A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTRE STUDY OF THE EFFICACY AND SAFETY OF NICOTINAMIDE IN PATIENTS WITH FRIEDREICH´S ATAXIA (NICOFA)

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Sponsor`s Study Code	15-138
EudraCT- Number	2017-002163-17
Investigational Product	Nicotinamide
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Status, Version, Date	V03.4, 05.12.2018

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Table of Contents

SYNOPSIS

Item	Description
Study Title	A randomized, double-blind, placebo-controlled, parallel-group, multicentre study of the efficacy and safety of nicotinamide in patients with Friedreich ataxia
Study Short Name	NICOFA
Study Number	15-138
EudraCT-Number	2017-002163-17
Phase	IIb/III
Protocol version	V03.4, 05.12.2018
Registration with ClinicalTrials.gov	NCT03761511
Regulations	In accordance to the Declaration of Helsinki, ICH E6 Guideline for Good Clinical Practice (GCP), German Medicine Act (AMG), Good Clinical Practice Act (GCP- V), Local Rules, regulations and applicable requirements.
Sponsor	RWTH Aachen University for the Medical Faculty, represented by Center for Translational & Clinical Research Aachen (CTC-A) Pauwelsstraße 30, 52074 Aachen, Germany Sponsor's Representative: Dr. med. Susanne Isfort, Managing Director CTC-A Phone: +49 241 80 80092 Fax +49 241 80 33 35849 E-Mail sisfort@ukaachen.de
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Item	Description
Financing	This is an investigator-initiated trial. The trial will be financed by research funding of the clinic (E-rare/DFG).
Insurance	A patient's insurance in accordance to § 40 (1) and (3) No.8 AMG will be completed by the sponsor (the insurance policy number will be filed subsequently).
Risk Benefit Assessment	Nicotinamide is a classical class III HDAC inhibitor (Vaquero et al., 2007), has a good bioavailability, rapidly penetrates all tissues, and readily crosses the blood brain barrier (Hoane et al., 2006; Spector and Kelley, 1979). Nicotinamide has over the past forty years been given at high doses for a variety of therapeutic applications. A review on safety of high-dose nicotinamide has revealed that the therapeutic index of nicotinamide is wide but at very high doses reversible hepatotoxicity has been reported in animals and humans (Knip et al., 2000). Minor abnormalities of liver enzymes can infrequently occur at the high or mega doses. There is no evidence of teratogenicity from animal studies and nicotinamide is not in itself oncogenic; at very high doses it does however potentiate islet tumor formation in rats treated with streptozotocin or alloxan. There is no evidence of oncogenicity in man. Growth inhibition can occur in rats but growth in children is unaffected. High-dose nicotinamide should still, however, be considered as a drug with toxic potential at adult doses in excess of 3 g/day and only applied under supervision. To our knowledge nicotinamide has been applied in Friedreich´s ataxia in such high doses (> 3 g) only in the exploratory, open-label, dose-escalation study in Friedreich´s ataxia in the UK (ClinicalTrials.gov, number NCT01589809) (Libri et al., 2014). Nicotinamide has been given safely for 5 years at about 3 g (1.2 g/m^2) per day to more than 250 individuals including children from 3 years and above, adolescents and adults in an attempt to prevent diabetes in an at-risk population (Gale et al., 2004). No serious adverse effects were observed. In a recent exploratory, open-label and dose-escalation study on ten patients with Friedreich ataxia, nicotinamide was given in single doses, 2-8 g per day oral nicotinamide for 5 days and 8 weeks (Libri et al., 2014). Nicotinamide was generally well tolerated with nausea being the most frequent dose-related adverse event in this study; this was readily controlled with the use of antiemetics and by modification of the dose. Here, nicotinamide was rapidly absorbed after oral administration and generally well tolerated in Friedreich´s ataxia patients after repeated daily dosing for 8 weeks.
Key Words	Rare disease, ZSEA, Nicotinamide, Friedreich ataxia

Item	Description
Study Drug INN	*Nicotinamide* Dose: 0.5 g per capsule Mode of administration: oral Adult: 4 g per os per day (8 capsules)
Comparator Drug(s) INN if applicable (International Nonproprietary Name)	Matching Placebo
Indication	Friedreich ataxia
Medical Study Rationale	Friedreich ataxia is the most frequent early-onset autosomal recessive hereditary ataxia. It is caused by a pathological expansion of a GAA repeat in the first intron of the frataxin gene (FXN) and results in decreased levels of FXN protein. FXN deficiency results in a relentlessly progressive neurodegenerative condition which frequently presents around puberty. Patients gradually lose coordination, become dysarthric and are frequently wheel-chair bound as adolescents. There is no disease modifying therapy and many patients die prematurely of cardiomyopathy. It was subsequently found that the FXN gene is silenced at the chromatin level by the formation of heterochromatin and that this heterochromatin formation can be antagonized by histone deacetylase inhibitors (HDACi) (Chan et al., 2013). A recent proof-of-concept clinical study on ten patients with Friedreich ataxia demonstrated that FXN levels can be restored to those seen in asymptomatic carriers using the class III HDACi nicotinamide at a dose that is well tolerated by patients (Libri et al., 2014). Since carriers are asymptomatic, this degree of restoration of FXN expression might be expected to halt disease progression. Nicotinamide readily crosses the blood brain barrier and has previously been given at high doses for long periods to normal individuals without serious adverse effects (Gale et al., 2004; Knip et al., 2000). This study will be the first to provide clinical evidence for the efficacy and safety of nicotinamide in patients with Friedreich´s ataxia.
Primary Objectives	To evaluate the efficacy of daily doses of nicotinamide in slowing disease progression as measured by changes in the Scale for the Assessment and Rating of Ataxia (SARA) as compared with placebo in patients with Friedreich´s ataxia.

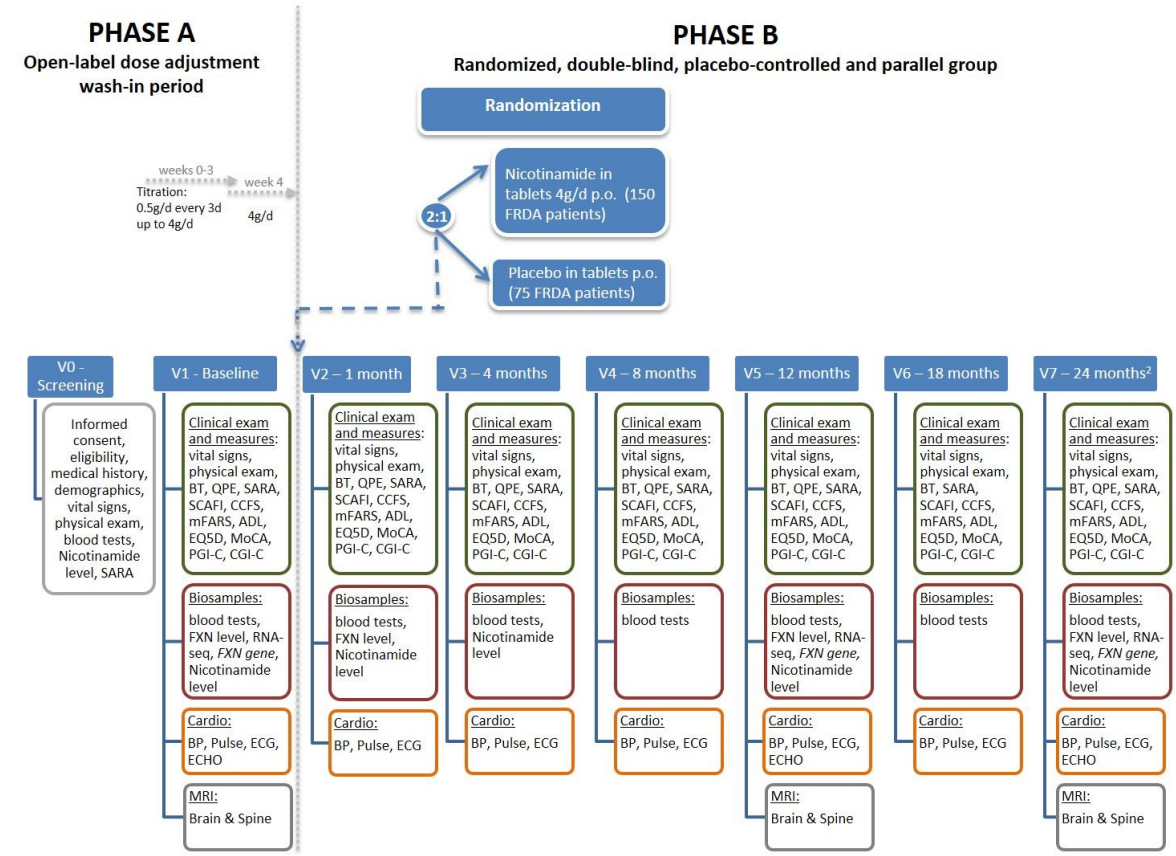
Item	Description
Secondary Objectives	To determine the change of secondary endpoints such as quality of life, functional motor and cognitive measures, clinician's and patient's global impression-change scales as well as frataxin protein level, safety reasons and survival/death under treatment of daily doses of nicotinamide as compared with placebo in patients with Friedreich´s ataxia.
Tertiary Objectives	To evaluate cognition, cardiac and spinal cord/brain measures.
Evaluation Criteria	**Primary endpoints:** ▪ Change in the Scale for the Assessment and Rating of Ataxia (SARA). **Secondary endpoint:** ▪ Quality of life (EQ5D, ADL), functional (SCAFI, CCFS), modified Friedreich Ataxia Ratings Scale (mFARS) and cognitive measures (MoCA), clinician's and patient's global impression-change scale (CGI-C, PGI-C), frataxin protein level, safety reasons and survival/death.
Study Design	***Phase A*** (weeks 1-4): Open-label dose adjustment wash-in period with nicotinamide immediately followed by ***Phase B*** (weeks 5-104): Multicentre, prospective, controlled, double-blind, randomized, two arm parallel, placebo-controlled, phase IIb/III study, with a 2:1 allocation ratio.
Study Duration	24 months per patient, in total 36 months including evaluation and clinical study report. The recruitment period will last 12 months, and data cleaning, processing, analysis and reporting about 3 months.
Patients Number	In total 225 patients (75 patients control arm and 150 patients treatment arm). Screening is expected to be necessary in 360 patients.

Item	Description
Inclusion Criteria	1. Patients must have a molecular genetic diagnosis of Friedreich ataxia with a GAA-repeat expansion on both alleles of the FXN gene and a SARA Score >7 and <28. 2. Patients must be ≥18 and <50 years old and have a weight of at least 50kg. 3. Written informed consent prior to study participation. 4. A female subject is eligible to participate if she is of: Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea or of childbearing potential and agrees to use of highly effective birth control methods (Pearl Index < 1).
Exclusion Criteria	1. Patients with any medical condition or illness that, in the opinion of the investigator would interfere with study compliance and/or impair the patient´s ability to participate or complete the study. 2. Any uncontrolled medical or neurological/neurodegenerative condition (other than Friedreich ataxia). 3. Clinically significant psychiatric illness (e.g., uncontrolled major depression, schizophrenia, bipolar affective disorder) within 6 months prior to screening. 4. Patients with significant clinical dysphagia. 5. Hypersensitivity to nicotinamide. 6. Patients known to be positive for human immunodeficiency virus (HIV). 7. Patients with a significant history of substance abuse (e.g. alcohol or drug abuse) within the previous six months before enrolment. 8. Patients with a history of severe allergies to medications. 9. Indication of impaired liver function as shown by an abnormal liver function profile at screening (e.g., repeated values of aspartate aminotransferase [AST], alanine aminotransferase [ALT] and bilirubin ≥3 × the upper limit of normal). 10. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor: • Subjects with cancers in remission more than 5 years prior to screening. • Subjects with a history of excised or treated basal cell or squamous carcinoma.

