# Clinical Study Report SynopsisVersion 01, 11.07.2023

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

**Sponsor's Protocol Code Number:** 15-138

**EudraCT Number:** 2017-002163-17

**National Competent Authority reference:**

- Germany (BfArM): 4042858
- Austria (BASG): 12230551
- United Kingdom (MHRA): 248392
- Spain (AEMPS): n.a.

**Initial National Authority Approval:**

- Germany: 25.10.2018
- Austria: 04.09.2019
- United Kingdom: 21.01.2020
- Spain: 08.04.2020

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|---|
| **Name of Sponsor:**<br>RWTH Aachen University, represented by the Rector,<br>represented by the Dean of the Medical Faculty Univ.-Prof. Dr. rer. nat. Stefan Uhlig<br>Pauwelsstraße 30, 52074 Aachen<br>Tel.: 0241 / 80 80092, Fax. 0241 / 80 3380092<br>Email: ctca-regaffairs@ukaachen.de |
| **Name of Finished Product(s):**<br>Nicotinamide |
| **Name of Active Substance(s):**<br>Nicotinamide |
| **Study Title:** A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTRE STUDY OF THE EFFICACY AND SAFETY OF NICOTINAMIDE IN PATIENTS WITH FRIEDREICH'S ATAXIA (NICOFA) |
| **Study design:** placebo-controlled, randomised, double blind, parallel group, multicentre study |
| **Final Protocol version:** Protocol version 3.5 |
| **Amendments:** |

| Amendment Identification [e.g., number] | Reason(s) for changes | Date of approval by the National Authorities |
|---|---|---|
| Substantial Amendment 01 in Germany | Change of sponsor representative, extension of IMP expiry to 9 months, change of personal at trial site | 29.05.2019 |
| Substantial Amendment 02 in Germany | Delay of recruitment start due to COVID-19 pandemic | 05.05.2020 |
| Substantial Amendment 03 in Germany | Start of recruitment, extension of IMP expiry to 13 months, update of Investigator's Brochure (version 03) | 17.06.2020 |
| Substantial Amendment 04 in Germany | Stop of recruitment | 02.05.2022 |

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**Publication (reference):**

Protocol of a randomized, double-blind, placebo-controlled, parallel-group, multicentre study of the efficacy and safety of nicotinamide in patients with Friedreich ataxia (NICOFA)
Reetz et al. 2019 Oct 15, Neurol Res Pract., doi: 10.1186/s42466-019-0038-9.

**Study period:**

**Date of first subject enrolment:** n.a.

**Date of last subject completed:** n.a.

No subjects have been enrolled.

**Phase of Development:** IIb/III

**Objectives and criteria for evaluation:**

Objective(s):

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's ataxia.

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

Primary endpoint:

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

Secondary endpoints will include:

1) Progression of quality of life measures such as the Activity of Daily Living (ADL) scores, part of the Friedreich's ataxia rating scale (FARS), and the EuroQoL five dimensions questionnaire (EQ-5D)

2) Modified Friedreich's 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's 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

