Official Title: A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase III Clinical Study to Evaluate the Efficacy and Safety of Intrathecally Administered RO7234292 (RG6042) in Patients With Manifest Huntington's Disease

NCT Number: NCT03761849

Document Dates: SAP Version 3: 12-May-2022

SAP Version 1: 16-December-2019

STATISTICAL ANALYSIS PLAN

TITLE:	**A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III CLINICAL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF INTRATHECALLY ADMINISTERED RO7234292 (RG6042) IN PATIENTS WITH MANIFEST HUNTINGTON'S DISEASE**
PROTOCOL NUMBER:	BN40423 Version 4 and onwards
STUDY DRUG:	RO7234292 (Tominersen)
VERSION NUMBER:	3
IND NUMBER:	137873
EUDRACT NUMBER:	2018-002987-14
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted], Ph.D. [redacted], M.Sc. [redacted], M.Sc.
DATE FINAL:	Version 1: 16 December 2019 Version 2: 1 April 2022
DATE AMENDED:	See electronic date stamp on the last page of this document.

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The Statistical Analysis Plan (SAP) for Study BN40423 has been amended in accordance with the Protocol BN40423 Version 4 and onwards.

Study BN40423 was originally designed (under Protocol Versions 1-3) to include three dosing regimens under a double-blinded monthly dosing paradigm: RO7234292 every 4 weeks (Q4W), RO7234292 every 8 weeks (Q8W) (with alternating placebo), and placebo Q4W. The Sponsor decided to stop enrollment under this original protocol containing this blinded monthly dosing paradigm and revised the protocol with a major protocol amendment in March 2019 to include three dosing regimens under a double-blinded bi-monthly dosing paradigm: RO7234292 Q8W, RO7234292 every 16 weeks (Q16W) arm (with alternating placebo), and placebo Q8W.

The details of this amendment including the rationale are in Protocol Version 4.

In March 2021, following the recommendation from the independent Data Monitoring Committee (iDMC) as a consequence of a regular iDMC safety review, the Sponsor issued an Urgent Safety Measure (USM) to permanently halt the dosing in the BN40423 study and implemented a new protocol amendment (Protocol Version 6).

Amendments made in the SAP from Version 1 to 2 includes following changes: Details on the study design were updated to reflect the study design as per Protocol Version 4 and onwards. Outcome measures were updated to consider outcome measures as per Protocol Version 6 and it was clarified that efficacy and biomarker outcome measures will be evaluated based on change from baseline at Week 69 due to Sponsor's decisions to discontinue study treatment as of 22 March 2021. Efficacy outcome measures (primary, secondary, and exploratory) and exploratory health status utility outcome measures were added and the order in which the different outcome measures are listed were adjusted for consistency with Protocol Version 6. Additionally, biomarker outcome measures were specified in accordance with Protocol Version 6.

Key changes made to the SAP from Version 2 to Version 3 are summarized below:

- Definition of baseline was updated in Sections 4.4, 4.9, 4.9.3, and 4.9.6.

Additional minor changes have been made to improve clarity and consistency.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. BACKGROUND

Study BN40423 is a Phase III, randomized, placebo-controlled, double-blind, multicenter clinical study to evaluate the efficacy, safety, pharmacokinetic (PK), and biomarker effects of intrathecally (IT) administered RO7234292 in patients with manifest Huntington's disease (HD).

Study BN40423 was originally designed (under Protocol Versions 1-3) to include three dosing regimens under a double-blinded monthly dosing paradigm: RO7234292 every 4 weeks (Q4W), RO7234292 every 8 weeks (Q8W) (with alternating placebo), and placebo Q4W. The Sponsor decided to stop enrollment under this original protocol containing this blinded monthly dosing paradigm and revised the protocol with a major protocol amendment in March 2019 to include three dosing regimens under a double-blinded bi-monthly dosing paradigm: RO7234292 Q8W, RO7234292 every 16 weeks (Q16W) arm (with alternating placebo), and placebo Q8W.

The details of this amendment including the rationale are in Protocol Version 4.

Prior to stopping the enrollment in Protocol Versions 1-3 on 29 March 2019, 108 patients were randomized, referred to as the "Original Design Cohort" (ODC). The ODC will not be included in the primary efficacy and safety analysis of the new study design (Protocol Version 4 and onwards). The Sponsor made this decision to prevent the potential bias that would have been introduced to the trial results if patients under different regimens (monthly and bi-monthly) were contained in the same analysis. Instead, ODC patients have been discontinued from Study BN40423 and offered enrollment into the long-term open-label extension study (BN40955).

Analysis for the Protocol Versions 1-3 (ODC) are described in Statistical Analysis Plan (SAP) Version 1.

In March 2021, following the recommendation from the independent Data Monitoring Committee (iDMC) as a consequence of a regular iDMC safety review, the Sponsor issued an Urgent Safety Measure (USM) to permanently halt the dosing in the BN40423 study and implemented a new protocol amendment (Protocol Version 6). This allowed patients to enter the off-treatment follow-up period, to monitor their safety and efficacy endpoints after the treatment discontinuation. At the same time, the Sponsor has been unblinded, to allow the start of exploratory analyses as soon as possible, for internal decision making on further clinical development of RO7234292.

This SAP will describe the statistical analysis of the efficacy and safety analyses of the cohort enrolled under Protocol Version 4 and onwards. The statistical analysis will be performed on the data collected up to the treatment termination (referred as "on-treatment period" thereafter) and data collected after the treatment termination (referred as "off-treatment follow-up period" thereafter).

2. STUDY DESIGN

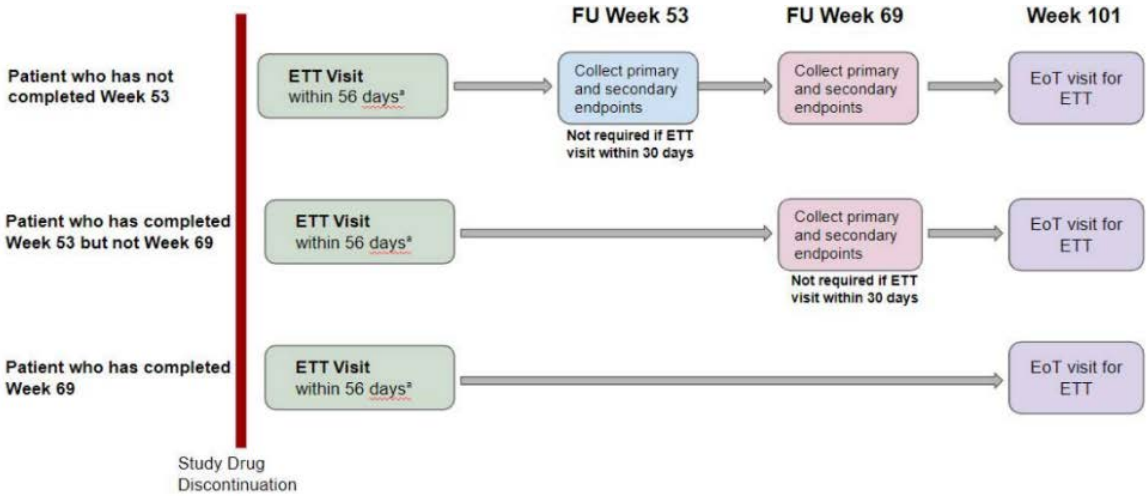
Approximately 801 patients will be enrolled in Study BN40423 under Protocol Version 4 and onwards. Prospective patients will undergo screening assessments during a 4-week screening period.

Upon completion of the screening period, eligible patients will be randomized in a 1:1:1 ratio to receive 120 mg RO7234292 Q8W, 120 mg RO7234292 Q16W, or placebo Q8W by IT injection. To maintain the study blind and integrity, patients in the 120 mg RO7234292 Q16W arm will also receive placebo every 8 weeks (i.e., alternating doses of active drug and placebo every 8 weeks).

Following the iDMC recommendation and Sponsor's decision to discontinue study treatment in this study, as of 22 March 2021, all patients will transition to the Early Treatment Termination (ETT) schedule within 56 days after treatment discontinuation as shown in Figure 1.

The language used in this SAP supersedes that in the protocol and protocol synopsis.

Figure 1 Visit Schedule Scenarios for Early Treatment Termination (Applicable to All Patients from 22 March 2021)



EoT=end of treatment; ETT=early treatment termination; FU=follow-up.

[a] The ETT visit should be performed within 56 days of the decision to discontinue study treatment. A telephone safety follow-up call will be conducted every 8 weeks between the clinic visits, to check for any change in patient status since the patient's last visit.

2.1 PROTOCOL SYNOPSIS

Please refer to Protocol Version 6 for the protocol synopsis. For additional details, see the Schedule of Assessments in Protocol Version 6, Appendix 1a and the Schedule of Assessments for Early Treatment Termination in Protocol Version 6, Appendix 1b.

2.2 ENDPOINTS

Following the iDMC recommendation and Sponsor's decision to discontinue study treatment in this study, as of 22 March 2021, only data collected up to 22 March 2021 will be used to evaluate the efficacy of RO7234292. By that date, approximately 80% of the participants reached their Week 69 visit, therefore the efficacy and biomarker outcome measures will be evaluated based on change from baseline at Week 69 (rather than change from baseline at Week 101).

However, all outcome measures are listed below as planned per protocol (i.e., referring to change from baseline at Week 101).

2.2.1 Primary Efficacy Endpoint

- Change from baseline in the composite Unified Huntington's Disease Rating Scale (cUHDRS) score at Week 101

  Note: The primary efficacy endpoint for the U.S. Food and Drug Administration (FDA) will be change from baseline in the Total Functional Capacity (TFC) score at Week 101.

Due to the iDMC recommendation as explained in Section 2.2 change from baseline at Week 69 (rather than change from baseline at Week 101) will be analyzed for endpoint listed above.

2.2.2 Secondary Efficacy Endpoints

- Change from baseline in scores for the following individual scales at Week 101:
  - TFC
  - Total Motor Score (TMS)
  - Symbol Digit Modalities Test (SDMT)
  - Stroop Word Reading (SWR) Test

  Note: For the U.S. FDA, the first secondary endpoint will be change from baseline in the cUHDRS score at Week 101 instead of TFC, as TFC will be the primary endpoint.
- Change from baseline in the Clinical Global Impression, Severity Scale (CGI-S) score at Week 101
- Proportion of patients with a decrease from baseline of at least 1 point on the TFC at Week 101
- Proportion of patients with a decline from baseline of at least 1.2 points on the cUHDRS at Week 101

- Proportion of patients with an unchanged or improved score on the Clinical Global Impression, Change Scale (CGI-C) score from baseline at Week 101

Due to the iDMC recommendation as explained in Section 2.2, change from baseline at Week 69 (rather than change from baseline at Week 101) will be analyzed for all endpoints listed above.

2.2.3 Exploratory Efficacy Endpoints

- Change from baseline in the Apathy Evaluation Scale (AES) score at Week 101
- Change from baseline in the Symptoms of Major Depressive Disorder Scale (SMDDS) score at Week 101
- Change from baseline in the Huntington's Disease Daily Activities Scale (HD-DAS) score at Week 93
- Change from baseline in the Patient Global Impression, Severity Scale (PGI-S) score at Week 101
- Change from baseline in the Quality of Life in Neurological Disorders (Neuro-Qol) Cognition Function Short Form at Week 101
- Change from baseline in the Huntington's Disease Speaking Difficulty Item Scale (HD-SDI) score at Week 101
- Change from baseline in the Huntington's Disease Companion-Reported Irritability and Angry Outbursts Scale (HD-CIAOS) score at Week 101
- Change from baseline in the in-clinic patient-reported EuroQol 5-Dimension Questionnaire (5-level version; EQ-5D-5L) index-score and visual analogue scale (VAS) at Week 101
- Change from baseline in the sensor-based measures collected by the Roche HD mobile application (app; smartphone and wrist-worn wearable) at Week 101

Due to the iDMC recommendation as explained in Section 2.2, change from baseline at Week 69 (rather than change from baseline at Week 101) will be analyzed for all endpoints listed above.