Item	Description
	• Subjects with prostate cancer in situ. 11. History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants. 12. History of clinically significant cardiac disease (ejection fraction < 40% [normal range 50-70%], cardiac insufficiency defined as New York Heart Association [NYHA] Class >2; clinically significant congenital or acquired valvular disease; symptomatic coronary disease such as prior myocardial infarction or angina, B-type natriuretic peptide (BNP) level increase more than 2 x of the normal age- and gender dependent range; history of unstable arrhythmias, history of atrial fibrillation). 13. The subject received an investigational drug within 30 days prior to inclusion into this study. 14. Patients taking sodium valproate, tranylcypromine or any other known histone deacetylase inhibitor. 15. Use of vitamin B1 (thiamine), withdrawal should be at least 3 months prior screening or 5 half-lives, whichever is longer. 16. Use of vitamin B3 (nicotinamide), withdrawal should be at least 3 months prior screening. 17. If patients are taking idebenone or coenzyme Q_{10} (CoQ), this should be stable over the last three months and not changed during the study. 18. The subject is unwilling or unable to provide written informed consent and to follow the procedures outlined in the protocol. 19. For subjects who will undergo an MRI: Any contraindications to MRI such as, but not limited to cardiac pacemaker, implanted cardiac defibrillator, aneurysm clips, carotid artery vascular clamp, neurostimulator, implanted drug infusion devices, metal fragments or foreign objects in the eyes, skin or body, bone growth/fusion stimulator, cochlear, otologic implant, severe claustrophobia or any condition that would counterindicate an MRI scan. 20. Patients participating at start or have been within 30 days before start of study in another pharmacological and non-pharmacological clinical trial, excluding natural history / observational studies. 21. The subject is mentally or legally incapacitated. 22. Pregnant females as determined by positive [serum or urine] hCG test at Screening or prior to dosing. Participants of child-

Item	Description
	bearing age should use adequate contraception as defined in the study protocol. 23. Lactating females.
Treatment and Visits	Treatment: ***Phase A*** (weeks 1-4): Open-label dose adjustment wash-in period with nicotinamide: All patients will be slowly titrated with an increase of 0.5 g nicotinamide every three days up to a dose of 4 g/day Thus, the titration period will be three weeks, patients should then be stable on 4g/d or the highest tolerated dose for one week. Phase A is immediately followed by a 2:1 randomization. ***Phase B*** (weeks 5-104): Multicentre, prospective, controlled, double-blind, randomized, two arm parallel, placebo-controlled, phase IIb/III study, with a 2:1 allocation ratio. Adult patients will receive *nicotinamide* 4 g p.d. or placebo for a period of 24 months (minimum dose: 2 g p.d.). The blood chemistry will be evaluated at screening, baseline as well as 1, 4, 8, 12, 18 and 24 months after initiation of the therapy. If a patient is eligible to participate in the study according to the in- and exclusion criteria the patient will randomly be assigned to one of the two treatment arms. The randomisation of eligible patients will take place after all screening examinations are completed and prior to the treatment phase. A randomisation code will be assigned for each randomised patient. This code will be used to label all information that are gathered for each patient (e.g. blood samples and case report forms (CRFs) and to label the study medication. The Randomisation list will be prepared by Department of Medical Statistics of the RWTH Aachen University Hospital, using randomizeR. The lists will be sent to the pharmacy for packaging the treatments to be applied and maintain concealment and double blinded treatment allocation.
Sample size and Statistics	Power calculation

1 Study Flow Chart



¹Duration of recruitment 1 year; ²starting open-label study; at all visits adverse events will be recorded, analysed and followed-up;. Abbr.: ADL, Activity of Daily Living; BP, blood pressure; BT, body temperature; CCFS, Composite Cerebellar Functional severity; CGI-C, Clinician's Global Impression-Change Scale; ECG, electrocardiogramm; ECHO, echocardiogramm, EQ5D, EuroQol five dimensions questionnaire; *FXN*, Fratxain; FARS, Friedreich Ataxia Rating Scale; MoCA, Montreal Cognitive Assessment; MRI, Magnetic Resonance Imaging; PGI-C, Patient's Global Impression-Change Scale; SARA, Scale for the Assessment and Rating Ataxia; SCAFI, Spinocerebellar Ataxia Functional Index; QPE, Questionnaire about physical exercise; V, visit

Visit Schedule

Study Period	**Screening**	**Phase A** 1 month	**Phase B** 23 months					
Visit No.		**1**	**2**	**3**	**4**	**5**	**6**	**7**
Activity		**Baseline**	**Randomization** 1 month	**4 month**	**8 month**	**12 month**	**18 month**	**EOS (End of Study)** 24 month
Visit window +/- calendar days			**±3 days**	**±1 week**	**±1 week**	**±1 week**	**±1 week**	**±1 week**
Informed consent	X							
Inclusion/ Exclusion criteria[1]	X							
Medical history	X							
Pregnancy test	X	X	X	X	X	X	X	X
Demography		X						
Vital signs[2], respiratory rate, resting pulse, height and weight	X	X	X	X	X	X	X	X
Blood pressure[2]	X	X	X	X	X	X	X	X
Body temperature	X	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)		X	X	X	X	X	X	X
Echocardiogram (ECHO)		X				X		X
Quest. about exercise (QPE)		X	X	X	X	X	X	X
Clinical measures[3] SCAFI, CCFS, mFARS, ADL, EQ5D, MoCA, CGI-C, PGI-C		X	X	X	X	X	X	X

Study Period	**Screening**	**Phase A** **1 month**	**Phase B** **23 months**					
Visit No.		**1**	**2**	**3**	**4**	**5**	**6**	**7**
Activity		**Baseline**	**Randomization** **1 month**	**4 month**	**8 month**	**12 month**	**18 month**	**EOS (End of Study)** **24 month**
Visit window +/- calendar days			**±3 days**	**±1 week**	**±1 week**	**±1 week**	**±1 week**	**±1 week**
Scale for the Assessment and Rating Ataxia (SARA)	X	X	X	X	X	X	X	X
Standard laboratory evaluation[4]	X	X	X	X	X	X	X	X
Up-regulation of Frataxin (FXN) protein level		X	X			X		X
Gene expression of *Frataxin (FXN)* gene		X				X		X
RNA-Sequencing of *Frataxin* gene		X				X		X
PK sampling (nicotinamide level)	X	X	X	X		X		X
MRI (brain and spine)		X				X		X
Concomitant medication	X	X	X	X	X	X	X	X
Adverse events evaluation		X	X	X	X	X	X	X

[1] might include genetic testing, if participants are not included in the EFACTS registry
[2] after at least 15 minutes of resting
[3] ADL, Activity of Daily Living; CCFS, Composite Cerebellar Functional severity; CGI-C, Clinician's Global Impression-Change Scale; EQ5D, EuroQol five dimensions questionnaire; INAS, Inventory of Non-Ataxia Signs; MoCA, Montreal Cognitive Assessment; PGI-C, Patient's Global Impression-Change Scale; SCAFI, Spinocerebellar Ataxia Functional Index
[4] Hematology (total and differential blood count) and blood chemistry

1.1 Abbreviations

AAV	Adeno-associated Virus
ADL	Activity of Daily Living
AE	Adverse Event
BfArM	Federal Institute for Drugs and Medical Devices
BNP	Brain Natriuretic Peptide
CCFS	Composite Cerebellar Functional Severity
CGI-C	Clinicians's Global Impression-Change Scale
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
CTC-A	Center for Translational & Clinical Research Aachen
DNA	Deoxyribonucleic Acid
DRG	Dorsal Root Ganglion
EBV	Epstein - Barr Virus
EC	Ethics Committee
ECG	Electrocardiogramm
eCRF	Electronic Case Report Form
EFACTS	European Friedreich´s Ataxia Consortium for Translational Studies
EOS	End of Study
FARS	Friedreich´s Ataxia Rating Scale
FAS	Full Analysis Set
FRDA	Friedreich´s Ataxia
FU	Follow up visits
FXN	Frataxin
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDACi	Histone Deacetylase Inhibitors
ICH	Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product

INAS	Inventory of Non-Ataxia Signs
IP	Investigational Product
IRB	Institutional Review Board
LMEM	Linear Mixed Effect Model
LV	Left ventricular
MMRM	Mixed effect Model Repeat Measurement
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
Nrf2	Nuclear factor (erythroid-derived 2) – like 2
PBMC	Peripheral Blood Mononuclear Cell
PGI-C	Patient's Global Impression-Change Scale
PEV	Position Effect Variegation
RNA	Ribonucleic Acid
RWTH	Rheinische Westfälische Technische Hochschule
SAE SAER	Serious Adverse Event Serious Adverse Event Report
SARA	Scale for the Assessment and Rating Ataxia
SCA	Spinocerebellar Ataxia
SCAFI	Spinocerebellar Ataxia Functional Index
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operation Procedure
QPE	Questionnaire about physical exercise
WOCBP	Women of Childbearing Potential
ZSEA	Zentrum für Seltene Erkrankungen Aachen

2 Study Rationale and Clinical Relevance

Friedreich ataxia is the most frequent early-onset autosomal recessive hereditary ataxia. It is caused by a pathological expansion of a GAA repeat in the first intron of the frataxin gene *(FXN)* and results in decreased levels of FXN protein. FXN deficiency results in a relentlessly progressive neurodegenerative condition which frequently presents around puberty. Patients gradually lose coordination, become dysarthric and are frequently wheel-chair bound as adolescents. There is no disease-modifying therapy and many patients die prematurely of cardiomyopathy. It was subsequently found that the *FXN* gene is silenced at the chromatin level by the formation of heterochromatin and that this heterochromatin formation can be antagonized by histone deacetylase inhibitors (HDACi) (Chan et al., 2013). A recent proof-of-concept clinical study on ten patients with Friedreich´s ataxia demonstrated that FXN levels can be restored to those seen in asymptomatic carriers using the class III HDACi nicotinamide at a dose that is well tolerated by patients (Libri et al., 2014). Since carriers are asymptomatic, this degree of restoration of FXN expression might be expected to halt disease progression. Nicotinamide readily crosses the blood brain barrier and has previously been given at high doses for long periods to normal individuals without serious adverse effects (Gale et al., 2004; Knip et al., 2000). This study will be the first to provide clinical evidence for the efficacy and safety of nicotinamide in patients with Friedreich ataxia.

2.1 Description of evidence and medical need

Friedreich ataxia (FRDA) is an autosomal recessive inherited ataxia. This devastating and incurable neurodegenerative disease often manifests in childhood and in many cases leads to severe disability by early adulthood. Although FRDA is the most common hereditary ataxia in caucasian populations, however, with an estimated prevalence of about 2–4/100,000 people, it remains a rare disease (Schulz et al., 2009) In 1996, the genetic mutation that underlies most Friedreich ataxia cases (Campuzano et al., 1996) was discovered as a homozygous pathological expansion of GAA triplet repeats in the first intron of the frataxin *(FXN)* gene, which encodes for the mitochondrial protein frataxin. *FXN* deficiency results in spinocerebellar ataxia, dysarthria, proximal weakness, sensory loss and cardiomyopathy, and leads to dependence on a wheelchair and reduced life expectancy with a mean of 20 years after disease onset. Many Friedreich ataxia patients die from cardiomyopathy. To date, there is no disease-modifying therapy for this disabling progressive disease.

