Final Report

1. Name of Sponsor/Company	Charité – Universitätsmedizin Berlin
2. Name of Finished Product	Niaspan®
3. Name of Active Substance	Nikotinsäure
4. Individual Study Table: Referring to Part of the Dossier (Volume, Page)	*Diese Angabe ist nur bei Einreichung in Zusammenhang mit einem Zulassungsdossier erforderlich.*
5. Title of Study	Evaluation of the effect of NICOtinic acid (niacin) on elevated Lipoprotein(a) levels (NICOLa Study)
5.1 Name or abbreviated title of the trial	NICOLa Study
5.2 Sponsor's protocol code number	Ep_Li 001_2006
5.3 EudraCT-number	2006-005710-12
6. Principial investigators	Prof. Dr. Elisabeth Steinhagen-Thiessen Charité Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin Tel. 030 / 450 -553 169, Fax: 030 / 450 -565 969 Stoffwechselcentrum@charite.de Co-Investigator: Dr. Anja Vogt + Dr. Ursula Kassner Charité Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin Tel. 030 / 450 -553 169, Fax: 030 / 450 -565 969 Stoffwechselcentrum@charite.de
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8. Publication (reference)	---
9. Studied period (years)	date of first enrolment: March 2009 date of last completed (dta analysis and data collection: April 2012 Due to difficulties in recruitment, study enrolment was terminated before the targeted sample size was achieved
10. Phase of development	III

11. Objectives

The objective was to evaluate the efficacy of niacin in lowering Lp(a) in patients with elevated Lp(a) levels in comparison to placebo.

12. Methodology

Multicenter, randomised, placebo-controlled, double-blind, 2-arm, parallel-group Phase III intervention study. Subjects were randomised to receive drug therapy (Niacin) or placebo for 20 weeks.

13. Number of patients	Planned: 149 Analysed: 120

14. Diagnosis and main criteria for inclusion/exclusion

Inclusion:

- Male or female subjects, aged 18 – 75 years
- Subjects with and without cardiovascular diseases
- Lp(a) plasma levels > 30 mg/dl
- Triglyceride levels < 400 mg/dl
- Cholesterol and triglyceride levels not requiring immediate change in medication according to current clinical guidelines
- If concurrent statin therapy, stable doses are required in the four weeks prior to study inclusion, and no changes in statin dosages were allowed during the study period

- Subjects willing to follow all study procedures including attendance at practices for scheduled study visits, fasting prior to blood draws and compliance with study treatment regimen
- Written informed consent to participate in the trial

Exclusion:

- Known hypertriglyceridaemia or fasting triglycerides > 400 mg/dl in the last four weeks before the randomisation visit
- Known heterozygous or homozygous familial hypercholesterolaemia or known type III hyperlipoproteinaemia (familial dysbetalipoproteinaemia)
- Documented secondary hypercholesterolaemia of any cause
- Initiation of a lipid-modifying drug treatment or a dose change of a lipid-modifying drug within the last four weeks
- Known hypersensitivity to nicotinic acid or any component of this medication or their derivatives
- Concurrent treatment with products containing significant amounts (more than 100 mg as daily dose) of nicotinic acid (niacin) or nicotinamide (e.g., vitamin preparations and nutritional supplements)
- Concurrent treatment with an immediate release formulation of nicotinic acid or a nicotinic acid analogue, e.g. supplements
- Treatment with an anticoagulant such as marcumar
- Cardiovascular diseases which are contra-indicated: unstable angina, acute myocardial infarction or uncontrolled cardiac arrhythmias within the preceding 3 months, stroke within the preceding 6 months, symptomatic heart failure (NYHA class III or IV), or severe peripheral artery disease
- Pregnant women, women who are breast feeding, and women of childbearing potential who are not using chemical or mechanical contraception (prescription oral contraceptives, abstinence, condoms with spermicide, surgical sterilisation, diaphragm with spermicide, or intrauterine device)
- History of malignancy, except subjects who have been disease free for more than 10 years or whose only malignancy has been basal or squamous cell skin carcinoma. Women with a history of cervical dysplasia were excluded unless 3 consecutive normal cervical smears have subsequently been recorded before entry into the study
- History of alcohol (more than 2 glasses of wine or alcohol equivalent per day) or drug abuse (within 12 months of screening), or both
- Active liver disease or hepatic dysfunction as defined by elevations of AST or ALT >1.5 times the ULN in the last 4 weeks before the randomisation visit
- Known uncontrolled or poorly controlled (HbA1C > 9 %) diabetes
- Persistent uncontrolled or untreated hypertension, defined as either resting diastolic blood pressure of > 95 mmHg or resting systolic blood pressure of > 200 mmHg
- Unexplained serum creatine phosphokinase (CK) > 3 times the ULN in the last 4 weeks before the randomisation visit (e.g. not due to recent trauma, intramuscular injections, heavy exercise etc)
- History of severe myalgia of unknown origin

- Arterial bleeding
- Active peptic ulcer
- Uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins
- Active gout symptoms
- Significant renal insufficiency (serum creatinine > 1.5 mg/dl)
- Planned hospitalizations for diagnostic or surgical procedures within the next 5 months
- Known infectious disease such as hepatitis or HIV
- Participation in another investigational drug trial within the four weeks prior to study entry
- Previous randomisation into this study
- Subjects with serious or unstable medical or psychological condition that, in the opinion of the investigator, would compromise the subject's safety or successful participation in the study.
- Persons who were detained officially or legally to an official institution.

15. Test product, dose and mode of administration, batch number

The active ingredient in the modified release tablets was nicotinic acid (niacin), a B-complex vitamin (Niaspan®). Subjects received an oral dose of 500 mg modified release niacin once a day during the first four weeks of treatment. Thereafter, the dose was gradually increased as follows:

- 1000 mg/day in the four following weeks (week 5-8),
- 1500 mg/day in the four following weeks (week 9-12),

and 2000 mg/day in the eight following weeks (week 13-20)

16. Duration of treatment

Following a run-in / wash-out phase, each subject underwent a screening phase (four weeks at most) and a treatment phase of 20 weeks. At the end of the screening phase, subjects who were eligible in terms of the inclusion and exclusion criteria entered the treatment phase, which started with Visit 1 (week 1) and ended with Visit 5 (week 20).

17. Reference therapy, dose and mode of administration, batch number

The placebo matched Niaspan® and was supplied in blister cards identical to those containing study medication. Quantities of placebo in blister cards and doses corresponded to the respective doses of study medication.

18. Criteria for evaluation:

Efficacy

Subjects were assessed at week –4 (run-in / wash-out), 0a+b (screening phase), 1, 5, 9, 13, and 20. The following variables were assessed prior randomisation: sozio-demographic factors, physical examinations, medical history, concurrent medication, health-related quality of life, costs prior study entry, and lipid as well as other laboratory parameters. Lipid parameters include Lp(a), total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

At follow-up, the respective laboratory analyses and physical examinations were e assessed at each visit. Subjects were investigated with regard to safety and tolerability. Health-related quality of life and costs were assessed at week 9 and 20.

Primary objective

To compare the effect of niacin therapy on mean change in Lp(a) levels to placebo.

Secondary objectives

- To compare the effect of niacin therapy on mean change in plasma lipids levels to placebo
- To compare the effect of niacin therapy on mean change in blood glucose levels to placebo.
- To compare the effect of niacin therapy on health-related quality of life (Short Form (SF)-12, EQ-5D)
- To compare the effect of niacin therapy on cumulative disease-related costs to placebo.
- To compare safety and tolerability in patients with niacin therapy and placebo
- To compare medication adherence with niacin therapy and placebo.

Safety

Adverse events and tolerability were assessed at each follow-up visit (Visit 2-Visit 5). Blood sampling for safety parameters (CK, creatinine, sodium, potassium, phosphorus, uric acid, blood glucose). With regard to laboratory safety data, levels at different Visits and percentages of values out-of-range were described unadjusted over time by treatment group and overall.

With regard to the safety analysis, the evaluable subject population were subjects who have received at least one dose of the trial medication. This was the case for all 120 randomised participants.

19. Statistical methods

The null hypothesis is that the mean change of Lp(a) levels (visit 5 - visit 1) will not differ between patients in the niacin group and patients in the placebo group. The null hypothesis is tested against the alternative hypothesis that the mean change of Lp(a) levels (visit 5 - visit 1) will be different in the niacin and the placebo group.

Sample size is based on the primary endpoint. A difference in mean Lp(a) plasma levels of –15 mg/dl (µ1-µ2, 19-34) with a common standard deviation σ of 24 was assumed. The significance level chosen is α=0.05 and the power 90%. The sample size calculation was based on the t test of equal means with unequal group size (ratio: treatment group / control group = 2:1). Sample size amounted to n2=82 in the niacin group and to n1=41 in the placebo group, yielding an overall sample size of N (n1 + n2) = 123. Assuming a drop out rate of 20%, the sample size increased to N=149 ((n1 + 20%) + (n2 + 20%) = 41 + 9 + 82 + 17 = 50 + 99 = 149).

