AMG 416 (velcalcetide) is a novel peptide for the treatment of secondary hyperparathyroidism in a single-dose study in hemodialysis patients

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AMG 416 (velcalcetide), a novel peptide agonist of the calcium-sensing receptor, lowers plasma parathyroid hormone in preclinical uremic animal models and in normal healthy individuals. Here, we studied its efficacy in hemodialysis patients suffering from secondary hyperparathyroidism. Major inclusion criteria were hemodialysis for at least 3 months, serum parathyroid hormone over 300 pg/ml, a corrected serum calcium of 9.0 mg/dl or more, and stable doses of vitamin D analogs for at least 3 weeks prior to screening. Twenty-eight patients were enrolled in one of five cohorts (5, 10, 20, 40, 60 mg). Cohorts 1–3 (four patients each) were treated in a two-period crossover design, while cohorts 4 and 5 (eight patients each) were randomized 1:1 to AMG 416 or placebo. Patients were admitted to a clinical research unit following hemodialysis and studied for 3 days prior to discharge for hemodialysis. Single intravenous doses of AMG 416 from 5 to 60 mg were well tolerated, and plasma levels increased in a dose-related manner. AMG 416 treatment was associated with significant, dose-dependent reductions in serum parathyroid hormone and fibroblast growth factor 23. Compared with placebo, all dose groups of 10 mg or more were associated with attenuation in the rise in serum phosphate during the interdialytic period. Dose-dependent reductions in serum calcium were observed and were well tolerated. Thus, AMG 416 represents a novel therapeutic approach for the treatment of secondary hyperparathyroidism in hemodialysis patients.

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Secondary hyperparathyroidism (SHPT) is a complex disorder associated with chronic kidney disease (CKD) in which the impairment of mineral homeostasis (calcium and phosphate) and vitamin D ($1,25(OH)_2D_3$) metabolism leads to excessive parathyroid hormone (PTH) levels. These changes begin early in CKD and gradually worsen as CKD progresses to end-stage renal disease.[1] Elevated PTH levels further exacerbate the disturbances in mineral metabolism and are linked to a variety of deleterious physiological effects including bone remodeling disorders, vascular calcification, and left ventricular hypertrophy. Increased levels of PTH, calcium, and phosphate are associated with an increased risk for cardiovascular events, hospitalization, all-cause and cardiovascular mortality.[2–9] The importance of the appropriate management of SHPT and the associated mineral disturbances is underscored by the various clinical practice guidelines used to manage this disorder.[10–14]

Treatment of SHPT in dialysis patients is complex and has relied on several approaches, including normalization of serum calcium, control of hyperphosphatemia, and treatment with nutritional and active vitamin D.[1,3] Dietary phosphorus restriction and oral phosphate binders are typically prescribed to reduce serum phosphate levels; however, they do not consistently normalize serum phosphate. Exogenously administered vitamin D analogs can decrease PTH gene transcription as well as increase calcium (and phosphate) absorption from the gut, thereby decreasing PTH synthesis and secretion.[15,16] However, vitamin D use is often limited by the development of hypercalcemia and hyperphosphatemia, leaving many patients with elevated PTH levels and poorly controlled calcium and phosphorus. PTH secretion by the parathyroid gland is primarily controlled by the action of a cell-surface calcium-sensing receptor (CaSR) residing on parathyroid chief cells.[17,18] Activation of the CaSR by calcium or by calcimimetics reduces PTH secretion from the parathyroid gland, lowering serum intact PTH (iPTH). Thus, with the introduction of the calcimimetic, cinacalcet hydrochloride, in 2004, a more direct approach to control PTH in SHPT became available. Treatment with cinacalcet, an

Table 1 | Demographics and baseline chemistries

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Total $N = 28$
Age (years)						
N	4	4	4	8	8	28
Mean (s.d.)	54.3 (10.4)	59.0 (14.5)	52.8 (21.2)	52.9 (14.6)	47.5 (10.9)	52.4 (13.6)
Median (range)	56 (40-65)	60.5 (40–75)	46.5 (35–83)	53.5 (28–78)	49.0 (28-60)	53.0 (28–83)
Sex (n, %)						
Male	3 (75)	4 (100)	3 (75)	4 (50)	6 (75)	20 (71)
Female	1 (25)	0	1 (25)	4 (50)	2 (25)	8 (29)
Race (n, %)						
White	1 (25)	0	1 (25)	0	1 (13)	3 (11)
African American	2 (50)	4 (100)	3 (75)	8 (100)	7 (88)	24 (86)
Asian	1 (25)	0	0	0	0	1 (4)
Duration of hemodialysis (years)						
N	4	4	4	8	8	28
Mean (s.d.)	7.76 (6.48)	7.15 (4.51)	9.43 (3.96)	5.45 (6.72)	4.59 (2.57)	6.35 (5.01)
Median (range)	5.36 (3.1–17.2)	6.48 (2.7–12.9)	11.31 (3.5–11.6)	3.35 (0.7–21.8)	4.02 (0.9–8.9)	4.35 (0.7–21.8)
Active vitamin D use (n, %)						
Yes	4 (100)	2 (50)	3 (75)	8 (100)	6 (75)	23 (82)
No	0	2 (50)	1 (25)	0	2 (75)	5 (18)
iPTH (pg/ml)						
Mean (s.d.)	449.8 (96.4)	632.0 (254.8)	1609.8 (1577.4)	910.8 (934.7)	820.9 (213.1)	879.3 (799.8)
Median (range)	419.7 (373.5–586.5)	562.7 (420.0–982.5)	880.2 (711.5–3967.5)	645.2 (315.5–3179.5)	830.7 (496.5–1116.5)	704.5 (315.5–3967.5)
Ionized calcium (mmol/l)						
Mean (s.d.)	1.08 (0.02)	1.10 (0.05)	1.13 (0.09)	1.04 (0.05)	1.01 (0.05)	1.06 (0.06)
Median (range)	1.07 (1.1–1.1)	1.11 (1.0–1.1)	1.13 (1.0–1.2)	1.03 (1.0–1.1)	1.01 (0.9–1.1)	1.04 (0.9–1.2)
Corrected calcium (mg/dl)						
Mean (s.d.)	9.45 (0.5)	10.0 (0.14)	10.5 (0.89)	9.45 (0.4)	9.46 (0.77)	9.68 (0.68)
Median (range)	9.5 (8.8–10.0)	10.05 (9.8–10.1)	10.2 (9.8–11.8)	9.4 (8.8–10.0)	9.35 (8.5–10.9)	9.8 (8.5–11.8)
Phosphate (mg/dl)						
Mean (s.d.)	3.15 (0.26)	3.28 (1.37)	3.92 (0.66)	3.02 (0.84)	3.74 (0.65)	3.41 (0.83)
Median (range)	3.07 (2.9–3.5)	3.01 (2.0–5.1)	3.76 (3.3–4.8)	3.07 (1.8–4.1)	3.76 (2.5–4.8)	3.5 (1.8–5.1)
Log FGF23						
Mean (s.d.)	8.87 (1.86)	7.43 (2.09)	9.14 (2.37)	9.29 (2.20)	9.02 (0.74)	9.65 (0.77)
Median (range)	9.27 (5.16–11.85)	6.87 (5.76–10.21)	10.08 (6.45–10.89)	10.16 (6.06–10.79)	8.94 (8.21–10.00)	9.89 (8.55–10.27)

Abbreviations: FGF23, fibroblast growth factor 23; iPTH, intact parathyroid hormone.
Subjects in cohort 1 received 5 mg AMG 416 and placebo in a crossover design.
Subjects in cohort 2 received 10 mg AMG 416 and placebo in a crossover design.
Subjects in cohort 3 received 20 mg AMG 416 and placebo in a crossover design.
In cohort 4, four subjects received 40 mg AMG 416 and four subjects received placebo.
In cohort 5, four subjects received 60 mg AMG 416 and four subjects received placebo.

allosteric agonist of the CaSR, results in an immediate left shift in the calcium–PTH curve. It has been demonstrated in numerous clinical trials that cinacalcet reduces PTH levels, while simultaneously reducing serum calcium and phosphate.[19]

AMG 416 is a novel, long-acting 8-amino-acid peptide agonist of the CaSR.[20,21] AMG 416 directly activates the CaSR with activity in the presence or absence of ambient serum calcium, a mechanism of action distinct from that of cinacalcet hydrochloride. Intravenous administration of AMG 416 to uremic animals reduced serum PTH and attenuated parathyroid hyperplasia and soft tissue calcification in a dose-dependent manner.[20,21] Furthermore, intravenous administration of AMG 416 to healthy male subjects was shown to be safe, well tolerated, and to reduce serum iPTH in a dose-dependent manner.[22] Similarly, AMG 416 reduced serum fibroblast growth factor 23 (FGF23) levels, a phosphaturic hormone, in a dose-dependent manner in healthy male subjects. FGF23, acting via the Klotho-FGF receptor 1,[23,24] is important in the bone–kidney axis controlling phosphorus homeostasis and vitamin D metabolism but more recently appears to have a role in the pathogenesis of SHPT and left ventricular hypertrophy.[25–27]

The present study was conducted, therefore, to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of escalating single doses of AMG 416 administered by intravenous (IV) bolus injection to hemodialysis subjects with SHPT.

RESULTS

Twenty-eight male and female subjects were randomized into five dose cohorts. Dose escalation was stopped when the maximum dose, 60 mg, was reached. Demographics and baseline blood chemistries (obtained post-dialysis and within 30 min before dosing) varied across cohorts consistent with the small sample size (Table 1). Baseline serum phosphate levels ranged from 1.8 to 5.1 mg/dl (mean 3.41 mg/dl), reflecting phosphate clearance during hemodialysis. To control for the variability in baseline chemistry levels and