Before a phase IIa trial (Libri et al., 2014) with nicotinamide was initiated in patients, careful preclinical studies were performed. First, nicotinamide was tested on EBV-transformed lymphoblastoid cell lines (Chan et al., 2013). Modest up-regulation of *FXN* mRNA levels was obtained in patient-derived cell lines with relatively little effect on FXN expression in the normal control cell line. Second, to assess the effect of nicotinamide under more physiological conditions, fresh primary lymphocytes derived from Friedreich ataxia-affected or normal healthy individuals were treated. A small effect (2-fold increase) in *FXN* mRNA level was produced for healthy primary cells after nicotinamide treatment suggesting that minor chromatin effects might occur at the healthy *FXN* locus. Notably, the increase in *FXN* mRNA level in Friedreich ataxia individuals was much larger (4.5-fold). Third, in Friedreich ataxia transgenic mice (Al-Mahdawi et al., 2006) treated with nicotinamide for 6 days with a dose of

750 mg/kg increases of *FXN* mRNA expression were found in all Friedreich´s ataxia – relevant tissues and the most substantial increases, in terms of fold up-regulation, were observed in spinal cord and cerebellum with 1.8-fold up-regulation of frataxin (Chan *et al.*, 2013). Taken together, these results strongly suggest that nicotinamide can reactivate the silenced *FXN* gene in both human Friedreich ataxia cells and *in vivo* transgenic Friedreich´s ataxia models. Also, mechanistic preclinical investigations were performed. Treating primary lymphocytes from Friedreich ataxia patients with nicotinamide strongly reduced the disease-associated increase in histone H3K9 and H3K27 trimethylations and increased the histone acetylation at the *FXN* gene. Furthermore, the DNase I accessibility at the *FXN* gene was increased in Friedreich ataxia patient cells. High-throughput RNA sequencing on libraries generated from untreated and nicotinamide-treated Friedreich ataxia primary lymphocytes revealed that 67% of the genes known to be dysregulated in Friedreich´s ataxia was ameliorated by the treatment. Thus, it was demonstrated that expanded GAA-triplet repeats can induce gene silencing *in vivo* leading to the archetypal epigenetic gene silencing phenomenon of position effect variegation (PEV) (Saveliev et al., 2003). This GAA-repeat silencing was exquisitely sensitive to the gene dosage of PEV modifiers which encode enzymes that modify chromatin. Moreover, it was demonstrated that the *FXN* gene is silenced at the chromatin level by the formation of heterochromatin. This heterochromatin formation can be antagonized by histone deacetylase inhibitors (HDACi) (Chan et al., 2013). Nicotinamide is a classical class III HDACi.

2.2 Rationale and Clinical Evidence

Friedreich ataxia is an autosomal-recessive inherited disorder due to a gene mutation resulting in expansion of a repeating DNA sequence (GAA) which partially switches off the frataxin gene. The deficiency of frataxin causes the disease. A recent exploratory, open-label and dose-escalation study on ten patients with Friedreich´s ataxia demonstrated that frataxin levels can be restored towards asymptomatic carrier levels using nicotinamide (Libri et al., 2014). Friedreich ataxia patients were given single doses, as well as repeated daily doses of 2-8 g oral nicotinamide for 5 days and 8 weeks. Nicotinamide was generally well tolerated with nausea being the most frequent dose-related adverse event in this study. In addition nicotinamide has a good bioavailability and rapidly penetrates all tissues, readily crosses the blood brain barrier, and has previously been given at high doses from 1.2 g/m^2 up to 3 g/d for long periods (up to 5 years) to normal individuals including children from 3 years and above, adolescents and adults without serious adverse effects (Gale et al., 2004). Moreover, a sensitive clinical rating measure to assess disease progression, the Scale for the Assessment and Rating of Ataxia (SARA) is now available, which was proved most suitable to measure clinical disease progression within the registry of the European Friedreich´s Ataxia Consortium for Translational Studies (EFACTS, www.e-facts.eu) framework. Other current clinical trials in Friedreich ataxia (based on www.clinicaltrials.gov) stratified by their mechanism of action are:

I. Antioxidants and mitochondrial enhancers: Two phase 3 trials using idebenone as a mitochondrial enhancer and antioxidant showed a negative outcome (Lynch et al., 2010) despite a very positive phase 2 trial (Di Prospero et al., 2007). The antioxidant α-tocopheryl quinone (A0001) was tested in a randomized placebo-controlled phase 2

trial for 28 days and resulted in a neurological improvement. There is no registered follow-up trial. The approach to scavenge mitochondrial iron overload with deferiprone resulted in a negative outcome in a randomized, placebo-controlled phase 2 trial. There is an ongoing phase 2 trial using the Nrf-2 activator RTA-408 to improve mitochondrial function (NCT02255435).

II. Frataxin stabilizers, enhancers and replacement: Erythropoietin has been shown to increase frataxin protein concentration by posttranscriptional/-translational mechanisms (Mariotti et al., 2013). However, a long term study of 48 weeks did not show any neurological improvement and did not replicate the findings of frataxin up-regulation in PBMCs (Sacca et al., 2016). Furthermore, frataxin up-regulation was not replicated in a phase 2 trial with carbamylated erythropoietin (Boesch et al., 2014).

III. Increase of frataxin gene expression by epigenetic mechanisms: In addition to the strategy of using nicotinamide as a HDAC inhibitor, a specific HDAC class 1 inhibitor, RG 2833 (or HDACi 109), was developed and similarly to nicotinamide showed an increase in frataxin mRNA and protein expression in the blood of patients with Friedreich ataxia in a phase 2 trial (Soragni et al., 2014). However, the development of this drug was discontinued due to side-effects and poor penetration of the blood brain barrier. An effect of resveratrol to increase frataxin expression in PBMCs could not be demonstrated in a phase 2 trial (Yiu et al., 2015). In a non-blinded twelve-week phase 2 trial subcutaneous injection of interferon γ-1b led to a small but significant increase in frataxin levels in red blood cells, platelets and PBMCs (Seyer et al., 2015). A phase 3 trial on interferon γ-1b in the US was initiated (NCT02415127) but had a negative outcome (press release).

IV. Increase of frataxin gene expression by virus-mediated gene transfer: In animal models, very promising results have been published to treat manifest cardiomyopathy with AAV-mediated gene (Perdomini et al., 2014). Similar results using viral gene transfer with tropism to DRG neurons do not exist so far.

Although our knowledge about the pathophysiological processes and clinical progression has increased substantially over the last years, all vigorous international attempts to establish a disease-modifying therapy for Friedreich ataxia have failed to show any beneficial effect. Thus, many patients are severely disabled by adulthood or die prematurely of cardiomyopathy. Previous clinical trials have all focussed on attempts to ameliorate the downstream effects of *FXN* deficiency (Perlman, 2012). They all lacked statistical significance, indicating that more specific and potent candidate drugs, as well as more sensitive clinical measures and better-powered clinical trial designs are needed. Recent research now provides both,

(1) a novel and radical therapeutic cost-effective approach to restore FXN expression, and

(2) sensitive clinical measures.

If successful, this therapeutic approach could be applied to the growing number of diseases which have been shown to be caused by a similar mechanism.

3 Aim of Study

The aim of the study will have a direct impact on health care – in terms of the first treatment for the chronic and devastating neurodegenerative disease Friedreich ataxia. To date, there is no cure or treatment that can slow down the disease which frequently results in severe disability by early adulthood. Patients become progressively more dependent on carers and frequently die prematurely of heart disease. This multinational study NICOFA will investigate whether nicotinamide is an effective treatment for Friedreich´s ataxia.

3.1 Primary objectives

The primary objective of the study is to evaluate the efficacy of daily doses of nicotinamide in slowing disease progression as measured by changes in the Scale for the Assessment and Rating of Ataxia (SARA) as compared with placebo in patients with Friedreich ataxia.

3.2 Secondary objective

Secondary objectives are to determine the change of secondary endpoints such as quality of life, functional motor and cognitive measures, clinician's and patient's global impression-change scales as well as the up-regulation of the frataxin protein level, safety and survival/death.

3.3 Tertiary objectives

Tertiary objectives are mainly neuroimaging measures of the central nervous system (spinal cord and brain).

4 Investigational Drug and Comparator

4.1 Investigational Drug

The investigational study drug nicotinamide (3-Pyridinecarboxamide), licensed in the EU, will be obtained from Euro OTC Pharma GmbH (Edisonstraße 6, 59199 Bönen) and will be produced according Good Manufacturing Practice (GMP) regulations by an approved manufacturer pharmacists at the University of Mainz in Germany.

4.1.1 Packaging, Labelling and re-supply of Investigational Product (IP)

The Randomization list prepared by Department of Medical Statistics of the RWTH Aachen University Hospital, Aachen in Germany using randomizeR is stratified by center. The lists will be sent to the pharmacy before packaging the treatments. The packaging will be done at the pharmacy of the University in Mainz, Germany. The pharmacy will send out the packages (placebo or drug) that are labelled according to the randomization list.

4.1.2 Management of IMP

Administration of IMP to patients will be delegated to the responsible study nurse by the investigator. The study nurse will document charge number, expire date and randomization number and will maintain the drug accountability log (including return of IMP by patients).

4.1.3 Administration of IMP

Subjects will receive an oral dose of 4 g/d nicotinamide (pyridine-3-carboxylic amide, [formula $C_6H_6N_2O$]) or a dose of placebo once a day for the time period of two years.

4.1.4 Advice for using the IMP

Subjects will be instructed to take the study medication once a day (4g/d or placebo, 8 capsules) in the morning after breakfast at approximately the same time a day throughout the study. Subjects will swallow the study medication whole, and will not manipulate or chew the medication prior to swallowing.

Daily dosing of 3.5-6 g has been shown to upregulate frataxin expression. However, treatment above 4 g/d (such as 6-8 g/d) is associated with nausea. Our experience is that if nicotinamide is introduced gradually nausea is frequently transient and resolves over a few days.

To maintain blinding, there will be a *Phase A (weeks 1-4):* All patients will be slowly titrated with an increase of 0.5 g nicotinamide every three days up to a dose of 4 g/day [titration would be: 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 g per day]. Thus, the titration period will be three weeks, patients should then be stable on 4g per day or the highest tolerated dose for one week. If nausea or vomiting occur it is at the discretion of the investigator to flexible reduce the dosing and then reach the highest possible dose. Domperidone as first choice medication (1-3 x 10 mg/day) and/or metoclopramide as second choice (1-3 x 10 mg/day) may be used individually as rescue treatments.

Phase B (week 5 - 104): Phase A is immediately followed by a 2:1 randomization. Randomization includes safety visit. ⅓ of the FRDA patients will be withdrawn from active

treatment and switched to placebo. ⅔ of the FRDA patients will stay on active treatment with 4 g nicotinamide per day or the highest tolerated dose of phase A. The switch from phase A to phase B will be done without discontinuation of treatment to prevent a second titration period.
Again, in the event of nausea, the dose will be adjusted and the patient will be maintained on the maximum tolerated dose (MTD). A telephone safety assessment following each dose increment will allow dose-adjustment if necessary. The minimal dose would be 2 g/d. Dose escalation will be adjusted or stopped on the basis of tolerability and anti-nausea treatments will be given when needed.
Drug will be dispensed to the subject at each clinic visit.
Between clinic visits, subjects will be responsible for establishing a process for reliable outpatient dosing to ensure dosing compliance. To facilitate compliance assessment, a dosing diary will be supplied to the subject, who will be instructed to record the time for each daily doses of study medication. Subjects will be instructed to bring the completed diary to the clinic at the time of each visit, along the used and in-use packs to assess compliance.
If a subject misses a scheduled dose, that dose should be taken as soon as possible, but not later than 12 hours beyond the scheduled time of administration. If it is greater than 12 hours beyond the scheduled dose, the subject should be instructed to skip that dose and resume dosing at the next regularly scheduled time. Missed doses and reasons for missed doses should be recorded on the dosing diary.

Storage conditions:
Receipt, usage and return must be documented on the respective forms for Drug Accountability of the Center for Translational & Clinical Research Aachen. Account will be given for any discrepancy. See instruction of use (SmPC).

4.2 Placebo
The approved manufacturer pharmacists at the University of Mainz in Germany will further provide an oral dose of placebo with identical appearance.

4.3 Preclinical data of Nicotinamide
See Summary of Product Characteristics (SmPC).

4.4 Benefit Risk Assessment
Nicotinamide is a classical class III HDAC inhibitor (Vaquero et al., 2007), has a good bioavailability and rapidly penetrates all tissues, readily crosses the blood brain barrier (Hoane et al., 2006; Spector and Kelley, 1979). Nicotinamide has over the past forty years been given at high doses for a variety of therapeutic applications. A review on safety of high-dose nicotinamide has revealed that the therapeutic index of nicotinamide is wide but at very high doses reversible hepatotoxicity has been reported in animals and humans (Knip et al., 2000). Minor abnormalities of liver enzymes can infrequently occur at the high or mega doses. There is no evidence of teratogenicity from animal studies and nicotinamide is not in itself oncogenic; at very high doses it does however potentiate islet tumor formation in rats treated with streptozotocin or alloxan. There is no evidence of oncogenicity in man. Growth inhibition can

occur in rats but growth in children is unaffected. High-dose nicotinamide should still, however, be considered as a drug with toxic potential at adult doses in excess of 3 g/day and only applied under supervision. To our knowledge nicotinamide has been applied in Friedreich ataxia in such high doses (> 3 g) only in the exploratory, open-label, dose-escalation study in Friedreich´s ataxia in the UK (ClinicalTrials.gov, number NCT01589809) (Libri et al., 2014). Nicotinamide having been given safely for 5 years at about 3 g (1.2 g/m^2) per day to more than 250 individuals including children from 3 years and above, adolescents and adults in an attempt to prevent diabetes in an at-risk population (Gale et al., 2004). No serious adverse effects were observed. In a recent exploratory, open-label and dose-escalation study on ten patients with Friedreich ataxia (Libri et al., 2014), nicotinamide was given single doses, repeated daily doses of 2-8 g oral nicotinamide for 5 days and 8 weeks. Nicotinamide was generally well tolerated with nausea being the most frequent dose-related adverse event in this study; this was readily controlled with the use of antiemetic's and by modification of the dose. Here, nicotinamide was rapidly absorbed after oral administration and generally well tolerated in Friedreich ataxia patients after repeated daily dosing for 8 weeks.

4.5 Known adverse events for Nicotinamide

The following most common adverse events have been described in the exploratory, open-label, dose-escalation study by (Libri et al., 2014): Nausea, headache, lightheadedness, vomiting, hypersomnia, fatigue, diarrhea, raised AST and ALT, falls, anorexia, migraine, dizziness, sore throat, retching, cold, fever, infections, cough, anemia, flu-like symptoms.

4.5.1 Dose-Response Assessment

The following section accords the Opinion of the Scientific Committee on Food on the tolerable upper intake levels of Nicotinamide, European Commission, Brussels, Belgium 17-April-2002:

Vasodilatory effects (flushing)

The flushing reported with nicotinic acid does not occur following nicotinamide, either given as an intravenous injection (Bean and Spies, 1940) or when it is given orally at high-doses to patients with diabetes (Knip et al., 2000).

Gastrointestinal effects

Gastrointestinal effects are rare following high-dose treatment with nicotinamide (Knip et al., 2000). Nausea was reported in a single subject who had taken nicotinamide 3 g daily followed by 9 g per day for several days (Winter and Boyer, 1973).

Hepatotoxicity

Only one patient has been reported to have developed hepatitis after nicotinamide alone, and this subject had been given 3 g daily followed by 9 g per day for several days (Winter and Boyer, 1973); other subjects who developed liver disease after nicotinamide had also received prolonged treatment with nicotinic acid (Rader et al., 1992).
Increased serum transaminase levels were reported for 17 out of 41 children with attention deficit disorders treated for 12 weeks with daily doses of 3 g nicotinamide, in combination with

1.2 g pantothenic acid, 3 g ascorbic acid and 0.6 g pyridoxine (Haslam et al., 1984).
Whether this hepatotoxic effect was related to the high dose of nicotinamide, or to the combination with the high doses of pantothenic acid, vitamin C and pyridoxine, cannot be concluded from this study, and therefore, this study cannot be used in risk assessment of nicotinamide.
The supplementation trials on the use of nicotinamide to prevent or delay the development of diabetes mellitus have not reported hepatitis as an adverse effect (Knip et al., 2000); however these have involved smaller number of subjects, have been of shorter duration and at lower doses than the trials on the use of nicotinic acid for the treatment of hypercholesterolaemia. Ten newly diagnosed Type 1 diabetic patients were given 1 g/day for 45 days (Mendola et al., 1989), and compared over the following year with a group who were treated with placebo; the authors reported that no adverse effects were observed when physical, biochemical and haematological parameters were considered (no details of the tests were given and the main aim of the paper was to study efficacy). A group of 35 patients, aged 6 to 18 years, were given either placebo (n=17), or up to 1.5 g/day of slow-release nicotinamide (n=18) for 12 months (Chase et al., 1990); various tests, including measurement of serum transaminases, alkaline phosphatase and bilirubin, were performed after 4 and 12 months, and remained normal in all subjects. No adverse effects were reported in a group of nine Type 1 diabetic patients with ketosis given 3 g of nicotinamide per day, three of whom were treated for up to 12 months, compared to 7 similar patients given placebo (Vague et al., 1987).
Major long-term studies in patients with Type 1 diabetes mellitus, at dosages of 2-3 g of nicotinamide per day, have been undertaken recently [ENDIT - (Pociot et al., 1993); IMDIAB III - (Pozzilli et al., 1995); DENIS - (Lampeter et al., 1998)]. The ENDIT (European Nicotinamide Diabetes Intervention Trial) has reviewed the safety data on nicotinamide before starting the clinical phase, but no results of the trial have yet been published (Knip et al., 2000; Pociot et al., 1993). The IMDIAB III study involved a double-blind trial in which 28 newly diagnosed patients with Type 1 diabetes mellitus were given 25 mg/kg bw of nicotinamide daily for 12 months, and a similar number treated with placebo; no adverse effects were reported and biochemical parameters including liver and kidney function were normal during follow-up (the publication describes the measurement of bilirubin). The DENIS trial (Deutsche Nicotinamide Intervention Study) was a study in young children (average age 3 years) at high risk of developing Type 1 diabetes mellitus in which 25 subjects were randomized to receive nicotinamide (1.2 g per m^2 per day), and 30 to receive placebo; the trial continued for 3 years and during this period all biochemical markers (including alanine aminotransferase, aspartate aminotransferase and bilirubin) were in the normal range.

Cardiac Events

In more than 40% of patients with FRDA the heart is affected as well. Hypertrophic cardiomyopathy is a recognized cause of premature death in Friedreich Ataxia, by arrhythmia or cardiac failure, reducing life expectancy to 29 to 38 years. Thus, we expect ongoing cardiac events during the study and the cardiac situation needs and will be controlled upon a regular basis (see study design).

Glucose intolerance

Nicotinamide has been studied in relation to reducing the risk of the development of diabetes mellitus; none of the studies (see above) has reported a worsening of symptoms in the treated groups.

Other effects and overall dose-response relationships

There have been no other adverse effects reported following the administration of nicotinamide in trials in patients with diabetes. Determination of the NOAEL from the intervention trials is difficult, because of the different dosage regimens employed. Studies have used fixed doses of 1 g/day (Mendola et al., 1989), 1.5 g/day (Chase et al., 1990), 3 g/day (Vague et al., 1987), 25 mg/kg bw/day (IMDIAB III trial) and 1.2 g/m^2/day (DENIS trial). These different doses can be calculated on a body weight basis using the data on body weights or ages in the different publications; the doses approximate to 17 mg/kg bw/day [(Mendola et al., 1989); average age 18.3 years), 37 mg/kg bw/day (Chase et al., 1990); average age 12.5 years), 43 mg/kg bw/day adults (Vague et al., 1987), 25 mg/kg bw/day (IMDIAB III trial; ages in the range 5-35 years) and 50-40 mg/kg bw/day (DENIS trial; ages 3-12 years]. The lowest of these values (25 mg/kg bw/day) was from one of the largest published studies, and this has been used as the NOAEL for nicotinamide.

5 Study Design and Duration

5.1 Study Design

This clinical trial contains two phases:

Phase A (weeks 1-4): Open-label dose adjustment wash-in period with nicotinamide: All patients will be slowly titrated with an increase of 0.5 g nicotinamide every three days up to a dose of 4 g/day [titration would be: 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 g per day]. Thus, the titration period will be three weeks, patients should then be stable on 4g/d or the highest tolerated dose for one week. Phase A is immediately followed by a 2:1 randomization.

Phase B (weeks 5-104): Multicentre, prospective, controlled, double-blind, randomized, two arm parallel, placebo-controlled, phase IIb/III study, with a 2:1 allocation ratio.

***Nicotinamide* Group (2/3):** *Nicotinamide* 4 g (capsules) or highest tolerated dose with a minimum of 2 g/d *per os* once daily

Placebo Group (1/3): Matching Placebo (capsules) once daily

5.2 Study Duration

The recruitment of patients for the inclusion of the study will start 2019. The expected duration of study inclusion will be 12 months; the study will be 24 months per patient and in total 36 months including evaluation and clinical study report.

5.3 Stratification

The study will be stratified according to center. There are ten centers to be included in the trial: Aachen, Bonn, Tübingen, Munich (all in Germany), Innsbruck (Austria), Milan (Italy), Paris (France), 2x London (ICL & UCL, UK) and Madrid (Spain).

Accordingly, the randomization list prepared by Department of Medical Statistics of the RWTH Aachen University Hospital, using randomizeR is stratified by center. The packaging following the randomization list will be done in Mainz, Germany, labelled and A or B. The allocation of the nicotinamide or placebo group to A or B will be balanced by study site. This will maintain concealment and double blinded treatment allocation.

5.4 Allocation Ratio

Patients will be allocated to treatment groups by randomization stratified by center. The Randomisation list will be prepared by Department of Medical Statistics of the RWTH Aachen University Hospital, using randomizeR. A 2:1 allocation ratio favouring the active treatment is intended. To make the trial more attractive to FRDA patients, we will use a 2:1 randomisation, in which the probability that a patient is assigned to the experimental treatment arm is 2/3. The best practice randomization procedure to minimize the impact of selection and time trend bias on the type one error will be selected *via* a simulation study (ERDO).

6 Study Population

6.1 Number of Patients

N=225 (n=75 control arm; N=150 treatment arm). Screening is expected to be necessary in 360 patients. Patients will be recruited *via* EFACTS, ataxia outpatient centers and patient advocacies.

6.2 Inclusion Criteria

Subjects, fulfilling the following inclusion criteria are suitable for participation in the study:

1. Patients must have a molecular genetic diagnosis of Friedreich ataxia with a GAA-repeat expansion on both alleles of the FXN gene and a SARA Score >7 and <28.
2. Patients must be >18 and <50 years old and have a weight of at least 50kg.
3. Written informed consent prior to study participation
4. A female subject is eligible to participate if she is of: Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of spontaneous amenorrhea or of childbearing potential and agrees to use of highly effective birth control methods (Pearl Index < 1).

6.3 Exclusion Criteria

Subjects, fulfilling one or more of the following exclusion criteria will not be included in the study:

1. Patients with any medical condition or illness that, in the opinion of the investigator would interfere with study compliance and/or impair the patient´s ability to participate or complete the study.
2. Any uncontrolled medical or neurological/neurodegenerative condition (other than Friedreich ataxia).
3. Clinically significant psychiatric illness (e.g., uncontrolled major depression, schizophrenia, bipolar affective disorder) within 6 months prior to screening.
4. Patients with significant clinical dysphagia that will be screened with dysphagia screening questionnaire.
5. Hypersensitivity to nicotinamide.
6. Patients known to be positive for human immunodeficiency virus (HIV).
7. Patients with a significant history of substance abuse (e.g. alcohol or drug abuse) within the previous six months before enrolment. Substance abuse refers to the harmful or hazardous use of psychoactive substances, including alcohol and illicit drugs.
8. Patients with a history of severe allergies.
9. Indication of impaired liver function as shown by an abnormal liver function profile at Screening (e.g., repeated values of aspartate aminotransferase [AST], alanine aminotransferase [ALT] and bilirubin ≥3 × the upper limit of normal).
10. History of malignancy or carcinoma. The following exceptions may be made after discussion with the Sponsor:

- Subjects with cancers in remission more than 5 years prior to screening.
- Subjects with a history of excised or treated basal cell or squamous carcinoma.
- Subjects with prostate cancer in situ.

11. History or evidence of an autoimmune disorder considered clinically significant by the Investigator or requiring chronic use of systemic corticosteroids or other immunosuppressants.
12. History of clinically significant cardiac disease (ejection fraction < 40% [normal range 50-70%], cardiac insufficiency defined as New York Heart Association [NYHA] Class >2; clinically significant congenital or acquired valvular disease; symptomatic coronary disease such as prior myocardial infarction or angina, B-type natriuretic peptide (BNP) level increase more than 2 x of the normal age- and gender dependent range; history of unstable arrhythmias, history of atrial fibrillation).
13. The subject received an investigational drug within 30 days prior to inclusion into this study.
14. Patients taking sodium valproate, tranylcypromine (monoamine oxidase inhibitor [MAOI]) or any other known histone deacetylase inhibitor.
15. Use of vitamin B1 (thiamine), withdrawal should be at least 3 months prior screening or 5 half-lives, whichever is longer.
16. Use of vitamin B3 (nicotinamide), withdrawal should be at least 3 months prior screening.
17. If patients are taking idebenone or coenzyme Q_{10} (CoQ), this should be stable over the last three months and not changed during the study.
18. The subject is unwilling or unable to provide written informed consent and to follow the procedures outlined in the protocol.
19. For subjects who will undergo an MRI: Any contraindications to MRI such as, but not limited to cardiac pacemaker, implanted cardiac defibrillator, aneurysm clips, carotid artery vascular clamp, neurostimulator, implanted drug infusion devices, metal fragments or foreign objects in the eyes, skin or body, bone growth/fusion stimulator, cochlear, otologic implant, sever claustrophobia or any condition that would counterindicate an MRI scan.
20. Patients participating at start or have been within 30 days before start of study in another interventional clinical trial.
21. The subject is mentally or legally incapacitated.
22. Pregnant females as determined by positive [serum or urine] hCG test at Screening or prior to dosing. Participants of child-bearing age should use adequate contraception as defined in the study protocol.
23. Lactating females.

6.4 Subjects of Reproductive Potential

Women during pregnancy and lactation must not be included in the study. Before entering the study and at every visit a pregnancy test has to be conducted to exclude pregnancy.

Female patients capable of bearing children should inform their sexual partner of their participation in this clinical study and use highly effective methods of birth control such as abstinence, sterilization, birth control pills, Depo-Provera injections, or contraceptive implants during treatment and for an additional 1 month after the end of treatment.

Male patients should inform their sexual partner of their participation in this clinical study and use highly effective methods of birth control such as abstinence, vasectomy, or condom in combination with hormonal birth control or barrier methods used by women during treatment and for an additional 3 months after the end of treatment.
Vasectomised partner is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

7 Study Procedures

7.1 Informed Consent

The patient must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed. The Patient information leaflet and Informed Consent Form to be used must be revised by the sponsor and approved by the Ethics committee of the study site. Each patient's chart will have his or her signed ICF and/or assent form for study participation attached to it. It must also be available for any required inspection. Written and verbal versions of the Patient Information Sheet and Informed Consent will be presented to the patients detailing all pertinent aspects of the study procedures to be taken no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the patient is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. The patient will be allowed as much time as wished to consider the information, and the opportunity to ask any question at any time to the Investigator, whether he/she will participate in the study. Written Informed Consent will be given voluntarily by the patients and obtained by means of a patient‘s dated signature and dated signature of the study principal investigator who presented and obtained the informed consent. Other physician investigator / study personnel who obtained the consent must be suitably qualified and experienced, and have been authorized to do so by Principal Investigator. A copy of the signed Informed Consent will be given to the patient. The original signed form will be retained at the study site (in the study file).

7.2 Overview Study Treatment

7.2.1 Screening and eligibility assessment

Patients are pre-screened by the study nurse of the centre to select those patients who meet the inclusion and exclusion criteria. Every patient fulfilling the inclusion criteria will be proposed by the investigator to participate to this trial. The subjects will voluntarily confirm their willingness after complete information about their disease, options of treatment, potential outcomes, risk and benefits of several therapies, and trial process, including number of visits, clinical and laboratory determinations, and time of follow-up. The informed consent of all aspects of the trial that are relevant to the subject's decision to participate has to be in writing and verbally by the investigator.

In detail, the screening procedures will be realized with the following information and determinations:

Demographics
The major demographic factors such as date of birth, gender, race, weight, height, smoking and drinking habits, and type of anticonception when applicable will be recorded on CRFs (see also Data Management and Validation Plan [DMVP]).

Medical History
Details of any history of disease, medical history, or clinical relevant surgical interventions.

Concomitant Medication
All over-the-counter or prescription medication, vitamins, and/or herbal supplements will be recorded on CRFs.

Physical Examination / Vital signs
Height, weight and body temperature will be recorded on CRFs.
Resting pulse, blood pressure (BP) and respiratory rate measurements will be measured after the participant has sat for at least five minutes.

Questionnaire about physical exercise (QPE)
At each visit, physical exercise performance of the study participants will be obtained (average duration in minutes per week, frequency, kind of exercise (e.g. aerobic, strength), change in contrast to exercise performance before). We will further request not to change their typical physical exercise performance during the study.

Laboratory tests
The following routinely used laboratory tests will be necessarily determined at baseline in all potential participants:

Hemoglobin levels, white blood cell count (total and differential blood count), creatinine, glomerular filtration rate, bilirubin levels, blood urea, aspartate aminotransferase [AST] and alanine aminotransferase [ALT], blood glucose, HbA1c, PTT, Quick/INR, CRP and BNP (should be measured in the morning, fasten and at rest [not after any exercise]). All laboratory results will be reviewed and the reports signed by the investigator who will record in the CRF whether they are normal, abnormal but not clinically significant, or abnormal and clinically significant. In the latter case the eligibility of the participants will be reviewed.

As the following are of particular interest in terms of safety, we apply the following definitions:

Liver function tests such as aspartate aminotransferase [AST] and alanine aminotransferase [ALT]: According to previous definitions used in the phase II study for nicotinamide in Friedreich ataxia, we define mild increase as 3-5x upper normal limit (Grade 1), moderate as >5-20x

upper the normal limit (Grade 2) and severe raised LFT as >20x upper the normal limit (Grade 3) (Libri et al., 2014).

Bilirubin: mild increase (Grade 1): < 1.5 x normal limit; moderate increase (Grade 2): >1.5 – 3 x upper normal limit; sever increase (Grade 3): > 3 – 10 x upper normal limit.

B-type natriuretic peptide (BNP) level: in general, a cut-off of > 200 pg/ml is used, however as these results are age- and gender-dependent, we extend this to values that are 2 times upper the normal level.

7.2.2 Subsequent assessment

For each visit, we will consider inclusion of:

1. Eligibility check.
2. Assessment of endpoints/outcome measures.
3. Assessments of safety including general (e.g. physical examination; electrocardiogram), specific safety assessments (e.g. specific laboratory tests according to the applicable product information and/or population, clinical assessments (e.g. specific questionnaires) and adverse event collection.
4. Dispensing of study drugs.
5. Assessment of compliance with study drugs.
6. Recording of concomitant medications.
7. Lab test to evaluate treatment response as defined in the schedule.

7.2.3 End of trial assessment

The end of trial will be the date of the last scheduled visit of the last participant. The end of trial study (EOT) visit form should include:

1. Assessment of endpoints/outcome measures.
2. Assessments of safety including general (e.g. physical examination; echocardiography; echocardiogram), specific safety assessments (e.g. specific laboratory tests according to the applicable product information and/or population; MRI), clinical assessments (e.g. specific questionnaires) and adverse event collection.
3. Assessment of compliance with study medication.
4. Recording of concomitant medications.

7.3 Blinding

This trial is double-blinded. After randomization neither the patients nor the investigator or sponsor will be aware of the treatment allocation. Patients assigned to one of the double-blinded treatment will take Nicotinamide capsules or matching placebo. The capsules will be identical in appearance. The involved staff of the Department of Medical Statistics of the RWTH Aachen University Hospital as well as the involved staff of the pharmacy are aware about the randomized treatment allocation sequence but keep the list and information concealed till closure of the database. Neither the Department of Medical Statistics of the RWTH Aachen University Hospital nor the pharmacy are involved in patient recruitment.

7.4 Unblinding Procedures

In the event of medical emergency which requires identification of an individual patient's treatment, investigators will be able to access information *via* decoding envelopes, which can be found along the packages, but not given to the patients and can be collected at the monitor visits. The randomization centre should be contacted before unblinding and the reason for unblinding should be documented in the medical records.

The responsible biostatistician from the Department for Medical Statistics at the RWTH Aachen University ensures best data quality and that no unblinded data will be given to the participating centers. Information provided to investigators, patients and raters will be limited as possible.

7.5 Package and Labelling of IMP and Placebo

Master Label for Primary and Secondary Packaging (German & English Version):

Hersteller: Apotheke der Universitätsmedizin, Langenbeckstr. 1, D-55131 Mainz, Tel. 06131-17-5359
Sponsor: Center for Translational & Clinical Research (CTC-A), Uniklinik RWTH Aachen, Pauwelsstr. 30, 52074 Aachen; Tel.: 0241 80 80092

NICOFA

Protocol No.: 15-138
EudraCT-Nr.: 2017-002163-17

Kruke enthält XXX Kapseln Nicotinamid oder Placebo zur oralen Einnahme
1 Kapsel enthält 500 mg Nicotinamid oder Placebo
Dosierung: _____ Kapseln pro Tag (vom Prüfarzt einzutragen)
Gruppe: _____ (A oder B)
Patientennummer: _____ (vom Prüfarzt einzutragen)

Medikationsnummer: _____

Verwendbar bis: DD.MM.JJJJ Ch.-B.: SJJJJ/XXX/XXX

Die Kapseln sind vor Licht geschützt und nicht über 25°C und für Kinder unzugänglich aufzubewahren!
Zur klinischen Prüfung bestimmt!

Producer: Apotheke der Universitätsmedizin, Langenbeckstr. 1, D-55131 Mainz, Tel. 06131-17-5359
Sponsor: Center for Translational & Clinical Research (CTC-A), Uniklinik RWTH Aachen, Pauwelsstr. 30, 52074 Aachen; Tel.: 0241 80 80092

NICOFA

Protocol No.: 15-138

EudraCT-No.: 2017-002163-17

Pot contains XXX capsules Nicotinamid or Placebo for oral intake
1 capsule contains 500 mg Nicotinamid or Placebo
Dose: _____ capsules per Day (entered by investigator)
Group: _____ (A or B)
Patient No.: _____ (entered by investigator)

Medication No.: _____

Useable till: DD.MM.YYYY Ch.-B.: SJJJJ/XXX/XXX

The capsules are to be stored in the packaging carton, protected from sunlight, not above 25°C and out of the reach of children. Destined for clinical trial!

7.6 Compliance

Patients will be asked to bring all trial medication to each trial visit. Capsules will be counted by the corresponding study nurse and compliance will be calculated in a worksheet which must be kept as a source document.

8 Treatment Details

8.1 Variables

8.1.1 Efficacy

To prove efficacy with respect to the primary and secondary endpoints, a linear mixed effects model (LMEM) will be used with the fixed effects of treatment, treatment-by-time interaction, center, baseline score and age as well as the random intercept and time. The primary as well as the secondary efficacy endpoints will be evaluated over the Full Analysis Set (FAS), which is the set of subjects who have been randomized and have taken at least one dose of nicotinamide or placebo.

8.1.1.1 Primary endpoints:

The primary endpoint is SARA, validated for Friedreich ataxia and shown to be the most suitable measure of disease progression in Friedreich ataxia (Burk et al., 2013; Reetz et al., 2015; Reetz et al., 2016).