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

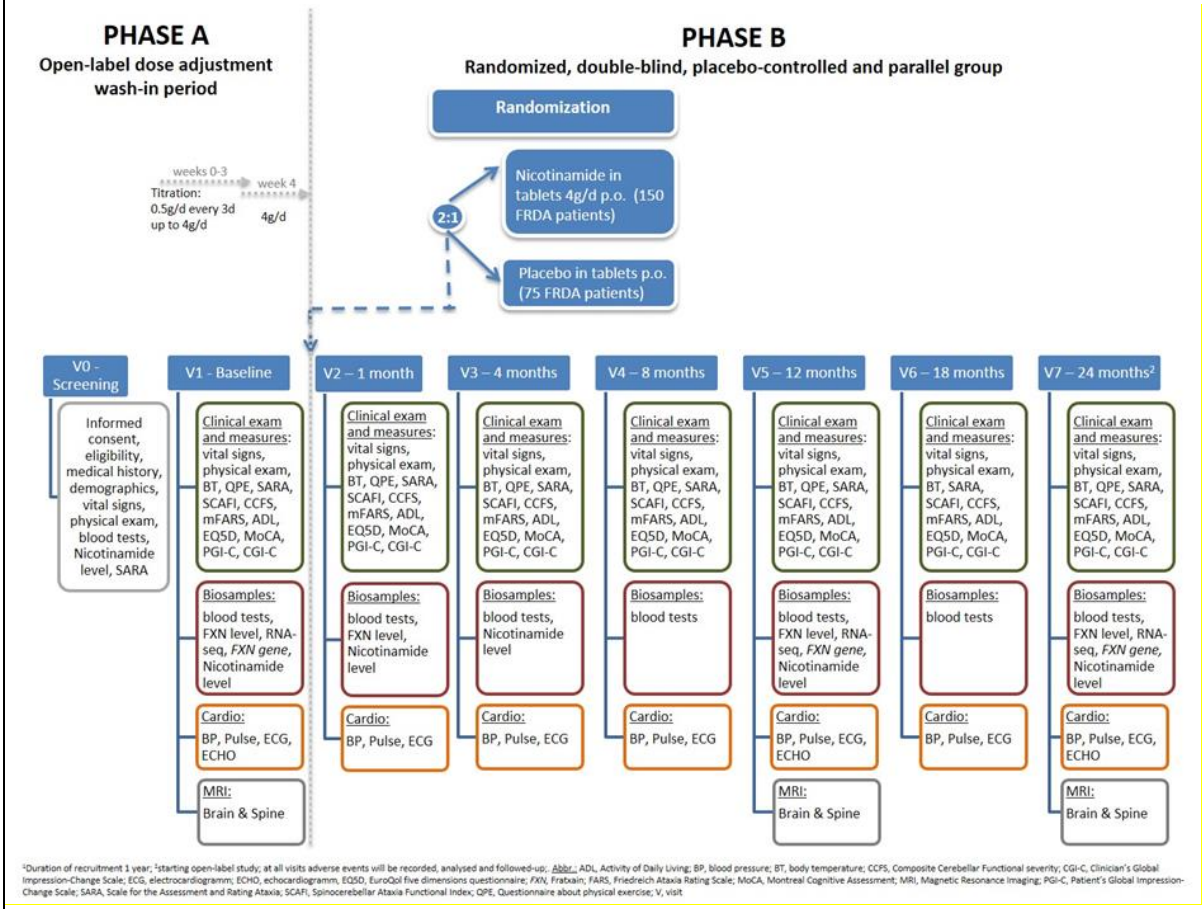
4) Structural and functional changes of the brain and spinal cord, measured by magnetic resonance imaging (MRI)

References:


- Burk, K., Schulz, S.R., Schulz, J.B., 2013. Monitoring progression in Friedreich's ataxia (FRDA): the use of clinical scales. J Neurochem. 126 Suppl 1, 118-24.
- Filipovic Pierucci, A., et al., 2015. Quantifiable evaluation of cerebellar signs in children. Neurology. 84, 1225-32.
- Reetz, K., et al., 2015. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. Lancet Neurol. 14, 174-82.
- Reetz, K., et al., 2016. Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 2 year cohort study. Lancet Neurol. 15, 1346-1354.
- Schmitz-Hubsch, T., et al., 2008. SCA Functional Index: a useful compound performance measure for spinocerebellar ataxia. Neurology. 71, 486-92.
- Subramony, S.H., et al., 2005. Measuring Friedreich's ataxia: Interrater reliability of a neurologic rating scale. Neurology. 64, 1261-2.

**Methodology:**

Study Flow Chart:




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, risks 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, Medical History, Concomitant Medication, Physical Examination/Vital signs, Questionnaire about physical exercise (QPE), Laboratory tests

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.

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.

