolongation secondary to hypocalcemia	Routine risk minimization measures: • SmPC Section 4.4 where advice on monitoring serum calcium levels in patients with a history of conditions that predispose to QT prolongation is included • SmPC Section 4.8 • PL Section 2 where advice for patients to tell their doctor if they have a history of heart problems, such as arrhythmias, or experience an unusually fast or pounding heartbeat or have heart rhythm problems while receiving etelcalcetide is included • PL Section 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

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Footnotes, including abbreviations, are defined on the last page of the table.

Table 20. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Potential Risks		
Ventricular arrhythmias	Routine risk minimization measures: • SmPC Section 4.4 where advice on monitoring serum calcium levels in patients with a history of conditions that predispose to ventricular arrhythmia is included • PL Section 2 where advice for patients to tell their doctor if they have a history of heart problems, such as arrhythmias, or experience an unusually fast or pounding heartbeat or have heart rhythm problems while receiving etelcalcetide is included Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Fractures	Routine risk minimization measures: • SmPC Section 4.4 where advice that if PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or etelcalcetide should be reduced or therapy discontinued is included • PL Section 1 • PL Section 2 where advice on monitoring PTH levels and reducing the dose of etelcalcetide if PTH levels become very low is included Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Missing information		
Use in pregnancy and lactation	Routine risk minimization measures: • SmPC Sections 4.6 and 5.3 • PL Section 2 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

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PL = Package Leaflet; PTH = parathyroid hormone; SmPC = Summary of Product Characteristics

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the RMP for etelcalcetide is presented below.

Summary of Risk Management Plan for Parsabiv® (Etelcalcetide)

This is a summary of the risk management plan (RMP) for Parsabiv. The RMP details important risks of Parsabiv, how these risks can be minimized, and how more information will be obtained about Parsabiv's risks and uncertainties (missing information).

Parsabiv's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Parsabiv should be used.

This summary of the RMP for Parsabiv should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Parsabiv's RMP.

I. The Medicine and What it is Used for

Parsabiv is authorized for the treatment of secondary hyperparathyroidism in adult patients with chronic kidney disease on hemodialysis therapy (see SmPC for the full indication). It contains etelcalcetide as the active substance and it is given by intravenous injection.

Further information about the evaluation of Parsabiv's benefits can be found in Parsabiv's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/Parsabiv.

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of Parsabiv, together with measures to minimize such risks and the proposed studies for learning more about Parsabiv's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the public (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Parsabiv is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Parsabiv are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Parsabiv. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Hypocalcemia Worsening heart failure QT prolongation secondary to hypocalcemia
Important potential risks	Ventricular arrhythmias Fractures
Missing information	Use in pregnancy and lactation

II.B. Summary of Important Risks

Important identified risk: Hypocalcemia	
Evidence for linking the risk to the medicine	This risk was identified in the clinical study setting; both asymptomatic and symptomatic events of low calcium (hypocalcemia) were reported more frequently in etelcalcetide-treated subjects compared with placebo-treated subjects in the phase 3 placebo controlled studies. Additionally, other products in the same pharmacological class have shown an increased incidence of hypocalcemia.
Risk factors and risk groups	Patients with chronic kidney disease who have low serum calcium due to concurrent medical conditions such as hyperphosphatemia, vitamin D deficiency, acute pancreatitis, calcitonin-producing tumors, low serum magnesium or who are treated with medications that lower the serum calcium.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 where advice on serum calcium level and administration of etelcalcetide, and monitoring of serum calcium is included • SmPC Section 4.4 where advice on serum calcium level and administration of etelcalcetide, seeking medical attention for symptoms of hypocalcemia, and monitoring of serum calcium is included • SmPC Section 4.9 where advice on monitoring serum calcium and symptoms of hypocalcemia in the event of etelcalcetide overdose is included • SmPC Sections 4.3, 4.5, 4.7, 4.8, 5.1, and 5.3 • PL Section 2 where advice on monitoring blood calcium levels and for patients to tell their doctor if they have symptoms of low calcium levels is included • PL Section 4 where advice for patients to tell their doctor if they have symptoms of low calcium levels is included Additional risk minimization measures: • None