2.2.4 Safety Endpoints

- Incidence and severity of adverse events (AEs), with severity determined according to the Adverse Event Severity Grading Scale
- Change from baseline in Montreal Cognitive Assessment (MoCA)
- Change from baseline in vital signs
- Change from baseline in ECG parameters
- Change from baseline in clinical laboratory results
- Proportion of patients with suicidal ideation or behavior, as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) score at each visit, including

detailed focus on any individual cases identified as having severe ideation or behavior during the study conduct

2.2.5 Pharmacokinetic Endpoints

- Concentration of RO7234292 in plasma at specified timepoints
- Trough concentration of RO7234292 in cerebrospinal fluid (CSF) at specified timepoints

The exploratory pharmacokinetic/pharmacodynamic (PK/PD) outcome measures are:

- Relationship between plasma profiles and/or trough CSF concentrations and/or PK parameters for RO7234292 and efficacy endpoints
- Relationship between plasma profiles and/or trough CSF concentrations and/or PK parameters for RO7234292 and safety endpoints

2.2.6 Immunogenicity Endpoints

- Incidence of anti-drug antibodies (ADAs) at specified timepoints relative to the prevalence of ADAs at baseline
- Titer and antibody subtype, determined if ADAs are identified

The exploratory immunogenicity outcome measure is:

- Relationship between ADA status and efficacy, safety, or PK endpoints

2.2.7 Biomarker Endpoints

2.2.7.1 Primary Biomarker Endpoint

- Change from baseline in CSF mutant huntingtin (mHTT) protein level at Week 101

2.2.7.2 Secondary Biomarker Endpoints

- Change from baseline in whole and regional brain volumes (caudate, whole brain, and ventricular), as determined by structural magnetic resonance imaging (MRI), at Week 101
- Change from baseline in CSF neurofilament light chain (NfL) protein level at Week 101

2.2.7.3 Exploratory Biomarker Endpoints

- Relationship between biomarkers in blood, plasma, and CSF and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between imaging biomarkers (e.g., putamen, cortical grey matter, cortical white matter volumes, resting state functional MRI signal) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

2.2.8 Exploratory Health Status Utility Endpoints

- Change from baseline in patient- and companion-reported EQ-5D-5L Index and VAS scores at specified timepoints

- Change from baseline in companion self-reported and proxy-reported Health Utilities Index Mark 2 (HUI2) and Health Utilities Mark 3 (HUI3) scores at specified timepoints
- Change from baseline in patient- and companion-reported Work Productivity and Activity Impairment (WPAI) scores at specified timepoints

2.3 DETERMINATION OF SAMPLE SIZE

The planned sample size is adequate to capture meaningful clinical decline on both the TFC and cUHDRS and was estimated applying a meta-analysis on data available from non-interventional studies (TRACK-HD, COHORT, ENROLL-HD) and a randomized placebo-controlled study (2CARE). Results of the meta-analysis on the change from baseline at 24 months in TFC suggested a natural decline of 1.36 points and a corresponding pooled standard deviation of 1.78. A conservative treatment discontinuation rate at Week 101 for patients receiving placebo or active is assumed to be 20% and 15% respectively.

Using these assumptions, 267 patients per arm was estimated to provide approximately 80% power, at a two-sided ≤0.025 level, to detect a 40% slowing of clinical decline for RO7234292 as compared with placebo at 101 weeks. The proposed sample size was estimated based on simulations (further described below). The assumed treatment effect translates into an expected average decline of ~0.82 points at 101 weeks for the RO7234292 arms. The minimal detectable difference with these assumptions is ~0.38 points.

Given the above sample size, the cUHDRS, the more sensitive outcome measure, is powered at 80%, at a two-sided ≤0.025 level, to detect a 30% slowing of clinical decline for RO7234292 as compared with placebo at 101 weeks. Since there are presently no therapies available to stop or slow clinical progression in HD, any slowing of clinical progression of overall functional decline or linked overall functional, cognitive, and motor decline may be considered meaningful, such that between a 20%-40% slowing of decline, translating to approximately 2.5-4.5 months per year of time saved from progression, would represent a meaningful treatment effect.

Description of simulations to derive the sample size

The design used for the simulation was simplified to consider only 2 treatment arms (placebo and active) and 2 post-baseline time-points (Week 49 and Week 101).

1. The following algorithm was run and repeated 500000 times:
   Generate change from baseline values in TFC at Week 49 and Week 101 for N **active patients** according to the following bivariate normal distribution:

$$\begin{pmatrix} y\_wk49 \\ y\_wk101 \end{pmatrix} = N\left(\mu = \begin{pmatrix} 0.47 \\ 0.82 \end{pmatrix}, \sum = \begin{pmatrix} 1.56^2 & 1.8 \\ 1.8 & 1.78^2 \end{pmatrix}\right)$$

where y_wk49 and y_wk101 is the change from baseline in TFC respectively at Week 49 and Week 101, μ is the assumed true change at those two timepoints and $\sum$ is the variance-covariance matrix. The assumed covariance of 1.8 corresponds to a correlation coefficient of 0.65. Subsequently:

- set to missing, due to any treatment and/or disease progression related reasons (TDPR), both values at Week 49 and Week 101 for 5% of the N active patients. Set to missing, due to non-treatment or disease progression related reasons (NTDPR), both values at Week 49 and Week 101 for additional 2.5% of the N active patients.
- set to missing, due TDPR, only the value at Week 101 for additional 5% of the N active patients. Set to missing, due to NTDPR, only the value at Week 101 for additional 2.5% of the N active patients.

2. Generate change from baseline values in TFC at Week 49 and Week 101 for N **placebo patients** according to the following bivariate normal distribution:

$$\begin{pmatrix} y\_wk49 \\ y\_wk101 \end{pmatrix} = N\left(\mu = \begin{pmatrix} 0.79 \\ 1.36 \end{pmatrix}, \sum = \begin{pmatrix} 1.56^2 & 1.8 \\ 1.8 & 1.78^2 \end{pmatrix}\right)$$

   where y_wk49 and y_wk101 is the change from baseline in TFC respectively at Week 49 and Week 101, μ is the assumed true change at those two timepoints and $\sum$ is the variance-covariance matrix. Subsequently:

   - set to missing both values at Week 49 and Week 101 for 10% of the N placebo patients
   - set to missing only the value at Week 101 for additional 10% of the N placebo patients

   Given how missing data will be imputed, it is not relevant to differentiate missing data into TDPR versus NTPDR for placebo patients.

3. Apply multiple imputation and derive 20 complete datasets. Missing data on placebo patients were imputed from the placebo arm. Missing data on active patients, depending if due to TDPR or NTDPR reasons, were imputed respectively from the active or the placebo arm.
4. Use a t-test to compare active versus placebo at Week 101 for each completed dataset and pool the result (Rubin 1987) to derive an estimate of the treatment effect, including a p-value.

Across the 500000 simulations, the power achieved, with the N patients per arm was calculated, by dividing the number of times the two-sided p-value (in Step 4) was below 2.5% by 500000. The above procedure was repeated by only changing the N until the calculated power was close to 80%.

2.4 ANALYSIS TIMING

The final analysis will be conducted once all patients have either reached Week 101 or withdrawn early from the study and data have been cleaned and verified and the database has been locked.

Following the iDMC recommendation and Sponsor's decision to discontinue study treatment in this study, as of 22 March 2021, the main statistical analysis will be performed on the data collected up to 22 March 2021. The data collected after 22 March 2021 will be analyzed in an exploratory off-treatment follow-up analysis.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Approximately 801 patients are planned to be randomized to receive placebo, RO7234292 Q8W 120 mg or RO7234292 Q16W 120 mg in a 1:1:1 ratio using permuted block randomization. An independent Interactive Voice or Web Response System (IxRS) provider will conduct randomization and hold the treatment assignment code. No stratification is applied in this study.

3.2 DATA MONITORING

An iDMC will be employed to monitor and evaluate cumulative patient safety throughout the study. It is anticipated those safety reviews will occur approximately every 4 months (further details are provided in a separate iDMC charter).

Following the iDMC recommendation to halt the dosing in Study BN40423, the scope of the iDMC has been revised and it is now focusing on a comparison of the on-treatment period (data collected up to treatment termination) against the off-treatment follow-up period (data collected after treatment termination). Further details are provided in the updated iDMC charter.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population will consist of all randomized patients who received any study treatment. Randomized patients who receive therapy different from the one assigned at randomization will be summarized in the group according to their planned randomized treatment.

The ITT population will be the primary population for all analyses of primary and secondary efficacy variables.

4.1.2 Safety Population

The ITT population will also be used for all analyses of safety data.

For the purpose of all safety analyses, at the time of unblinding, it will be assessed whether at any time during the course of the study, patients received a treatment different from the one they were randomized to.

For patients who were randomized to placebo but received any active treatment by error, if there is any safety signal of concern present, they will be summarized under the active treatment group; otherwise will be summarized under placebo.

The safety data during such switching period will be provided separately.

The final decision on this will only be possible after unblinding.

4.1.3 PK Population

The PK population will include all patients randomized after implementation of Protocol Version 4 who received at least one dose of RO7234292, and had sufficient sampling to permit PK evaluation.

4.2 ANALYSIS OF STUDY CONDUCT

The numbers of patients who enroll in the study, discontinue from the study (during on-treatment period or during off-treatment follow-up period), and complete the study will be summarized overall and by treatment arm. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. In addition, major protocol deviations that are considered related to Coronavirus Disease 2019(COVID-19) will be listed and summarized descriptively.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics will be summarized by treatment group using means, standard deviations, medians and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment.

4.4 EFFICACY ANALYSIS

Given the date of the public announcement of the Sponsor halting dosing in Study BN40423 (following the iDMC recommendation), only data collected up to 22 March 2021 will be used to evaluate the efficacy of RO7234292 (to avoid any bias from data collected after the official announcement).

For all efficacy endpoints, the baseline will be defined as the last assessment on Day 1. Further reporting windows are defined in Appendix 1.

4.4.1 Covariate Adjustment

Unless otherwise noted, analyses of efficacy endpoints (primary, secondary, and exploratory) will include the following covariates in the model:

- Treatment: Placebo, RO7234292 Q8W, and RO7234292 Q16W
- CAG at baseline
- CAG-Age Product (CAP) at baseline (defined as (CAG-33.66)*age)
- Age at baseline

For continuous endpoint the baseline of the endpoint will also be included in the model unless stated otherwise.

4.4.2 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo on the basis of cUHDRS score.

Following the iDMC recommendation and Sponsor's decision to discontinue study treatment in this study, as of 22 March 2021, the primary estimand as described in Protocol Section 6.6.1 and the planned analysis method as described in Protocol Section 6.6.2 will not be considered for the analysis of the primary efficacy endpoint.

Instead of analysis of variance (ANCOVA) as planned per protocol, the primary efficacy endpoint will be evaluated by means of a Mixed Model Repeated Measurements (MMRM) analysis using the covariates described in Section 4.4.1 as fixed effects. The model will also include visit (as a categorical factor) and visit-by-treatment interaction. An unstructured (UN) variance-covariance structure will be applied to model the within patients' errors; if the model fails to converge, the following variance-covariance structures will be tested as alternatives in the pre-specified order: Heterogeneous Toeplitz (TOEPH), Antedependence (ANTE[1]) and Heterogeneous Compound Symmetry (CSH). On the basis of this analysis, least squares means for the treatment differences at Week 69 and corresponding 95% confidence intervals (CIs) will be derived. Unlike as planned per protocol, no adjustments for multiple comparisons will be incorporated into the analyses.

The MMRM analysis is equivalent to a 'hypothetical' strategy, estimating the treatment effect as if patients would have fully adhered to their intended treatment regimen. This hypothetical strategy is generally considered, but actual off-treatment values assessed after treatment discontinuation before 22 March 2021 are included in the analysis. Missing values (because no data was collected) will not be imputed but will be handled via the MMRM. The MMRM assumes that missing data are missing at random (MAR). That is, MMRM assumes that given the statistical model and given the observed values of the endpoint, missing data are independent of the unobserved values (O'Kelly and Ratitch 2014).

The primary endpoint will also be summarized using descriptive statistics.

4.4.3 Secondary Efficacy Endpoints

The continuous secondary efficacy endpoints will be analyzed via an MMRM as described in Section 4.4.2.

Similar as for the primary endpoint, the MMRM analysis will be performed instead of per protocol planned analyses via ANCOVA. For these analyses, least squares means for the treatment differences at Week 69 and corresponding 95% CIs will be reported. No adjustments for multiple comparisons will be incorporated into the analyses, especially the testing strategy described in Protocol Section 6.3 is not considered for any analyses.

Change from baseline at Week 69 will be analyzed for the following secondary endpoints:

- TFC
- TMS
- SDMT
- SWR Test
- CGI-S

The categorical secondary endpoints will be analyzed descriptively and by means of logistic regression including treatment (categorical), CAG repeat length, and CAP score as covariates.

- Analyses will be conducted for the following categorical secondary endpoints: Proportion of patients with a decrease from baseline of at least 1 point on the TFC at Week 53 and at Week 69
- Proportion of patients with a decline from baseline of at least 1.2 points on the cUHDRS at Week 53 and at Week 69
- Proportion of patients with an unchanged or improved score on the CGI-C score from baseline at Week 53 and at Week 69

4.4.4 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are listed in Section 2.2.3.

The exploratory endpoints will be analyzed via an MMRM as described in Section 4.4.2.

Results for the digital endpoints (including HD-SDI, HD-CIAOS, and sensor-based measures collected by the Roche HD mobile) will not be reported in the Clinical Study Report (CSR).

4.4.5 Subgroup Analyses

Subgroup analyses will be performed for the following endpoints:

- Change from baseline in cUHDRS and the individual components (TMS, TFC, SDMT, SWRT) at Week 69
- Change from baseline in CSF NfL protein level at Week 69
- Change from baseline in CSF mHTT protein level at Week 69 (due to data availability, the analyses of CSF mHTT protein level might not be completed by the time of the CSR writing so results of this subgroup analysis may be reported in an addendum to the CSR)
- Annualized percent change from baseline in whole and regional brain (caudate and ventricular) boundary shift integrals (BSI) at Week 69

The thresholds for the categories for each variable were chosen on the basis of median or frequency distribution in the population, thus the definitions of the subgroups actually chosen differ slightly from the definitions as specified in the protocol:

- Sex (male versus [vs.] female)
- Age at baseline (≤48 years vs. >48 years (instead of ≤45 years vs. >45 years as planned per protocol))
- CAG repeat length (≤44 vs. >44 [instead of ≤43 vs. >43 as planned per protocol])
- Stage at baseline (Stage I vs. Stage II-IV [instead of Stage I vs. Stage II vs. Stage III as planned per protocol])

For subgroups defined by 'baseline variables' (e.g., baseline_CAG≤44 vs. baseline_CAG>44), a similar MMRM as the one described in Section 4.4.2 will be used, with the addition of the following covariates: subgroup (as categorical; the corresponding continuous variable will be excluded from the model if it was considered as a covariate in the original model), visit-by-subgroup interaction, treatment-by-subgroup interaction and visit-by-treatment-by-subgroup interaction.

4.4.6 Post-Hoc Exploratory Analysis

Following the recommendation from the iDMC to halt dosing in Study BN40423, the sponsor decided to perform post hoc exploratory analysis in subgroups defined by baseline age and CAP (thresholds defined based on approximate median splits; i.e., Age <48 and CAP<500; Age≥48 and CAP<500; Age<48 and CAP≥500; and Age≥48 and CAP≥500). A similar MMRM analysis as the one described in Section 4.4.2 was used, with the addition of the following covariates: subgroup (as categorical), visit-by-subgroup interaction, treatment-by-subgroup interaction and visit-by-treatment-by-subgroup interaction. Age and CAP at baseline were removed from the MMRM analysis. Analyses for this subgroup were performed for the endpoints as listed in Section 4.4.5. For these subgroups defined by baseline age and CAP, strata were defined by post-randomization variables (e.g., patients with low or high exposure) and propensity score methodology was used in order to define the right 'control group',

by assigning weights (defined as (PS/[1-PS]), where PS is the propensity score as estimated using a logistic regression) to placebo patients (to balance out potential confounders) and then employing a weighted regression. The standard errors of the fixed-effects parameters were estimated by using the asymptotically consistent and robust estimator (commonly referred to as the "sandwich" estimator, Liang and Zeger 1986).

Analyses were performed for the treatment group comparisons of Placebo vs. RO7234292 Q16W.

The following strata were considered:

- Strata split by median of average concentration at Week 21
- Strata split by median of average percent change from baseline in mHTT at Week 21 (due to data availability, the analyses of strata by mHTT might not be completed by the time of the CSR writing so results of this analysis may be reported in an addendum to the CSR)

Those analyses will be re-run on the final data after database lock.

In addition, demographic and baseline characteristics will be summarized by subgroups defined by above mentioned baseline age and CAP using means, standard deviations, medians and ranges for continuous variables and proportions for categorical variables, as appropriate.

4.5 PHARMACOKINETIC ANALYSES

For all patients in the PK population, CSF, and plasma concentrations of RO7234292 will be presented descriptively, including arithmetic and geometric means, median, range, standard deviations, and coefficients of variation.

In addition, nonlinear mixed-effects modeling will be used to analyze the concentration–time data for RO7234292 in CSF and plasma following IT administration. A covariate analysis will be conducted to evaluate the effect of covariates such as body weight, age, and sex on RO7234292 exposure. Population and individual estimates of primary PK parameters (e.g., clearance, distribution volume) and secondary PK parameters (e.g., area under the plasma concentration–time curve, average trough plasma concentration) will be computed and used to explore exposure-response relationship on primary and key secondary endpoints, as well as safety measures. The data from this study may be pooled with data from other studies conducted with RO7234292 to support the population PK/PD modeling. Details of this mixed-effects modeling and exploration of exposure-response analysis and results will be described and reported in a document separate from the CSR.

4.6 IMMUNOGENICITY ANALYSES

For the analysis, the following definitions based on Shankar et al. (2014) as well as a Sponsor's definition for ADA with neutralizing potential, will be used to describe patients' RO7234292 immunogenicity as follows:

- **ADA Negative**
  - ADA negative all samples: Patients who have no pre-existing ADA (i.e., antibodies reactive with the drug that are present in patients before treatment) or are missing ADA data before drug administration and who have all negative ADA results following drug administration, and treatment unaffected ADA-negative patients.
  - Treatment unaffected ADA: Subset of ADA negative patients who have pre-existing ADA but do not have a $\geq$4 fold increase in ADA titer following drug administration compared to baseline measurement.
- **ADA Positive**
  - Treatment induced: ADA developed de novo (seroconversion) following drug administration. Patients who have no pre-existing ADA or are missing ADA data before drug administration and who have at least one ADA positive sample following drug administration.
  - Treatment boosted: Patients who have pre-existing ADA and have a$\geq$4 fold increase in ADA titer following drug administration compared to baseline measurement.
- **Transient ADA**
  - Treatment-induced ADA detected only at one sampling time point during the on-treatment or off-treatment follow-up period (excluding the last sampling time point).
- **Persistent ADA**
  - Treatment-induced ADA detected at 2 or more sampling time points during the on-treatment or off-treatment follow-up period; or detected on last sampling time point.
- **ADA with Neutralizing Potential**
  - An ADA positive patient with declining or increasing PK based on visual assessment, and corroborated by PD markers.

Immunogenicity will be analyzed in patients included in the safety population who had at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned. The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) will be summarized by treatment group. For those who are ADA-positive, titers will be estimated as well as antibody subtype. In addition, the numbers and proportions of ADA-positive patients and ADA-negative

patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized for patients on active treatment only.

4.7 BIOMARKER ANALYSES

For statistical modelling, raw concentration values of fluid biomarkers in their respective units will be log-transformed.

Change from Baseline in CSF mHTT Protein Level

The same MMRM model as for efficacy endpoints (see Section 4.4) will be used to model the change from baseline in mHTT (after log-transformation of mHTT). Results from the model will be back-transformed, in order to present model-based percent change in geometric means.

Due to data availability, the analyses of CSF mHTT protein level might not be completed by the time of the CSR writing so results of this analysis may be reported in an addendum to the CSR.

Annualised Percentage Change from Baseline in Whole and Regional Brain (Caudate, and Ventricular) Volume Measured by BSI, as Determined by Structural MRI

The same MMRM model as for efficacy endpoints (see Section 4.4), but without adjusting for baseline volume (as this is already taken into account by considering the percent change from baseline), will be used to model the annualized percent change from baseline in BSI, which means that the measured percent change from baseline to the analysis timepoint will be converted to reflect percent change from baseline normalized for the duration between baseline assessment and post-baseline assessment in years.

Change from Baseline in CSF NfL Protein Level

The same MMRM model as for efficacy endpoints (see Section 4.4) will be used to model the change from baseline in NfL (after log-transformation of NfL). Results from the model will be back-transformed, in order to present model-based percent change in geometric means.

4.8 EXPLORATORY HEALTH STATUS UTILITY ANALYSES

The exploratory health status utility endpoints are listed in Section 2.2.8.

Results for the exploratory health status utility endpoints will not be reported in the CSR.

4.9 SAFETY ANALYSES

Following the iDMC recommendation, effective 22 March 2021, no further study treatment was administered in this study. Patients in the study were continued to be followed for safety and efficacy outcomes until study completion.

All safety endpoints will be analyzed overall, i.e., disregarding if data was collected during on-treatment period or during off treatment follow-up period. On-treatment period is defined as time from first dose to last dose plus 5 months. Off-treatment follow-up period is defined as the time more than 5 months after last dose of study drug.

Analyses addressing the on-treatment period and off-treatment follow-up period are described in Section 5.

For all safety endpoints, if not stated otherwise, the baseline will be defined as the last assessment prior to the first lumbar puncture procedure or last assessment on Day 1, whichever occurred first.

4.9.1 Exposure of Study Medication

Exposure to RO7234292 and placebo over the course of the study will be summarized using descriptive statistics for the safety evaluable population and the PK population. The duration of exposure, defined as number of days from first dose of study treatment to last dose plus 5 months (i.e., 152 days) as well as the duration of the off treatment follow-up period will be summarized descriptively.

4.9.2 Adverse Events

All verbatim AE terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and AE severity will be graded.

The incidence of AEs will be summarized on the basis of body systems and dictionary preferred terms and reported in individual listings and tables by treatment arm. The incidence of AEs by severity and relationship to study drug or study procedure and outcome will be provided.

The following AEs will be summarized by body system and preferred term:

- Any AE
- SAE
- AEs related to study treatment (any AE, SAE)
- AEs related to lumbar puncture
- AEs leading to discontinuation of study treatment
- AEs leading to dose modification or interruption
- AEs resulting in death
- Selected AEs

- Liver function
- Abuse potential
- Peripheral neurological events
- Central neurological events
- CSF proteins and leukocytes events
- Events potentially associated to brain ventricular expansion
- Renal function
- Thrombocytopenia
- Lumbar puncture associated (any time, occurring within 5 days)

The above mentioned summaries for AEs will be provided for AEs reporting during the on-treatment period. In addition, summary tables will be provided for on treatment AEs by ADA status, acknowledging that subgroups are defined by post-baseline data. AEs reported during the off-treatment period will be listed.

Adverse events are considered on-treatment if the AE onset date was before or at the date of last exposure to treatment plus 5 months, i.e., $\leq$ last dose + 152 days.

Adverse events are considered post-treatment if the AE onset date was after the date of last exposure to treatment plus 5 months, i.e., $>$ last dose + 152 days.

In addition, COVID-19 related AEs will be summarized.

4.9.3 Laboratory Data

Abnormal laboratory outcomes will be reported. A summary of the number and percentage of patients with abnormal laboratory outcomes will be produced at each visit by treatment group.

Absolute values and change from baseline values for all laboratory assessments will be summarized by descriptive statistics at each visit by treatment group. The baseline for the laboratory, except for the CSF safety lab parameters, will be defined as the last assessment prior to the first lumbar puncture or last assessment on Day 1, whichever occurred first. For the CSF safety lab parameters, the baseline will be defined as the last assessment prior to the first dosing administration or last assessment on Day 1, whichever occurred first.

For the measurement reported as '$<$x' or '$>$x', the value will be set to x.

In addition, the shifts (relative to the normal range) from baseline to the minimum and maximum post-baseline values will be presented. If a subject is missing a baseline value but had a post-baseline value, then the baseline assessment is labeled as

"unknown". Likewise, if a subject had a baseline value but had no post-baseline values, then the minimum and maximum are labeled as "unknown".

The number of patients with abnormal and marked abnormal absolute values for the CSF safety labs, according to the parameter ranges presented in Table 1, will be summarized by treatment and visit.

Table 1 CSF Safety Laboratory Normal Ranges

Parameter	Low	Normal	High	Marked High
Glucose (mmol/L)	<2.2	2.2-3.9	>3.9	>4.4
Protein (g/L)	<0.15	0.15-0.5	>0.5	
Erythrocytes (cells/μL)		0	>0	>5
Leucocytes (cells/μL)		0-5	>5	

CSF = cerebrospinal fluid.

4.9.4 Vital Signs and ECG

Absolute values and change from baseline values for vital signs and ECG data will be summarized by descriptive statistics at each visit by treatment group.

4.9.5 Columbia-Suicide Severity Rating Scale

Clinical assessments of suicidality data from CSSR-S will be summarized by descriptive statistics at each visit by treatment group.

4.9.6 Montreal Cognitive Assessment

The MoCA is an 11-item clinician-reported assessment that is used to detect cognitive impairment. It contains a series of basic assessments, including attention and visuospatial tasks. The total score ranges from 0–30, where lower scores indicate greater impairment. A scoring $\geq 26/30$ is considered normal. Individual components contributing to the total score are listed below:

- Visuospatial/executive (0 to 5)
- Naming (0 to 3)
- Attention (0 to 6)
- Language (0 to 3)
- Abstraction (0 to 2)
- Delayed recall (0 to 5)
- Orientation (0 to 6)

The total score is given by the sum of all sub scores; one point can be added for subject who has 12 years or fewer of formal education, for a possible maximum of 30 points.

Absolute values and change from baseline values for the MoCA assessment will be summarized by descriptive statistics at each visit by treatment group. The baseline for MoCA will be defined as the last assessment on Day 1.

4.9.7 Safety MRI

Clinical assessments from the safety MRI will be summarized by descriptive statistics at each visit by treatment group. Radiographic hydrocephalus cases will be listed.

5. ANALYSIS OF OFF-TREATMENT FOLLOW-UP DATA

Following the recommendation from the iDMC to halt dosing in Study BN40423, patients entered the off-treatment follow-up period to monitor their safety and efficacy endpoints after the treatment discontinuation. This section describes the statistical analyses that will use data collected after treatment termination.

5.1 MIXED MODEL REPEATED MEASUREMENTS

Data collected up to Week 101 will be analyzed by an MMRM model as defined in Section 4.4.2. Different approaches will be defined for these MMRM analyses:

1. ITT analysis will include all patients in the ITT population
2. iDMC ad-hoc completer analysis will include patients who completed Week 101
3. Completer analysis will include patients who completed Week 101 and who had their last dose of study drug more than 5 months ($>$152 days) prior to their Week 101 visit

The statistical modeling will be applied to the following endpoints:

- cUHDRS and its individual components
- MRI (BSI data, annualized percentage change from baseline)
- cUHDRS and components for age and CAP subgroups (if number of patients in the subgroup is sufficiently large, especially for the completers analyses)

5.2 SLOPE ANALYSIS

All analyses will be limited to patients who 1) received their last dose of any study treatment within 3 months (3*28 days) before 22 March 2021 (the date when it was publicly announced to stop treatment in Study BN40423) and 2) have at least one measurement collected during the off-treatment period for the selected outcome.

The statistical modeling will be applied to the following endpoints:

- cUHDRS and its individual components
- MoCA

This analysis will consider two periods: the on-treatment period and the off-treatment follow-up period, in order to compare the different slopes.

Two different approaches will be applied to define those periods:

1. Cut-off at date of last study drug intake (on-treatment period up to date of last dose)
2. Cut-off at date of last study drug intake plus 5 months (on-treatment period up to date of last dose + 152 days)

A linear mixed effect model (LMM) will be performed using time as a continuous variable and including a random intercept and a random slope to investigate the treatment effect by comparing the slopes. Baseline age, CAP score, and CAG will also be included in the model.

- **Within Treatment Comparison While on Treatment Versus After Treatment Stop:**
  Within each treatment, the rate of declining in clinical endpoints during the off-treatment follow-up period is compared with the rate of declining during the on-treatment period.
- **Between Treatment Comparison of the Slopes After Treatment Stop**:
  The slope after treatment stop of the active treatment (individually per treatment schedule) will be compared with that of placebo group.

If the model fails to converge, the following steps might be adapted:

1. Relaxing the assumption of different variance of the random effect of change in slope for each treatment group
2. Excluding the random effect of change in the slope after treatment stop
3. Relaxing the assumption of different variance of the random slope for each treatment group

5.3 OTHER ANALYSES OF OFF-TREATMENT FOLLOW-UP DATA

A descriptive summary of values during on-treatment period compared with values during off-treatment follow-up period will be shown using boxplots for the following endpoints:

- Annualized percent change in ventricle volume – maximum on-treatment versus maximum off-treatment value will be used
- CSF protein – maximum on-treatment versus last off-treatment value will be used
- CSF Leukocytes – maximum on-treatment versus last off-treatment value will be used

For these analyses the off-treatment period will start at the day after the last dose of study treatment plus 5 months (152 days).

6. REFERENCES

Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika. 1986;73(1):13-22.

O'Kelly M, Ratitch B. Clinical trials with missing data: a guide for practitioners. Chichester, UK: John Wiley & Sons. 2014.

Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons. 1987.

Shankar G, Arkin S, Cocea L, et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. AAPS J 2014;16:658-73.

Appendix 1 Reporting Windows by Endpoints

All visits are used as labeled in the data.

Data collected at the early termination visit (for endpoints Unified Huntington's Disease Rating Scale [UHDRS], Clinical Global Impression, Change Scale [CGI-C], Patient Global Impression of Change [PGI-C], and Companion-Reported Global Impression, Change (CrGI-C): also unscheduled visits) will be mapped to the visits applying reporting windows depending on the endpoint as described in Table 1.

If there are two or more assessments for an endpoint within the same visit due to the remapping of early termination or unscheduled visits, the mean of all assessments within the same visit will be considered in the analysis. If there are two or more assessments for an endpoint within the same visit but not due to the remapping of early termination or unscheduled visits, the last available assessment will be considered in the data analysis.

Table 1 Reporting Windows by Endpoints

Scheduled Week	Reporting Window (based on study day) All Endpoints except UHDRS, CGI-C, PGI-C and CrGI-C			Reporting Window (based on study day) Endpoints UHDRS, CGI-C, PGI-C and CrGI-C		
1	1	to	13	1	to	13
5	14	to	55	14	to	83
13	56	to	111			
21	112	to	167	84	to	195
29	168	to	223			
37	224	to	279	196	to	307
45	280	to	335			
53	336	to	391	308	to	419
61	392	to	447			
69	448	to	503	420	to	531
77	504	to	559			
85	560	to	615	532	to	643
93	616	to	671			
101	≥ 672			≥ 644		

CGI-C = Clinical Global Impression; Change Scale, CrGI-C = Companion-Reported Global Impression, Change; PGI-C = Patient Global Impression of Change; UHDRS = Unified Huntington's Disease Rating Scale.

Signature Page for: System identifier:RIM-CLIN-439389
Statistical Analysis Plan - BN40423 - Published

Approval Task	[redacted] Scientific content approver 12-May-2022 17:17:08 GMT+0000

STATISTICAL ANALYSIS PLAN

TITLE: **A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III CLINICAL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF INTRATHECALLY ADMINISTERED RO7234292 (RG6042) IN PATIENTS WITH MANIFEST HUNTINGTON'S DISEASE**

PROTOCOL NUMBER: BN40423 version 1-3

STUDY DRUG: RO7234292

VERSION NUMBER: 1

IND NUMBER: 137873

EUDRACT NUMBER: 2018-002987-14

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted] Ph.D.
[redacted], Ph.D.

DATE FINAL: See electronic date stamp below

STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
16-Dec-2019 09:09:31	Company Signatory	[redacted]

CONFIDENTIAL

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. BACKGROUND

Study BN40423 is a Phase III, randomized, placebo-controlled, double-blind, multicenter clinical study to evaluate the efficacy, safety, pharmacokinetic (PK), and biomarker effects of intrathecally (IT) administered RO7234292 in patients with manifest Huntington's disease (HD).

Study BN40423 was originally designed (under Protocol Versions 1-3) to include three dosing regimens under a blinded monthly dosing paradigm: RO7234292 every 4 weeks (Q4W), RO7234292 every 8 weeks (Q8W) (with alternating placebo), and placebo Q4W. The Sponsor decided to stop enrollment under this original protocol containing this blinded monthly dosing paradigm and revised the protocol with a major protocol amendment in March 2019 to a include 3 dosing regimens under a blinded bi-monthly dosing paradigm: RO7234292 Q8W, RO7234292 every 16 weeks (Q16W) arm (with alternating placebo), and placebo Q8W.

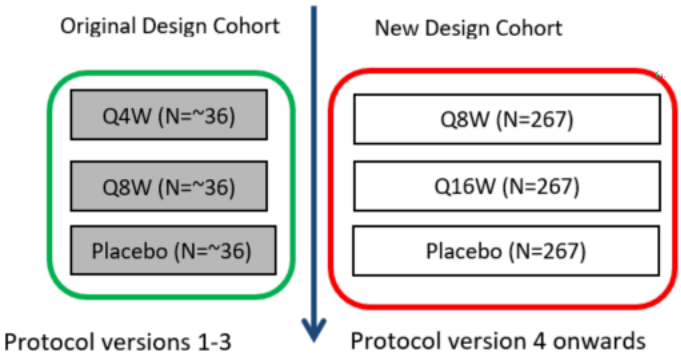
The details of this amendment including rationale are in Protocol Version 4, and a comparison of old (Versions 1-3) and new study designs (version 4+) in Figure 1.

Prior to stopping the enrollment in Protocol versions 1-3 on 29 March 2019, 108 patients were randomized in Canada, USA and Spain referred to as the "Original Design Cohort" (ODC). The ODC will not be included in the primary efficacy and safety analysis of the new study design (Protocol version 4 onwards). The Sponsor made this decision to prevent the potential bias that would have been introduced to the trial results if patients under different regimens (monthly and bi-monthly) were contained in the same analysis. Instead, ODC patients have been discontinued from Study BN40423 and offered enrollment into the long-term open label extension study (BN40955).

This Statistical Analysis Plan (SAP) will describe the statistical analysis of the ODC only. A separate SAP will be provided for the analysis of the new cohort (Protocol Version 4 onwards).

Because the study design was changed, patients in the ODC received less than two years of treatment and did not reach the Week 101 assessment. The analysis of clinical endpoints will be deemed as exploratory analysis. No formal hypothesis testing will be performed and all the *p*-values will be descriptive.

Figure 1 Phase III Protocol BN40423 Cohorts



Q4W= every 4 weeks; Q8W= every 8 weeks; Q16W= every 16 weeks

2. STUDY DESIGN

One hundred and eight patients were enrolled in the ODC of Study BN40423. Prospective patients went through screening assessments during a 4-week screening period.

Upon completion of the screening period, eligible patients were randomly allocated in a 1:1:1 ratio to receive 120 mg RO7234292 Q4W, 120 mg RO7234292 Q8W, or placebo Q4W by IT injection. To maintain the study blind and integrity, patients in the RO7234292 Q8W arm also receive placebo (i.e., alternating Q4W administrations of active drug and placebo).

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

2.2.1 Pharmacodynamic Endpoints

- **Biomarkers**
  - Cerebrospinal fluid (CSF) levels of –
    - mHTT
    - neurofilament light chain (NFL)
    - Chitinase-3-like protein 1 (YKL-40)
    - Tau
    - Total protein levels
  - Plasma levels of NFL
- **Neuroimaging volumes (Structural Magnetic Resonance Imaging [MRI])**
  - Baseline Caudate volume and Caudate Boundary Shift Integral (CBSI)

- Baseline Whole brain volume and whole-brain BSI (KNBBSI)
- Baseline Ventricular volume and ventricle BSI (VBSI)

- **Clinical endpoints**
  - Unified Huntington's Disease Rating Scale (cUHDRS)
  - Total Functional Capacity (TFC) scale score
  - Total Motor Score (TMS)
  - Symbol Digit Modalities Test (SDMT)
  - Stroop Word Reading Testing (SWR)

- **Digital endpoints**
  - Chorea
  - Speed tapping
  - Symbol digit modality test (SDMT)
  - Stroop Word Reading Test (SWT)
  - 2 minute walking
  - U turn
  - Balance test
  - Draw a shape

2.2.2 Pharmacokinetic Endpoints

The PK endpoints are as follows:

- Concentration of RO7234292 in plasma at all available timepoints
- Trough concentration of RO7234292 in CSF at all available timepoints

2.2.3 Immunogenicity Endpoints

The immunogenicity endpoints are as follows:

- Incidence of anti-drug antibodies (ADAs) at specified time-points relative to the prevalence of ADAs at baseline
- Titer and antibody subtype, determined if ADAs are identified

2.2.4 Safety Outcome Endpoints

Safety will be assessed on the basis of the following endpoints:

- Incidence and severity of adverse events (AEs)
- Change from baseline in Montreal Cognitive Assessment (MoCA)
- Change from baseline in vital signs
- Change from baseline in ECG parameters
- Change from baseline in clinical laboratory results including CSF findings

- Proportion of patients with suicidal ideation or behavior, as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) score at each visit, including detailed focus on any individual cases identified as having severe ideation or behavior during the study conduct

2.3 ANALYSIS TIMING

The analysis will be conducted once the last patient among the 108 patients has either withdrawn early from the study or enrolled to the BN40955 study and when all data of the 108 patients needed for the planned analysis have been made available, cleaned and verified and the database has been locked.

3. STATISTICAL METHODS

3.1 ANALYSIS POPULATIONS

3.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population will consist of all patients who were randomized and received any study treatment. Randomized patients who receive therapy different from the one assigned at randomization will be summarized in the group according to their planned randomized treatment.

The ITT population will be the primary population for all clinical efficacy endpoints, CSF biomarker and MRI analysis.

3.1.2 Safety Population

The ITT population will also be used for all analyses of safety data.

For the purpose of all safety analyses, at the time of unblinding, it will be assessed whether at any time during the course of the study, patients received a treatment different from the one they were randomized to.

For patients who were randomized to placebo but received any active treatment by error, if there is any safety signal of concern present, they will be summarized under the active treatment group; otherwise will be summarized under placebo.

The final decision on this will only be possible after unblinding.

3.1.3 Pharmacokinetic-Evaluable Population

The PK population will include all randomized patients who received at least one dose, and had sufficient sampling to permit PK evaluation.

3.1.4 Immunogenicity

The immunogenicity population will include all randomized patients who received any study treatment and with at least one post-dose ADA assessment. Patients will be grouped according to the treatment received.

3.2 ANALYSIS OF STUDY CONDUCT

The numbers of patients who enrolled in the ODC, discontinued from the treatment, and the study early and whether they roll-over or not to the BN40955 study will be summarized overall and by treatment arm. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. The population for the analysis of study conduct will be all randomized patients, unless stated otherwise.

3.3 BASELINE DEFINITION

The baseline will be defined as the last non-missing assessment prior to the randomization date or the first dosing date, whichever is the latest.

3.4 STUDY DAY DEFINITION

Day 1 will be defined as the randomization date or the first dosing date, whichever is the latest. Study Day will be calculated relative to the Day 1 as defined:

If the assessment date is on or after the Day 1,

$$\text{Study Day} = \text{assessment date} - \text{Day 1} + 1$$

If the assessment date is before the Day 1,

$$\text{Study Day} = \text{assessment date} - \text{Day 1}$$

3.5 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics will be summarized by treatment group using means, SD, medians and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment.

3.6 CSF AND PLASMA BIOMARKER ANALYSES

Absolute values and change from baseline values for all biomarker assessments (as listed in Section 2.2.1) will be summarized by descriptive statistics at each visit by treatment group.

For all biomarkers, the measurement that is below the limit of quantification (BLQ), the value will be set to BLQ divided by two (BLQ / 2). A summary table for subjects who were BLQ by regimen and visit will be presented.

All biomarkers will be log-transformed in the statistical modelling and correlation analyses.

- **Analysis of Longitudinal Changes Over Time**

The mixed-effect model repeated measures (MMRM) analysis will be performed for each individual parameter including data from baseline up to 7 months. The fixed effects in the model will include the corresponding baseline value of the biomarker analyzed (with log transformation), visit (as categorical variable), treatment, treatment by visit interaction, baseline age, baseline cytosine-adenine-guanine (CAG) repeat length and CAP score (the latter defined as CAP = [CAG-33.66]*Baseline age). Visit will be fitted as a repeated variable within a patient. An unstructured (UN) variance-covariance structure will be applied to model the within-patients' errors; if the model fails to converge, the following variance-covariance structures will be tested as alternatives in the pre-specified order: Heterogeneous Toeplitz (TOEPH), Antedependence (ANTE[1]) and Heterogeneous Compound Symmetry (CSH).

Least squares means (LSM) estimates based on the MMRM model, at each time-point, along with corresponding standard error, 95% CI and unadjusted *p*-value will be presented (back-transformation) for each regimen as well as for the comparison of each active arm against placebo.

The full list of analyses is summarized in Table 1.

Technical details of the MMRM and sample SAS code are included in the Appendix 3.

- **Analysis of Relationship Between Selected Parameters**

The following analyses will be conducted to describe the relationship between selected pairs of parameters:

  - the association of baseline CSF mHTT with baseline CSF biomarkers (Tau, NfL YKL-40, and total protein levels)
  - the prognostic value of baseline CSF mHTT for the changes in CSF biomarkers at 3, 5 and 7 months, respectively
  - the association of the changes in CSF mHTT with the changes in CSF biomarkers at 3, 5 and 7 months, respectively
  - the association of baseline CSF NfL with the baseline plasma NfL
  - the association of the changes in CSF NfL with the changes in plasma NfL at 3 and 5 months, respectively
  - the association of baseline CSF mHTT with the baseline MRI volumes.
  - the association of the changes in CSF mHTT with the BSI at 3 months
  - the association of baseline CSF biomarkers with the baseline MRI volumes.
  - the association of the changes in CSF biomarkers with the BSI at 3 months
  - the association of the baseline CSF mHTT with the clinical endpoints at baseline

- the association of the baseline CSF biomarkers with the clinical endpoints at baseline
- the association of the baseline CSF mHTT with the change in the clinical endpoints at 3 months and 5 months, respectively
- the association of the baseline CSF biomarkers with the change in the clinical endpoints at 3 months and 5 months, respectively
- the association of the changes in CSF mHTT with the changes in the clinical endpoints at 3 months and 5 months, respectively
- the association of the changes in CSF biomarkers with the changes in the clinical endpoints at 3 months and 5 months, respectively

Both descriptive statistics (scatter plots) and model-based analyses will be applied.

Descriptive analyses - Scatter plots between selected pairs of parameters will be presented by time point and by treatment. Spearman correlation coefficients will be calculated.

Model-based analyses - In order to model the relationship between a continuous response variable (e.g. the change in CSF Tau at 3 months) and a main predictor (e.g., baseline value of mHTT), a linear regression model (LRM) will be used. The model will include treatment and treatment by main predictor interaction terms as independent variables. Age, CAG repeat length and CAP scores will be included for covariate adjustment.

The full list of analyses, together with specifications about additional covariates to account for, is provided in Table 2.

A similar model, with a term for the main predictor but without any term including treatment, will also be considered to allow estimating the relationship between the response and the main predictor based on a pooled (across treatments) population.

The LSM estimates for the slope of the main predictor (X-variable in Table 2) along with corresponding standard error, 95% CI and unadjusted *p*-value will be presented. The estimated effect represents the effect of the main predictor on the response adjusted for all other covariates in the model. Distributional assumptions underlying the model used for analysis will be examined to gain confidence that the model assumptions are reasonable and where needed, sensitivity analyses will be performed.

Additional analyses, not listed in this SAP, may be conducted to better understand any safety concern which may arise.

3.7 CLINICAL ENDPOINTS

The Composite Unified Huntington's Disease Rating Scale (cUHDRS) (Schobel, et al., 2017) and its individual components will be analyzed. The cUHDRS is defined as a combination of the following first four individual assessments:

- **Total Functional Capacity**

  The Total Functional Capacity (TFC) represents the Investigator's assessment of the patient's capacity to perform a wide range of activities of daily living including working, chores, managing finances, eating, dressing and bathing. It is based on a brief interview with the patient and the study companion. Individual item scores range from 0 to 3 (by 1), total score ranges from 0 to 13 and higher scores represent better functioning. The total score is the sum of the individual item scores.

  The scale is considered completed if there are no missing values. There will be no imputation for missing values. The total score will be derived only if each of the individual item scores is not missing.

- **Total Motor Scale**

  The Total Motor Scale (TMS) is the sum of the individual motor ratings obtained during administration of the motor assessment portion of the UHDRS. Individual item scores range from 0 to 4 (by 1), total score range from 0 to 124 and higher scores represent more severe impairment.

  For each of the scores (total or domains) if any of items is missing then there will be no imputation for missing data and the score will not be computed.

  In addition to TMS, the 'maximal chorea in upper limb' item as well the maximal chorea (from TMS) will also be considered. The maximal chorea score is the sum of the seven maximal chorea items

- **Symbol Digit Modalities Test**

  The Symbol Digit Modalities Test (SDMT) is used to assess attention, visuoperceptual processing, working memory and psychomotor speed. It has been shown to have strong reliability and validity (Smith, 1982). The patient must pair abstract symbols with specific numbers according to a translation key. The test measures the number of items correctly paired (maximum of 110) in 90 seconds.

- **Stroop Word Reading Test**

  The Stroop Word Reading Test (SWRT) is a measure of attention, processing and psychomotor speed. Patients are presented with a page of color names printed in black ink and are asked to read aloud as many words as possible within a given amount of time (typically within 45 seconds). The number of words read correctly is counted and higher scores indicate better cognitive performance.

Based on the aforementioned assessments, the following formula is used to derive the cUHDRS where TFC, TMS, SDMT and SWRT are the raw total scores of each assessment:

$$\mathbf{cUHDRS} = \left(\frac{\mathrm{TFC} - 8.8}{2.8}\right) - \left(\frac{\mathrm{TMS} - 34.4}{17.4}\right) + \left(\frac{\mathrm{SDMT} - 25.2}{12.4}\right) + \left(\frac{\mathrm{SWRT} - 58}{21.2}\right) + 10.0$$

The cUHDRS will be derived only if each of the individual components is not missing. No imputation for missing values will be conducted. The minimum possible score is -3.06. The maximum is not defined.

Descriptive statistics will be provided for all available data.

Due to the limited number of patients reaching the 9-months visit, the statistical modelling will be performed including the data up to 5 months.

Analysis of longitudinal change from baseline over time: The MMRM will be performed for the cUHDRS and its four components respectively. The fixed effects in the model will include the corresponding endpoint at baseline, visit, treatment, treatment by visit interaction, baseline age, baseline CAG repeat length, CAP score and region. Visit will be fitted as a repeated variable within a patient. An unstructured (UN) variance-covariance structure will be applied to model the within-patients' errors; if the model fails to converge, the following variance-covariance structures will be tested as alternatives in the pre-specified order: TOEPH, ANTE[1] and CSH. (See Appendix 3 for technical details)

Least squares means estimates based on the MMRM model, at each time-point, along with corresponding standard error, 95% CI and *p*-value will be presented for each regimen as well as for the comparison of each active arm against placebo.

Model-based analyses for the association between the clinical endpoints and the CSF biomarkers: In order to model the relationship between a continuous response variable (e.g. the change in cUHDRS from baseline at 5 months) and a main predictor (e.g., baseline value of mHTT), a LRM will be used. The model will include treatment and treatment by main predictor interaction terms as independent variables. Age, CAG repeat length, CAP scores and region will be included for covariate adjustment.

3.8 MRI ANALYSES

A 3D T1-weighted structural MRI scan will be used to quantitate whole brain, caudate and intraventricular volumes. The only absolute measures are baseline volumes, while boundary shift integral (BSI) are used to assess changes in volumes over time. Three boundary shift integrals will be considered: K-means ventricular boundary shift integral (VBSI), K-means CBSI and K-means brain boundary shift integral (KNBBSI). To be noticed is that BSI values represent already a measure of change from baseline.

Only data with a QC flag equals to 'Pass' will be used in the analysis.

Descriptive tables and plots will be performed. The relationship between the MRI at baseline and CSF mHTT at baseline will be performed using the methods as described in Section 3.4.

In addition, the analysis of covariance (ANCOVA) will be performed to compare the percentage change of BSI at 3 months between the treatment groups. The model will include baseline age, CAG repeat length, baseline CAP score and treatment as covariate. The estimated treatment difference at 3 months and corresponding 95% CIs will presented.

3.9 DIGITAL ENDPOINTS

The statistical analyses of digital endpoints will be described in a dedicated SAP.

3.10 PHARMACOKINETIC AND PHARMACOKINETIC-PHARMACODYNAMIC ANALYSES

All patients in the PK population (Section 3.1.3), CSF and plasma concentrations of RO7234292 will be presented descriptively, including arithmetic and geometric means, median, range, SD, and coefficients of variation.

3.11 IMMUNOGENICITY ANALYSES

For patients under treatment, there is a potential for them to develop ADA over time. The serum sampling for ADA assessment data will be available for baseline and pre-dose at each time point post-baseline. The immunogenicity analysis population will be used for the analysis. Data will be presented in summary tables (proportions of baseline prevalence and incidence of ADA by treatment arm) and a listing of patients who tested positive for ADA.

The following definitions based on (Shankar, et al., 2014) as well as a Sponsor's definition for ADA with neutralizing potential will be used to describe patients' immunogenicity:

- ADA-Positive
  - Treatment induced: ADA developed de novo (seroconversion) following drug administration. Patients who have no pre-existing ADA or are missing ADA data before drug administration and who have at least one ADA-positive sample following drug administration.
  - Treatment boosted: Patients who have pre-existing ADA and have a ≥4 fold increase in ADA titer following drug administration compared to baseline measurement.
- ADA-Negative
  - ADA-negative all samples: Patients who have no pre-existing ADA (i.e. antibodies reactive with the drug that are present in patients before treatment) or are missing ADA data before drug administration and who have all negative

ADA results following drug administration, and treatment unaffected ADA-negative patients.

- Treatment unaffected ADA: Patients who had positive sample at baseline and post-baseline were either negative or positive but do not have a ≥4 fold increase in ADA titer following drug administration compared to baseline measurement.

- Transient ADA
  - Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point).
- Persistent ADA
  - Treatment-induced ADA detected at 2 or more sampling time points during the treatment or follow-up observation period, or detected on last sampling time point.

Table 1 Overview of Planned Analysis for the Longitudinal Changes Over Time

Parameter	Output presentation		Data Type			Time-points for descriptive statistics	Time points for MMRM	MMRM
	Plot	Table	Absolute	Change	% Change			
mHTT	Y	Y	Y	Y	Y	all available	BSL 1 month to 7 months	Yes
CSF Biomarker (NFL, YKL-40, Tau, and CSF total protein)	Y	Y	Y	Y	Y	all available	BSL 1 month to 7 months	Yes
Plasma NFL	Y	Y	Y	Y	Y	all available	BSL 3 months, 5 months	Yes
UHDRS	Y	Y	Y	Y	Y	all available	BSL 1month, 5 months	Yes
BSI*	Y	Y		Y*	Y‡	all available	3 months	No**
BSL MRI Volume		Y	Y			all available	Screening	No
PK	Y	Y	Y			all available		No
ADA		Y	Y			all available		No

ADA= anti-drug antibody; BSI= Boundary Shift Integral; BSL=Baseline; CSF= cerebrospinal fluid; MRI= magnetic resonance imaging; MMRM= mixed-model repeated measures; mHTT= mutant huntingtin (protein); NFL= neurofilament light chain (protein); PK= pharmacokinetic; UHDRS= Unified Huntington's Disease Rating Scale; Y= Yes.

Absolute=measured data at a given time point.

Change (%Change)= change from baseline from a given post-baseline measurement (expressed as a percentage)

*BSI is already a measure of change in volume (thus the change is not derived as for the other variables)

‡ %-Change for BSI is derived as $\left(\frac{BSI}{baseline\ volume}\right) \cdot 100$

** ANCOVA will be applied to compare the percentage of change of BSI at 3 months between the treatment groups.

Table 2 Overview of Planned Outputs to Describe the Association Between Selected Pairs of Parameters

Paired Variables	Data Type				Time points**	Additional covariates in statistical models
	X-variable		Y-variable			
	Absolute	Change	Absolute	Change		
X=mHTT, Y= CSF Biomarkers (NFL, YKL-40 Tau Total Protein)	Y		Y		X and Y=BSL	BSL Age, CAG, CAP
	Y			Y	X=BSL, Y=3M, 5M, 7M	BSL Age, CAG, CAP BSL CSF BM
		Y		Y	X and Y=3M, 5M, 7M	BSL Age, CAG, CAP BSL CSF BM, BSL mHTT
X= CSF Biomarkers (mHTT, NFL, YKL-40 Tau, and CSF total protein) Y=Clinical endpoints (cUHDRS, TFC, TMS, SDMT, and SWR)	Y		Y		X and Y=BSL	BSL Age, CAG, CAP, Region
	Y			Y	X=BSL, Y=5M	BSL Age, CAG, CAP, Region BSL ClinEP
		Y		Y	X=3M, 5M, Y=5M	BSL Age, CAG, CAP, Region BSL ClinEP, BSL CSF BM
X=**CSF-Nfl**, Y=**Plasma-Nfl**	Y		Y		X and Y=BSL	NA
		Y		Y	X and Y=3M,5M	NA
X=**mHTT**, Y=**MRI**	Y		Y		X and Y=BSL	BSL Age, CAG, CAP

BM=biomarker; BSL=baseline; ClinEP=clinical endpoints; Change = Change from baseline; CSF= cerebrospinal fluid; MRI= magnetic resonance imaging; mHTT= mutant huntingtin (protein); NA=not applicable; NFL= neurofilament light chain (protein).

3.12 SAFETY ANALYSES

3.12.1 Exposure of Study Medication

Exposure to RO7234292 and placebo over the course of the study will be summarized using descriptive statistics.

Duration of treatment exposure (in days) to study drug will be calculated as**:**

Last follow-up visit date – treatment start date +1

3.12.2 Adverse Events

All treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) will be summarized for each treatment arm and for all patients using the Medical Dictionary for Regulatory Activities (MedDRA) coding by system organ class, preferred term, relationship to study drug, and severity. Percentages presented in AE tables will display the percentage of patients within a treatment arm experiencing the AE at least once.

An AE will be regarded as TEAE if the event occurs after the first dose of treatment or if event occurs before the first dose of treatment and worsens after the first dose.

Adverse events that occur before first dose administration and are not related to study procedure will be included in data listings only. SAEs and non-serious AEs that lead to treatment discontinuation or treatment interruption will be listed separately. Selected adverse events, for instance procedure related AEs, will be summarized and listed separately.

3.12.3 Laboratory Data

Abnormal laboratory outcomes will be reported. A summary of the number and percentage of patients with abnormal laboratory outcomes will be produced at each visit and overall by treatment group.

Absolute values and change from baseline values for all laboratory assessments will be summarized by descriptive statistics at each visit by treatment group.

3.12.4 Vital Signs and ECG

Absolute values and change from baseline values for vital signs and ECG data will be summarized by descriptive statistics at each visit by treatment group.

A listing of patients meeting any of the abnormality criteria as presented in Table 3 (according to Roche data analysis standards [GDSR]) will be provided.

Abnormal findings and clinical significance for the finding for ECG parameters will be listed.

Table 3 Vital Signs Ranges

Parameter	Low	Normal	High
Pulse/HR (bpm)	<60	60-100	>100
SBP (mmHg)	<90	90-130	>130
DBP (mmHg)	<60	60-80	>80
Temperature (C)	<36.5	36.5-37.5	>37.5
RR (bpm)	<8	8-20	>20

DBP= diastolic blood pressure; HR=heart rate; RR=refractory rate; SBP=systolic blood pressure.
Note: The boxplots of vital signs and ECG by visit and by treatment group will be provided.

3.12.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a structured tool to assess suicidal ideation and behavior. Four constructs will be assessed: severity of ideation, intensity of ideation, behavior and lethality of actual suicide attempts.

The C-SSRS collects binary responses to 11 categories: five subtypes of suicidal ideation, five subtypes of suicidal behavior, and self-injurious behavior without suicidal intent. Specifically, the following outcomes are C-SSRS categories and have binary (Yes/No) responses. The categories have been re-ordered from the actual scale to facilitate the definitions of the composite endpoints and to enable clarity in the presentation of the results.

Suicidal Ideation:

- **Category 1** - Wish to Be Dead
- **Category 2** - Non-specific Active Suicidal Thoughts
- **Category 3** - Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- **Category 4** - Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- **Category 5** - Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior:

- **Category 6** - Preparatory Acts or Behavior
- **Category 7** - Aborted Attempt
- **Category 8** - Interrupted Attempt
- **Category 9** - Actual Attempt (non-fatal)
- **Category 10** - Completed Suicide

Other:

- **Category 11** - Non-suicidal Self-injurious Behavior

In addition, a numerical score, the Suicidal Ideation Score, will be defined as the highest suicide ideation category (1-5) at which the patient responded "Yes" for the given visit. If the patient did not respond “Yes” to any of these categories, the score will be set to zero.

For each of the aforementioned 11 categories, the number and percent of patients with a “Yes” response at any time post-baseline (regardless of baseline response) will be summarized by treatment arm. Emergent suicidal ideation or behavior will be summarized.

The listed binary categories and the Suicidal Ideation Score will be used to identify a number of composite suicidal endpoints. Note that "recent history" for these composite endpoints is defined as the 12 months prior to Screening and the Screening period. At the Screening visit, C-SSRS data is collected for the prior 12 months. Therefore, analyses that utilize data from “recent history'” will include the historical 12-month data collected at Screening as well as all on-study C-SSRS data collected prior to first dose. The endpoints are defined as follows:

- **Suicidal Ideation**: A “Yes" answer at any time post-first-dose to any one of the five suicidal ideation questions (Categories 1-5), regardless of the pre-dose responses
- **Suicidal Behavior**: A “Yes" answer at any time post-first-dose to any one of the five suicidal behavior questions (Categories 6-10), regardless of the pre-dose responses.
- **Suicidal Ideation or Behavior**: A "Yes" answer at any time post-first-dose to any one of the ten suicidal ideation or behavior questions (Categories -10), regardless of the pre-dose responses.
- **Treatment-Emergent Suicidal Ideation compared to recent history**: A maximum post-first-dose suicidal ideation score that is increased from the maximum suicidal ideation score in recent history.
- **Treatment-Emergent Serious Suicidal Ideation compared to recent history**: A maximum post-first-dose suicidal ideation score of 4 or 5 when the maximum suicidal ideation score during recent history was less than 4 (i.e., scores of 0-3). Only patients with a recent history score of 0-3 will be considered evaluable for this outcome.
- **Emergence of Serious Suicidal Ideation compared to recent history**: A maximum post-first-dose suicidal ideation score of 4 or 5 when the maximum suicidal ideation score during recent history was 0. Only patients with a recent history score of 0 will be considered evaluable for this outcome.
- **Improvement in Suicidal Ideation compared to baseline**: A decrease in the suicidal ideation score at the patient's week 13 (3 months), week 21 (5 months) and week 29 (7 months) C-SSRS assessment compared to the baseline score, defined as the minimum score obtained during the Screening Period (i.e., assessments collected from the Screening Visit through pre-dose on Study Day 1). Only patients with a baseline score >0 will be considered evaluable for these outcomes.

- **Emergence of Suicidal Behavior compared to all prior history**: The occurrence of suicidal behavior (a "Yes" response to one or more of Categories 6-10) post-first dose from not having suicidal behavior prior to first dose (includes the "lifetime" score collected at the Screening Visit as well as all C-SSRS assessments collected from the Screening Visit through pre-dose on Study Day 1).

Each of the composite endpoints will be summarized by treatment arm and by visit. For each treatment emergent outcome listed, only those patients with the specified screening condition will be considered evaluable. In addition, patients who discontinue from the study with no post-first dose C-SSRS assessment will be considered unevaluable for analyses of suicidality. Percentages will be based on the number of evaluable patients for each outcome.

In addition, a shift table will be created to demonstrate the change in suicidal ideation score from recent history to treatment period and/or post-treatment period. The maximum suicidal ideation score in each period will be used to create the shift table. If a patient's recent history suicidal ideation score is missing but has a post-first-dose score, then the recent history assessment will be labeled as "unknown". Likewise, if a patient's recent history suicidal ideation score is available but has no post-first-dose score, then the scores during the treatment and post-treatment period will be labeled as "unknown".

3.12.6 Montreal Cognitive Assessment (MoCA)

The MoCA is an 11-item clinician-reported assessment that is used to detect cognitive impairment. It contains a series of basic assessments, including attention and visuospatial tasks. The total score ranges from 0–30, where lower scores indicate greater impairment. A scoring $\geq$ 26/30 is considered normal. Individual components contributing to the total score are listed below:

- Visuospatial /executive (0 to 5)
- Naming (0 to 3)
- Attention (0 to 6)
- Language (0 to 3)
- Abstraction (0 to 2)
- Delayed recall (0 to 5)
- Orientation (0 to 6)

The total score is given by the sum of all sub scores; one point can be added for subject who has 12 years or fewer of formal education, for a possible maximum of 30 points.

Descriptive tables of the baseline overall score will be provided.

3.12.7 Safety MRI

Clinical assessments from the safety MRI will be summarized by descriptive statistics at each visit by treatment group. In addition, a shift table will be created to demonstrate the change in safety MRI status from baseline to post-baseline.

3.13 MISSING DATA

Incomplete dates for AEs and laboratory data will be handled as described in the Roche GDSR.

Missing values for labs, biomarkers and clinical endpoints will not be imputed unless otherwise specified.

4. REFERENCES

Schobel SA, Palermo G, Auinger P, et al. Motor, cognitive, and functional declines contribute to a single progressive factor in early HD. Neurology 2017;89:2495–2502.

Shankar G, Arkin S, Cocea L, et al. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. AAPS J 2014;16:658−73.

Smith, A. Symbol Digit Modalities Test (SDMT). Manual (rev.). Los Angeles: Western Psychological Services, 1982.

Appendix 1
Protocol Synopsis

TITLE:	**A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III CLINICAL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF INTRATHECALLY ADMINISTERED RO7234292 (RG6042) IN PATIENTS WITH MANIFEST HUNTINGTON'S DISEASE**
PROTOCOL NUMBER:	BN40423
VERSION NUMBER:	3 (VHP)
EUDRACT NUMBER:	2018-002987-14
IND NUMBER:	137873
TEST PRODUCT:	RO7234292
PHASE:	Phase III
INDICATION:	Huntington's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, pharmacokinetic (PK), and biomarker effects of RO7234292 compared with placebo in patients with manifest Huntington's disease (HD). Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo on the basis of the following endpoint:

- Change from baseline in the composite Unified Huntington's Disease Rating Scale (cUHDRS) score at Week 101

  Note: The primary efficacy endpoint for the U.S. Food and Drug Administration (FDA) will be change from baseline in the TFC score at Week 101

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo on the basis of the following endpoints:

- Change from baseline in scores for the following individual scales at Week 101:
  - TFC
  - Total Motor Score (TMS)
  - Symbol Digit Modalities Test (SDMT)
  - Stroop Word Reading Test (SWR)

  Note: For the U.S. FDA, the first secondary endpoint will be change from baseline in the cUHDRS score at Week 101 instead of TFC, as TFC will be the primary endpoint.

- Change from baseline in the Clinical Global Impression, Severity Scale (CGI-S) score at Week 101
- Proportion of patients with a decrease from baseline of ≥ 1 point on the TFC at Week 101
- Proportion of patients with a decline from baseline of ≥ 1.2 points on the cUHDRS at Week 101
- Proportion of patients with an unchanged or improved score on the Clinical Global Impression, Change Scale (CGI-C) score from baseline at Week 101

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of RO7234292 compared with placebo on the basis of the following endpoints:

- Change from baseline in the Apathy Evaluation Scale (AES) score at Week 101
- Change from baseline in the Symptoms of Major Depressive Disorder Scale (SMDDS) score at Week 101
- Change from baseline in the Huntington's Disease Daily Activities Scale (HD-DAS) score at Week 93
- Change from baseline in the Patient Global Impression, Severity Scale (PGI-S) score at Week 101
- Change from baseline in the Quality of Life in Neurological Disorders (Neuro-Qol) Cognition Function Short Form at Week 101
- Change from baseline in the Huntington's Disease Speaking Difficulty Item Scale (HD-SDI) score at Week 101
- Change from baseline in the Huntington's Disease Companion-Reported Irritability and Angry Outbursts Scale (HD-CIAOS) score at Week 101
- Change from baseline in the in-clinic patient-reported EuroQol 5-Dimension Questionnaire (5-level version; EQ-5D-5L) index-score and visual analogue scale (VAS) at Week 101
- Change from baseline in the sensor-based measures collected by the Roche HD mobile application (app; smartphone and wrist-worn wearable) at Week 101

Safety Objective

The safety objective for this study is to evaluate the safety and tolerability of RO7234292 compared with placebo on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the Adverse Event Severity Grading Scale
- Change from baseline in Montreal Cognitive Assessment (MoCA)
- Change from baseline in vital signs
- Change from baseline in ECG parameters
- Change from baseline in clinical laboratory results
- Proportion of patients with suicidal ideation or behavior, as assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) score at each visit, including detailed focus on any individual cases identified as having severe ideation or behavior during the study conduct

Pharmacokinetic Objectives

The PK objective for this study is to characterize the RO7234292 PK profile in plasma and trough CSF on the basis of the following endpoints:

- Concentration of RO7234292 in plasma at specified timepoints
- Trough concentration of RO7234292 in CSF at specified timepoints

The exploratory pharmacokinetic/pharmacodynamic (PK/PD) objective for this study is to evaluate potential relationships between drug exposure and the efficacy and safety of RO7234292 on the basis of the following endpoints:

- Relationship between plasma profiles and/or trough CSF concentrations of PK parameters for RO7234292 and efficacy endpoints
- Relationship between plasma profiles and/or trough CSF concentrations of PK parameters for RO7234292 and safety endpoints

Immunogenicity Objectives

The immunogenicity objective for this study is to evaluate the immune response to RO7234292 on the basis of the following endpoints:

- Incidence of anti-drug antibodies (ADAs) at specified timepoints relative to the prevalence of ADAs at baseline
- Titer and antibody subtype, determined if ADAs are identified

The exploratory immunogenicity objective for this study is to evaluate potential effects of ADAs on the basis of the following endpoint:

- Relationship between ADA status and efficacy, safety, or PK endpoints

Biomarker Objectives

Primary Biomarker Objective

The primary biomarker objective for this study is to evaluate the effects of RO7234292 compared with placebo on the basis of the following endpoint:

- Change from baseline in CSF mHTT protein level at Week 101

Secondary Biomarker Objective

The secondary biomarker objective for this study is to evaluate the effects of RO7234292 compared with placebo on the basis of the following endpoints:

- Change from baseline in whole and regional brain volumes (caudate, whole brain, and ventricular), as determined by structural magnetic resonance imaging (MRI), at Week 101
- Change from baseline in CSF neurofilament light chain (NfL) protein level at Week 101

Exploratory Biomarker Objective

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to RO7234292 (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to RO7234292, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of RO7234292 activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between biomarkers in blood, plasma, and CSF and efficacy, safety, PK, immunogenicity, or other biomarker endpoints
- Relationship between imaging biomarkers (e.g., putamen, cortical grey matter, cortical white matter volumes, resting state functional MRI signal) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

Health Status Utility Objective

The exploratory health status utility objective for this study is to evaluate health status utility scores of patients treated with RO7234292 on the basis of the following endpoint:

- Change from baseline in patient- and companion-reported EQ-5D-5L Index and VAS scores at specified timepoints
- Change from baseline in companion self-reported and proxy-reported Health Utilities Index Mark 2 (HUI2) and Mark 3 (HUI3) scores at specified timepoints
- Change from baseline in patient- and companion-reported Work Productivity and Activity Impairment (WPAI) scores at specified timepoints

Study Design

Description of Study

Study BN40423 is a Phase III, randomized, placebo-controlled, double-blind, multicenter clinical study to evaluate the efficacy, safety, PK, and biomarker effects of intrathecally administered RO7234292 in patients with manifest HD.