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 |
| Electrocardio-gram (ECG) | | X | X | X | X | X | X | X |
| Echocardio-gram (ECHO) | | X | | | | X | | X |
| Quest. about exercise (QPE) | | X | X | X | X | X | X | X |
| Clinical measures[3]<br><br>SCAFI, CCFS, mFARS, ADL, EQ5D, MoCA, CGI-C, PGI-C | | X | X | X | X | X | X | X |
| Scale for the Assessment and Rating of 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<br><br>(nicotinamide level) | X | X | X | X | | X | | X |

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|---|---|---|---|---|---|---|---|---|
| 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

**Number of subjects:**

Planned: 225 (75 control arm and 150 patients treatment arm)

Analysed: 0 since no subjects have been enrolled in the study

**Diagnosis and main criteria for inclusion and exclusion:** Study population: Adult (≥18 and <50 years), female and male Friedreich's ataxia patients with a molecular genetic diagnosis with GAA-repeat expansion on both alleles of the FXN gene and a SARA Score >7 and <28.

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 and age <50 years.
2. Patients must be ≥18 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 appropriate contraceptive measures.

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's 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 Q10 (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 or otologic implant, sever claustrophobia, or any condition that would counterindicate an MRI scan.
20. Patients participating in another interventional clinical trial, excluding natural history/observational studies, at start of the study or within the last 30 days before study start.

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.

**Test product(s):**

Name of finished product(s): Nicotinamide

Marketing authorization number(s): n.a.

Name of active substance(s): pyridine-3-carboxylic amide

Dose(s): 4g daily (8 capsules á 500 mg)

Mode of administration: oral

Batch number(s): n.a. since no subjects were enrolled

**Duration of treatment:** 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. Within the first 3 weeks 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).

**Reference therapy:**

Product name(s): Placebo

Dose: 8 capsules daily

Mode of administration: oral

Batch number(s): n.a. since no subjects were enrolled

**Statistical methods:**

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.

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. 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, EQ-5D 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.

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.

Bias protection

To minimize selection bias and chronological bias, the treatment allocation will use the appropriate randomization procedure and randomization is stratified by the 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 at 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.

References:

- Mallinckrodt, C.H., Clark, W.S., David, S.R., 2001. Accounting for dropout bias using mixed-effects models. J Biopharm Stat. 11, 9-21.
- Reetz, K., et al., 2015. Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data. Lancet Neurol. 14, 174-82.
- Reetz, K., et al., 2016. Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 2 year cohort study. Lancet Neurol. 15, 1346-1354.
- Romano, S., et al., 2015. Riluzole in patients with hereditary cerebellar ataxia: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 14, 985-91.

**Treatment 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.

**Efficacy and safety variables:** see objectives and criteria for evaluation

**Data Quality Assurance:**

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 according to GCP guidelines and the respective SOPs.

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 must be entered first in the subject file. 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 not required.

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.

Data management

All data to be collected will be entered on a case report form (CRF) and are to be considered as source data. Automatic print outs as well as patient records and electronic patients are considered as 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. 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.

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.

Monitoring

This study will be monitored regularly by a qualified monitor chosen by the sponsor 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; 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 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 required time periods.
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.

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).

**Risk Evaluation/Protocol Deviations:** As no subjects were enrolled in the study, no deviations occurred, and no risk management procedures were implemented.

**Safety Evaluation:** As no subjects were enrolled in the study, no (serious) adverse events occurred.

**Summary of results:** As no subjects were enrolled in the study, no results can be concluded.

**The undersigned authors agree to the content of this clinical study report by giving their signatures. The clinical trial reported here was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and applicable laws.**

**Sponsor**

RWTH Aachen, represented by the Rector, represented by the Dean of the Medical Faculty

Univ.-Prof. Dr. rer. nat. Stefan Uhlig

Place, Date:

Signature:

**Principal Investigator and Author**

Univ.-Prof. Dr. med. Jörg Schulz

Place, Date:

Signature: