The Calcimimetic AMG 073 as a Potential Treatment for Secondary Hyperparathyroidism of End-Stage Renal Disease

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Abstract. Current treatment of secondary hyperparathyroidism in chronic kidney failure with calcium and active vitamin D is potentially limited by hypercalcemia and hyperphosphatemia. AMG 073 represents a new class of compounds for the treatment of hyperparathyroidism known as calcimimetics, which reduce parathyroid hormone (PTH) synthesis and secretion by increasing the sensitivity of the parathyroid calcium-sensing receptor (CaR) to extracellular calcium. The current study evaluates the efficacy and safety of AMG 073 when added to conventional treatment of secondary hyperparathyroidism in end-stage renal disease (ESRD). Seventy-one hemodialysis patients with uncontrolled secondary hyperparathyroidism, despite standard therapy with calcium, phosphate binders, and active vitamin D sterols, were treated in this 18-wk, dose-titration study with single daily oral doses of AMG 073/placebo up to 100 mg. Changes in plasma PTH, serum calcium, serum phosphorus, and calcium × phosphorus levels were compared between AMG 073 and placebo groups. Mean PTH decreased by 33% in the AMG 073 patients compared with an increase of 3% in placebo patients ($P = 0.001$). A significantly greater proportion of AMG 073 patients (44%) had a mean PTH ≤ 250 pg/ml compared with placebo patients (20%; $P = 0.029$). Also, a significantly greater proportion of AMG 073 patients (53%) had a decrease in PTH ≥30% compared with placebo patients (23%; $P = 0.009$). Calcium × phosphorus levels decreased by 7.9% in AMG 073 patients compared with an increase of 11.3% in placebo patients ($P = 0.013$). Adverse event rates were low and mostly mild to moderate in severity; however, the incidence of vomiting was higher in AMG 073 patients. In this study, the calcimimetic AMG 073 at doses up to 100 mg for 18 wk provided a safe and effective means to attain significant reductions in PTH and calcium × phosphorus levels in ESRD patients. AMG 073 represents a novel and promising therapy to improve the management of secondary hyperparathyroidism.

The current standard treatment for secondary hyperparathyroidism in ESRD uses calcium supplementation, phosphate binders, and active vitamin D sterols in various combinations to attempt correction of hypocalcemia, hyperphosphatemia, and 1,25 $(OH)_2$ vitamin D_3 deficiency (1,2). Each component of this combined treatment strategy addresses abnormalities responsible for the pathogenesis of hyperparathyroidism, but each has limitations due to potential undesirable side effects at doses required to effectively suppress PTH hypersecretion (3–6). In this regard, treatment with vitamin D sterols is often complicated by hypercalcemia and hyperphosphatemia (7–10), resulting in elevate calcium × phosphorus levels, predisposition to soft tissue calcification, and increased mortality risk in the ESRD population (11–15). Large doses of orally administered calcium to control hyperphosphatemia also predispose patients to episodes of hypercalcemia, chronic positive calcium balance, and increased soft tissue calcification in dialysis patients (15,16). Treatment with calcium and vitamin D sterols may also be associated with development of adynamic bone disease (10). Finally, severe hyperparathyroidism can be refractory to this treatment regimen (17). Consequently, an unmet medical need exists for a therapeutic agent that can control PTH without raising serum calcium and/or phosphorus concentrations.

AMG 073 represents a new class of compounds known as calcimimetics that act on the parathyroid calcium-sensing receptor to increase its sensitivity to extracellular calcium (18,19). AMG 073 has potential advantages as a therapy for secondary hyperparathyroidism because it mimics the effects of extracellular calcium to suppress PTH secretion, even in the presence of hyperphosphatemia (4), without the risk of causing hypercalcemia and/or hyperphosphatemia. More importantly, pre-clinical studies indicate that calcimimetics rapidly inhibit PTH release from parathyroid cells both *in vitro* and *in vivo*

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and prevent the development of parathyroid cell hyperplasia *in vivo* without the risk of positive calcium balance induced by high-dose calcium therapy (18,19,20–23). Current clinical trials, however, are restricted to short-term studies using limited doses of AMG 073 (24–26).

In the present study, we evaluated the efficacy and safety of single, daily doses of AMG 073 up to 100 mg in treating secondary hyperparathyroidism over an 18-wk period. The addition of a calcimimetic to standard treatment caused a dose-dependent reduction in PTH and calcium × phosphorus concentrations in patients on chronic maintenance hemodialysis with secondary hyperparathyroidism.