The ITT population for the efficacy analysis consists of subjects who had a pre-dosing assessment of the primary outcome (the assessment taken prior to randomisation), one post-baseline

assessment and have received at least one dose of trial medication. Additional analyses were performed excluding those patients who were mis-randomised.
The per-protocol population includes all subjects who have been treated according to protocol and fulfilled the following criteria:

- All inclusion / exclusion criteria satisfied
- Adequate study medication compliance
- Dose titration according to the study protocol
- Measurements of laboratory values at visit 1 and visit 5

With regard to the safety analysis, the evaluable subject population were subjects who have received at least one dose of the trial medication.
Health related quality of life (Qol) was assessed using two validated questionnaires. The Short Form-12 Health Survey (SF-12) and the EuroQol-5D (EQ-5D). Qol assessment was conducted at baseline, Visit 3 (8 weeks) and Visit 5 (20 weeks). SF-12 values were aggregated and presented as the mean mental and physical summary score (MSS and PSS, respectively). Similarly, the EQ-5D was aggregated and converted to a single summary index by the application of specifically derived German weights.

Statistical Analysis

Descriptive statistics were used to summarize continuous and categorical variables, including the number of subjects (N), and mean, standard deviation (SD), standard error of the mean (SEM), median, minimum, maximum values, and 95 % confidence intervals (CI) where appropriate. In addition to laboratory values, the demographic characteristics of age, height, weight, body mass index, race, blood pressure and smoking status were presented overall and by treatment group. Data regarding medical history, physical examination findings, and concomitant medications were also summarized in a descriptive way overall and by treatment group.

The primary outcome is the change of Lp(a) levels between visit 5 (week 20) and Visit 1 (visit 5 minus visit 1). The primary efficacy analysis compared mean changes of Lp(a) levels between treatment and placebo group for the ITT population. For missing outcome data, the last observation was carried forward (LOCF). Comparisons between groups were performed using analysis of covariance (ANCOVA) adjusting for Lp(a) levels at baseline. Results are presented as adjusted mean differences (week 20 – baseline) for both groups, with associated 95% confidence intervals and the p-value for the group comparison. Tests are two-sided with level of significance alpha=0.05.

Further analysis for the primary outcome included unadjusted analyses, evaluation of the change over time of Lp(a) levels using repeated measures ANCOVA, and analyses with further adjustments for baseline characteristics. In addition, efficacy outcomes were analyzed for the PP-population

Secondary laboratory outcomes were analyzed similarly to the primary outcome (adjusted for the respective baseline value). For health-related quality of life and disease specific costs, absolute values at Visit 5 were compared, adjusted for baseline values. The incidence of AE was summarised by treatment group and given by unadjusted frequencies and percentages. With regard to laboratory safety data, levels at different Visits and percentages of values out-of-range were described unadjusted over time by treatment group and overall.

Treatment compliance was calculated on the basis of documented returned tablets at visits 2 to 5. Accordingly, participants were classified as compliant with study medication (compliance 80-120%), non-compliant (< 80% compliance), and over-compliant (>120% compliance).

20. Summary – Conclusions

Observational studies and systematic reviews confirm, that Lp(a) is independently and continuously associated with the risk for cardiovascular diseases under a broad range of circumstances (15). The present randomized double blind placebo controlled clinical trial showed, that in patients with elevated Lp(a) levels, treatment with niacin can lead to clinically relevant and statistically significant reductions in Lp(a) compared to placebo. The mean difference in change in Lp(a) was about 18 mg/dl in favour of the niacin group. In addition, niacin therapy resulted in further favourable lipid profile changes including total cholesterol, HDL-cholesterol, LDL-cholesterol, and a trend towards lower triglyceride levels. In contest, a modest but statistically significant increase in glucose levels was observed in participants treated with niacin compared to placebo.
During the treatment period 246 adverse events (excluding flushes) were recorded, at a similar rate in both groups. Although no statistically significant difference in AEs between intervention groups was found, there was a trend towards more AEs, and AEs more frequently leading to action on study medication or withdrawal from the study, in the niacin group. Most common AEs were related to gastrointestinal and muscular symptoms, as well as headaches and migraine. Furthermore, the frequency of flushes in the intervention group was high (84%) and significantly more common in participants treated with niacin compared to placebo (18%).
Despite these differences in incidence of AEs and particularly flushes, Qol was similar in both intervention groups throughout the study. Also, direct, indirect, and total costs during the study did not differ significantly between both intervention groups.

