UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

Statistical Analysis Plan

Version: 1.0 Date: 18.09.2025

A randomized, double blind, parallel group, placebo controlled, Phase 3 trial of orally administered nicotinamide riboside over one year as a potential disease modifying treatment for Parkinson's disease

NOPARK

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Approval of the Statistical Analysis Plan

A randomized, double blind, parallel group, placebo controlled, Phase 3 trial of orally administered nicotinamide riboside over one year as a potential disease modifying treatment for Parkinson's disease

Protocol Version No: 6.0 / 01.04.2025

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Table of Contents

List of Figures

No table of figures entries found.

List of Tables

List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
BP	Blood Pressure
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation due to Adverse Event
DT	Dopaminergic Treatment
EC	Ethics Committee
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IP	Investigational Product (includes active comparator and placebo)
ITT	Intention to treat
MDS-UPDRS	Movement Disorders Unified Parkinson's Disease Rating Scale
NMSQ	Non-Motor Symptoms Questionnaire
NMSS	Non-Motor Symptom assessment scale for Parkinson's Disease
MoCA	Montreal Cognitive Assessment
NAD	Nicotinamide Adenine Dinucleotide
NR	Nicotinamide Riboside
PD	Parkinson's Disease
SAE	Serious Adverse Event
SD	Stable Disease
SOP	Standard Operating Procedure

1 Introduction

This document has been written based on the study protocol, Version 6.0.

Affecting 1-2% of the population over the age of 65, Parkinson's disease (PD) is a major cause of death and disability with a devastating global socioeconomic impact. In Europe alone, PD affects an estimated 1.2 million people at a cost of €14 billion per year. Current treatments for PD are symptomatic and have no impact on disease progression. As a result, patients face a future of progressive disability, early institutionalization and premature death.

1.1 Background and Rationale

Previous research has shown that nicotinamide riboside (NR) holds promise as a potential neuroprotective, disease-modifying therapy for PD (see Study Protocol Section 1.3/1.4).

NOPARK aims to determine whether daily oral administration of NR will slow/inhibit the progression of PD. See the study protocol for more details on the background and rationale of the NOPARK study.

1.2 Objectives and Endpoints

The NOPARK study investigates the hypothesis that oral administration of NR can ameliorate neuronal metabolism, increase neuronal resilience, and inhibit neurodegeneration, resulting in amelioration of clinical symptoms and delayed PD progression. Primary and secondary endpoints are listed in Table 1.

Table 1 Objectives and related endpoints

	Objective	Endpoint
Primary	To compare the effectiveness of orally administered nicotinamide riboside (NR) 500 mg twice per day versus placebo on delaying disease progression in PD.	Change from baseline in MDS-UPDRS Total Score (sum of parts I, II and III) in the ON-medication state at week 52.
Key secondary	To compare the effectiveness of orally administered nicotinamide riboside (NR) 500 mg twice per day versus placebo on delaying the progression of motor symptoms in PD.	Change from baseline in the MDS-UPDRS Part III in the ON-medication state at Week 52.
	To compare the effectiveness of orally administered nicotinamide riboside (NR) 500 mg twice per day versus placebo on delaying the progression of dopaminergic nigrostriatal denervation in PD.	Change from baseline in the mean striatal binding ratio (SBR) of the putamen, bilaterally, as measured [^{123}I]FP-CIT Single-Photon Emission Computed Tomography (SPECT) Imaging of the Dopamine Transporter (DaT, DaTscan) at Week 52.
	To compare the effectiveness of orally administered nicotinamide riboside (NR) 500 mg twice per day versus placebo on delaying the progression	Change from baseline in the MDS-UPDRS Part I in the ON-medication state at Week 52.