Materials and Methods

Patients

This study enrolled 71 patients from 17 centers in the United States who signed Institutional Review Board-approved informed consents to participate in the study. Patients were treated for at least 3 mo with hemodialysis and had uncontrolled secondary hyperparathyroidism (mean PTH ≥300 pg/ml, despite availability of standard care [phosphate binders and/or vitamin D sterols]). Patients were eligible if they met certain criteria, which included the following: age ≥ 18 yr; serum calcium ≥ 8.8 mg/dl and < 11.0 mg/dl; serum phosphorus ≥ 2.5 mg/dl; and calcium × phosphorus < 70 $(mg/dl)^2$. Patients receiving vitamin D sterols must have been on a stable dose for at least 21 d before enrollment. Dialysis calcium concentration, the dose of any supplements, and the dose of oral phosphate binders must not have been changed during the 7 d before enrollment. Patients were required to be medically stable with no evidence of an active infectious or malignant process or diseases known to cause hypercalcemia. Patients were also required to have a hemoglobin concentration > 9.0 g/dl or a hematocrit > 27% as well as liver transaminases and bilirubin concentrations no more than twice the upper limit of normal.

Study Design

This was a placebo-controlled, double-blind, randomized study consisting of two phases: a 12-wk dose-titration phase, during which four possible doses were evaluated sequentially (25, 50, 75, and 100 mg AMG 073 or placebo); and a maintenance phase, in which the final dose from the end of the dose-titration phase was maintained for 6 wk (Figure 1). Patients were randomized by the interactive voice response system (IVRS) at a 1:1 ratio to AMG 073 or placebo. No stratification factors were applied to the randomization. All patients received two tablets of study medication once daily, regardless of dose level and whether they were assigned to the AMG 073 or placebo group. AMG 073 and placebo tablets were manufactured for Amgen and were identical in appearance to maintain the double-blind status of the study. Study drug was administered immediately before dialysis and at approximately the same time of day each day. Compliance with study drug was assessed using patient dosing diaries and returned medication blister cards.

All patients began the study on 25 mg of AMG 073 or placebo. Sequential dose increases in either AMG 073 or placebo were managed by the IVRS, based on input of central laboratory PTH and serum calcium values and safety information by a site representative. Dose increases were permitted at week 3, 6, and 9 of the study, based on the mean PTH of the two previous study weeks. The dose of AMG 073 or placebo was increased until patients had achieved both a reduction in PTH of ≥ 30% from baseline and an absolute PTH ≤ 250 pg/ml. These dose increases were permitted provided the serum calcium was ≥ 7.8 mg/dl, the patient was not receiving the 100 mg/d dose of AMG 073 or placebo, and the patient was not experiencing an adverse event that would preclude a dose increase. Dose reductions occurred if the mean PTH was < 100 pg/ml.

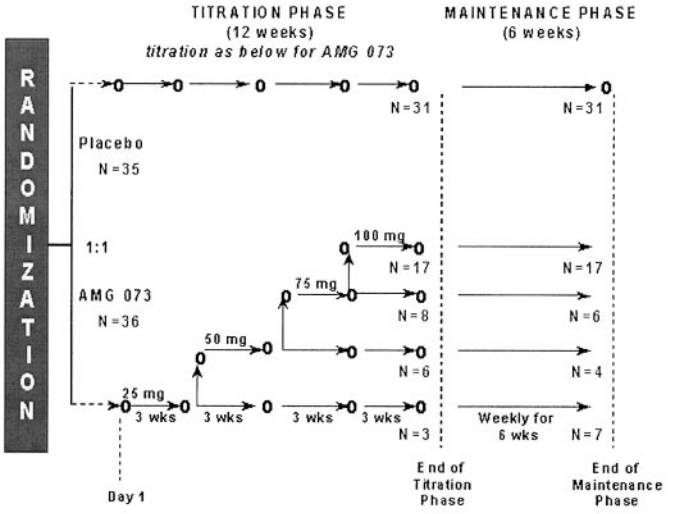

Figure 1. Schematic representation of the study design. Patients were treated with escalating does of AMG 073 over a 12-wk period and then maintained on treatment for an additional 6 wk as described in Materials and Methods. *n* = number of patients at each dose level at the end of the titration and maintenance phases.

In the 30 d before the first dose of study drug, three measurements of PTH, serum calcium, and serum phosphorus were obtained at least 2 d apart to calculate the baseline PTH, serum calcium, serum phosphorus, and calcium × phosphorus level. On study, biochemical assessments were made at weekly visits throughout the study to determine the effect of AMG 073 on PTH, serum calcium, phosphorus, and calcium × phosphorus levels. These assessments were made immediately before administering the daily dose of study medication (24 h after the dose on the preceding day). In addition, at week 18 of the study, patients remained at the dialysis unit after their dose of study drug to have PTH and serum calcium assessments collected at 2, 4, and 8 h post-dose to examine the pharmacodynamic effects of AMG 073 or placebo immediately after dosing. Safety information was collected from physical exams, electrocardiograms, safety chemistry and hematology laboratory assessments, and patient-reported symptoms and hospitalizations.