Important identified risk: Worsening heart failure	
Evidence for linking the risk to the medicine	This risk was originally identified from postmarketing data with another calcimimetic therapy. Thus, it was investigated in clinical trials for etelcalcetide. Some numerical differences were noted in the subject incidence of adjudicated congestive heart failure requiring hospitalization in the clinical trial setting. The subject incidence of cardiac failure (Standardized Medical Dictionary for Regulatory Activities [MedDRA] Query) in the etelcalcetide treatment group of Study 20120360 (3.0%) was similar to that reported in the etelcalcetide treatment groups of the placebo-controlled studies (3.2%).
Risk factors and risk groups	Pre-existing cardiomyopathy or congestive heart failure, coronary artery disease, hypertension, and valvular heart disease appear to be risk factors for the development of heart failure (Kenchaiah et al, *Med Clin North Am*, 2004;88(5):1145-1172; Levy et al, *JAMA*, 1996;275(20):1557-1562).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where advice on monitoring serum calcium levels in patients with a history of congestive heart failure is included • SmPC Section 4.8 • PL Section 2 where advice for patients to tell their doctor if they have a history of heart problems such as heart failure or experience heart failure while receiving etelcalcetide is included • PL Section 4 Additional risk minimization measures: • None

Important identified risk: QT prolongation secondary to hypocalcemia	
Evidence for linking the risk to the medicine	This risk was identified in the nonclinical setting on the basis of the pharmacologic action of etelcalcetide to lower serum calcium. Nonclinical studies in the dog indicate that etelcalcetide causes QT prolongation in association with maximal decreases in serum calcium, but not in association with maximal plasma drug levels, suggesting that etelcalcetide does not directly affect cardiac repolarization. Administration of etelcalcetide is associated with corrected QT interval prolongation secondary to reductions in serum calcium in both etelcalcetide nonclinical and clinical studies.
Risk factors and risk groups	Subjects with a congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT prolongation and ventricular arrhythmia.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where advice on monitoring serum calcium levels in patients with a history of conditions that predispose to QT prolongation is included • SmPC Section 4.8 • PL Section 2 where advice for patients to tell their doctor if they have a history of heart problems, such as arrhythmias, or experience an unusually fast or pounding heartbeat or have heart rhythm problems while receiving etelcalcetide is included • PL Section 4 Additional risk minimization measures: • None

Important potential risk: Ventricular arrhythmias	
Evidence for linking the risk to the medicine	Data to evaluate this safety concern derives from the nonclinical setting on the basis of the pharmacological action of etelcalcetide to lower serum calcium.
Risk factors and risk groups	Subjects with a congenital long QT syndrome, previous history of QT prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT prolongation and ventricular arrhythmia.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where advice on monitoring serum calcium levels in patients with a history of conditions that predispose to ventricular arrhythmia is included • PL Section 2 where advice for patients to tell their doctor if they have a history of heart problems, such as arrhythmias, or experience an unusually fast or pounding heartbeat or have heart rhythm problems while receiving etelcalcetide is included Additional risk minimization measures: • None

Important potential risk: Fractures	
Evidence for linking the risk to the medicine	Data to evaluate this safety concern derives from the documented association in the literature between oversuppression of parathyroid hormone and adynamic bone.
Risk factors and risk groups	Older age, women, prior kidney transplant, low serum albumin, selective serotonin reuptake inhibitors, combination narcotic medications, and parathyroid hormone > 900 pg/mL (versus parathyroid hormone 150 to 300 pg/mL) were associated with an increased risk of new fractures (Jadoul et al, *Kidney Int*, 2006:70;1358-1366). In a study of the elderly (≥ 75 years of age in the United Kingdom), an estimated glomerular filtration rate < 45 mL/min/1.73 m^2 was associated with an almost 2-fold increase in hip-fracture-related mortality (Nitsch et al, *Nephrol Dial Transplant*, 2009;24(5):1539-1544). Risks for hip and vertebral fracture had a U-shaped relationship with parathyroid hormone concentration, with the lowest risk observed with a parathyroid hormone concentration of approximately 300 pg/mL.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 where advice that if parathyroid hormone levels decrease below the recommended target range, the dose of vitamin D sterols and/or etelcalcetide should be reduced or therapy discontinued is included • PL Section 1 • PL Section 2 where advice on monitoring parathyroid hormone levels and reducing the dose of etelcalcetide if parathyroid hormone levels become very low is included Additional risk minimization measures: • None

Missing information: Use in pregnancy and lactation	
Risk minimization measures	Routine risk minimization measures: • SmPC Sections 4.6 and 5.3 • PL Section 2 Additional risk minimization measures: • None

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Parsabiv.

II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for Parsabiv.

PART VII: ANNEXES

Table of Contents

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

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AMGEN®

ETELCALCETIDE HYPOCALCEMIA QUESTIONNAIRE

AER #

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Do not provide any information by or through which a patient can be identified, other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

1. PATIENT INFORMATION (all dates dd/mm/yyyy)

Patient Initials (Confidential)

Age at Time of Event or Date of Birth:

Gender: ☐ Male ☐ Female

Weight: _____lb _____kg

Date of Event Onset

Date Event Resolved

Date of this Report

Hospitalization Admit Date

Hospitalization Discharge Date

Relationship to Product: Is there a reasonable possibility that this event may have been caused by etelcalcetide? ☐ Yes ☐ No

Action taken: ☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug withdrawn ☐ Drug rechallenge

Outcome: ☐ Resolved ☐ Resolved w/ sequelae ☐ Resolving ☐ Event ongoing ☐ Died of event

2. MEDICATION ADMINISTERED (all dates dd/mm/yyyy)

Etelcalcetide Information
(include dosing changes/titration)

Dose	Frequency	Route	Start Date	Stop Date
Dose	Frequency	Route	Start Date	Stop Date

Indication (check all that apply)

☐ SHPT on dialysis

☐ Other (please specify): _____

Co-suspect Medications: _____

PLEASE BE SURE TO COMPLETE THE ENTIRE POSTMARKET ADVERSE EVENT (PMAE) FORM AND QUESTIONNAIRE

3. SIGNS AND SYMPTOMS (Check all that apply)

☐ Arrhythmia

Date (dd/mm/yyyy): _____ Specify type: _____ QTc interval (msec): _____

Baseline EKG findings prior to hypocalcemia related arrhythmia (including dd/mm/yyyy): _____

If abnormal, please specify / include QTc values: _____

☐ Convulsion
If yes, type: _____

☐ Hypotension
If yes, BP: _____

☐ Paraesthesia
If yes, specify locations: _____

☐ Heart failure
☐ Laryngospasm
☐ Syncope
☐ Muscle cramping

☐ Muscle twitching
☐ Tetany
☐ Other _____

4. EVALUATIONS, DIAGNOSIS & LABORATORY MEASURES (Please attach copy of report)

AT TIME OF HYPOCALCEMIA EVENT:

Diagnostic	Value	Units	Date	Unknown	Report Attached Y	Report Attached N
Serum Calcium ☐ Corrected ☐ Ionized ☐ Total						
Phosphorus						
Magnesium						
Potassium						
Albumin						
Serum Bicarbonate						
pH						
Other _____						

MOST RECENT SERUM CALCIUM AND ALBUMIN PRIOR TO HYPOCALCEMIA EVENT:

Diagnostic	Value	Units	Date	Unknown	Report Attached Y	Report Attached N
Serum Calcium ☐ Corrected ☐ Ionized ☐ Total						
Albumin						

Amgen
Office Fax:

REPORTER

Name:

Address:

City:

State/ Province:

Country:

Postal Code:

Email:

Phone: (include country code)

Signature _____

Title _____ Date _____

CONTINUED ON NEXT PAGE

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ETELCALCETIDE HYPOCALCEMIA QUESTIONNARE (continued)

AER #

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Do not provide any information by or through which a patient can be identified, other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

1. PATIENT INFORMATION (all dates dd/mm/yyyy should match page 1)

Patient Initials (Confidential)

Age at Time of Event or Date of Birth:

Gender: ☐ Male ☐ Female

Weight: _____lb _____kg

Date of Event Onset

Date Event Resolved

Date of this Report

Hospitalization Admit Date

Hospitalization Discharge Date

5. RISK FACTORS (Check all that apply, provide dates and attach available reports)

☐ History of hypoparathyroidism
☐ History of chronic renal failure
☐ Hyperphosphatemia
☐ Vitamin D deficiency
☐ Other: _____

☐ Hypoproteinemia
☐ Magnesium deficiency/hypomagnesemia
☐ Sepsis
☐ Acute pancreatitis

☐ Recent surgery (specify): _____

6. MEDICATION HISTORY (Check all that apply, provide dates as dd/mm/yyyy and attach available reports)

☐ Prior cinacalcet use: ☐ Yes ☐ No If yes, please list start date: _____ stop date: _____

Please indicate if patient was on any of the following medications at time of hypocalcemia event

☐ Nutritional vitamin D supplement ☐ Yes ☐ No
If yes, Brand/Generic name _____ Dose / Units _____ Start date _____ Stop date _____ This is a suspect drug ☐ Yes ☐ No

☐ Active vitamin D supplement ☐ Yes ☐ No
If yes, Brand/Generic name _____ Dose / Units _____ Start date _____ Stop date _____ This is a suspect drug ☐ Yes ☐ No

☐ Calcium supplement ☐ Yes ☐ No
If yes, Brand/Generic name _____ Dose / Units _____ Start date _____ Stop date _____ This is a suspect drug ☐ Yes ☐ No

☐ Calcium containing phosphate binder ☐ Yes ☐ No
If yes, Brand/Generic name _____ Dose / Units _____ Start date _____ Stop date _____ This is a suspect drug ☐ Yes ☐ No

☐ Citrate containing anticoagulation ☐ Yes ☐ No
If yes, Brand/Generic name _____ Dose / Units _____ Start date _____ Stop date _____ This is a suspect drug ☐ Yes ☐ No

☐ Patient received other drugs or treatments which are known to cause hypocalcemia ☐ Yes ☐ No

If yes, Brand/Generic name _____ Dose / Units _____ Route _____ Start date _____ Stop date _____ This is a suspect drug ☐ Yes ☐ No

If yes, Brand/Generic name _____ Dose / Units _____ Route _____ Start date _____ Stop date _____ This is a suspect drug ☐ Yes ☐ No

7. TREATMENT OF HYPOCALCEMIA (Check all that apply, provide dates as dd/mm/yyyy and attach available reports)

☐ Treatment medication for hypocalcemia (starting or increasing calcium supplements, vitamin D sterols, increased dialysate calcium concentration, anti-arrhythmic medications, anti-arrhythmic medications, anti-convulsants, etc.)

If yes, Brand/Generic name _____ Dose / Units _____ Route _____ Frequency _____ Start date _____ Stop date _____

If yes, Brand/Generic name _____ Dose / Units _____ Route _____ Frequency _____ Start date _____ Stop date _____

☐ Other symptomatic treatment _____

☐ Additional information (ie. icu admission, hospitalization) _____

REPORTER Name:

Address:

City:

City:

Country:

Email:

State/Province:

Postal Code:

Phone: (include country code)

Amgen
Office Fax:

Signature _____

Title _____ Date _____

CONTINUED FROM PREVIOUS PAGE (page 2 of 2)

Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)

Not applicable.