	Objective	Endpoint
	of non-motor symptoms in daily living in PD.	
	To compare the effectiveness of orally administered nicotinamide riboside (NR) 500 mg twice per day versus placebo on delaying the progression of motor aspects of experiences of daily living in PD.	Change from baseline in the MDS-UPDRS Part II in the ON-medication state at Week 52.
	To compare the effect of orally administered nicotinamide riboside (NR) 500 mg twice per day versus placebo on the progression of non-motor symptoms in PD.	Change from baseline in the NMSS Score in the ON-medication state at Week 52.
Other secondary	To compare the effect of orally administered nicotinamide riboside (NR) 500 mg twice per day versus placebo on the progression of cognitive dysfunction in PD.	Change from baseline in the MoCA score in the ON-medication state at Week 52.
	To compare the effect of orally administered nicotinamide riboside (NR) 500 mg twice per day versus placebo on quality of life in PD.	Change from baseline in the EQ-5D-5L index value, at week 52.
	To compare the effect of orally administered nicotinamide riboside (NR) 500 mg twice per day versus placebo on the progression of Hoehn and Yahr stage.	Hoehn and Yahr stage at Week 52.
Exploratory	To compare the effect of orally administered nicotinamide riboside (NR) 500 mg twice per day versus placebo on brain NAD levels in PD.	Change from baseline in brain NAD/ATP-α ratio measured by 31 Phosphorus magnetic resonance spectroscopy (31P-MRS) in the posterior brain (encompassing the occipital, parietooccipital and posterior parts of the temporal cortex), at 52 weeks between participants according to treatment allocation.
	To compare the effect of orally administered nicotinamide riboside (NR) 500 mg twice per day versus placebo on systemic NAD metabolism	Comparison of the change from baseline in the NAD metabolome in whole blood, measured by liquid chromatography mass spectrometry (LC-MS), at 52 weeks between participants according to treatment allocation.
	To compare the effect of orally administered nicotinamide riboside (NR) 500 mg twice per day versus placebo on neuronal damage	Comparison of the change from baseline in serum neurofilament light-chain (NfL) levels, measured by Simoa analysis, at 52 weeks between participants according to treatment allocation.
Safety	To determine whether NR is safe and well tolerated.	Report of all Adverse Events (AE) of moderate or severe intensity and Serious Adverse Events (SAE).

1.3 Primary objective and endpoint

The primary endpoint is measured by MDS-UPDRS Total Score (Sum of Part I, II and III). The MDS-UPDRS is a questionnaire developed to evaluate non-motor and motor experiences of daily living and motor complications in PD. Higher scores indicate more severe symptoms of PD. For more information see Section 5.1.

1.4 Secondary objectives and endpoints

Key and other secondary endpoints are listed in Table 1. For further details on the definition of the endpoints, see Section 5.1.

1.5 Exploratory objectives and endpoints

Exploratory endpoints are listed in Table 1. For further details on the definition of the endpoints, see Section 5.1.

1.6 Safety

Recording AE and SAE will begin after baseline (week 0) and continue to be monitored and registered throughout the duration of the study up until 7 days after last study visit.

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

If a patient has experienced AE(s), the following information will be recorded:

- The nature of the event described by precise standard medical terminology.
- The duration of the event (event onset and event end date; resolved/still ongoing).
- The intensity of the adverse event: **Only intensity 2 (moderate) and 3 (severe) is registered as AE in eCRF.**
- The causal relationship of the event to the study medication
- The outcome of the AE.
- The action taken.

Table 2 Definition of causal relationship and intensity in AEs.

Causal relationship:	Intensity:
• **Unrelated:** No temporal relationship to investigational product administration or a reasonable causal relationship between the AE and non-	1. **Mild**: An event that is easily tolerated by the participant, causing minimal

investigational product, concurrent disease, or circumstance. • **Unlikely:** A temporal relationship to investigational product administration without a reasonable causal relationship to the AE. • **Possible:** A reasonable causal relationship to the investigational product. Dechallenge information is lacking or unclear. • **Probable:** A reasonable causal relationship to the investigational product. The event responds to dechallenge. Rechallenge is not required. • **Definite:** A reasonable causal relationship to the investigational product.	discomfort and not interfering with everyday activities. 2. **Moderate**: An event that causes sufficient discomfort to interfere with normal everyday activities. 3. **Severe**: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Hospitalization for administrative reasons (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalization.

2 Study methods

2.1 Trial design

NOPARK is a national, multicenter, randomized, double-blinded, placebo controlled, phase 3 trial of oral NR supplementation in patients with PD. Patients are screened and randomized either to NR or placebo group and followed-up 52 weeks after baseline.

2.2 Randomization

Randomization is done upon enrolment to the study. Patients are randomized in a 1:1 ratio to Placebo or NR stratified by site.

2.3 Sample Size

For sample size calculation we assume a common standard deviation of 16 points in the total MDS-UPDRS (parts I, II and III) and an overall type 1 error rate of 5%. Such a standard deviation was seen in Holden et al (2018). This estimate is further supported by a blinded sample size review performed on a blinded data export from August 23, 2024. A sample size of 162 participants per group gives an 80% power given a difference of 5 points in the total MDS-UPDRS at 52 weeks between the NR and the placebo group (324 in total). A difference of this magnitude was reported to be within the clinically meaningful range (see Wyman-Chick et al (2018)). Accounting for approx. 20% drop out, 200 participants per group (400 in total) are required.

2.4 Framework

Unless stated otherwise, all endpoints are tested for superiority of NR over placebo.

2.5 Statistical Interim Analyses and Stopping Guidance

No interim analyses are planned.

The whole trial may be discontinued at the discretion of the PI or the sponsor in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration.
- Medical or ethical reasons affecting the continued performance of the trial.
- Difficulties in the recruitment of patients.

The sponsor and principal investigator will inform all investigators and the Ethics Committees of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety and Ethics Committees will be informed within 15 days.

2.6 Timing of the Final Analysis

The final analysis will take place when all outcomes have been collected and the database is locked.

2.7 Timing of Outcome Assessments

Data is collected over a period of 52 weeks with multiple measurement points (see Table 2). Patients must be on stable dopaminergic treatment at Baseline (see Study Protocol, Section 5.4). When the patient is on stable dopaminergic treatment (DT), screening (up to 3 months) is completed and the patient can join the study. DatScan and MRI should be performed within 6 weeks prior to Baseline and 2 weeks prior to the 52 weeks visit.

Table 3 Trial flow chart

	Screening Period		Treatment period					End of study
Time	**First screening**	**Last screening**	**Baseline**	**W4**	**W13**	**W26**	**W39**	**W52**
Stable DT	X	X						X
MDS Clinical diagnosis Criteria (MDS CDC)			X					
Inclusion/exclusion Evaluation	X		X					
Informed consent biobank, optional			X					
Anamnestic information[1]	X		X					
Physical Examination	X							
Concomitant medication	X		X		X	X	X	X
Medical history	X		X					
DatScan/MRI			X					X
Vital signs: BP, pulse, weight; height (Baseline)			X		X	X	X	X
MDS-UPDRS			X		X	X	X	X
NMSS & NMSQ			X			X		X
MOCA			X					X
EQ-5D-5L			X					X
Blood samples[2]			X		X	X	X	X
PBMC[3]			X			X		X
Treatment dispensation			X		(X) [4]	(X)[4]	(X)[4]	
Adverse event			X	X	X	X	X	X

3 Statistical Principles

3.1 Confidence intervals and p-values

Unless specified otherwise, all tests will be performed two-sided on a significance level of 5%. Consequently, confidence intervals (CI) will be reported with 95% confidence level.

[1]Includes: family history of neurological illness, smoking history, anamnestic months since first clinical PD symptoms, occurrence and duration of REM sleep behaviour disorder symptoms, occurrence and duration of loss of smell.

[2] CRP, ALAT, ASAT, GT, bilirubin, ALP, creatinine, urea, RBC, Hb, WBC with differential, platelets, CK, FT4, TSH, B12, folic acid, homocysteine, methylmalonic acid, sodium, potassium.

[3] PBMC analysis is discontinued for new patients enrolled after 16.04.23. Patients enrolled before 16.04.23 will complete PBMC as described.

[4] If necessary to resupply.

3.2 Adherence and protocol deviations

Adherence to the study protocol is monitored. All significant protocol deviations will be recorded in the trial data base. Procedures are detailed in the Protocol Deviation Handling Plan provided in the appendix.

3.3 Analysis populations

The primary analysis will follow the intention-to-treat (ITT) principle. The **ITT population** contains all randomized patients with at least two post-baseline measurements, regardless of protocol adherence.

The **safety population** contains all enrolled patients with treatment as actually received.

In a secondary **per-protocol analysis set**, participants are excluded if any of the following apply:

- Failure to meet eligibility criteria
- Incorrect randomization
- Missing primary outcome at any visit
- Treatment compliance < 90%
- Change in standard-of-care PD regimen during the trial

4 Trial population

4.1 Screening data

Screening data will be reported and described within a CONSORT flowchart.

4.2 Eligibility

The eligibility criteria are listed in Table 4. All inclusion criteria must be fulfilled. If at least one of the exclusion criteria is met, patients are excluded. Informed consent needs to be signed prior to enrolment to the study.

Table 4 Eligibility criteria

Inclusion criteria:	Exclusion criteria:
• Clinical diagnosis of idiopathic PD according to the MDS clinical diagnostic criteria for Parkinson's disease. • FP-CIT Single-Photon Emission Computed Tomography Imaging of the Dopamine Transporter confirming nigrostriatal denervation. • Diagnosed with PD within 2 years from enrolment.	• Dementia or other neurodegenerative disorder at baseline. • Diagnosed with atypical or vascular Parkinsonism. • Any psychiatric disorder that would interfere with compliance in the study. • Any severe somatic illness that would make the individual unable to comply and participate in the study.

• Hoehn & Yahr Score < 3 at enrolment. • Optimal symptomatic therapy, not requiring adjustments, for at least 1 month. • Age ≥35 years at time of enrolment.	• Use of high dose vitamin B3 supplementation within 30 days of enrolment. • Metabolic, neoplastic, or other physically or mentally debilitating disorder at baseline. • Genetically confirmed mitochondrial disease.

4.3 Recruitment

Recruitment numbers will be reported and described within a CONSORT flowchart.

4.4 Withdrawal/follow-up

Reasons for withdrawal will be documented using a CONSORT flowchart. Reasons for drop-out are collected in a corresponding form within the trial data base. Patients who are withdrawn from the study before the start of treatment, will be replaced.

4.5 Baseline patient characteristics

All baseline patient characteristics will be summarized using descriptive statistics (e.g. mean, standard deviation, median, IQR for continuous variables and frequencies (percentages) for categorical variables) and appropriate graphical methods (e.g. boxplots, histograms, barplots) depending on the data type.

5 Analysis

5.1 Outcome definitions

Instrument	Description	Missing values
Movement Disorder Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [1]	MDS-UPDRS is a 4-subscale scale assessing clinical impairment and disability in PD. Part IV is not applicable. All items are scored on a scale from 0 (normal) to 4 (severe). • Part I: Non-motor experiences of daily living (Range: 0-52). Part IA has 6 items (R: 0-24) and Part IB 7 items (R: 0-28). • Part II: Motor experiences of daily living (13 items, R: 0-52). • Part III evaluates motor severity and contains 33 scores based on 18 items being assessed by a rater (R: 0-132). • For all parts the score is the sum of the scored items. The total score is the sum of all parts (Range: 0-236).	Any missing value invalidates the total score.
Hoehn & Yahr Scale	• Assessed by the Hoehn & Yahr stage in MDS-UPDRS. • Classification: 0 = Asymptomatic, 1 = Unilateral involvement, 2 = Bilateral involvement, 3 = Bilateral involvement with postural instability, 4 = Severe disability, 5 = wheelchair bound	
Movement disorder PD clinical	• The diagnosis of clinically established PD requires 1. Absence of absolute exclusion criteria 2. At least two supportive criteria	

diagnosis criteria (MDSCDCPD) [2]	3. No red flags • Diagnosis of Clinically Probable PD requires: 1. Absence of absolute exclusion criteria 2. Presence of red flags counterbalanced by supportive criteria. If 1 red flag is present, there must also be at least 1 supportive criterion. If 2 red flags, at least 2 supportive criteria are needed. No more than 2 red flags are allowed for this category.	
Non-Motor Symptom assessment scale for Parkinson's Disease (NMSS) [3]	• 30-item scale assessing frequency and severity of non-motor symptoms in PD, covering nine domains: cardiovascular, sleep/fatigue, mood/cognition, perceptual problems, attention/memory, gastrointestinal, urinary, sexual function, and miscellany. • Each item is scored based on the severity from 0 to 3 points and frequency from 1 to 4, if severity is ≥1. • The total score ranges from 0 to 360.	Any missing value invalidates the total score.
Montreal Cognitive Assessment (MoCA) [4]	• 30 items questionnaire used for assessing cognition • Score: Sum of points, range 0-30 ○ If the score is <30 and education ≤12 years, an extra point is added. • Higher values indicate a healthier state	Any missing value invalidates the total score.
EQ-5D-5L [5]	• Used to measure QoL • 5 items scored 1-5 and a visual analogue scale (EQ-VAS, range 0-100) • Index values summarize the health state, range from less than 0 (0 indicates a health state equivalent to dead, negative values a health state as worse than dead) to 1 (full health) Index values are calculated using the R package *eq5d* [6]: eq5d::eq5d(scores = data %>% dplyr::select(MO = "eq5d_1", SC = "eq5d_2", UA = "eq5d_3", PD = "eq5d_4", AD = "eq5d_5"), country = "Sweden2022", version = "5L", type = "VT", ignore.invalid = TRUE)	In case of death, the index value is set on 0. Index value cannot be calculated if a dimension value is missing.

NAD metabolome	• Nicotinamide adenine dinucleotide total (NAD^+ and NADH) • Nicotinamide adenine dinucleotide oxidized (NAD^+) • Nicotinamide adenine dinucleotide reduced (NADH) • NAD^+/NADH ratio • Nicotinamide adenine dinucleotide phosphate total ($NADP^+$ and NADPH) • Nicotinamide adenine dinucleotide phosphate oxidized ($NADP^+$) • Nicotinamide adenine dinucleotide phosphate reduced (NADPH) • $NADP^+$/NADPH ratio • 1-methyl nicotinamide (Me-Nam) • Nicotinic acid-adenine dinucleotide (NAAD) • N1-methyl-2-pyridone-5-carboxamide (Me-2-PY) • N-Methyl-4-pyridone-5-carboxamide • Nicotinamide (Nam) • Nicotinamide N-oxide (Nam N-oxide) • Nicotinic acid riboside (NAR) • Nicotinamide riboside (NR) • Nicotinamide mononucleotide (NMN) • Nicotinic acid (NA)	-

5.2 Analysis methods

Primary endpoint analysis

The primary endpoint, the MDS-UPDRS changes from baseline to week 52 between the NR and placebo group, will be analyzed using Gaussian linear models for repeated measures (MMRM) with intervention, center, time (week 13, 26, 39, and 52), and intervention-by-time interaction as factors, and baseline MDS-UPDRS score as covariate. Centers with fewer than 20 patients are pooled into one center. The error terms are assumed to follow a multivariate normal distribution with unstructured covariance. Least square mean changes for both groups as well as the difference between the least squares treatment group means will be reported with 95% CIs and p-value testing the null hypothesis of no treatment effect.

```
library(mmrm)
library(emmeans)
dataEndpoints_long <- dataEndpoints_long %>%
      mutate(updrs_diff = updrs - updrs_BL)
model <- mmrm(updrs_diff ~ updrs_BL + group * time + center,
                  covariance = cov_struct("us", "time",
                  subject = "SubjectId"), data = dataEndpoints_long)
# report least square group differences
tmt.means <- lsmeans(model, specs = trt.vs.ctrlk ~ group | time,
                     reverse = T, adjust = 'none')
```

Secondary endpoints analyses

The analyses of continuous secondary endpoints with multiple measurement times, namely the MDS-UPDRS part I, II and III and the NMSS total and domain scores, are compared between the

treatment groups by the MMRM model as described for the primary endpoint. The change in the mean Striatal Binding Ratio (SBR), in the total MOCA score and in the EQ-5D-5L index value are compared between the treatment groups by analysis of covariance (ANCOVA) with intervention and center as factors and baseline value as covariate. Least square mean changes for both groups as well as the difference between the least squares treatment group means will be reported with 95% CIs and p-value testing the null hypothesis of no treatment effect. The family-wise error rate across the key secondary endpoints, namely MDS-UPDRS part 1, 2 and 3, mean striatal binding ratio and NMSS total score, will be controlled by application of the Hochberg procedure. The key secondary endpoints are only tested for significance if the primary endpoint is statistically significant. The analyses of other secondary endpoints and safety parameters will have an exploratory character and will therefore not be adjusted for multiple testing.

```
library(emmeans)
dataEndpoints <- dataEndpoints %>%
      mutate(sbr_diff = sbr_w52 - sbr_BL)
model <- lm(sbr_diff ~ sbr_BL + group + center, data = dataEndpoints)
# report least square group differences
tmt.means <- lsmeans(model, specs = trt.vs.ctrlk ~ group, reverse = T, d
                     adjust = 'none')
tmt.means$contrasts; tmt.means$lsmeans
```

The Hoehn and Yahr stage at 52 weeks will be compared between the treatment groups by ordinal regression with intervention, center and baseline stage as factors.

```
library(ordinal)
library(emmeans)
library(rstatix)
mod.sec <- clm(HoehnYahr_w52 ~ HoehnYahr.BL + group + center,
                  link = 'logit', data = dataEndpoints)
emm.ord <- emmeans(mod.sec, ~ HoehnYahr_w52 | group, mode = 'prob',
                   adjust = 'none') %>% as.data.frame()%>%
mutate(Prob = sprintf('%.3f (%.3f, %.3f)', prob, asymp.LCL, asymp.UCL)) %>%
dplyr::select(HoehnYahr.V10, RANDTRT, Prob) %>%
pivot_wider(values_from = Prob, names_from = group)
comp <- pairs(emmeans(mod.sec, specs = 'group'))
# Display probabilities and p-value of pairwise contrast
qflextable(emm.ord) %>%
set_caption(paste0("Probabilities for the Hoehn & Yahr stage at 52 weeks in
the treatment groups (", p_format(comp$p.value, digits = 3, add.p =
T),")"))
```

Exploratory analyses

The change from baseline to week 52 in the NAD metabolome, serum NfL levels, and NAD/ATP-α ratio, will be compared between the treatment groups by MMRM, following the same lines as the primary outcome. Least square mean changes for both groups as well as the difference between the least squares treatment group means will be reported with 95% CIs and p-value testing the null hypothesis of no treatment effect.

Furthermore, the primary endpoint will be analyzed using the per-protocol set as defined in Section 3.3. If the selection between the treatment arms is skewed, a propensity score based method will be applied to adjust for potential confounding.

5.3 Missing data

While the MMRM model described above is robust to a certain extent to missing data (in particular when missing at random (MAR)), a sensitivity analysis using multiple imputation will be conducted to assess the robustness of the results. For this purpose, reference based multiple imputation will be performed using the R package *rbmi* (without MAR assumption).

5.4 Additional analyses

Sensitivity analysis of the primary analysis

To assess the robustness of the primary analysis, sensitivity analysis will be performed by using multiple imputation as described in the previous section.

In addition, the change in Levodopa dose (part of the standard-of-care PD regimen) and the time elapsed from levodopa intake until performance of the visit will be compared between the groups. If there are differences between the groups, we will model the hypothetical effect if the levodopa dose was constant and could not be changed.

In addition, the presence of dyskinesia during examination (from the MDS-UPDRS III scale) will be compared between the groups. If there are differences between the groups, we will model the hypothetical effect if dyskinesia was not present during the examination.

Subgroup analysis

Subgroups analyses are planned to be performed for:

- Age (median split; i.e. ≤ median vs > median)
- Hoehn & Yahr (Score ≤ 1 vs >1)
- Sex (Male/Female)
- Disease duration (Time from anamnestic onset of PD to randomization; dichotomized by median split)
- Motor phenotype (Postural Instability and Gait Difficulty [PIGD] vs non-PIGD)
- Dopaminergic therapy dose (3 groups: 300, 450, 600 mg levodopa).

The described MMRM for the primary endpoint will be extended to include the respective baseline factor and its interaction with treatment. Results will be graphically summarized in a forest plot.

For continuous variables such as age and disease duration the interaction with the treatment effect will be modeled using flexible splines. The treatment effects with confidence intervals will be plotted against the baseline variable.

5.5 Harms

Safety endpoints will be analyzed descriptively by treatment group using standard statistic measures depending on the data type (e.g. frequencies and percentages for categorical variables and mean, standard deviation, median and IQR for continuous variables). For events of particular interest (e.g. neoplastic disease and cardiovascular events) Kaplan-Meier curves or cumulative incidence functions in case of competing events stratified by treatment group will be computed and compared by log-rank tests resp. Gray’s test. For recurrent events and to account for variable

follow-up times, event rates will be reported with rate ratios comparing NR with placebo and 95% CI. We will use Poisson regression with adjustment for over dispersion or negative binomial regression models with offset for follow-up time and possibly a mixture component to account for zero-inflation.

```
library(gtsummary)
library(survival)
library(ggsurvfit)
library(tidycmprsk)
library(MASS)
# On patient level
tbl_summary(
      data = dataEndpoints, by = group, missing = "no",
      include = c(sae_pat,n_sae, ...),
      label = list(sae_pat ~ "Number of Patients with a SAE",
                   n_sae ~ "Number of SAE", ...),
      type = all_continuous() ~ "continuous2",
      statistic = list(all_continuous()~ c("{N_nonmiss}", "{mean}\u00B1{sd}",
                        "{median} ({p25}-{p75})"),
                        all_categorical() ~ "{n}/{N_nonmiss} ({p}%)"))%>%
      add_p(pvalue_fun = label_style_pvalue(digits = 3),
            test = list(
                  all_categorical()~ "chisq.test",
                  all_continuous()~ "t.test"))
# On the events in each group
tbl_summary(
      data = dataSAEs, by = group, missing = "no",
      include = c(sae_outcome, sae_serious, ...),
      label = list(sae_outcome ~ "Outcome of SAE",
                   sae_serious ~ "Seriousness of SAE", ...),
      type = all_continuous() ~ "continuous2",
      statistic = list(all_continuous()~ c("{N_nonmiss}", "{mean}\u00B1{sd}",
                        "{median} ({p25}-{p75})"),
                        all_categorical() ~ "{n}/{N_nonmiss} ({p}%)"))

# Kaplan-Meier curves with log-rank tests
SurvObj   <-   Surv(event_time,   event_status,   data   =   dataEndpoints)
km.by.treat <- survfit(SurvObj ~ group, data = dataEndpoints,
                        conf.type = "log-log")
plot(km.by.treat)
dataEndpoints %>%
  gtsummary::tbl_survfit(y = Surv(time, status),
                          label_header = "**{time} weeks**",
                          include = "group", times = 364/7) %>%
  gtsummary::add_p()

# Cumulative incidence functions with Gray's test
cuminc(Surv(event_time, event_status) ~ group, data = dataEndpoints) %>%
  ggcuminc() +
  ylim(c(0, 1)) + labs(x = "Days") +
  add_confidence_interval() +
  add_risktable()

cuminc(Surv(event_time, event_status) ~ group, data = dataEndpoints) %>%
  tbl_cuminc(times = 364/7, label_header = "**{times} weeks cuminc**") %>%
  tidycmprsk::add_p()

# Negative binomial Regression for recurrent events
mod.les <- glm.nb(event_rate ~ intervention + center +
                   offset(log(FUtime)), data = secEndpoints)
tmt.means <- emmeans(mod.les, ~ intervention , type = "response",
```

5.6 Statistical software

All analyses will be performed in the current version of R or SAS (SAS Institute Inc., Cary, NC, USA). Employed R packages and the specific version are documented within the statistical report.

5.7 References

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[6] Morton F, Nijjar JS (2024). eq5d: Methods for Analysing 'EQ-5D' Data and Calculating 'EQ-5D' Index Scores. R package version 0.15.3, https://CRAN.R-project.org/package=eq5d.

See Study Protocol Section 16.

6 Appendix

Protocol Deviation Handling Plan, v1.0, 14 Sep 2025

Protocol deviations (PDs) are defined as any departure from the approved NOPARK protocol, GCP, or applicable regulations. Deviations are classified as **Major** or **Minor** depending on their potential impact on participant safety, trial integrity, or interpretability of efficacy/safety endpoints.

Major Protocol Deviations

1. Enrolment of a participant not meeting inclusion/exclusion criteria (e.g., PD diagnosis >2 years, H&Y ≥3, no DAT confirmation, use of high-dose vitamin B3).
2. Informed consent not obtained prior to study procedures.
3. Incorrect randomization or failure to randomize per protocol.
4. Non-adherence to investigational product (IP) administration with < 90% compliance or not taking study medication for > 14 days consecutively, or not taking study medication within 3 days from the last visit.
5. Non-adherence to the standardized dopaminergic regimen (Regimens A–C, see study protocol) after baseline.
6. Missing primary efficacy endpoint assessment (MDS-UPDRS Total) at any visit.

Minor Protocol Deviations

1. Missed non-primary efficacy assessments (e.g., MoCA, NMSS, EQ-5D-5L).
2. Missed safety laboratory samples at any visit (baseline, Week 13, 26, 39, 52).
3. Missed research biobank samples.
4. Incomplete eCRF entry not affecting data integrity.
5. Missing DaTscan at Week 52 when baseline DatTscan is done.

Handling and Analysis

- All deviations will be evaluated by the Sponsor (HUS).
- Each deviation will be reviewed for impact on patient safety, study integrity, and evaluability.
- The frequency and type of deviations (major/minor) will be summarized by treatment arm (the denominator for percentages will be the Full Analysis Set (FAS)).
- No formal statistical testing will be performed.
- Patients with major deviations may be excluded from the Per Protocol Set (PPS), but will remain in the FAS.

Category	Protocol Deviation	Rationale / Potential Impact	Include in FAS	Include in PPS
Major	Enrolment of participant not meeting inclusion/exclusion criteria	Threatens study validity and endpoint interpretability	Yes	No
Major	Informed consent not obtained prior to study procedures	Regulatory and ethical violation; invalidates data	Yes	Yes
Major	Incorrect randomization or failure to randomize per protocol	Compromises trial integrity and treatment balance	No	No
Major	Non-adherence to investigational product (IP): <90% compliance	Affects treatment exposure and efficacy/safety interpretability	Yes	No
Major	Non-adherence to standardized dopaminergic regimen (Regimens A–C) post-baseline	Confounds efficacy outcomes	Yes	No
Major	Missing primary efficacy endpoint (MDS-UPDRS Total at any visit)	Primary endpoint not assessable	Yes	No