Concomitant Medication

Patients were allowed to continue receiving vitamin D sterols during this study if they were prescribed; therefore, guidance was provided for changes in the dose of vitamin D. These guidelines were established to preserve patient safety while allowing the efficacy of AMG 073 in reducing PTH concentrations to be distinguished from that of vitamin D. Decreases in vitamin D doses or discontinuations of vitamin D sterols were allowed if the serum calcium was ≥ 11.0 mg/dl, serum phosphorus was ≥ 6.5 mg/dl, calcium × phosphorus was ≥ 70 $(mg/dl)^2$, or PTH was < 100 pg/ml on the lowest dose of study drug. Increases in vitamin D doses or initiations of vitamin D sterols were allowed if the PTH was ≥ 50% of baseline and the PTH was > 600 pg/ml or if the serum calcium was < 8.4 mg/dl.

Patients were also permitted to continue to receive phosphate-binding agents and participate in this study. All brands of phosphate-

binding agents were permitted. Phosphate binder dose and brand could be changed as needed after enrollment. In addition, dialysate calcium concentration could also be changed as needed after enrollment.

Biochemical Determinations

All chemistries and PTH determinations were performed at a central laboratory (Covance Laboratory Services, Inc, Indianapolis, IN). Biochemical determinations at the central laboratory of calcium and phosphorus levels were performed using standard methodology. Plasma PTH concentrations at the central laboratory were determined using a double-antibody immunoradiometric assay for the intact hormone (Nichols Institute Diagnostics, San Juan Capistrano, CA). Serum calcium was reported as corrected values for patients with a serum albumin below 4.0 g/dl according to the following equation:

corrected serum calcium = 0.8 × (4.0 − serum albumin) + uncorrected serum calcium

Statistical Analyses

The study enrolled 71 patients. This sample size allowed an 84% power to show a 33% difference between treatment groups in the proportion of patients who could achieve a mean reduction in PTH of ≥30% during the maintenance phase of the study. The study was not powered for the secondary endpoints.

The intention-to-treat data set (ITT) was used to analyze all endpoints. The efficacy analyses were based on data collected during the 6-wk maintenance phase. Data are presented as the mean ± standard error (SE). Mean percent changes from baseline for PTH, serum calcium, serum phosphorus, and calcium × phosphorus were calculated using the six weekly maintenance phase values, compared with the mean of the three baseline values. The mean percent change from baseline for PTH, serum calcium, phosphorus, and calcium × phosphorus were among between treatment groups using an ANOVA model. Although this was a multicenter study, center effect was not examined in the analysis due to the small number of patients enrolled at each center. The safety of AMG 073 was assessed by review of adverse events and changes in laboratory parameters.

Results

Baseline Characteristics

The AMG 073 and placebo-treated groups did not differ with regard to age, race, or duration of hemodialysis (Table 1). There were fewer females in the AMG 073 group. This gender difference did not affect the analysis of efficacy in this study. In accordance with the intention to recruit patients with circulating PTH levels ≥300 pg/ml, mean (SE) baseline PTH was 626 ± 53 pg/ml in the AMG 073 group and 583 ± 72 pg/ml in the placebo group, which represents moderately severe hyperparathyroidism (Table 2). Consistent with the selection of patients receiving standard care for secondary hyperparathyroidism at the time of enrollment, serum calcium concentrations were in the normal range in both groups, serum phosphorus was slightly elevated, and mean calcium × phosphorus levels at baseline were < 70 $(mg/dl)^2$ (Table 2). There were no significant differences between treatment groups in baseline laboratory values for PTH, serum calcium, phosphorus, and calcium × phosphorus levels.

By design, patients enrolled in the study were receiving treatment for secondary hyperparathyroidism according to the standard of care at the participating centers. Therefore, 61% of AMG 073 patients and 69% of placebo patients were receiving vitamin D sterols at the start of the study (Tables 1 and 3). In addition, 100% of AMG 073 patients and 94% of placebo patients were receiving phosphate binders at the start of the study (Tables 1 and 3). The dose of vitamin D sterols and phosphate binders were not different between the AMG 073 and placebo groups at baseline (Table 3), although almost twice as many AMG 073 patients were prescribed sevelamer hydrochloride (14 AMG 073 patients *versus* 8 placebo patients). Sevelamer hydrochloride was used as a phosphate binder in 40% of patients in the AMG 073 group and 20% in the placebo group (Table 3). The prescribed dose of calcium averaged slightly less than 2 g of elemental calcium per day in both groups at baseline. Doses of elemental calcium from calcium-containing phosphate binders are reported as mg/d in Table 3.

Table 1. Baseline demographics

	AMG 073 $n = 36$	Placebo $n = 35$
Gender		
female[a]	9 (25%)	18 (51%)
male	27 (75%)	17 (49%)
Race		
African American	27 (75%)	23 (66%)
White	9 (25%)	11 (31%)
Hispanic	0 (0%)	1 (3%)
Age (yr)		
mean	49.6	47.9
SD	8.5	14.2
Duration of dialysis (mo)		
mean	71.3	71.1
SD	54.3	66.2
range	6 to 205	4 to 283
Vitamin D sterol use at baseline (proportion of patients receiving)	22 (61%)	24 (69%)
Phosphate binder use at baseline (proportion of patients receiving)	36 (100%)	33 (94%)

[a] Significant difference between AMG 073 and placebo in the number of females per treatment group ($P = 0.022$).

AMG 073 Dose Levels

The starting dose of AMG 073 was 25 mg/d and could be increased to a maximum dose of 100 mg/d. Two AMG 073 (both at the 25-mg dose) and four placebo patients withdrew from the study during the dose-titration phase. No patients withdrew from study during the maintenance phase. Of the patients completing the titration phase (34 patients), 50% reached and sustained the 100 mg/d maximum dose. Intermediate daily doses of 75 and 50 mg were reached in 41% of the patients, whereas 9% of the patients did not escalate above the initial dose. During the maintenance phase, dose reduction

Table 2. PTH, serum calcium, serum phosphorus, and Ca × P at baseline and during the maintenance phase

	AMG 073		Placebo	
	Mean (SE)	*n*	Mean (SE)	*n*
PTH (pg/ml)				
baseline	626 ± 53	36	583 ± 72	35
maintenance phase	451 ± 74	34	552 ± 87	31
% change[a]	−32.5 ± 7.6	34	3.0 ± 8.5	31
Serum calcium (mg/dl)				
baseline	9.6 ± 0.1	36	9.7 ± 0.1	35
maintenance phase	9.2 ± 0.1	34	9.9 ± 0.1	31
% change[a]	−4.6 ± 1.4	34	2.6 ± 1.3	31
Serum phosphorus (mg/dl)				
baseline	6.0 ± 0.2	36	5.5 ± 0.2	35
maintenance phase	5.8 ± 0.2	34	5.7 ± 0.2	31
% change[b]	−2.6 ± 3.4	34	7.0 ± 5.5	31
Ca × P (mg^2/dl^2)				
baseline	57.6 ± 1.6	36	53.4 ± 2.3	35
maintenance phase	53.1 ± 1.8	34	56.6 ± 2.3	31
% change[c]	−7.9 ± 2.9	34	11.0 ± 6.5	31

[a] $P < 0.001$ comparing treatment groups.
[b] $P = 0.217$ comparing treatment groups.
[c] $P = 0.013$ comparing treatment groups.

Table 3. Mean (SE) dose at baseline and maintenance phase of vitamin D/phosphate binders

	AMG 073		Placebo	
	Mean (SE)	*n*	Mean (SE)	*n*
Calcitriol injection dose (μg/wk)				
baseline	4.3 ± 0.6	14	4.5 ± 0.6	17
maintenance phase[a]	3.4 ± 0.5	24	3.2 ± 0.5	20
Paricalcitol injection dose (μg/wk)				
baseline	22.1 ± 5.9	8	21.0 ± 5.2	5
maintenance phase[a]	15.6 ± 4.2	12	14.0 ± 3.8	9
Elemental calcium dose from calcium-containing phosphate binders (mg/d)				
baseline	1903 ± 193	27	1630 ± 138	27
maintenance phase[a]	1901 ± 163	26	1924 ± 307	26
Sevelamer hydrochloride dose (mg/d)				
baseline	5094 ± 1014	14	3777 ± 1035	8
maintenance phase[a]	4983 ± 507	15	3930 ± 618	6

[a] Values were not different between groups ($P > 0.05$).

from 75 to 50 mg was required in one patient, dose reduction from 75 to 25 mg was required in one patient, and dose reduction from 50 to 25 mg was required in three patients. All dose reductions occurred due to PTH < 100 pg/ml (Figure 1). Mean (SE) compliance with study medication was 96.0 (1.3)% in the placebo group and 96.8 (1.1)% in the AMG 073 group.

Changes in Biochemical Parameters in Response to Treatment

Maintenance Phase PTH Response. Efficacy was assessed in this study using PTH values obtained at the end of the dosing interval (*i.e.*, 24 h after the previous dose of study drug). Figure 2 demonstrates that 24 h post-dose PTH decreased progressively during the dose-titration phase, as the patients' doses of AMG 073 were being escalated. In the maintenance phase, the reduction in PTH was sustained in the AMG 073 group. Minimal change from baseline was observed in the placebo group. During the maintenance phase, PTH concentrations in the AMG 073 group were reduced by 33% 24 h after dosing (Figure 2 and Table 2), compared with an increase of 3% in the placebo group ($P < 0.001$). Indeed, significantly more patients in the AMG 073 group achieved the primary

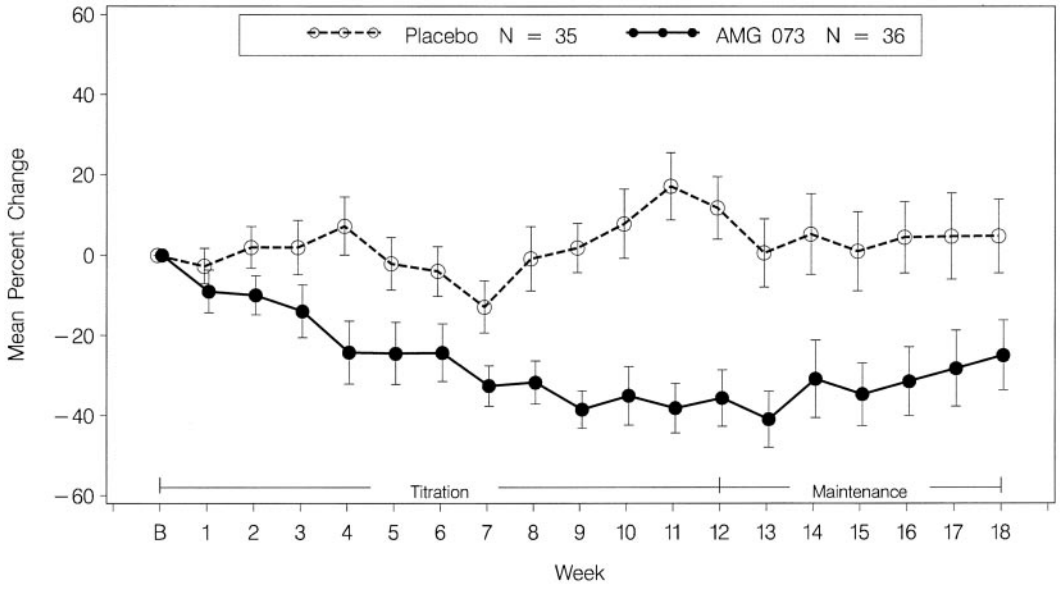

Figure 2. Changes in serum parathyroid hormone (PTH) levels in AMG 073 and placebo-treated groups during titration and maintenance periods. Values represent the mean (± SE) percent change in PTH from baseline levels to each measurement time point. Patient numbers are shown for those patients providing samples at baseline in each treatment group. $P < 0.001$ for the treatment comparison of weeks 13 to 18.

endpoint (≥30% from baseline in mean PTH) during the maintenance phase (53% of AMG 073 patients and 23% of placebo patients, $P = 0.009$). In addition, the study was designed to assess the proportion of patients in each treatment group who had reductions in PTH to ≤ 250 pg/ml during the maintenance phase. This endpoint was achieved in 44% of AMG 073 patients and 20% of placebo patients ($P = 0.029$). Finally, the relationship between serum calcium and PTH indicated that AMG 073 suppressed PTH at any given serum calcium concentration.

Post-Dose PTH Response. The mean (SE) PTH suppression from baseline immediately after dosing with AMG 073 and placebo treatments was assessed during and after hemodialysis at week 18 (Figure 3). Although these data reflect mean (SE) percent changes from variable baseline (pre-treatment) PTH levels, and do not necessarily indicate adequate control of PTH, they do indicate the time course of PTH suppression at 18 wk, when patients had attained their final AMG 073 dose. The mean ± SEM final dose of AMG 073 was 74 ± 5.3 mg. After dosing at week 18, AMG 073 resulted in a maximal

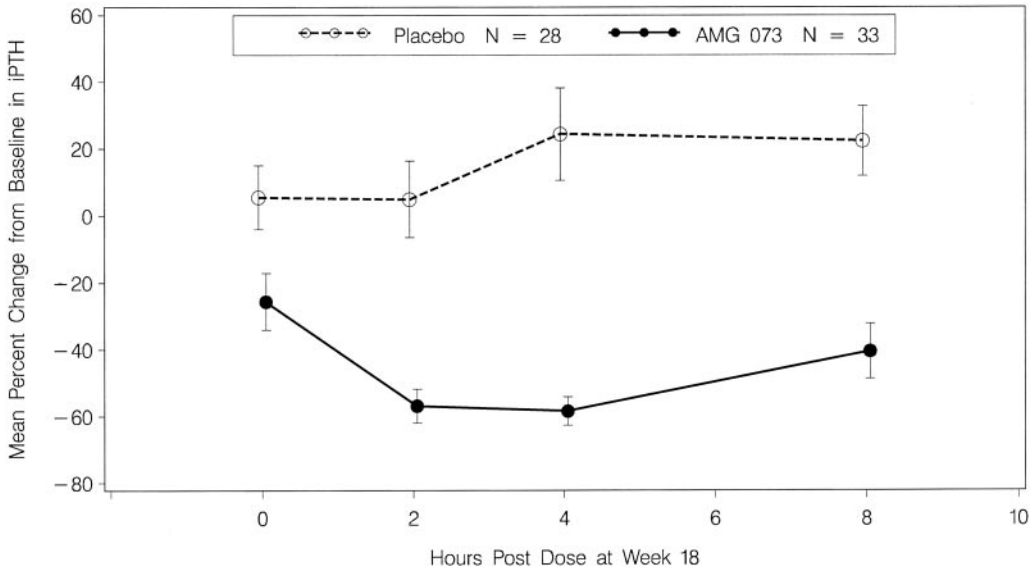

Figure 3. Time-course of PTH suppression after administration of AMG 073. Values represent the mean (± SE) percent change in PTH from baseline levels over the 8 h post-dose at week 18. n = the number of patients participating in the pharmacokinetic study at week 18 in each treatment group.

reduction in PTH at approximately 4 h after dosing. At this time point, the mean maximal reduction in PTH from baseline was approximately 60%. The maximal PTH suppression observed at 4 h after dosing trended upwards over the remainder of the dosing interval, but it remained below baseline for the entire dosing interval.

Changes in Calcium, Phosphorus, and Calcium × Phosphorus. Mean serum calcium decreased in the AMG 073 group (−4.6%) compared with a slight increase in the placebo group (2.6%) ($P < 0.001$; Figure 4A; Table 2). Mean percent change from baseline to the maintenance phase in serum phosphorus was not different between treatment groups ($P = 0.217$), although there appeared to be a trend toward a reduction in serum phosphorus in the AMG 073 group (Figure 4B). As a consequence, mean calcium × phosphorus decreased 7.9% in the AMG 073 group compared with an 11.0% increase in the placebo group ($P = 0.013$; Figure 4C; Table 2). Changes in PTH and calcium × phosphorus were not explained by adjustments in concomitant therapy (Table 3).

Effects of Concomitant Therapy. Complete flexibility was permitted in phosphate binder dosing during the study. Table 3 demonstrates that the dose of elemental calcium and the number of patients prescribed calcium-containing phosphate binders did not differ between treatment groups and remained relatively constant during the study. Table 3 also shows that the proportion of patients receiving sevelamer hydrochloride at enrollment was higher in the AMG 073 group compared with the placebo group (40% AMG 073 *versus* 20% placebo). Baseline PTH value and percent change from baseline PTH were similar regardless of whether the patient received sevelamer hydrochloride or not during the study.

Dose changes in vitamin D sterol therapy were permitted during the study for safety reasons under the conditions described in Materials and Methods. At baseline, the proportion of patients receiving vitamin D sterols was similar between treatment groups (61% AMG 073 *versus* 69% placebo). Because dose changes in vitamin D sterols were permitted during the study, the effect of these vitamin D dose changes on percent change from baseline in PTH was examined. Patients were subdivided into one of 3 groups on the basis of whether they had an increase, decrease, or no change in vitamin D sterol dose from enrollment to the maintenance phase of the study. Percent change from baseline in PTH was compared between among groups for each of these subgroups. In each subgroup, greater percent reductions from baseline in PTH were observed in the AMG 073 group compared with the placebo group regardless of whether patients had an increase, decrease, or no change in vitamin D sterol dose from baseline ($P = 0.008$ for percent change in PTH, adjusted for vitamin D dose changes).

Safety Profile. The safety profile of AMG 073 was similar to that of placebo with respect to the incidence and severity of adverse events, with only vomiting occurring more frequently in the AMG 073 group. Other studies conducted with AMG 073 have not demonstrated higher rates of vomiting compared with placebo. Most adverse events were mild to moderate in severity. A review of safety laboratory parameters revealed no differences between AMG 073 and placebo groups, other than the expected changes in PTH, serum calcium, and phosphorus due to the pharmacodynamic effects of AMG 073.

Discussion

The current study evaluates the efficacy and safety of AMG 073, a member of a new class of calcimimetic drugs that increase the sensitivity of the calcium sensing receptor to extracellular calcium (17). Treatment with AMG 073 was effective in suppressing circulating PTH levels. Suppression of PTH was attained without causing hypercalcemia and hyperphosphatemia, which frequently limit current treatment regimens (13 27–29). In fact, treatment with AMG 073 significantly reduced calcium × phosphorus levels. Whereas PTH levels were not further suppressed in the placebo group (Figure 2, Table 2), the mean plasma PTH in the AMG 073 group decreased progressively during the 12-wk titration phase and remained suppressed during the 6-wk maintenance phase (Figure 2, Table 2). Overall, addition of the calcimimetic AMG 073 achieved a 33% further suppression of PTH than attained with standard therapy (Table 2). Although these percent changes from variable baseline PTH levels do not necessarily indicate adequate control of PTH, we found that this reduction resulted in 44% of AMG 073 patients achieving adequate control of PTH (defined as a mean PTH ≤ 250 pg/ml) compared with 20% of placebo patients ($P = 0.029$).

The suppression of PTH concentrations by AMG 073 was time-dependent (Figure 3), with the maximal suppression occurring 4 h after oral administration of AMG 073. Over the 24-h dosing interval, the PTH reduction gradually lessened; despite this trend, the reduction in plasma PTH 24 h after the dose of AMG 073 remained clinically significant (Figure 2). Although secondary hyperparathyroidism in some patients was managed with AMG 073 doses of 25 mg, most required doses more than 50 mg to suppress PTH (mean dose of 74 mg/d at the end of the titration phase). The current study did not assess the effects of daily doses greater than 100 mg.

The overall effect of AMG 073 is to increase the sensitivity of CaR to ambient calcium (17); therefore, AMG 073-mediated suppression of PTH occurred without increasing serum calcium concentrations; indeed, serum calcium concentrations were decreased slightly compared with baseline (Table 2). These results contrast to the hypercalcemic response observed after therapy with vitamin D sterols (27,29). The mechanism underlying the observed reductions in serum calcium in response to AMG 073 was not defined in the current study but may be explained by the reductions in PTH leading to "hungry bone" effect that can follow parathyroidectomy (30). Another possible mechanism for the observed reductions in serum calcium could be stimulation of the CaR in the thyroid C-cells to increase calcitonin secretion. The latter explanation seems unlikely, however, based on other studies indicating that calcitonin stimulation does not occur at the doses studied here (31). The underlying mechanism of the serum calcium reduction deserves further investigation.

Administration of AMG 073 also did not exacerbate hyperphosphatemia (Table 2, Figure 4), which is a common complication of treatment with vitamin D sterols (27,32). Serum

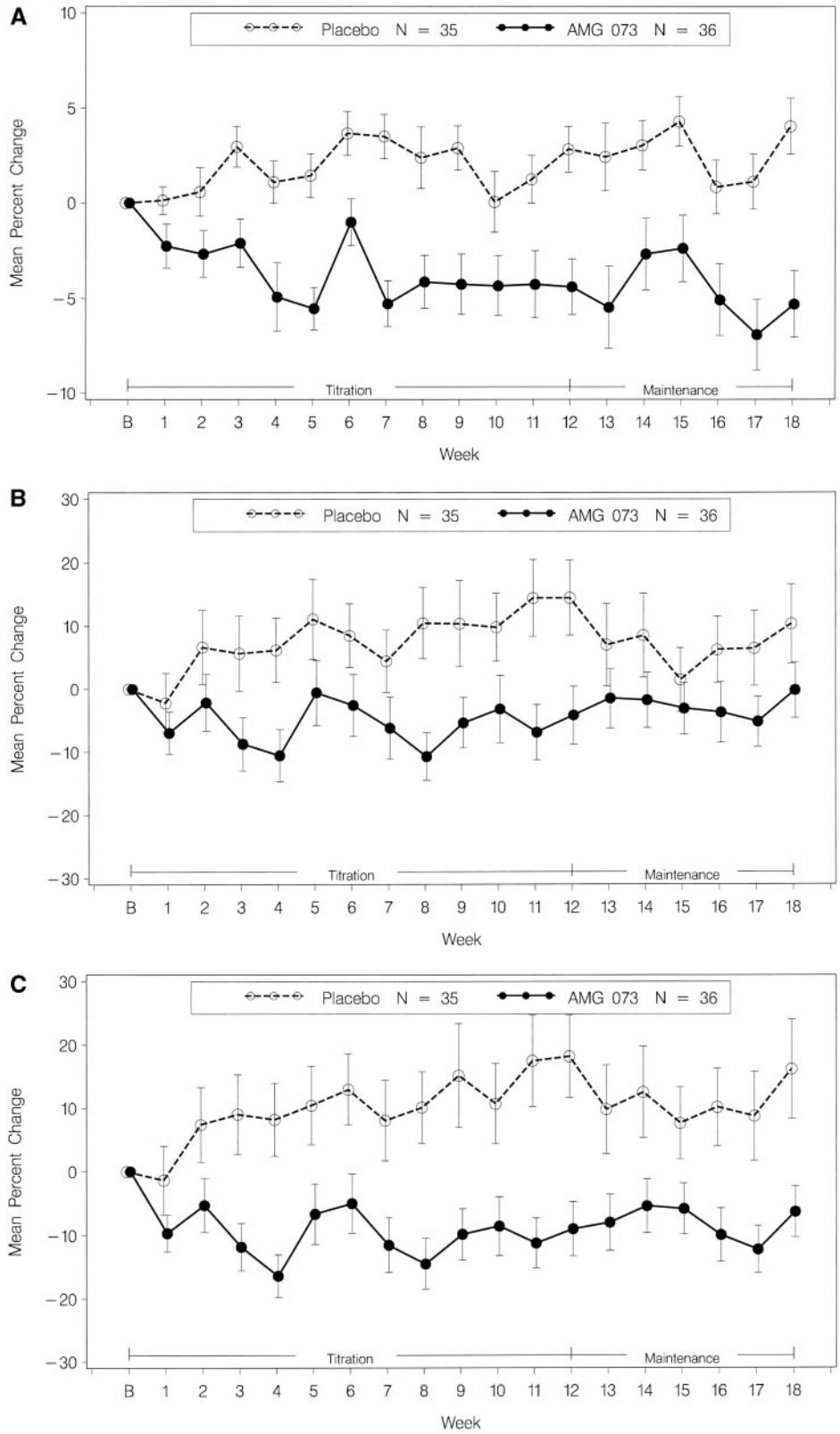

Figure 4. Changes in serum calcium, phosphorus, and calcium × phosphorus product in AMG 073 and placebo-treated groups during titration and maintenance periods. Values represent mean (± SE) percent change in serum calcium (A), serum phosphorus (B), and calcium × phosphorus (C) from baseline levels to each measurement time point. Patient numbers are shown for those patients providing samples at baseline in each treatment group. $P < 0.001$ for serum calcium; $P = 0.217$ for serum phosphorus, and $P = 0.013$ for calcium × phosphorus for the treatment comparison of weeks 13 to 18.

phosphorus concentrations tended to be lower in the AMG 073 group (Table 2), possibly reflecting a hungry bone–like effect on serum phosphorus or other mechanisms not yet identified. Although the reduction in serum phosphorus was not statistically significant, calcium × phosphorus levels were significantly lower in the AMG 073 group compared with placebo (Figure 4C and Table 2). Hyperphosphatemia and elevated calcium × phosphorus product results in parathyroid gland dysfunction (33), soft tissue calcification (34), and possibly mortality of dialysis patients (11,16); therefore, the favorable calcium and phosphorus profiles in AMG 073-treated patients may be advantageous.

In the current study, all but two patients in the AMG 073 and placebo groups were already receiving phosphate binders, and 65% of patients were receiving vitamin D sterols (Table 3), at doses similar to those reported in other prospective studies evaluating combined therapy (27). The effects of AMG 073 on PTH and calcium × phosphorus levels were not due to on-study adjustments in calcium supplements, phosphate binders, or vitamin D sterol supplementation. Furthermore, approximately one third of patients (35%) enrolled in this study were not receiving vitamin D sterols at baseline, and the effects of AMG 073 on PTH were independent of whether patients were receiving vitamin D sterols at baseline. The proportion of patients in each treatment group by race, an independent determinant of uremic secondary hyperparathyroidism (35), did not differ. A greater proportion of females were enrolled in the placebo group, but no data are available to support an effect of gender on the suppression of PTH in clinical trials.

Despite the compelling results of the current study, the optimal use of AMG 073 may not have yet been defined. It is of note that all patients displayed a greater reduction of PTH at 4 h (Figure 3) after the administration of AMG 073 than at the 24 h time point used to monitor the efficacy of treatment (Figure 2). In addition, the response to AMG 073 at 24 h after dosing was heterogeneous, with some patients displaying sensitivity to AMG 073 at low doses and others with less PTH suppression despite doses up to 100 mg/d used in this study. The basis for this heterogeneity was not examined, but could be due to individual differences in metabolism of the drug or to intrinsic alterations of the parathyroid gland that alter the effectiveness of calcimimetics. Reductions in CaR expression that characterize adenomatous transformation of parathyroid glands may explain individual variation in response to AMG 073, although AMG 073 has also been shown to be effective in patients with primary hyperparathyroidism (36). Current studies are evaluating the efficacy of higher once-daily doses of AMG 073. In addition, at the time these studies were performed, the use of newer vitamin D sterols and non-calcium containing phosphate binders were in limited use. Additional studies will be needed to evaluate the effects of AMG 073 in comparison to or in combination with newer approaches to suppress PTH in chronic kidney failure patients.

These studies did not evaluate AMG 073 as a primary therapy. Recent studies in mice lacking the vitamin D receptor (VDR), however, suggest that calcium alone may be sufficient to prevent secondary hyperparathyroidism under certain conditions (20), although other interventions may be needed to treat the hyperphosphatemia and $1,25(OH)_2$ vitamin D deficiency in ESRD. In support of the potential to use AMG 073 as primary therapy in chronic kidney failure, high-dose calcium therapy without concomitant therapy with active vitamin D sterols can suppress PTH concentrations and control serum phosphorus concentrations in hemodialysis patients with mild hyperparathyroidism, but the doses of calcium required lead to chronic calcium overload (27). It is possible that AMG 073 might achieve similar reduction in PTH while minimizing the need to administer large doses of calcium.

In conclusion, AMG 073 represents a novel pharmacologic therapy to treat hyperparathyroidism in ESRD. Calcimimetic compounds, by directly targeting CaR in the parathyroid gland, may provide an alternative and/or an adjunct to intensive calcium and vitamin D sterol treatment of secondary hyperparathyroidism and permit further suppression of PTH without increases in serum calcium or worsening hyperphosphatemia. Thus, AMG 073 has the potential to reduce the prevalence of hyperparathyroidism and limit the potential toxicity of current treatment strategies. Long-term treatment and follow up with AMG 073 are needed to determine if AMG 073 improves survival and the quality of life of patients with ESRD.

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