Although the study followed a randomized and placebo controlled study design, some differences between niacin and placebo group at baseline were noted. These differences, however, did not uniformly favour one intervention group and additional adjustments for potentially confounding factors did not alter the results meaningfully. Also, findings were robust in sensitivity analyses. It is therefore unlikely, that the observed effects are a result of confounding.

After adjustment for baseline values in disease specific costs, mean adjusted costs of about 892€ and 1617€ during the 20 week study period in niacin and placebo group, respectively. However, these estimates showed a large variation, were not statistically significant and were mainly driven by few participants in the placebo group that reported very high indirect costs. In contrast, two participants of the niacin group that had high indirect costs at baseline were lost to follow-up which could have influenced the lower indirect costs in this group.

Despite the randomized study design, some limitations of the present study should be noted. Firstly, recruitment to the study was markedly delayed. For that reason, recruitment had to be stopped before the originally targeted sample size could be reached. Secondly, although the study was sufficiently large to provide strong evidence for a difference in the primary endpoint, the study was not powered to detect differences in certain secondary outcomes. Especially with regard to disease specific costs, the observed large difference in mean costs did not translate into statistically significant findings. Thirdly, due to the restrictive selection process of study participants, generalizability of the findings is limited considerably.

Conclusion

In patients with elevated levels of Lp(a) niacin therapy resulted in clinically relevant and statistically significant reductions in Lp(a) and improvements in other lipid parameters. Despite a trend towards more frequent AEs and a large proportion of patients experiencing flushes under niacin therapy, Qol was similar in both groups. Similarly, no statistically significant differences in disease specific costs were found.

20.1 Efficacy Results Change in mean Lp(a) showed a significantly greater reduction in niacin (-11.4 mg/dl; 95% CI: -16.9 to -5.9) compared to participants in the placebo group (6.7 mg/dl, 95% CI: -1.1 to 14.4) (p<0.001). Also, a significantly greater reduction in total cholesterol, high-density-lipoprotein cholesterol, and low-density-lipoprotein cholesterol was observed in niacin participants. With regard to triglycerides no significant difference between groups was observed. A small but statistically significant increase in blood glucose was noted in favour of the placebo group (niacin: 5.9 mg/dl, 95% CI: 2.7 to 9.1; placebo: -1.0 mg/dl, 95% CI -5.5 to 3.5, p=0.016).
20.2 Safety Results With regard to safety outcomes, a trend towards more frequent adverse events and adverse events leading to withdrawal was observed in the niacin group and flushes were significantly more frequent in niacin patients.
20.3 Conclusion In patients with elevated levels of Lp(a) niacin therapy resulted in clinically relevant and statistically significant reductions in Lp(a) and improvements in other lipid parameters. Despite a trend towards more frequent AEs and a large proportion of patients experiencing flushes under niacin therapy, Qol was similar in both groups. Similarly, no statistically significant differences in disease specific costs were found.

21. Date of report	12.07.2021

Annex II Principal or coordinating investigator(s) signature(s)
Annex III a, b Study design and schedule of Assessments
Annex IV b Disposition of Patients

Annex II

PRINCIPAL OR COORDINATING

INVESTIGATOR(S) SIGNATURE(S)

OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE: *Evaluation of the effect of NICOtinic acid (niacin) on elevated Lipoprotein(a) levels (NICOLa Study)*

STUDY AUTHOR(S): Dr. Anja Vogt
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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

INVESTIGATOR: Prof. Dr. Elisabeth Steinhagen-Thiessen
OR SPONSOR'S

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Annex III a

Study design and schedule of Assessments

Study Flow Chart

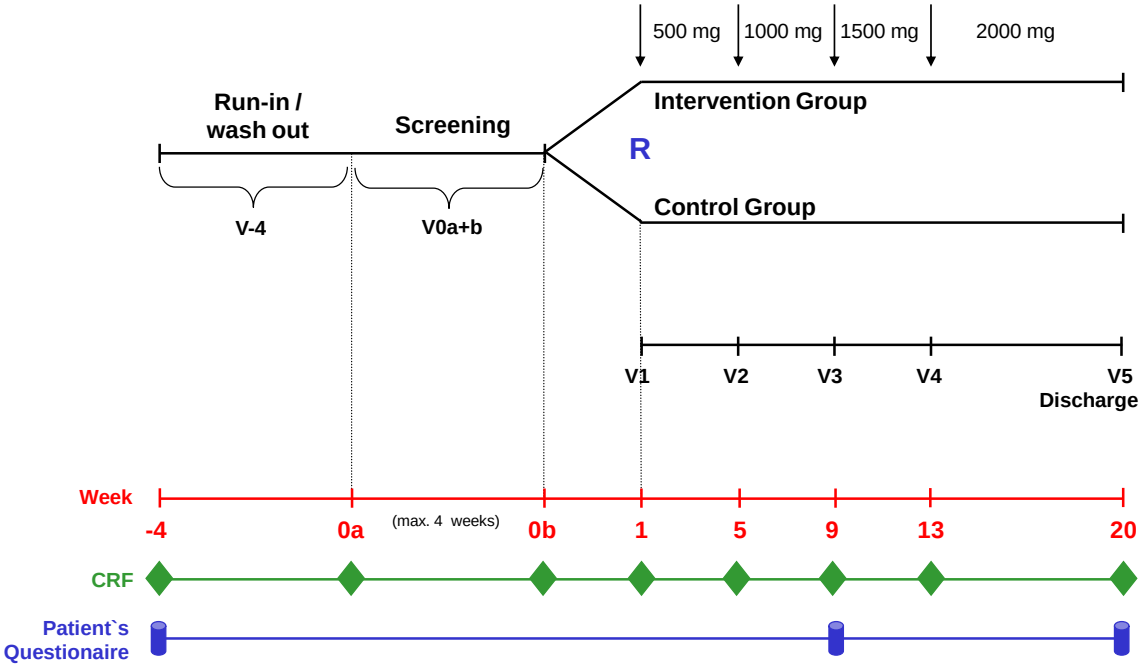
	Run in / wash out	Screening	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	V-4	V0a	V0b	V1	V2	V3	V4	V5
Duration	4 wks	4 wks (maximum)		4 wks ± 3 d	4 wks ± 3 d	4 wks ± 3 d	8 wks ± 3 d	Discharge ± 7 d
Written Informed Consent	✓							
Subject Information	✓							
Medical History	✓							
Inclusion & Exclusion Criteria	✓	✓	✓	✓				
Pregnancy Test*	✓							
Randomisation				✓				
Physical Examination	✓				✓	✓	✓	✓
Laboratory analyses	✓	✓	✓	✓	✓	✓	✓	✓
Begin / End of Treatment				✓				✓
Study Drug Dispensing				✓	✓	✓	✓	
Control Treatment Schedule					✓	✓	✓	✓
Return Study Medication					✓	✓	✓	✓
Concomitant Medication	✓	✓	✓	✓	✓	✓	✓	✓
Safety / Adverse Events					✓	✓	✓	✓
Tablet count (compliance)					✓	✓	✓	✓
Follow up Appointment	✓	✓	✓	✓	✓	✓	✓	
Examination at discharge†								✓
Patient´s Questionnaire	✓					✓		✓

* Women of childbearing potential; as defined by up to 2 years after menopause.
† In case of discontinuation, the examination scheduled for discharge should be performed.

Annex III b

Study design and schedule of Assessments

Study flow



Week	-4	-3	-2	-1	max 4 wks		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	20
Visit	V-4				V0a+b		V1				V2				V3				V4								V5
Medication	run-in / wash-out	run-in / wash-out	run-in / wash-out	run-in / wash-out	screening	screening	500 mg / day	500 mg / day	500 mg / day	500 mg / day	1000 mg / day	1000 mg / day	1000 mg / day	1000 mg / day	1500 mg / day	1500 mg / day	1500 mg / day	1500 mg / day	2000 mg / day	2000 mg / day	2000 mg / day	2000 mg / day	2000 mg / day	2000 mg / day	2000 mg / day	2000 mg / day	Discharge
Laboratory examinations	a)				b)	c)	d)				e)				e)				e)								f)
Vital signs	√				√		√				√				√				√								√
Height	√																										
Weight	√				√		√				√				√				√								√
Waist circumference	√																										√
Waist-to-hip ratio	√																										√
Quality of life	√														√				√								√
Costs	√														√				√								√

Laboratory examinations:

a) Lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), Lp(a), haematology, biochemistry including HbA1c and TSH, coagulation, pregnancy test in women of childbearing age
b) Lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), Lp(a), biochemistry including HbA1c, coagulation
c) Lp(a) indicated only if value 30-45 at V0a

d) Lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, ApoB), Lp(a) including phenotype, liver enzymes, CK

e) Lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, ApoB), Lp(a), liver enzymes, CK, creatinine, sodium, potassium, phosphorus, uric acid, blood glucose

f) Lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, ApoB), Lp(a), haematology, biochemistry including HbA1c,
coagulation

Annex IV b

Disposition of Patients