8.1.1.2 Secondary endpoints:

Secondary endpoints will include:

1) Progression of quality of life measures such as the `Activity of Daily Living´ (ADL) scores, part of the `Friedreich ataxia rating scale´ (FARS), and the EuroQol five dimensions questionnaire (EQ-5D)
2) Modified Friedreich Ataxia Rating Scale (mFARS) (Subramony et al., 2005). Modified FARS scores are defined as the sum of scores for bulbar function, upper limb coordination, lower limb coordination, and upright stability (or the total FARS score minus the PNS score)
3) Progression of `Spinocerebellar Ataxia Functional Index´ (SCAFI) (Schmitz-Hubsch et al., 2008)
4) Progression of `Composite Cerebellar Functional Severity´ (CCFS), which has been validated in children and adults with Friedreich ataxia (Filipovic Pierucci et al., 2015)
5) Up-regulation of frataxin protein level
6) Clinician's Global Impression-Change Scale (CGI-C) including comparison of change to the last visit
7) Patient's Global Impression-Change Scale (PGI-C) including comparison of change to the last visit
8) Safety
9) Survival/ death

8.1.1.3 Tertiary endpoints:

Tertiary endpoints will include:

1) Progression of the `Montreal Cognitive Assessment´ (MoCA)
2) Active modification of the *FXN* locus, as measured by chromatin immunoprecipitation and chromosome confirmation capture sequencing
3) Percentual change in left ventricular mass index as measured by echocardiogram

4) Structural and functional changes of the brain and spinal cord, measured by magnetic resonance imaging (MRI)

All recruiting centers will be asked to perform spinal/brain tertiary measures, however they will be optional, as they are of explorative nature and partly depending on existing infrastructure (e.g. MRI scanner).

8.2 Methods

8.2.1 Blood Collection for serum chemistry and biomarkers

At V1, V5, V7 approx. 50 ml; V3, V4 and V6 approx. 30 ml and at V2 approx. 20 ml blood sampling will be performed as shown below:

Visit	Parameter	Material collected [mL]
V1, V2, V3, V4, V5, V6 and V7	**Central Lab**	20 or 30
V1, V5 and V7	**Research Lab**	20
Total amount / visit		**20-50 mL**
Total amount / study		**260 mL**

Measurements for serum chemistry and haematology are performed by the central labs at the sites. The liver enzymes need to be monitored by a medical team member. When abnormal liver enzymes are recognized, medication will be adjusted or even terminated (as described in section 10).

All patients that are included in the EFACTS registry (www. e-facts.eu) will have genetic testing performed at the Laboratory of Experimental Neurology at the Université Libre de Bruxelles in Brussels, Belgium. In the case of participating only in the NICOFA clinical trial but not in EFACTS, we will require blood samples evaluating genetic analyses. This should be send to Prof. Dr. Massimo Pandolfo, Laboratoire de neurologie expérimentale [Laboratory of Experimental Neurology], Campus Erasme, Hopital Erasme et bâtiment C, niveaux 2 et 3, campus universitaire Erasme, Bruxelles, Belgium (phone: +32-2-555.39.92/ 41.15/ 42.17/ 41.16/ 64.08, fax +32-2-555.39.42, email: massimo.pandolfo@ulb.ac.be).

Blood samples for evaluating nicotinamide level, RNA-Sequencing of Frataxin gene or gene expression of Frataxin (FXN) gene are send to Prof. Dr. Jörg B. Schulz at the Department of Neurology, RWTH Aachen University, Pauwelsstr. 30, 52074 Aachen, Germany (phone: +49 241 808900, E-mail: jschulz@ukaachen.de). Nicotinamide level will be measured by the

Institute for Occupational and Social Medicine at the RWTH Aachen University Hospital (Prof. Thomas Kraus).

Blood samples for evaluating frataxin level are send to Prof. Dr. Richard Festenstein at the Department of Medicine, Imperial College London, Room 2003, MRC Building, Hammersmith Campus, Du Cane Road, London, W12 ONN, United Kingdom (phone: +44 20 3313 8310, E-mail: r.festenstein@imperial.ac.uk).

8.2.2 Transthoracic echocardiography (ECHO)

For systolic function: Left ventricular ejection fraction (EF), LV end-systolic volume and LV end-diastolic volume will be determined by manual tracing of end-systolic and end-diastolic endocardial borders using apical 4-chamber and 2-chamber views, employing biplane Simpson's Method. Left atrial volume will be determined by manual tracing of end-systolic endocardial borders using apical 4-chamber and 2-chamber views with LA volume being calculated by (0.85 x A1 (LA area 4-chamber view) x A2 (LA are 2-chamber view))/ L (length of the left atrium in 4-chamber view). Endsystole will be marked as aortic valve closure in apical long axis views. For regional wall motion LV segments were defined according to the standardized myocardial segmentation model of the American Heart Association.
For diastolic function: Peak E: early diastolic mitral inflow velocity, LA volume and LV annular flow (e') by tissue doppler technique, E/e' ratio and 2D and novel 3D parameter global Strain Rate E by myocardial deformation imaging.

8.2.3 Pregnancy Test

For all females of child-bearing potential, pregnancy testing (urine β-hCG pregnancy) will be performed at each visit.

8.2.4 Vital signs and physical exam

Will include resting systolic and diastolic blood pressure and pulse including respiratory rates at a supine position after at least 5 minutes resting and will be measured at every visit. The physical exam includes a basic medical including cardiological, pulmonal and gastro-intestinal, and neurological clinical examination.

8.2.5 Clinical measures and rating scales

Modified Friedreich Ataxia Rating Scale (mFARS)

The modified Friedreich Ataxia Rating Scale (mFARS) scores are defined as the sum of scores for bulbar function, upper limb coordination, lower limb coordination, and upright stability or the total FARS score minus the PNS score (Subramony et al., 2005).

Activity of Daily Living (ADL)

Activities of Daily Living (ADLs) are tasks related to personal care. The ADL score looks at four of these tasks: transfer, bed mobility, toileting and eating. For functional staging we will use the ADL assessment that is incorporated into the Friedreich ataxia rating scale (FARS).

EuroQol five dimensions questionnaire (EQ-5D)

Applicable to a wide range of health conditions and treatments, the EQ-5D health questionnaire provides a simple descriptive profile and a single index value for health status.

Spinocerebellar Ataxia Functional Index (SCAFI)
Quantitative performance measures or timed tests are used to supplement the results of clinical rating scales. Presumed advantages include high interrater and retest reliabilities. The SCAFI is composed of a timed 8m walk at maximum speed (8MW), the 9-hole peg test (9HPT), and the PATA rate, a measure of speech performance. SCAFI was validated in a large multi-center cohort of SCA patients.

Composite Cerebellar Functional Severity (CCFS)
The CCFS is a simple and validated method for assessing cerebellar ataxia over a wide range of severity. The pegboard and click tests are easy to perform and accurately reflect the severity of the disease.

Montreal Cognitive Assessment (MoCA)
The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visual constructional skills, conceptual thinking, calculations, and orientation.

Scale for the Assessment and Rating Ataxia (SARA)
SARA is a clinical scale that is based on a semi quantitative assessment of cerebellar ataxia on an impairment level. SARA has 8 items that are related to gait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements and heel-shin test. Although the cerebellum is directly involved in the coordination of eye movements, oculomotor functions are not considered, as the validation trials indicated that they are determined by other factors than appendicular and midline ataxia. SARA underwent a rigorous validation procedure involving three large multi-center trials in SCA and non-SCA ataxia patients, as well as controls.

Global Impression-Change Scale (CGI-C and PGI-C)
The Clinical Global Impressions-Change (CGI-C) Scale is used for the clinician to quantify and track patient progress and treatment response over time. The self-report Patient Global Impressions-Change (PGI-C) Scale is used for the patient to quantify and track patient progress and treatment response over time.

8.2.6 Electrocardiogram (ECG)
The 12-lead ECG records the electrical activity of your heart at rest. It provides information about your heart rate and rhythm, and shows if there is enlargement of the heart due to high blood pressure (hypertension) or evidence of a previous heart attack (myocardial infarction).

8.2.7 MRI

For subjects who consent to an MRI scan, contraindications to having a brain MRI (e.g., pacemaker; MRI-incompatible aneurysm clips, artificial heart valves, or other metal foreign body; claustrophobia) need to be checked. The spinal and brain MRI scan will contain structural (anatomical, T1, T2) and functional (resting-state, brain only) MRI measurements. Subjects will lie on a kind of couch, which slides for the measurements into the MR scanner. Subjects are asked to move as little as possible and will receive headphones and earplugs to protect the ears from the MR noise. The whole procedure takes about 45 minutes.

8.2.8 AEs

AEs may be volunteered spontaneously by the patient, or discovered as a result of general non-directed questioning by the study personnel or by physical examination. All AEs will be followed until the event resolves or stabilizes at a level acceptable to the investigator.
For further detailed description see section 10.

9 Safety Data Collection, Recording and Reporting

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of haematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.
The investigator will be provided with AE and SAE reporting forms by CTC-A, receive training for AE/SAE definition, documentation and reporting. AE and SAE documentation and reporting will be monitored on site.

9.1 Definition of Adverse Events (AEs)

An adverse event (AE) is defined in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) as “any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.” (ICH E6:1.2)

9.1.1 Instructions for completing adverse event case report forms

Each adverse event is to be reported on an Adverse Event Case Report Form. As far as possible, each adverse event must also be described by:

1. its duration (start and end dates),

2. its severity grade (mild, moderate, severe)

3. its relationship to the study drug (suspected / not suspected)

4. treatment required and action taken with trial drug

5. outcome

6. seriousness

Examples of the severity grade, relationship to study treatment and actions taken, as presented in the case report form, are provided below.
The severity grade of an adverse event provides a qualitative assessment of the extent or intensity of an adverse event, as determined by the investigator or as reported by the subject. The severity grade does not reflect the clinical seriousness of the event, only the degree or extent of the affliction or occurrence (e.g. severe nausea = nausea including vomiting, mild seizure), and does not reflect the relationship to study drug.

Severity grade for an adverse event
The intensity of the AE should be judged based on the following

1 = Mild	Awareness of sign(s) or symptom(s) which is/are easily tolerated
2 = Moderate	Enough discomfort to cause interference with usual activity
3 = Severe	Incapacitating or causing inability to work or to perform usual activities

Causal relationship of adverse event
Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship must be recorded for each adverse event.

Causality will be reported as either “Yes” or “No”.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

Examples for clinically notable laboratory abnormalities

Blood glucose:	fasting glucose > 240 mg/dl or randomly determined glucose level of > 400 mg/dl and confirmed by a second measurement (not the same day).
Liver parameters:	serum AST, ALT, y-GT, AP and bilirubin, please see page 35
Renal parameters:	change of estimated GFR (abbreviated MDRD formula) < 70 %, serum potassium above normal range
Hematological parameters:	Abnormal blood cell counts

9.2 Definition of Serious Adverse Events (SAEs)
A serious adverse event (SAE) is defined as an adverse event that

- results in death (fatal);
- is immediately life-threatening;
- results in persistent or significant disability/incapacity;
- requires or prolongs patient hospitalization;
- is a congenital anomaly/birth defect;

or

- based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the afore listed outcomes from occurring (e.g. intensive treatment in an emergency room without hospitalization).

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious (eg, emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other significant medical hazard” criterion for classification as a serious adverse event.

An event does not need to be reported as a SAE if it represents only a relapse or an expected change or progression of the condition that was the cause of treatment without any other symptoms and signs than those present before treatment. This type of event needs only to be reported as an AE.

9.3 Reporting Procedures of SAEs

All serious adverse events (SAEs) will be reported by the principle investigator to the sponsor (CTC-A) within 24 hours of discovery or notification of the event. The sponsor will forward all SAE reports to the BfArM within 24 hours after receipt.
More information on filling in the SAE form is provided in the “General Instructions for Completion of SAE Form” you find in the investigator site file.

9.4 Pregnancy

If a subject becomes pregnant or fathers a child during the study or within one month after treatment, the investigator should report to the sponsor within 1 working day and use the provided pregnancy notification form. The sponsor will inform BfArM and provide respective initial and follow-up information in cooperation with the investigator.

10 Adjustment of Study Medication and Study Termination

Adjustment of Study Medication

- The main well-known adverse event when taking nicotinamide is nausea. This can be treated with usage of antinausea drugs and/ or dose reduction. If nausea or vomiting occurs it is at the discretion of the investigator and/or a medical team member to flexible reduce the dosing and then reach the highest possible dose. Domperidone as first choice medication (1-3 x 10 mg/day) and/or metoclopramide as second choice (1-3 x 10 mg/day) may be used individually as rescue treatments.
- Mild to moderate increases in abnormal results from liver function tests. Study medication should be reduced and liver function controlled, until normal levels are reached.
- The dose should be 4g/d p.o.. If side effects or any other situation requires a dose reduction, this will be allowed up to the smallest unit of 2 g/d p.o..
- Study medication will be stopped immediately in patients with severe nausea including vomiting and/or severe increased liver enzymes (Grade 3, see chapter 7.2.1). If this occurs during phase A, we will wait for clinical recovery and normalization of liver function tests (serum AST, ALT, y-GT, AP and bilirubin), and ask the patient for a second attempt to take the study medication. This requires a new begin of phase A with the above mentioned titration procedure. If this occurs in phase B, the participant needs to drop out of the study.

Termination

The study will be prematurely terminated for an individual subject, if one of the following criteria is fulfilled:

- The subject experiences severe and nausea including vomiting, that cannot be sufficiently treated with antinausea drugs (prokinetica such as metoclopramide and domperidone) and/ or dose reduction.
- Severe increases in abnormal results from liver function tests (serum AST, ALT, y-GT, AP and bilirubin Grade 3, see chapter 7.2.1).
- Severe progression and/or unstable cardiac situation (cardiomyopathy, unstable arrhythmias).
- The subject experiences an AE that does not resolve or requires continued treatment that meets exclusion criteria.
- Pregnancy (to be reported to Sponsor on Pregnancy Notification Form)
- Non-compliance.
- Subject withdraws informed consent.

- Severe and unforeseen administrative problems that impact the study design and procedures.
- Occurrence of a contraindication or a serious adverse reaction of the study medication, e.g. severe infection.
- Appearance of an illness that interferes with study assessments.
- Death of patient.
- Subjects may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a subject from the study for any safety reason or if it is in the subject's best interests.
- Subject lost to follow-up: the subject cannot be located. The investigator must make every effort to reconnect with the subject (and record his attempts in the source file), at least to determine whether the subject is alive or dead.
- If a subject exits the trial prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

Reason, time point, and specific reason for premature study termination of each subject will be documented. The investigator should determine a primary reason for premature study termination of each subject. All relevant safety data until subject's study termination will be collected and reported.

This study may be prematurely terminated if there is sufficient reasonable cause related to the benefit risk assessment of participating in the study or for regulatory or medical reasons.

Reasons for terminating the study may include, but are not limited to, the following:

- Determination of unexpected, significant, or unacceptable risk to participants
- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Recommendation of DMC for safety issue
- Determination of futility (endpoint cannot be reached given the trial design and number of enrolled participants)
- Non-compliance with the International Council for Harmonization (ICH) guideline for Good Clinical Practice and the Declaration of Helsinki
- Insufficient compliance to protocol requirements

The study will entirely be terminated in case the risk-benefit-ratio changes in such way, that premature study termination is indicated in order to protect subject's health.

If the study is prematurely terminated, the sponsor will notify the principal investigator, the involved ethics committees as well as the competent authorities (BfArM) and will provide the reason(s) for the termination.

11 Statistics

11.1 Statistical analysis

Analysis will be performed within the Full Analysis Set (FAS), which is the set of subjects who have been randomized and have taken at least one dose of the trial medication. No other exclusion is eligible. 95% confidence intervals based on the contrast of the treatment progression derived from the above mentions linear mixed effects model will be used taking into account the sequential nature of the trial, i.e. a linear mixed effects model (LMEM) with the fixed effects of treatment, treatment-by-time interaction, center, SARA baseline score and age as well as the random intercept and time. Similar models will be used to test the treatment effects for FARS, SCAFI, CCFS, EQ-5D and ADL.

Details of the statistical analysis (in particular for the secondary endpoints), including statistical design aspects, primary hypotheses, statistical model, risk of error probabilities, definition of analysis set, statistical software and reporting (e.g. MOC tables and graphs) will be included the trial statistical analysis plan (TSAP). Connected to this document is the data management and validation plan (DMVP).

By slope (progression) analysis we assume a progression of 1.18/year increase in control patients with a SARA score between 8 and 28 at baseline. We estimate a reduction of this progression by 50% i.e. 0.59/year in the treatment group, giving a mean difference after 2 years of 1.19. A SARA score of 1 has been used in former studies as a meaningful difference between placebo and vehicle treatment (Romano et al., 2015).

Within the range of observed SARA measurements, it has been shown, that SARA progression is perfectly linear over time (Reetz et al., 2015; Reetz et al., 2016). Due to the specific type of disease and health care a strong physician-patient-relationship ensures a low withdrawal rate. Thus, with respect to withdrawals and intercurrent events, we assume that our linear mixed effects model the bias, i.e. overestimation of the treatment effect is negligible. Taking into account the concept paper on an addendum to ICH E9, we will further model estimands by an advanced sensitivity analysis, i.e. fitting a MMRM model to the data (Mallinckrodt et al., 2001).

We not intend to perform futility stops, taken into account, that nicotinamide has no major side effects and that patient's perspective is expressed by deriving a convincing level of evidence data from a convincing sized study. Due to potential biased effects and with regard to the above-mentioned uncertainty of the effect estimands, results in the suggestion to conduct the trial without interim analyses.

11.2 Interim analyses

No interim analysis will be applied.

11.3 Data analyses

Efficacy of nicotinamide versus placebo is tested by the linear contrast of the time by treatment interaction applied to the linear mixed effects model (LMEM, assumed variance – covariance error structure = unstructured) with treatment, treatment-by-time interaction, center, SARA baseline score and age as fixed effect and random intercept and time. Test of the primary hypothesis will be tested by the linear contrast on the treatment by time interaction at the

overall 5% significance level. Analysis will be performed within the Full Analysis Set (FAS), which is the set of subjects who have been randomized and have taken at least one dose of the trial medication. No other exclusion is eligible. 95% confidence intervals based on the contrast of the treatment progression will be used taking into account the sequential nature of the trial. Equal models will be used to test the treatment effects for INAS, SCAFI, CCFS, EQ5D and ADL. In a sensitivity analysis a mixed effects repeated measures model (MMRM) using the method described in Mallinckrodt (2001) with the fixed effects treatment, time and treatment by time interaction as well as the covariates baseline SARA score and the baseline-by-visit interaction age of onset, age will be fitted to the data.

11.4 Power calculation

Within the EFACTS register (Reetz et al, 2015 and 2016), inclusion of patients with a SARA < 28 and an age < 50 years the slope is 1.19 with a treatment effect after 2 years of 2.38. With an intended 2:1 allocation ratio, a sample size of 150 + 75 = 225 is required (90% power). An overall type one error rate by 5% (two-sided) is used to test the primary hypothesis at a power of 90%. A reduction of 0.5 is assumed for the treatment effect after 2 years.

11.5 Bias protection

To minimize selection bias and chronological bias the treatment allocation will use the appropriate randomization procedure and randomization is stratified by center. The selection of the randomization procedure will be based on an evaluation of the risks of bias prior to the generation of the randomization list. Details will be given in a randomization report by the Institute for Medical Statistics at the RWTH Aachen University, which will be kept concealed until closure of the database. Performance bias will be minimized by definition of the eligible co-treatments in the protocol and monitoring during the trial. Compliance will be documented in patient diaries and visits. Attrition bias will be reduced by strict follow-up of the patients, which are closely linked to the treating physician, as is usual for patients with rare diseases. Ascertainment and concealment bias will be kept as low as possible, by double-blinding, although the investigators are aware of the effect of unblinding due to observed side effects. With a sensitivity analysis, a statistical model including the selection bias and chronological bias effect will be fitted to the data. Details are given in the TSAP.

12 Ethical and Legal Aspects

12.1 Independent Ethics Committees

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

In accordance with the Declaration of Helsinki, the German Medicines Act (Deutsches Arzneimittelgesetz (AMG)) as well as the Good clinical practice (GCP)-guideline the study will be presented to the competent Ethics Committee for RWTH Aachen University and its endorsement will be obtained prior to inclusion of any subject into the study.

In accordance with local legal requirements, study documents also have to be submitted to the respective regulatory authority(ies) for separate approval.

Any change in the study protocol and/or informed consent form will be presented to the named Ethics Committee. They have to be approved by the Ethics Committee before implementation (except for changes in logistics and administration or when necessary to eliminate immediate hazards).

12.2 Authorization of the Competent Authority

The sponsor will request approval from the respective competent authority (Federal Institute for Drugs and Medical Devices (BfArM), Germany). The trial will only start after the competent authority has approved it. The sponsor will provide copies of the approval documentation to the principle investigator for his files. Any change in the study protocol will be presented to the named Competent Authority. They have to be approved by the Competent Authority before implementation (except for changes in logistics and administration or when necessary to eliminate immediate hazards).

12.3 Notification Requirements

The notification of the clinical trial according to § 67 German Medical Act to the local supervising authority before trial start and in case of any amendments as well as after the end of the study will with consent of investigator be performed by the sponsor according to SOP. The sponsor will provide a copy of the notification to the principle investigator for his files.

12.4 Informed Consent

According to AMG and GCP-guideline, informed consent must be obtained from subjects prior to participation in the trial.

The subjects will voluntarily confirm their willingness to participate in the trial, after having been informed by a physician in writing and verbally of all aspects of the trial that are relevant to the subject's decision to participate. They will be informed about requirements concerning data protection and have to agree to the direct access to their individual data.

The subjects will sign an informed consent form for study participation as well as disclosure of individual data.

The informed consent form has to be signed and personally dated by the subject and one of the sub-investigators.

Before informed consent is obtained, the investigator has to provide the subject ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial have to be answered to the satisfaction of the subject.
Copies of the informed consent forms will be given to the volunteers. The subject information and informed consent form will be prepared and informed consent will be obtained from the subject according to sponsors SOPs.
The subject will be informed by a physician in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be documented. The subject will receive a copy of any amendments to the written information and a copy of the signed and dated consent form updates.
Subjects will be informed that they are free to withdraw from the study at any time at their own discretion without necessarily giving reasons.
The participation in the clinical trial must be documented on the patient’s health records.

12.4.1 Subject card

A subject card will be given to the subjects who will be instructed to keep it in their possession at all times. The subject card will contain the following printed information:

- The name, address and telephone number of the investigator or institution, as the main contact for product information.
- The name, address, and telephone number of the sponsor
- A 24-hour hotline number for emergencies.

12.4.2 Post-study treatment

No specific post-study arrangements are made and no specific post-study care will be performed after this study. All subjects will return to their standard medical care after the study, as needed. This also applies to subjects who withdraw their consent during the course of the study.

12.4.3 Subject privacy

Patients will be informed about data protection and that data will be pseudonymized and handed to third party anonymized. Access to encoded data or source documents will only be given to authorized bodies or persons (sponsor, authorized staff, auditors, competent authorities or ethics commission) for validation of data. Also in case of publication confidentiality of collected data will be warranted.

12.4.4 Contact point

All subjects will be provided in the informed consent form with a contact address where they may obtain further information regarding clinical studies.

12.5 Duties of the Investigator

The responsibilities of investigator are stated in a separate agreement, which will be prepared by the sponsor, CTC-A; according SOP CTC01 and will be signed by all parties.

12.6 Delegation of Investigator's Duties

The investigator will ensure, that all assisting study personnel will be adequately qualified and informed about the study protocol, any amendments, the study medication and their study related responsibilities and functions.
The investigator will maintain a study staff authorization log according to the coordination to SOP, on which all persons he delegated which responsibilities to are listed.

12.7 Protocol Changes

The authorization of relevant competent authority and approval of the ethics committee for any amendments, which will become necessary during the study, will be applied by the sponsor, CTC-A, according to SOPs.
Reportable amendments are changes which may affect following aspects:

- Safety of subjects
- Integrity and credibility of data
- Protocol amendment
- Changes in risk evaluation of drugs consisting/ including genetically modified organisms

Every amendment of the protocol has to be signed by the coordinating investigator, the sponsor and the biostatistician.

12.8 Data Protection

All subjects will be identified by a unique randomization number. Each investigator holds a subject identification list according to the Sponsors SOP which will allow the identification of the subjects by holding information about the subject's personal data and randomization number. This list will be safely filed by the investigator in the investigator's file and a room/locker with limited access.
The subject's informed consent, which bears subject's printed name and signature will accordingly filed separately in the investigators file.
Monitors, auditors or the competent ethics committee will have access to personal data, but under no circumstances may copy the subject identification list or an informed consent.
Where required, personal data, and health data in particular, may be:

- hold for inspection by the competent ethics committee for monitoring the orderly performance of the study,
- to be passed on to the investigators or an authorized party for analysis in an pseudonymized manner.

13 Data Quality Assurance

Inspections by regulatory authority representatives and IECs/IRBs are possible at any time, even after the end of study. The investigator is to notify the sponsor immediately of any such inspection. The investigator and institution will permit study-related monitoring, audits, reviews by the IEC/IRB and/or regulatory authorities, and will allow direct access to source data and source documents for such monitoring, audits, and reviews.

13.1 Quality control

Standardization procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including methods to ensure standardization among sites (e.g., training, newsletters, investigator meetings, monitoring, central laboratories, centralized evaluations, and validation methods).

The monitors will be trained during a monitoring kick-off meeting. To prepare the investigators and to standardize performance a training will be held during an investigators' meeting before study start.

This study will be monitored regularly by a qualified monitor from the CTC-A according to GCP guidelines and the respective SOPs (see Section Monitoring).

13.2 Source documentation requirements

All data collected from a subject during the course of a clinical study should be entered and/or filed in the respective subject file. This includes a copy of the letter sent to the subject's primary physician about the subject's participation in the study (provided the subject has a primary physician and has agreed to the primary physician being informed).

The subject file must also contain a descriptive statement on the informed consent procedure (see Section "Informed consent").

All entries have to be entered first in the subject file (CRF-Case Report Forms). The subject's participation in this study must be appropriately documented in the subject file with study number, subject number, date of subject information, date of informed consent, date of each visit, and date of each telephone contact.

If a study site is using an electronic system for documenting source data, a member of the site staff must print out the source data after each visit. The paper print-outs must be overlapping, if possible (i.e., must contain at least the last row of data from the subject's previous visit). If it is not possible to obtain overlapping paper print-outs, the completeness of source data must be ensured by other suitable means. The print-out must be signed and dated by a member of the site staff who can confirm the accuracy and completeness of data in the paper print-out. The monitor should also sign and date after verifying the source data. The paper print-out should be stored in the ISF. If source data information is entered retrospectively, this must be done directly on the paper print-out and should be initiated and dated. The same applies to any corrections of initial data.

If the site is using a validated computer system including audit trail with a separate access for the monitor (i.e., the monitor can only access the data of the study subjects), then no such paper print-outs are required.

If corrections are necessary, the subject should be instructed to make a correction by drawing only a single line through the error, leaving the incorrect entry legible. The subject should date the correction, but not initial it. The investigator should not make any changes to these documents.
The sponsor's data management function will be responsible for data processing, in accordance with the sponsor's data management procedures. Database lock will occur only after quality assurance procedures have been completed.

13.3 Data management

All data to be collected will be entered on a case report form (CRF) and are to be considered source data. Automatic print outs as well as patient records and electronic patients are considered source data.
Investigators will enter the information required by the protocol into an electronic data collection system via internet (eCRF). The eCRF will be developed by the data manager for the study. Detailed information on the eCRF completion will be provided during the site initiation visits. Each site will also be provided with an eCRF completion manual. In general, all persons who will enter data into the eCRF will be trained by an e-learning tool. After the successful completion of the training all participants will receive a training certificate. The access to the e-learning tool and to the eCRF is password controlled. Plausibility checks will be performed according to a data validation plan. Inconsistencies in the data will be queried to the investigators via the electronic data collection system; answers to queries or changes of the data will directly be documented in the system. Laboratory and antibody test data will be received electronically. Plausibility checks will be performed to ensure correctness and completeness of these data. After all data are entered and all queries are solved, the database will be closed.

13.4 Direct Access to Source Data

The investigator is obliged to allow study specific monitoring, auditing, and inspections by the competent ethics committee, enable direct access at source data and source documents as well as support the respective person at his best knowledge.

13.5 Monitoring

This study will be monitored regularly by a qualified monitor chosen by the CTC-A according to GCP guidelines and the respective SOPs. Monitoring procedures include one or more visits designed to clarify all prerequisites before the study commences. Interim monitoring visits will take place on a regular basis according to a mutually agreed schedule.
During these visits, the monitor will check for completion of the entries on the eCRF/CRF; for compliance with the clinical study protocol, ICH-GCP principles, the Declaration of Helsinki, and regulatory authority requirements; for the integrity of the source data with the eCRF/ CRF entries; and for subject eligibility. Monitoring also will be aimed at detecting any misconduct or fraud. In addition, the monitor will check whether all AEs and SAEs have been reported appropriately within the time periods required.

The investigator and all staff will be expected to cooperate with the monitor by providing any missing information whenever possible. The investigator must be available to answer questions arising during regular monitoring visits. In addition, the investigator is required to:

- Have all data properly recorded in the eCRF and subject files prior to each monitoring visit.
- Have the source documentation available at the monitoring visits.
- Record all IP dispensed in the eCRF and the drug inventory records.

All subjects who give their informed consent, including those screened, but not entered into the study, will be listed on the subject screening/enrolment log. Further details of monitoring activities will be set forth in the monitoring manual.

13.6 Auditing

Audits will be performed according to the corresponding audit program, including the possibility that a member of the sponsor's quality assurance function may arrange to visit the investigator in order to audit the performance of the study at the study site, as well as all study documents originating there. Auditors conduct their work independently of the clinical study and its performance.

Audits may also be performed by contract auditors. In this case, the sponsor's quality assurance function will agree with the contract auditor regarding the timing and extent of the audit(s). In case of audits at the investigational site, the monitor will usually accompany the auditor(s).

14 Data Handling and Record Keeping

14.1 Conclusion of Documentation

By signing the CRF (eCRF/ eSignature), the investigator confirms that all investigations have been completed and conducted in compliance with the clinical study protocol, and that reliable and complete data have been entered into the eCRF.

14.2 Corrections to data

If corrections are necessary, the subject should be instructed to make a correction by drawing only a single line through the error, leaving the incorrect entry legible. The subject should date the correction, but not initial it. The investigator should not make any changes to these documents.

The sponsor's data management function will be responsible for data processing, in accordance with the sponsor's data management procedures. Database lock will occur only after quality assurance procedures have been completed.

14.3 Record keeping

Essential documents should be retained until at least 2 years after the last approval of a marketing application (whether pending or contemplated) in an ICH region, or at least 2 years have elapsed since the formal discontinuation of IP clinical development. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by agreement with the sponsor.

Essential documents at the investigational site include (among other documents):

- Subject files.
- Subject identification code list (i.e., provided by template to the investigator, along with the ISF, at the beginning of the study), which identifies the subject by number, name, and date of birth.
- A signed copy of the final clinical study protocol and any amendment.
- CD/DVD with eCRF data, and any associated subject-related source data (or, where applicable, authorized copies of source data).
- Signed informed consent forms.
- Copies of site investigators' and co-workers' curricula vitae.
- Copies of all direct correspondence with the IEC/IRB and with the regulatory authority(ies).
- Copies of laboratory normal ranges and methods.
- Copies of study supply receipt forms and drug inventory forms.
- Copies of all correspondence between the investigator and the monitor, and between the investigator and the sponsor.

- Copies of safety information reported during the study and submitted by the sponsor.

14.4 Archiving of Documents

The investigator will keep the subject's files and original data as long as possible and according to the local methods and facilities. The investigator should maintain the trial documents as specified in the ICH-GCP-Guideline for at least 10 years. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

14.5 Destruction of study documents

Study documents may not be destroyed by study site personnel prior to the retention period specified above without the prior written consent of the sponsor. The principal investigator must inform the sponsor in due time if the principal investigator leaves the institution during the retention period. This rule also applies when the institution closes within the retention period.

15 Oversight Committee

15.1 Data Monitoring Committee

The Data Monitoring Committee (DMC) will be formed of an independent group of experts that advises NICOFA and the study investigators. The members of the DMC serve in an individual capacity and provide their expertise and recommendations. The DMC will periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and make recommendations to NICOFA concerning the continuation, modification, or termination of the trial. The DMC considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study (see DMC Charta).

16 Publication Policy

The study results will be published in appropriate international scientific journals, and publishing details will be given in the clinical study agreement. The study will be registered and study results will be disclosed by the principal investigator in one or more public clinical study registry(ies), according to national/international use. The registration will include a list of the investigational sites.

17 Finance and Insurance

17.1 Financing

This is an investigator-initiated study. The study is financed by the German Research Foundation (DFG). The financial aspects of this study are specified in separate agreements between the institution, the sponsor (CTC-A) and the investigator.

17.2 Insurance

From the beginning of the study until its termination, each subject is insured against any health impairment occurring as a result of participation in the study in accordance with the laws and regulations of the country in which the study is performed.

The subject will be informed by the investigator and through the subject's informed consent form about the existence of this insurance and the resulting obligations. The insurance conditions will be handed out to the subject, if requested or if required by local law. Any medical deviation from the clinical study protocol that is deemed to have occurred through the subject's own fault is not covered by this insurance.

The sponsor is usually not liable for injuries/cases of death that occur solely as a consequence of the subject's underlying disease or condition, or from diagnostic or therapeutic measures not specifically required by the agreed clinical study protocol. The sponsor is also usually not liable for events resulting from negligence of the investigator, clinical study staff, and/or CRO, including failure to act according to ICH-GCP principles or to comply strictly with the agreed clinical study protocol. A patient's insurance in accordance with § 40 (1) and (3) No.8 AMG is submitted (the insurance policy number will be filed subsequently).

In addition, a travel accident insurance is completed.

18 Statement of compliance

Investigational Site(s)

I have thoroughly read and reviewed the clinical study protocol. Having understood the requirements and conditions of the clinical study protocol, I agree to perform the clinical study according to the clinical study protocol, the case report form, ICH-GCP principles (EU Directive 2001/20/EG), the Declaration of Helsinki, and regulatory authority requirements (§40-42 AMG). I have received the current SmPC (instruction of use). Having been adequately informed about the IP development to date, I also agree to:

- Sign this clinical study protocol before the study formally starts.
- Wait until I have received approval from the appropriate IEC/IRB before enrolling any subject in this study.
- Obtain informed consent for all subjects prior to any study-related action performed.
- Start the study only after all legal requirements in my country have been fulfilled.
- Permit study-related monitoring, audits, IEC/IRB review, and regulatory inspections.
- Provide direct access to all study-related records, source documents, and subject files
    - for the monitor, auditor, IEC/IRB, or regulatory authority upon request.
- Use the IP and all study materials only as specified in the clinical study protocol.
- Report to the responsible drug safety officer, within 24 hours, any adverse event (AE) that is serious, whether considered treatment related or not.

Furthermore, I understand that:

- Changes to the clinical study protocol must be made in the form of an amendment that has the prior written approval of RWTH University and – as applicable – of the appropriate IEC/IRB and regulatory authority.
- The content of the clinical study protocol is confidential and proprietary to RWTH University
- Any deviation from the clinical study protocol may lead to early termination of the study site.
- With my signature below, I also acknowledge receipt of the study protocol.

19 Signatures

The study protocol is accepted by

The Sponsor's Representative

Dr. med. Susanne Isfort
Managing Director CTC-A
RWTH Aachen University Hospital

Aachen, 05. December 2018

The Biostatistician

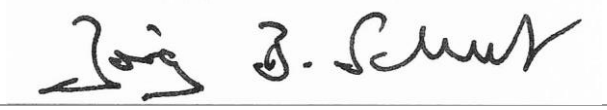
Prof. Dr. Ralf-Dieter Hilgers
Chair of Department of Medical Statistics
RWTH Aachen University Hospital

Aachen, 05. December 2018

Principal Sponsor- Investigator

Univ.-Prof. Dr. med. Jörg Schulz
Head of Department of Neurology,
RWTH Aachen University Hospital

Aachen, 06. December 2018



Co-Investigator

Univ.-Prof. Dr. med. Kathrin Reetz
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RWTH Aachen University Hospital

Aachen, 06. December 2018

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