Efficacy and Safety of a Novel Nicotinamide Modified-Release Formulation in the Treatment of Refractory Hyperphosphatemia in Patients Receiving Hemodialysis—A Randomized Clinical Trial

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Introduction: Despite widespread use of phosphate binders (PBs), phosphate control is insufficient in many hemodialysis patients. Preliminary clinical observations suggest that nicotinamide may act synergistically with PBs to improve phosphate control.

Methods: This multinational, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of nicotinamide modified release (NAMR) in combination with oral PB in a large cohort of hemodialysis patients with abnormal serum phosphate concentration (>4.5 mg/dl) despite treatment with PB. Patients entered a proof-of-efficacy phase (12 weeks [W12]) in which adjustments of relevant comedication were not permitted, followed by a safety extension phase for up to 52 weeks. Here, we report the results of the first phase.

Results: The intention-to-treat (ITT) population consisted of 539 patients in the NAMR and 183 patients in the placebo group. NAMR and placebo were orally administered once daily (250–1500 mg/d). Mean age of patients was 61.8 years, and 63.0% were men. In the confirmatory analysis that estimated the difference in serum phosphate concentration after 12 weeks, NAMR proved superior over placebo with a significant difference of -0.51 mg/dl (95% confidence interval [CI] -0.72, -0.29; $P < 0.0001$). This effect was associated with significantly lower intact parathyroid hormone (iPTH) values (NAMR: 292.4 ± 300.4 pg/ml vs. placebo: 337.0 ± 302.7 pg/ml; $P = 0.04$) and an improved calcification propensity (T50 time; NAMR: 23.8 ± 97.1 minutes vs. placebo: 2.3 ± 100.7 minutes; $P = 0.02$). Diarrhea and pruritus were more frequent in the NAMR group.

Conclusion: NAMR combined with oral PB significantly improved phosphate control in hemodialysis patients.

C hronic kidney disease–mineral and bone disorder (CKD-MBD) is characterized by progressive loss of renal function as well as dysregulation of mineral

and bone metabolism, leading frequently to hyperphosphatemia. Multiple studies have consistently shown that hyperphosphatemia is associated with cardiovascular events and increased morbidity and mortality in end-stage renal disease (ESRD) patients.[1–9] A recent meta-analysis based on 200,000 patients suggests a 40% higher all-cause mortality risk for patients with elevated serum phosphate concentrations compared to

patients with sufficiently controlled serum phosphate (risk ratio [RR] 1.39, 95% CI 1.31, 1.47).[10] The detrimental effects of hyperphosphatemia are thought to be related to phosphate-induced progressive cardiovascular calcification.[11] Importantly, use of phosphate-binding agents and reduction of serum phosphate concentration are associated with a lower risk of mortality.[9,12] Along these lines, lowering of serum phosphate concentration toward the normal range (4.5 mg/dl) represents a current guideline recommendation.[13] However, in Europe, roughly 70% of patients receiving maintenance hemodialysis do not meet this phosphate target.[14,15] This shows that there is a substantial gap between guideline recommendations and clinical practice despite widespread use of phosphate binders (PBs).

Our current understanding of pleiotropic effects of PB do not speak in favor of more aggressive PB regimens. These effects include, for example, accumulation of metals in different organs, disturbances of the gut microbiome, and binding of important nutrients such as vitamin K and may adversely affect clinical outcomes.[16] Therefore, therapy approaches that combine different modes of action may represent a reasonable alternative to improve phosphate control.

Limiting intestinal phosphate absorption is a major aim of hyperphosphatemia management and currently relies on dietary phosphate restriction and prescription of PB. Two processes govern absorption of phosphate in the human small intestine. Although passive paracellular transport occurs primarily at high luminal phosphate concentrations, sodium-dependent transcellular transport becomes important in situations of low luminal phosphate availability.[17–20]

Dietary phosphate restriction as well as physicochemical precipitation of phosphate using PB lowers the phosphate gradient between intestinal lumen and circulation and, hence, is supposed to reduce paracellular phosphate absorption. Experimental studies suggest that both strategies enhance intestinal expression of the sodium-dependent phosphate cotransporter 2b (NaPiIIb) that is responsible for up to 90% of active transcellular phosphate absorption.[21–28] These observations provide a reasonable pathophysiological explanation for insufficient phosphate control with current standard of care.[29]

Based on preclinical research, nicotinamide (NA) is known to inhibit NaPiIIb-dependent intestinal phosphate absorption via modulation of the NaPiIIb expression levels.[21,30,31] The compensatory upregulation of NaPiIIb in the presence of PB can be prevented by coadministration of NA.[28] However, the results of the COMBINE study suggest that the combined use of NA and PB does not affect serum phosphate in predialysis

patients (CKD stage 3b/4).[32] In contrast, randomized placebo-controlled studies with small patient populations showed that combining immediate-release NA with PB could be a strategy to improve phosphate control in patients with ESRD.[33–35] Yet, rapid attainment of high NA serum concentrations has been linked to acute adverse drug reactions such as gastrointestinal symptoms and headache.[36,37] In addition, it may promote drug-drug interactions, for example, with inhibitors of poly(ADP-ribose) polymerase.[38]

In the current study, efficacy and safety of a novel NA modified-release (NAMR) formulation in the treatment of ESRD patients with hyperphosphatemia were compared to placebo in a double-blind setting. Both NAMR and placebo were administered in addition to the individual therapy with approved oral PBs. Patients initially went through a first phase (12 weeks) in which adjustments of relevant comedication were not permitted and then entered a long-term safety follow-up for up to 52 weeks. Here, we report efficacy and safety results after 12 weeks of randomized treatment. Whereas the primary endpoint investigated difference in serum phosphate concentration after 12 weeks in the ITT population, secondary endpoints included phosphate target range achievement and serum iPTH and lipids. Serum calcification propensity was investigated as an exploratory endpoint.

METHODS

Study Design

This study was designed as a multicenter, randomized, prospective, double-blind, placebo-controlled, parallel group study conducted in 96 sites across Germany ($n = 57$ sites), Poland ($n = 25$ sites), and Austria ($n = 14$ sites). The study was approved by the national regulatory authorities as well as by all institutional review boards involved. The study was conducted in accordance with the principles of the International Council for Harmonization and the Declaration of Helsinki and was registered in the EU Clinical Trials Register (EudraCT Number 2013-000488-95). Until reaching the primary endpoint (serum phosphate concentration at W12) doses of concomitant PBs, calcimimetics, calcitriol, and vitamin D analogues were advised to be kept constant. Patients who permanently discontinued the intake of the study medication were asked to remain in the study and to complete regular visits including adverse event documentation and laboratory analyses.

Participants

After giving informed consent, adult male or female patients undergoing regular maintenance hemodialysis

(thrice a week) were screened for eligibility. Eligible patients had a serum phosphate concentration of >4.5 and <8.7 mg/dl and received a therapy with 1 or 2 oral phosphate-binding agents and, if necessary, active vitamin D analogues as well as calcimimetics. The dosage of these agents had to be stable for at least 1 month prior to screening. Patients with platelet numbers lower than 120/nl at screening were excluded. Concomitant intake of oral vitamin/food supplements containing >150 mg/wk NA or nicotinic acid were not allowed. Instead, the sponsor provided vitamin supplements without NA. See supplementary methods for a complete list of inclusion and exclusion criteria.

Dosing of Study Medication

Patients directly received study medication in addition to their individual PB therapy without passing through a washout phase. Nicotinamide MR and placebo capsules were orally administered once daily before the patient went to bed (250–1500 mg/d, equivalent to 1–6 capsules per day). The initial dose was 500 mg/d for 2 weeks and could then be adjusted at every further visit. For patient groups with a screening phosphate concentration of <6.25 or ≥6.25 mg/dl, the dose was to be increased by 1 capsule until serum phosphate of <4.5 or <5.5 mg/dl was reached. In case of adverse reactions, the dose was advised to be decreased by 1 capsule. Once adverse reactions had resolved, the dose could be titrated up again by 1 capsule per day. After temporal discontinuation due to adverse reactions or hospital admissions, re-exposition had to be started with 500 mg/d. Subsequent dose adjustments of 1 capsule per week were allowed.

Endpoints

The primary endpoint of this study was the difference in serum phosphate concentration at week 12 in the ITT population. Secondary endpoints relating to serum phosphate concentration included the effect on absolute values, change from screening, and response analyses. Response criteria were (i) ≤5.5 mg/dl, (ii) ≤4.5 mg/dl, (iii) target range achieved (≤4.5 mg/dl for patients with screening phosphate <6.25 mg/dl; ≤5.5 mg/dl for patients with screening serum phosphate concentration ≥6.25 mg/dl), and (iv) improvement ≥0.6 mg/dl. Further secondary efficacy endpoints were calcium, intact parathyroid hormone (iPTH), and lipids (high-density lipoprotein, low-density lipoprotein, and triglycerides). Carboxy-terminal fibroblast growth factor 23 (cFGF23) and lipoprotein(a) were considered prespecified exploratory endpoints. T50 was determined as an additional exploratory endpoint in frozen blood samples after discussion with clinical experts. This parameter (in

minutes) is determined in an *in vitro* nanoparticle-based assay that monitors the transformation of primary calciprotein particles (CPPs) to crystalline secondary CPPs. The test integrates the status of serum phosphate and other important CKD-MBD parameters that trigger calcium phosphate crystallization. Hence, T50 represents a quantitative read-out for the serum calcification propensity. It has been shown to be associated with cardiovascular morbidity and mortality in patients with CKD/ESRD.[39–41]

A central laboratory analyzed the blood samples that were taken after a long dialysis-free interval (i.e., 3 days; on Mondays or Tuesdays) immediately before dialysis. There were no stipulations with respect to prior food intake because patients could receive dialysis at different time points during the day. Up to W12 serum phosphate and calcium concentrations were measured at baseline and every 2 weeks up to week 12. Serum concentrations of iPTH, cFGF23, lipids, and T50 were measured at baseline and at week 12. Assay details are summarized in Supplementary Table S1. Safety evaluation included standard adverse event reporting and safety laboratory. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA, versions 16.1–19.1).

Sample Size

A randomization ratio of 3:1 (NAMR vs. placebo) was chosen, in order to ensure sufficient exposure to NAMR as required according to relevant ICH guidelines. Considering this ratio and assuming a standard deviation of 1.7 mg/dl, about 480 patients were required in order to detect a minimal difference of 0.7 mg/dl with a power of 95% at an α-level of 0.025 (2-sided t test). We decided to extend this sample size by about 30% to a total of 700 patients to collect sufficient long-term safety follow-up data for patients who received NAMR and to account for potential dropouts.

Randomization and Blinding

Randomization was stratified by study site, screening serum phosphate concentration (<6.25 vs. ≥6.25 mg/dl), and leading PB therapy (calcium-containing binders vs. lanthanum carbonate/aluminum vs. other PBs). The rationale for the latter stratification factor was to distinguish between divalent cationic binders (calcium, magnesium), trivalent cationic binders (lanthanum, aluminum), and other binders (mostly nonabsorbable organic polymers such as sevelamer and colestilan). Randomization was carried out using a validated web-based central randomization tool (TENALEA; Trans European Network for Clinical Trials Services). A member of the sponsor's galenics department, who was not involved in further study
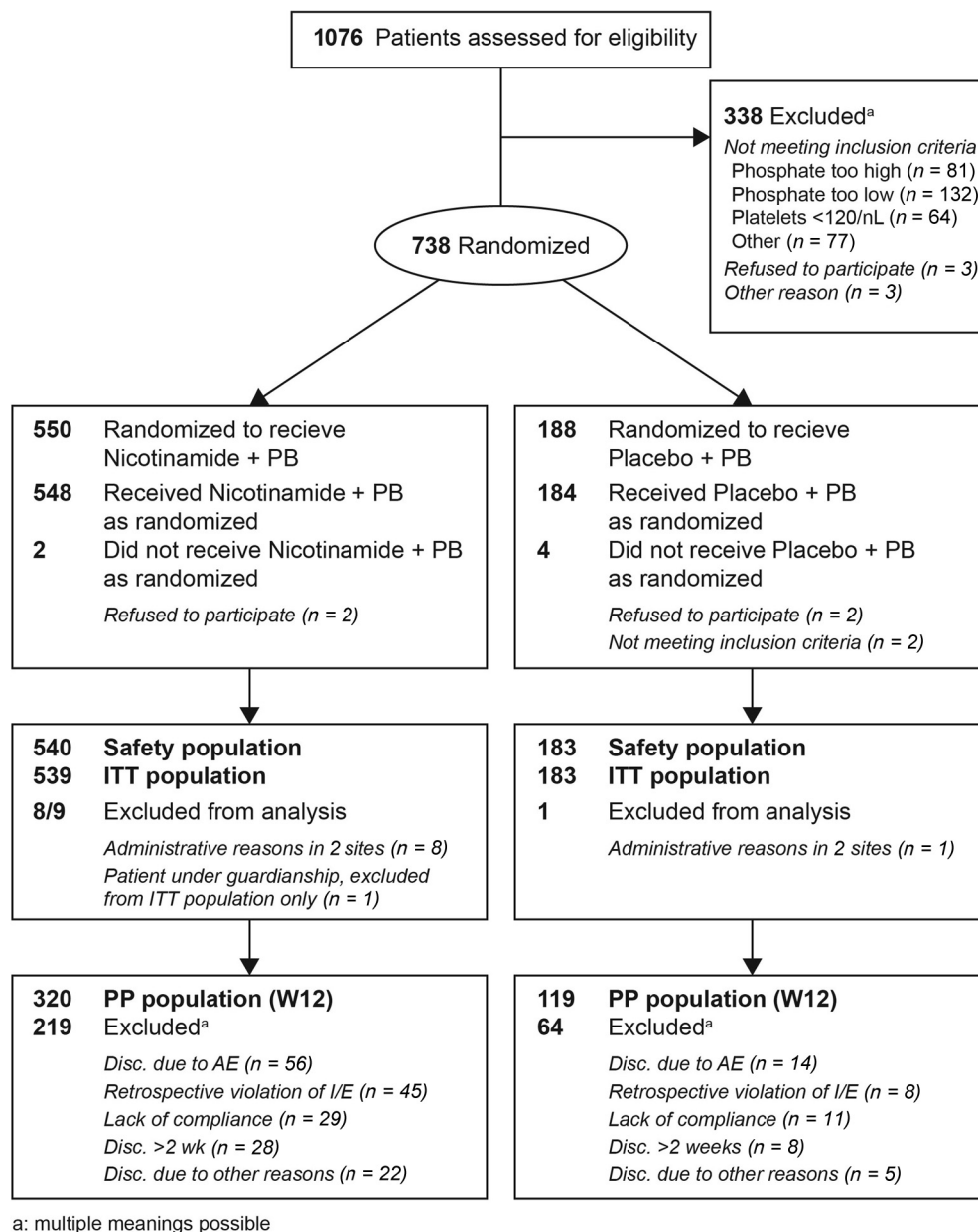
Figure 1. CONSORT patient flow chart. AE, adverse event; I/E, inclusion/exclusion criteria; ITT, intention to treat; PB, phosphate binder; PP, per protocol; W12, week 12.

conduct, provided a randomization code that assigned the patient number to the study medication.

Statistical Methods

The primary confirmatory analysis was carried out in the ITT population and was based on a linear mixed model to address the stratification factors of the randomization. *Medication group* was included as fixed effect, whereas *screening phosphate* and *type of leading PB* were included as fixed effect covariates. *Trial site* was modeled as random effect. Small sites with fewer than 10 patients were pooled by region. The claim of superiority was based on a 2-sided *P* value related to the Wald-type test statistic for the treatment effect

with a significance level of 2.5%. Missing data were imputed using the placebo multiple imputation approach to obtain the effectiveness estimand of Mallinckrodt. This is a conservative approach and commonly used as worst-case analysis. The model assumes that serum phosphate goes back to placebo level after discontinuation of NAMR.[42] Repetitions of the analysis in the PP population and in patients excluded from the PP population were conducted as prespecified sensitivity analyses. Secondary endpoints were analyzed using the Mann-Whitney *U* test for continuous variables and Monte Carlo estimation of exact χ^2 *P* values for binary or nominal variables. With respect to the response analyses, patients were considered

Table 1. Baseline characteristics in the ITT population of the NOPHOS study

Parameter	Nicotinamide + PB (n = 539)	Placebo + PB (n = 183)
Age, yr (mean±SD)	61.8±13.8	62.0±14.2
Sex, n (%)		
Female	204 (37.8)	63 (34.4)
Male	335 (62.2)	120 (65.6)
Cause of CKD[a,b], n (%)	n = 540	
Nephrosclerosis/hypertension	137 (25.4)	46 (25.1)
Glomerulonephritis	136 (25.2)	39 (21.3)
Type 2 diabetes	117 (21.7)	32 (17.5)
Other	75 (13.9)	24 (13.1)
Polycystic kidney disease	62 (11.5)	23 (12.6)
Etiology unknown	25 (4.6)	20 (10.9)
Interstitial nephritis	27 (5.0)	17 (9.3)
Time from first RRT to screening, mo, median (IQR)	41 (20–77)	44 (23–84)
Dialysis mode, n (%)		
Hemodialysis	434 (80.5)	146 (79.8)
Hemodiafiltration	104 (19.3)	37 (20.2)
Hemofiltration	1 (0.2)	0 (0.0)
Time of dialysis, n (%)		
Morning	275 (51.0)	97 (53.0)
Midday/afternoon	160 (29.7)	54 (29.5)
Evening	88 (16.3)	27 (14.8)
Night	16 (3.0)	5 (2.7)
Kt/V, mean±SD	1.5±0.4	1.5±0.3
PB therapy, n (%)		
Monotherapy	421 (78.1)	150 (82.0)
Combination therapy	118 (21.9)	33 (18.0)
Calcium-containing PB, n (%)	278 (51.6)	94 (51.4)
Phosphate binder[a], n (%)		
Sevelamer	191 (35.4)	59 (32.2)
Calcium acetate	127 (23.6)	50 (27.3)
Calcium acetate and magnesium carbonate	112 (20.8)	28 (15.3)
Lanthanum carbonate	94 (17.4)	31 (16.9)
Calcium carbonate	84 (15.6)	29 (15.8)
Aluminum	43 (8.0)	17 (9.3)
Colestilan	5 (0.9)	1 (0.5)
Sucroferric oxyhydroxide	1 (0.2)	1 (0.5)
Active vitamin D, n (%)	259 (48.1)	89 (48.6)
Calcimimetics, n (%)	110 (20.4)	46 (25.1)

CKD, chronic kidney disease; ITT, intention to treat; NOPHOS, Efficacy and tolerability of nicotinamide as add-on therapy compared to placebo in dialysis-dependent patients with hyperphosphatemia; PB, phosphate binder; RRT, renal replacement therapy
[a]Multiple meanings possible.
[b]≥5% in either treatment group.

nonresponder in case of missing values. All statistical analyses were carried out using SAS statistical software, version 9.4.

RESULTS

Participant Flow
Overall, 1,076 dialysis patients were screened for eligibility between November 2013 and March 2016 (Figure 1). Of these, 738 patients were randomly assigned to NAMR (n = 550) or placebo (n = 188). The ITT population (n = 722) consisted of 539 patients in the NAMR group and 183 patients in the placebo group. The per-protocol (PP) population (n = 439) was

defined as all patients who completed randomized treatment from baseline to W12 without major protocol violations. The 5 most frequent protocol violations are given in Figure 1. The number of protocol violations due to changes to PBs, calcimimetics, calcitriol, and vitamin D analogues was low in both treatment groups (NAMR: n = 13 vs. placebo: n = 3). The last patient completed the study in March 2017.

Baseline Characteristics
Baseline (i.e., screening visit) demographic and clinical characteristics are shown in Table 1. Table 2 shows baseline serum concentrations for phosphate and other markers of CKD-MBD. Supplementary Table S2 shows further baseline parameters. Overall, baseline characteristics were well balanced across both treatment groups of the ITT population. Mean (±SD) age of the entire ITT population was 61.8±13.9 years, and 63.0% of patients were male. More than half of all patients (51.5%) received dialysis at morning. One-third (29.6%) received dialysis at midday/afternoon. The other patients had dialysis sessions either in the evening (15.9%) or at night (2.9%). A PB combination therapy was documented for 20.9% of the patients. The 3 most frequently used PBs were sevelamer, calcium acetate, and calcium acetate/magnesium carbonate. Overall, more than half of the patients received a PB containing calcium. At screening, the mean (±SD) serum phosphate and calcium concentrations in the ITT population were 6.02±0.90 mg/dl and 2.18±0.21 mmol/l, respectively.

Dosing
Supplementary Figure S1A depicts the mean number of capsules used per day based on drug accountability between week 2 and week 12. On average, patients randomized to NAMR or placebo used 3.8 capsules (equivalent to 950 mg/d) and 4.9 capsules per day, respectively, at week 12.

Efficacy at W12—ITT Population
Primary Efficacy Endpoint
The time course for serum phosphate within the first 12 weeks is given in Supplementary Figure S1B. Within the first 2 weeks (2 capsules per day), serum phosphate dropped in patients randomized to NAMR and was significantly lower compared to patients randomized to placebo. After 12 weeks of randomized treatment, serum phosphate concentration was 5.36±1.38 mg/dl in patients randomized to NAMR and 5.88±1.32 mg/dl in patients randomized to placebo ($P < 0.0001$) (Table 2). The confirmatory analysis demonstrated superiority of NAMR over placebo with a significant between-group difference of −0.51 mg/dl (95% CI −0.72, −0.29; $P < 0.0001$). Protocol adherence appeared

Table 2. Baseline and W12 values for phosphate and other CKD-MBD markers in the ITT and PP population

| | Baseline | | | | | Week 12 | | | | |
| | Nicotinamide + PB | | Placebo + PB | | | Nicotinamide + PB | | Placebo + PB | | |
Parameter	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]	P Value[a]	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]	P Value[a]
Phosphate (mg/dl)										
ITT population	6.03±0.91 (n=539)	5.90 [5.30–6.60]	6.02±0.85 (n=183)	5.90 [5.40–6.60]	0.97	5.36±1.38 (n=499)	5.20 [4.40–6.20]	5.88±1.32 (n=174)	5.80 [4.80–6.80]	<0.0001
PP population	6.00±0.91 (n=320)	5.90 [5.30–6.60]	5.98±0.84 (n=119)	5.80 [5.30–6.60]	0.95	5.25±1.22 (n=320)	5.10 [4.40–6.00]	5.84±1.36 (n=119)	5.60 [4.80–6.80]	<0.0001
Calcium (mmol/l)										
ITT population	2.19±0.20 (n=538)	2.19 [2.06–2.32]	2.16±0.22 (n=183)	2.16 [2.02–2.29]	0.16	2.25±0.21 (n=499)	2.26 [2.14–2.39]	2.16±0.20 (n=174)	2.18 [2.03–2.30]	<0.0001
PP population	2.19±0.19 (n=320)	2.19 [2.06–2.31]	2.16±0.23 (n=119)	2.16 [2.02–2.28]	0.28	2.26±0.21 (n=320)	2.28 [2.14–2.40]	2.16±0.20 (n=119)	2.18 [2.03–2.31]	<0.0001
iPTH (pg/ml)										
ITT population	325.9±330.1 (n=527)	244 [130–412]	318.7±241.6 (n=177)	257 [154–433]	0.40	292.4±300.4 (n=493)	227 [121–366]	337.0±302.7 (n=173)	252 [141–447]	0.04
PP population	331.0±280.8 (n=318)	269 [159–416]	305.7±248.3 (n=114)	242 [136–425]	0.42	301.5±307.9 (n=318)	239 [121–376]	310.1±277.0 (n=118)	237 [141–403]	0.52
cFGF23 (RU/ml)										
ITT population	5,306±321.5 (n=508)	2,778 [1,190–6,214]	5,422±502.2 (n=173)	2,691 [1,269–6,986]	0.64	5,060±391.7 (n=465)	2,267 [1,000–5,785]	6,236±762.8 (n=172)	2,539 [1,018–6,005]	0.41
PP population	5,230±407.7 (n=305)	2,627 [1,196–6,111]	5,232±652.5 (n=111)	2,213 [1,082–6,096]	0.72	4,723±426.0 (n=300)	2,092 [931–5,436]	6,227±965.4 (n=117)	2,292 [1,010–5,182]	0.42
T50 (min)[b]	151.2±75.1 (n=481)	128.0 [93.0–189.0]	155.0±83.8 (n=170)	124.5 [94.0–200.0]	0.90	174.3±88.7 (n=464)	153.5 [100.5–235.5]	157.8±84.4 (n=166)	129.5 [90.0–199.0]	0.02

[a] P value of Mann-Whitney U test.
[b] Only presented for ITT population due to post hoc analysis.

to influence the results, as the treatment effect was more pronounced in the PP population (−0.61 mg/dl, 95% CI −0.85, −0.37; P < 0.0001) and reduced in patients excluded from the PP population (−0.33 mg/dl, 95% CI −0.75, 0.10; P = 0.13).

Secondary Endpoints: Phosphate

At week 12, change from screening was significantly larger for patients in the NAMR group compared with the placebo group (NAMR: −0.67±1.31 mg/dl vs. placebo: −0.11±1.33 mg/dl; P < 0.0001) (Supplementary Table S3). In the placebo group, mean and median change from screening were nearly identical (median value: −0.10 mg/dl). In contrast, the median change from screening in the NAMR group was slightly larger than the respective mean value (median value: −0.80 mg/dl) (Supplementary Table S3).

The response analyses for all response criteria yielded statistically significant differences favoring NAMR based on the ITT population at W12 (Figure 2). One hundred seventy patients (31.5%) in the NAMR group compared to 38 patients (20.8%) in the placebo group achieved their individual phosphate target range (RR 1.52, 95% CI 1.12, 2.07; P = 0.008). Although 131 patients (24.3%) in the NAMR group had a serum phosphate concentration lower than 4.5 mg/dl, 25 patients (13.7%) in the placebo group met this response criterion (RR 1.78, 95% CI 1.20, 2.64; P = 0.004). In addition, 235 patients (43.6%) in the NAMR group compared to 54 patients (29.5%) in the placebo group had a reduction of the serum phosphate concentration of ≥0.6 mg/dl compared to baseline (RR 1.48, 95% CI 1.16, 1.89; P = 0.002).

Secondary Endpoints—Other CKD-MBD Marker

Table 2 and Supplementary Table S3 show differential changes in calcium, iPTH, and cFGF23 between both treatment groups. Although serum calcium did not change in the placebo group, it was higher in the NAMR group at week 12 compared with baseline, leading to significantly different values (NAMR: 2.25±0.21 mmol/l vs. placebo: 2.16±0.20 mmol/l; P < 0.0001). Serum iPTH concentration was significantly lower in the NAMR group compared with the placebo group at week 12 (NAMR: 292.4±300.4 pg/ml vs. placebo: 337.0±302.7 pg/ml; P = 0.04). Although change of serum cFGF23 concentration from baseline at week 12 was not significantly different between both treatment groups in the ITT population (NAMR: −15.2±256.5 RU/ml vs. placebo: 730.6±575.3 RU/ml; P = 0.13), it was significantly different in the PP population (NAMR: −282.9±318.7 RU/ml vs. placebo: 1,128±736.6 RU/ml; P = 0.02).

Supplementary Table S4 shows the results for the lipid analyses. Except for a slight reduction in serum
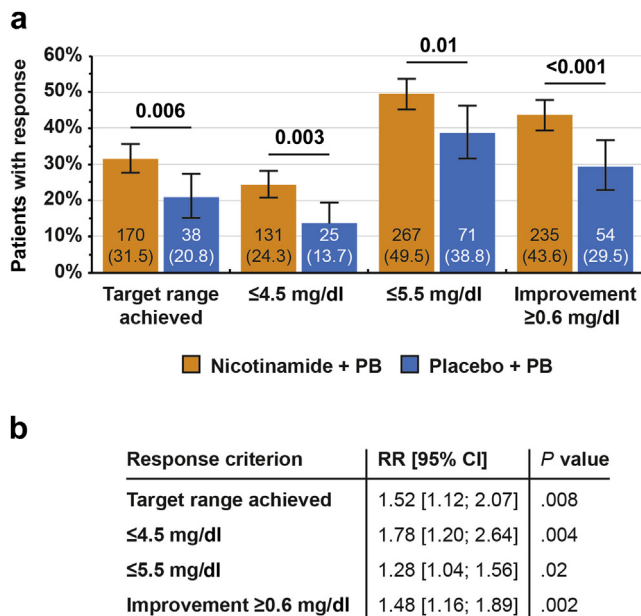
Figure 2. Response analyses at week 12 in the ITT population. (a) Bar diagrams showing the responder rates for all response criteria. (b) Tabular overview of the RRs resulting from the respective responder rates. CI, confidence interval; ITT, intention to treat; PB, phosphate binder; RR, risk ratio.

triglycerides concentration, lipid parameters did not notably change in patients randomized to placebo. In contrast, serum high-density lipoprotein concentration increased whereas values for low-density lipoprotein, triglycerides, and lipoprotein(a) decreased in patients randomized to NAMR.

Calcification Propensity

In line with the reduction in serum phosphate concentration in the NAMR group, T50 was prolonged in the NAMR group at week 12 compared with baseline. In contrast, T50 did not notably change in the placebo group between baseline and week 12. As a result, the change from screening was significantly different between both treatment groups (NAMR: 23.8 ± 97.1 minutes vs. placebo: 2.3 ± 100.7 minutes; $P = 0.02$) (Table 2 and Supplementary Table S3).

Frequent Adverse Events

Treatment-emergent adverse events that occurred with a frequency of $\geq2\%$ and $\geq1\%$ in either treatment group are listed in Table 3 and Supplementary Table S5, respectively. Until W12, 21 adverse events were reported with an incidence of $\geq2\%$ in either treatment group. Diarrhea and pruritus were the 2 most frequent adverse events and occurred more often in the NAMR group compared with the placebo group.

Platelets

Platelet numbers were comparable across both treatment groups at screening (NAMR: 216.4 ± 69.7/nl vs.

Table 3. Most frequent treatment-emergent adverse events ($\geq2\%$ in either treatment group) until week 12 in the safety population

MedDRA PT ($\geq2\%$)	Nicotinamide + PB, n (%) ($n=540$)	Placebo + PB, n (%) ($n=183$)
Diarrhea	166 (30.7)	23 (12.6)
Pruritus	53 (9.8)	5 (2.7)
Nasopharyngitis	39 (7.2)	11 (6.0)
Nausea	39 (7.2)	6 (3.3)
Vomiting	32 (5.9)	7 (3.8)
Hypertension	31 (5.7)	7 (3.8)
Headache	26 (4.8)	6 (3.3)
Bronchitis	24 (4.4)	5 (2.7)
Anemia	22 (4.1)	4 (2.2)
Hypotension	5 (0.9)	7 (3.8)
Decreased appetite	19 (3.5)	4 (2.2)
Muscle spasms	17 (3.1)	6 (3.3)
Cough	15 (2.8)	3 (1.6)
Flatulence	2 (0.4)	5 (2.7)
Sleep disorder	14 (2.6)	3 (1.6)
Fatigue	14 (2.6)	0 (0.0)
Rash	13 (2.4)	1 (0.5)
Influenza	7 (1.3)	4 (2.2)
Arthralgia	5 (0.9)	4 (2.2)
Hypocalcaemia	2 (0.4)	4 (2.2)
Abdominal pain upper	11 (2.0)	1 (0.5)

Treatment-emergent adverse event: defined as all adverse events that occurred between the first intake of study medication and the week 12 visit, withdrawal or permanent discontinuation of study medication.

placebo: 216.0 ± 65.0/nl). At week 12, the platelet number was significantly lower in the NAMR group compared to the placebo group (NAMR: 194.1 ± 66.0/nl vs. placebo: 209.0 ± 69.3/nl; $P = 0.01$). Adverse events associated with reduced platelet numbers occasionally occurred mainly in patients randomized to NAMR (NAMR vs. placebo; thrombocytopenia: 1.5% vs. 0.5%; platelet count decreased: 0.7% vs. 0.0%).

DISCUSSION

The phosphate-lowering capability of NAMR administered in combination with PBs was evaluated for the first time in a large cohort of patients with ESRD receiving maintenance hemodialysis. Eligible patients could have been on a therapy with all approved and available PBs. Serum phosphate decreased within the first 2 weeks in patients randomized to NAMR (2 capsules; 500 mg/d). After 12 weeks of randomized treatment, a mean daily dose of 950 mg NAMR proved superior over placebo in the primary and in all secondary endpoints. The results of this study are in line with preliminary observations from smaller studies[33–35,43] and demonstrate the potential of NAMR for improving phosphate control in maintenance hemodialysis patients.

This phase III study aimed at superiority over placebo in combination with PB in a double-blind setting. Previous phase III studies with other phosphate-

lowering agents were powered to show noninferiority to other PBs in an open-label setting[44,45] or superiority over placebo after a double-blind randomized withdrawal period.[46] Following prior washout of PBs, change from baseline in serum phosphate was necessarily higher in those studies compared with this study in which eligible patients did not pass through a washout phase. Therefore, the additional reduction of serum phosphate concentration observed in patients randomized to NAMR represents an improved phosphate control relative to screening where patients only received standard of care. In the NAMR group, 50% of patients achieved a phosphate reduction of at least –0.8 mg/dl after 12 weeks of randomized treatment. This was accompanied by a significantly lower serum iPTH concentration compared with placebo. In addition, change of cFGF23 from baseline was significantly different across both treatment groups in a PP analysis. These observations prove the physiological relevance of the additional phosphate reduction and suggest a lower systemic phosphate burden in patients of the NAMR group.

The pan-European prospective observational study COSMOS (Current Management of Secondary hyperparathyroidism – a Multicenter Observational Study) and data from the DOPPS registry demonstrated that 70% of hemodialysis patients do not reach the KDIGO phosphate recommendation of 4.5 mg/dl (i.e., upper level of normal). More than 40% of patients do not meet the less stringent K/DOQI target of 5.5 mg/dl.[14] In our study, the results of the response analyses demonstrate an enhanced target range achievement for patients in the NAMR group. These patients had a 78% higher chance to reach a normal serum phosphate concentration (i.e., KDIGO target of 4.5 mg/dl) compared to patients in the placebo group. As expected, the effect on reaching the K/DOQI target was less pronounced, because some patients could have had a serum phosphate concentration lower than 5.5 mg/dl at screening. Still, the chance to reach this guideline target was 28% higher for patients randomized to NAMR.

Reduction of the serum phosphate concentration in patients randomized to NAMR (mean change of –0.67 mg/dl) was associated with prolongation of the T50 value (mean change of 23.8 minutes), a measure of serum calcification propensity, indicating a relevant biological and potentially vasculoprotective effect of the intervention.[39] These observations are comparable to the EVOLVE study that enrolled more than 3000 hemodialysis patients. In EVOLVE, low T50 values were associated with a higher risk for cardiovascular events and mortality. In a multivariate linear regression analysis using the EVOLVE data, an increase in serum phosphate concentration by 1.49 mg/dl led to a shortening of T50 by around 45 minutes.[40] In a further recent prospective cohort study with a follow-up of 2 years, an increase of 1 minute predicted a reduction in all-cause mortality risk of 0.4% in ESRD patients.[47] Assuming a similar predictive value in the present study, the mean prolongation of T50 by 23.8 minutes would translate into a reduction in all-cause mortality risk of about 10%.

With respect to safety aspects, the results of this study do not allow for a quantitative comparison to other NA-containing preparations. In line with previous observations,[33–35,48–51] the most frequent adverse events associated with the intake of NAMR were gastrointestinal disturbances (diarrhea, nausea, vomiting). In addition, pruritus was reported more often for patients randomized to NAMR compared to patients randomized to placebo. Both, gastrointestinal symptoms and pruritus, often occurred at the beginning of the treatment and resolved either spontaneously or after dose reduction or discontinuation of the study medication. We also observed a reduction of the mean platelet number in the NAMR group of about 10% between screening and W12. A reversible NA-associated reduction of platelets has been consistently reported in the past.[35,48,51,52] The molecular mechanism presumably involves inhibition of poly(ADP-ribose) polymerase by NA itself as well as accumulation of the terminal NA metabolite N-methyl-2-pyridone-5-carboxamide (2PY).[38,53] Along these lines, accumulation of 2PY was documented in patients randomized to NA in the NICOREN study that compared efficacy and safety of NA with sevelamer over the course of 24 weeks after washout of the prior PB therapy. Four patients receiving a daily NA dose of 1000 mg experienced a fall in platelets to <70/nl. In each case, thrombocytopenia resolved within 4 weeks after permanent discontinuation of NA.[48] In this study, platelet reduction occasionally translated into respective adverse events. Importantly, post hoc analysis demonstrated that platelet numbers recovered after permanent discontinuation (data not shown).

Apart from serum phosphate being a surrogate endpoint, this study had some methodologic limitations. Patients started randomized treatment without passing through a run-in phase with repeated measurement of serum phosphate. Thus, we cannot exclude that some patients may have entered the study because of a single elevated serum phosphate concentration value and thus did not bona fide represent patients with therapy-refractory hyperphosphatemia.

All patients received randomized treatment based on a dose titration regimen. Apart from dose adjustments due to adverse events, dose titration was primarily

driven by efficacy. Lack of efficacy necessarily led to higher doses in the placebo group that may have promoted partial unblinding.

Apart from gastrointestinal absorption, excessive bone turnover contributes to elevated serum phosphate concentrations in patients with ESRD. We did not exclude patients with severe secondary hyperparathyroidism and thus did not control for phosphate released from bone. This aspect may have led to an underestimation of the treatment effect.

In conclusion, the results of this phase III study prove the phosphate-lowering potential of NAMR as an add-on therapeutic approach to established, but insufficiently effective, PB therapy in hemodialysis patients. They also show that the additional phosphate reduction achieved may be associated with favorable changes of other CKD-MBD parameters. The improved phosphate control was further accompanied by a reduced serum calcification propensity, thus potentially decreasing the risk of progressive cardiovascular calcification. Therefore, NAMR used in combination with oral PBs is a valid treatment option for hyperphosphatemia in patients receiving maintenance hemodialysis.

DISCLOSURES

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Characteristics and performances of employed assays.

Table S2. Further baseline patient characteristics in the intention-to-treat (ITT) population.

Table S3. Baseline and week 12 (W12) values for high-density lipoprotein, low-density lipoprotein, triglycerides, and lipoprotein(a).

Table S4. Change from baseline to W12 for phosphate and other chronic kidney disease–mineral and bone disorder markers in the ITT population.

Table S5. Frequent treatment-emergent adverse events (≥1% in either treatment group) until W12 in the safety population.

Table S6. CONSORT Checklist

Figure S1. Mean number of capsules between week 2 and week 12.

Supplementary Methods. Inclusion and exclusion criteria according to Protocol Version 3.0

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