Synopsis

Trial title:	Dose-Finding Trial of Nicotinamide in Dialysis-Dependent Patients with Hyperphosphataemia – DONATO- trial –	
Director of clinical investigation:	Prof. Dr. Walter Zidek Charité, Campus Benjamin Franklin, Clinic IV for Internal Medicine, WE 28 Hindenburgdamm 30, D-12200 Berlin	
EudraCT Nr.:	2009-015821-34	
Trial sites:	Multicenter trial in 32 trial sites in Germany	
Publication: -		
Phase: II	First patient in: 15SEP2010	Last patient out: 24JUN2011

Trial objective:

This randomised dose-finding trial compared modified-release nicotinamide at various dose levels and immediate-release nicotinamide in order to find a minimal, tolerated and effective dose for reducing elevated phosphate concentrations in dialysis-dependent patients.

Methods:

National, multisite, randomised, controlled and double-blind (i.e. double-blind to dose in the dose finding part), parallel-group trial. For the dose finding part 4 dose levels of modified-release nicotinamide were administered: 250mg, 500mg, 750mg and 1000mg. For the formulation part a 5th group received 1000mg immediate-release nicotinamide.

Patient numbers:	Screened:	N=361
	ITT population	N=252
	PP population	N=190
	Completed trial	N=152

Diagnostic and main inclusion criteria:

- Male or female patients aged 18 years or older
- Patient dependent on dialysis for more than 3 months
- Patient attends 3 times a week for haemodialysis
- Serum phosphate concentration prior to washout phase < 2.42 mmol/l (7.5 mg/dl)
- Serum phosphate concentration after washout phase > 1.52 mmol/l (4.7 mg/dl)
- Unmodified phosphate binder therapy at least 1 month prior to screening

Main exclusion criteria:

- Patient with severely impaired vision (e.g. macular oedema)
- Decompensated heart failure
- Acute bleeding
- Gastrointestinal bleeding in the last 6 months prior to trial commencement
- Acute myocardial infarction
- Peptic ulcers
- Severe liver parenchymal diseases
- Poorly controlled diabetes
- Uncontrolled hypertension
- Existing or previous vasculitis
- HIV infection
- Patient with dysphagia or swallowing difficulties
- Patient with impaired intestinal motility, pseudo-obstruction, megacolon, mechanical obstruction
- If the patient is on vitamin D replacement therapy, the dose must have remained stable for at least 1 month prior to screening

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History of thrombocytopenia or a platelet count at screening < 120/nl
Active gastroparesis, identifiable from nausea and vomiting
Pathological creatine kinase value (men > 174 U/l, women > 140 U/l) at the start of the trial; the creatine kinase values ≥ 5 times the normal range during the trial (such cases had to be reported as SAE, see the safety chapters below)

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<tr><td colspan="2">Duration of therapy: 1-3 weeks wash-out, 8 weeks treatment phase</td></tr>
<tr><td colspan="2">Dosage: For the dose finding part 4 doses of modified-release (MR) nicotinamide capsules were administered: 250mg, 500mg, 750mg and 1000mg. For the formulation part a 5th group received 1000mg immediate-release (IR) nicotinamide tablets.</td></tr>
<tr><td>Investigational substance:</td><td>modified-release nicotinamide 250 mg capsule: PL4881</td></tr>
<tr><td>Control:</td><td>immediate-release nicotinamide tablets: PL4855</td></tr>
<tr><td>Primary criterion:</td><td>Serum phosphate concentration in mmol/l at Week 4. Comparison of modified-release (MR) nicotinamide at 4 dose levels</td></tr>
<tr><td>Secondary criteria:</td><td>

Comparison of serum phosphate concentration for modified-release (MR) vs. nicotinamide immediate-release (IR) nicotinamide tablets
Serum phosphate concentration: difference baseline versus end value 4 and 8 weeks post randomisation
Number of responders - definition 1: serum phosphate concentration < 1.78 mmol/l (5.5 mg/dl) and < 1.52 mmol/l (4.7 mg/dl) 4 and 8 weeks post randomisation, respectively
Number of responders - definition 2: percentage drop in serum phosphate concentration after 4 and 8 weeks ≥ 20% relative to baseline (post washout)
Serum calcium and iPTH 4 and 8 weeks post randomisation

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<tr><td>Safety analysis:</td><td>

Adverse events
Structured Adverse Events Checklist (AEL), Laboratory parameters and vital signs
Cardiovascular disease
Incidence of fractures during the trial

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<tr><td colspan="2">Statistical methods: The primary efficacy variable was serum phosphate level in mmol/l at week 4. Missing data were replaced by carrying forward the last non-missing observation (LOCF), 47 values had to be imputed this way. The confirmatory analysis was the statistical test for a dose-response relationship between modified release nicotinamide in the dose range 0 to 1000 mg per day and serum phosphate levels, following the intent-to-treat principle (ITT). This test with one-sided significance level of 0.025 is part of the MCPMod framework for dose finding studies. The test takes into account the possibility of different shapes of the dose-response relationship. It also includes the determination of the minimum effective dose (MED) that leads to a significant difference in efficacy in comparison to the control arm (“Compare” group).

It is important to note that the “Compare” group is not the independent placebo group required by the standard method of the MCPMod framework. For ethical reasons, a placebo group was not justifiable in the DONATO trial. Instead, the baseline data of the treatment group 1000 mg IR were used as a surrogate for the Week 4 data of the non-existent placebo group.

Additional sensitivity analyses were performed to test the robustness of the primary analysis with regard to the imputed data (best case, worst case, and no imputation), subgroups, multicentre design and methodology (changes from baseline, linear (mixed) models).

All secondary criteria were analysed exploratively accounting for the variable scale.</td></tr>
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Summary of results:

This Phase II trial was conducted as a national, multisite, randomised, controlled and double-blind (i.e. double-blind to dose in the dose-finding part), parallel-group trial with the purpose of finding an optimum dose of modified-release nicotinamide in dialysis patients with hyperphosphataemia.

For the dose-finding part 4 dose levels of modified-release nicotinamide were administered: 250mg, 500mg, 750mg and 1000mg. For the formulation part a 5th group received 1000mg immediate-release nicotinamide.

After a wash-out period of up to 3 weeks and a 4-weeks medication phase after randomisation, the primary endpoint of serum phosphate concentration was measured. The trial treatment was then continued until week 8 after randomisation.

A total of 361 patients was screened, 252 of which were randomised and received treatment. No patients were lost to follow up. The main reason for trial discontinuation was adverse events (N=61), followed by lack of efficacy (N=10). 159 (63.1%) male and 93 (36.9%) female patients were included in the trial. The mean age was 65 years.

Efficacy:

The main question of this trial was whether there is a dose-response dependency between the 5 dose groups (Compare group, 250 mg, 500 mg, 750 mg and 1000 mg MR). It is important to note that the "Compare" group is not an independent placebo group because, for ethical reasons, a placebo group was not justifiable in the DONATO trial. Instead, the baseline data of the treatment group 1000 mg IR were used as a surrogate for the Week 4 data of the non-existent placebo group. The confirmatory analysis showed a significant ($p<0.0001$) quadratic dose-response shape in reduction of the phosphate level at week 4.

The group medians of the primary analysis differed significantly at W4, and pairwise Mann-Whitney-Wilcoxon testing showed significant differences between the Compare group (2.2 ± 0.5 mmol/l) and the groups 750 mg MR (1.9 ± 0.5 mmol/l) and 1000 mg MR (1.8 ± 0.5 mmol/l). A significant difference was even found for the comparison of the 500 mg MR group (2 ± 0.4 mmol/l) versus the Compare group. This fits the results of the dose finding analysis.

The confirmatory analysis summarized so far relies on LOCF imputation. Using other imputation methods (no replacement, including only completers, using PP-Population or replacing missing values by worst or best individual values) changed the overall means only slightly and did not change the significance of the relationship. The dose-response relationship for nicotinamide MR could also be shown if the 250 mg MR group was used as "Compare group".

A mixed model accounting for the repeated measurements and the multicentre type of the trial showed that there was a significant time component, which was different for the individual treatment groups. This difference in the time component may be connected to the positive dose finding result. The mean phosphate levels between the galenic groups 1000 mg MR and 1000 mg IR did not differ significantly in any week of the trial, and no group had consistently higher means than the other. This was also true for the PP and Completers population.

As another secondary variable, the difference of phosphate levels during the 8 treatment weeks to baseline values was analyzed. The median improvements were significantly different in all weeks with the 1000 mg MR group having the biggest improvements in all weeks, i.e. -0.344 mmol/l in week 4.

On computing the differences between serum phosphate levels during the 8 treatment weeks to screening values, most of the observed differences were positive, which means that levels at

screening were generally lower than those during the trial. In week 4, for example, the minimum difference to screening was +0.065 mmol/l (750 mg MR group), while the maximum difference to screening was 0.309 mmol/l (500 mg MR group). This means that the phosphate levels under the trial medication were generally higher than at screening when patients took their normal phosphate binding medication.

There were three alternative definitions of therapy response. In the first definition a responder had to have a phosphate level below 1.52 mmol/l. Therapy response increased from 0 for the 250 mg MR group to 29% for the 1000 mg MR group in week 4, the global chi square test was significant. The second definition of response demanded a phosphate level below 1.78 mmol/l. The percentages of responders seen in the different groups were about 20% higher as compared to the first definition. Again, the response rates increased with increasing dose, starting from 21% (250 mg MR) and ending at 52% (1000 mg MR) in week 4, resulting in a significant chi square test. The percentage of responders in the two 1000 mg groups did not differ very much for both responder definitions. The third definition of therapy response was a decrease in phosphate level by at least 20% of the baseline value. Again, the percentage of responders increased with dose, starting at 5% for 250 mg MR, ending at 44% for 1000 mg MR in week 4. In this definition 1000 mg MR had 44% responders and was 7% points above the IR group. The global chi square test was again significant.

For calcium levels no trend across dose groups could be observed. The overall mean at screening was 2.24 $\pm$ 0.19 mmol/l and there was a decrease during the wash-out-phase to 2.16 $\pm$ 0.22 mmol/l (baseline), i.e., a decrease from screening to baseline of -0.08 mol/l $\pm$ 0.17 mmol/l and in week 8: 2.22 $\pm$ 0.19 mmol/l.

For iPTH, there were no notably different group mean or median levels or differences to baseline at week 4 or week 8. This is also true for the four galenic groups. More than 67% of the patients had iPTH values between 13.80 and 63.60 pmol/l in week 8 (all patients pooled).

Additionally to the primary and secondary variables the assessment of efficacy was measured with the Clinical Global Impressions Scale (CGI). These efficacy scores were not significant. For all CGI Scores group means generally improved uniformly by small amounts when regarding the PP population. For all scores except the severity subscore (which had no uniform trend across doses) a slightly better efficacy was observed in higher doses, e.g., when the 750 and 1000 mg MR groups were compared to the lower dose groups.

Safety:

Under investigational treatment 485 adverse events were reported in 182 out of 252 patients (72%). 71 events occurred in 30 patients (63%) in the treatment group 250 mg MR, and 138 events occurred in 47 patients (89%) in the treatment group 1000 mg MR (p-value for chi-square test: 0.0022). In the treatment group 500 mg MR the AE were assessed as less severe than in the other treatment groups. 84% of the AE were resolved. 36% of the AE were assessed as possibly or probably related. This number was higher in the treatment group 1000 mg IR (44%), which was the only unblinded treatment group.

AE were also investigated for the subgroups gender, additional statin therapy and for patients with elevated nicotinamide metabolite levels, which occurred only in the treatment groups 750 mg, 1000 mg MR and 1000 mg IR. There is no evidence of a different AE incidence in these subgroups.

1 SAE (chest pain with uncertain myocardial infarction) in the treatment group 250 mg was fatal and 1 SAE (calciphylaxis) that had started before the patient received the investigational product was also fatal.

23 patients suffered from 30 SAE after receiving the investigational product. 7 of the 30 SAE seen in

this trial were hospitalisations due to examinations and shunt revision. 2 SAE were hospitalisation due to renal transplantations and 15 SAE were of cardiovascular nature.

Additionally to the AE reported by the investigator, fractures during the trial, changes in cardiovascular disease and a structured Adverse Events Checklist (AEL) consisting of 21 items were used. The checklist included known side effects of both nicotinamide and nicotinic acid and was handed out as a patient questionnaire.

6[1] patients suffered from a non-fatal myocardial infarction during the trial and 2 patients suffered from a cerebral infarction during the trial. TIA symptomatic did not occur during this trial. 4 patients showed improvements and 4 patients aggravations for the following cardiovascular disease: coronary heart disease, peripheral artery occlusive disease, chronic heart failure, angina pectoris.

No case of fractures occurred during this trial.

The results of the AEL-List are described together with the adverse events reported by the investigator. In general the symptoms of the AEL-list improved during the trial.

The following adverse drug reactions listed in the SmPC of Nicotinamide/Nicotinic acid or mentioned in the IB were confirmed by adverse events and or AEL list seen in this trial: Tachycardia, thrombocytopenia (only some cases of decreased thrombocyte values were seen, but no thrombocytopenia was assessed) or platelet count decreased, palpitations, nausea, diarrhoea, vomiting, abdominal pain, ALT increased, CK increased, glucose tolerance decreased, dizziness, dyspnoea, rash, hyperhidrosis, dry skin, change in anti-diabetic drug medication, flush/flushing.

In the DONATO trial we saw an increased incidence of AE in comparison to the adverse drug reactions listed in the SmPC of Nicotinamide/Nicotinic acid or mentioned in the IB for the following: Visual impairment, atrial fibrillation and arrhythmia, flatulence, fatigue, NAD increased, HDL increased, glucose increased, myalgia, muscle spasms, headache, migraine, insomnia, hypotension, collapse, phosphate decreased.

For some AE the intake of a higher dose of nicotinamide is associated with an increased frequency of AE. This applies to: Diarrhoea, abdominal pain, vomiting and nausea, headache, appetite decreased, glucose increased, NAD and other metabolized products of nicotinamide increased, HDL increased, visual impairment, tachycardia, restlessness, rash, dyspnoea and myalgia.

In this trial we saw some AE that are not listed in the SmPC of Nicotinamide/Nicotinic acid or mentioned in the IB. A decrease in haemoglobin and haematocrit and erythrocytes is seen in the treatment group 1000 mg. AE concerning hypertension or increased blood pressure occurred 35 times and are evenly distributed in the dose groups, but the trial was discontinuated for 6 patients because of elevated blood pressure. Decreased appetite is not listed in the SmPC but was seen 12 times in this trial, with the highest incidence seen in the treatment group 1000 mg. Restlessness was not listed in the SmPC but was seen 9 times in this trial. In this trial we also saw a high rate of myocardial infarctions (N=6), one of which was considered as a SAR.

The following events were observed in lower frequency than in the SmPC of nicotinamide and/or nicotinic acid: Paraesthesia, flush, urticaria, AST increased, ALT increased, uric acid increased.

Flush was reported only in two patients receiving 250 mg nicotinamide. In clinical trials investigating extended release nicotinic acid, nearly all patients experienced flushing. Thus the DONATO trial

[1] In one of these cases this diagnosis was found to be an incorrect interpretation of laboratory values. It is uncertain whether this patient actually suffered from myocardial infarction since expert opinions differ

revealed remarkable differences in the adverse event profile between nicotinamide and nicotinic acid. Beneath flushing another adverse reaction reported for nicotinic acid is liver toxicity including enhanced serum levels of liver enzymes. The DONATO trial revealed no evidence for liver toxicity of nicotinamide. Enhanced AST was not reported and enhancement of ALT was observed only in one patient.

A general assessment of safety measured with the CGI subscore of undesired effects showed a deterioration that increased with dose. 70% of the patients had no undesired effects but for 3% of patients the undesired effects outweighed the therapeutic effect.

Conclusions:

The main question of this trial is whether there is a dose-response dependency. The confirmatory analysis showed a significant ($p<0.0001$) quadratic dose-response shape in reducing of the phosphate level. This was confirmed by several sensitity analyses.

In comparison with other trials investigating fixed doses of phosphate binders, DONATO reveals the efficacy of a 1.000 mg dose of modified-release nicotinamide to be in the same range as that of Lanthanum Carbonate, which is known to be an efficient phosphate binder in comparison to other available therapeutic options.

The DONATO trial revealed significant and relevant serum phosphate reduction (difference to baseline values) only for daily nicotinamide doses of 750 and 1.000 mg. If the difference to screening values was calculated instead, most of the observed differences were positive, which means that the levels at screening were generally lower than those during the trial. This means that the phosphate levels under the trial medication were generally higher than at screening when patients took their normal phosphate binding medication. This is most obvious for the subgroup of patients that received multiple phosphate binding agents, suggesting that a dose limited to 1.000 mg is inadequate for patients with highly elevated phosphate loads. Therefore, future confirmatory trials should also include daily doses higher than 1.000 mg, if they are well-tolerated by the patient. Published studies have shown that nicotinamide can be titrated up to daily doses of 1.750 mg.

Beneath phosphate lowering, DONATO revealed changes in the lipid status in course of nicotinamide treatment. HDL values increased significantly with nicotinamide dose. The highest mean and median values were found in the treatment groups 750, 1000 mg MR and 1000 mg IR at week 4. The opposite effect to HDL was observed for the laboratory values of LDL in the Safety Population. The lowest median values are found in the treatment groups 750 and 1000 mg MR. The effect of nicotinamide on lipid metabolism may have important benefits for dialysis patients and warrants further investigation.

Many of the adverse events described in this trial are typical attendant symptoms or diseases of patients suffering from end stage renal disease (asthenia, fatigue, peripheral oedema, pruritus, nausea, glucose tolerance decreased, dry skin, dizziness, hypertension, myocardial infarction, palpitations, nasopharyngitis, insomnia, blood pressure increased, C-reactive protein increased).

All 6 patients who had myocardial infarction suffered from prior coronary heart diseases and/or multiple risk factors. This reflects the fact that hemodialysis patients generally suffer from strongly increased rates of cardiovascular morbidity and mortality. In the United States, 42% of hemodialysis patients had a history of myocardial infarction or coronary artery revascularization and 40% of hemodialysis patients had a previous episode of cardiac failure. The annual mortality rate due to cardiovascular reasons is 11.2% for hemodialysis patients.

Gastrointestinal disturbances with the leading symptom diarrhoea were observed in most clinical nicotinamide trials in patients with end-stage renal disease. DONATO data confirm and reinforce these findings, since diarrhoea was very common (76 findings in 66 patients) with the highest incidences seen in the high dosage treatment groups. Additionally, nausea, vomiting and abdominal pain are common adverse events.

In summary, it is difficult to assess the safety of nicotinamide in a dose-finding trial, because no comparator (placebo, standard therapy) exists and patients suffering from this indication are multi-morbid. Aspects of patient safety such as occurrence of adverse events need to be assessed in more detail and should be compared to standard phosphate binder and/or placebo therapy. This approach is recommended for further phase III trials.

Patients who received 500 mg nicotinamide MR showed the best safety profile. The self-assessments of adverse events (AEL) for these patients show a low rate of adverse events already at baseline, and these good assessments persist during the whole trial. The phosphate reduction, however, was not sufficient in the treatment group 500 mg. The safety profile of the treatment group 750 mg was better than the safety profile of the 1000 mg (MR and IR) treatment groups. We would recommend that doses be individually titrated in further trials to improve patient safety and to avoid a high rate of discontinuation due to AE.

Clinically relevant improvements in phosphate reduction were visible only in the treatment groups 750 mg MR, 1000 mg MR and 1000 mg IR. Therefore we would recommend that doses in the range of 750 mg to 1000 mg should be individually titrated in further trials to improve patient safety and to avoid a high rate of discontinuation due to AE. In patients who show good tolerance in higher dose ranges, doses even higher than 1000 mg daily should be evaluated.

Date: 21Jun2012