Approximately 660 patients will be enrolled in the study. Prospective patients will undergo screening assessments during a 4-week screening period. A maximum of one re-screening will be allowed within 8 weeks of the initial screening failure for patients who fail the initial screening.

Upon completion of the screening period, eligible patients will be randomly allocated in a 1:1:1 ratio to receive RO7234292 every 4 weeks (RO7234292 Q4W arm), RO7234292 every 8 weeks (RO7234292 Q8W arm), or placebo Q4W (placebo arm) by IT injection. To maintain the study blind and integrity, patients in the RO7234292 Q8W arm will also receive placebo (i.e., alternating doses of active drug and placebo).

Patients

will undergo safety and tolerability evaluations that include neurologic examinations, vital signs, ECGs, clinical laboratory tests, MoCA, C-SSRS, neuroimaging assessments (neurologic safety sequences), and adverse events including related concomitant medications.

Patients who complete the treatment period will return to the clinic for an end-of-treatment visit at Week 101. Patients will then be given the option on an individual basis of receiving RO7234292 in an OLE study (BN40955) upon completion of Study BN40423, provided they meet eligibility criteria and the data from the ongoing RO7234292 program support continued development. Approval of the open-label extension (OLE) study must also be granted by the relevant competent authority and Ethics Committee (EC)/Investigational Review Board (IRB).

All patients who discontinue study treatment prematurely but do not withdraw consent for continued participation in the study will return to the clinic for study visits at Weeks 53 and 69 (if not already completed) for collection of at least the data for the primary and secondary endpoints. If the early treatment termination visit falls within $\pm$30 days of either scheduled visits at Week 53 or Week 69, then only early treatment termination visit will be considered. The early treatment termination visit should be performed 28 days ($\pm$3 days) after the last dose. Patients will also attend the scheduled end-of-treatment visit at Week 101.

An independent Data Monitoring Committee (iDMC) and independent Data Coordinating Center (iDCC) will be employed to monitor and evaluate patient safety throughout the study as well as to evaluate evidence of early efficacy.

Number of Patients

Approximately 660 patients with HD will be enrolled in this global study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry during screening (some will be reassessed at baseline):

- Signed Informed Consent Form
- Age 25 to 65 years, inclusive, at the time of signing Informed Consent Form
- Manifest HD diagnosis, defined as a diagnostic confidence level (DCL) score of 4

- Independence Scale (IS) score ≥ 70
- Genetically confirmed disease by direct DNA testing with a CAP score > 400 (Zhang et al. 2011), calculated as follows:

  $$\text{CAP} = \text{Age} \times (\text{CAG repeat length} - 33.66)$$

- Ability to read the words "red," "blue," and "green" in native language
- Ability to walk unassisted without a cane or walker and move about without a wheelchair on a daily basis as determined at screening and baseline visit
  - Long-distance (e.g., > 50 meters) use of wheelchairs for convenience or transfer is permitted.
- Body mass index 16–32 kg/m^2; total body weight > 40 kg
- Ability to undergo and tolerate MRI scans (e.g., no claustrophobia, no severe chorea or other condition that precludes MRI scans or renders scanning intolerable for the patient, no MRI-incompatible intrauterine devices, metallic dental braces, or other metal implants)
- Ability to tolerate blood draws and lumbar punctures
- Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min (Cockcroft-Gault formula)
- Ability and willingness, in the investigator's judgment, to comply with all aspects of the protocol including completion of interviews and questionnaires for the duration of the study
- Ability and willingness, in the investigator's judgment, to carry a smartphone, wear a digital monitoring device, and complete smartphone-based tasks
- Stable medical, psychiatric, and neurological status for at least 12 weeks prior to screening and at the time of enrollment
- Signed study companion consent for participation if a study companion is available who fulfills all of the following criteria:
  - Age ≥ 18 years
  - Reliable and competent, in the investigator's judgment
  - Sufficiently knowledgeable of the patient's condition to complete study companion assessments of the patient, and likely to remain sufficiently knowledgeable throughout the study, in the investigator's judgment
  - Able to comment on study participant's symptoms and functioning experience

  Note: Companions with genetic confirmation of the mutant gene can only participate if they do not have confirmation of motor symptom onset and, in the opinion of the investigator, do not display any disease symptoms (i.e., the companion must have a DCL < 4, as well as no cognitive or behavioral change that would question the validity of the acquired observer-reported data).

  All effort should be made to retain the study companion; however, should this not be possible, a study companion can be replaced and new consent obtained.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, as defined below:

  Women must remain abstinent or use two methods of contraception, including at least one method with a failure rate of $< 1\%$ per year, during the treatment period and for 5 months after the final dose of study drug.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. A vasectomized man must undergo a medical

assessment that confirms the success of the surgery before he can be considered surgically sterile.

Hormonal contraceptive methods must be supplemented by a barrier method.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 5 months after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of preventing drug exposure.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- History of attempted suicide or suicidal ideation with plan (i.e., active suicidal ideation) that required hospital visit and/or change in level of care within 12 months prior to screening

  Current suicidal ideation is demonstrated by the C-SSRS per judgment of the investigator. If suicidal ideation is present, a risk assessment should be done by an appropriately qualified mental health professional to assess whether it is safe for the patient to participate in the study. Mild passive suicidal ideation (i.e., occasional thoughts that life is not worth living or is hard) without history of attempts or hospitalization over the past 12 months is generally acceptable for study participation, but final decision on participation should be made carefully and in consultation with an appropriately qualified mental health professional.

- Current active psychosis, confusional state, or violent behavior
- Any serious medical condition or clinically significant laboratory, or vital sign abnormality at screening that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- History known to the investigator or presence of an abnormal ECG that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree atrioventricular heart block, or evidence of prior myocardial infarction
- Clinical diagnosis of chronic migraines
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 5 months after the final dose of study drug

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.
- Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter
- Positive for hepatitis C virus (HCV) antibody or hepatitis B surface antigen (HBsAg) at screening
- Known HIV infection
- Current or previous use of an antisense oligonucleotide (including small interfering RNA)
- Current or previous use of anti-psychotics prescribed for a primary independent psychotic disorder (i.e., schizophrenia, schizoaffective disorder, bipolar disorder type I, severe with psychotic features), cholinesterase inhibitors, memantine, amantadine, or riluzole within 12 weeks from initiation of study treatment

- Current use of antipsychotics for motor symptoms or mood stabilization (i.e., irritability or aggressive behavior) and/or tetrabenazine, valbenazine, or deutetrabenazine at a dose that has not been stable for at least 12 weeks prior to screening or is anticipated to change between screening and treatment initiation
- Current use of supplements (e.g., coenzyme Q10, vitamins, creatine) at a dose that has not been stable for at least 6 weeks prior to screening or is anticipated to change during the study
- Current use of an antidepressant or benzodiazepine at a dose that has not been stable for at least 12 weeks prior to screening or is anticipated to change between screening and treatment initiation
- Treatment with investigational therapy within 4 weeks or 5 drug-elimination half-lives prior to screening, whichever is longer
- Antiplatelet or anticoagulant therapy within 14 days prior to screening or anticipated use during the study, including, but not limited to, aspirin (unless ≤ 81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban, and apixaban
- History of bleeding diathesis or coagulopathy
- Platelet count less than the lower limit of normal

  Platelet counts between 125,000 and 150,000 mm3 are permissible as long as the investigator confirms there is no evidence of current bleeding diathesis or coagulopathy.
- History of gene therapy, cell transplantation, or any experimental brain surgery
- Concurrent or planned concurrent participation in any interventional clinical study, including explicit pharmacological and non-pharmacological interventions (e.g., lumbar puncture)

  Observational studies (e.g., ENROLL-HD prospective study) are acceptable.
- Illicit drug (i.e., cannabis, opioid, stimulant, hallucinogen, designer) or alcohol abuse within 12 months prior to screening, as per the investigator's judgment
- Poor peripheral venous access
- Scoliosis or spinal deformity or surgery making IT injection not feasible in an outpatient setting
- Serious infection requiring oral or IV antibiotics within 14 days prior to screening
- Antiretroviral medications
- Malignancy within 5 years prior to screening, except basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated
- Preexisting structural brain lesion (e.g., tumor, arterio-venous malformation) as assessed by a centrally read MRI scan during the screening period

End of Study

The end of this study is defined as the date when the last patient, last visit occurs. The end of the study is expected to occur approximately 117 weeks (29 months) after the last patient is enrolled.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4 years.

Investigational Medicinal Products

The investigational medicinal products (IMPs) for this study are RO7234292 and RO7234292 placebo.

Test Product (Investigational Drug)

RO7234292 will be supplied by the Sponsor as sterile, preservative-free liquid in a 20-mL single-use vial containing 10 mL of 6.0 mg/mL RO7234292 drug product for IT injection. For a 120-mg dose (20-mL dosing volume), two vials containing 10 mL of 6.0 mg/mL RO7234292 will be pooled by drawing them up into the same injection syringe containing 20 mL of study drug.

For information on the formulation, preparation, and handling of RO7234292, refer to the pharmacy manual.

Placebo

RO7234292 placebo will be supplied by the Sponsor as a sterile, preservative-free liquid in a 20-mL single-use vial containing 10 mL RO7234292 placebo drug product for IT injection. The liquid is no different in color than the active drug.

For a 20 mL dosing volume, two vials containing 10 mL of RO7234292 placebo will have to be pooled by drawing them up into the same injection syringe containing 20 mL of placebo drug product.

For information on the formulation, preparation, and handling of RO7234292 placebo, refer to the pharmacy manual.

Statistical Methods

Primary Analysis

The primary efficacy endpoint is the change from baseline in cUHDRS score at Week 101. This is defined as the attribute "variable" of the primary estimand.

Note: The primary efficacy endpoint for the U.S. FDA will be change from baseline in the TFC score at Week 101. TFC will be analyzed the same way as the cUHDRS.

The primary efficacy analysis for this study will compare each active treatment arm, RO7234292 Q4W and RO7234292 Q8W, against the placebo arm. To account for the multiple comparison, an appropriate procedure will be used to maintain the overall two-sided type I error at 5% (details will be given in the SAP).

The analysis of the primary endpoint will be performed by means of analysis of covariance (ANCOVA). The model will include the corresponding endpoint baseline score, CAG repeat length, baseline CAP score, and treatment as covariates; the final list of covariates will be defined in the SAP. On the basis of this analysis, least squares mean for the treatment differences at Week 101 and corresponding 95% CIs will be derived.

The robustness of the primary method of estimation described above may be explored by alternative sensitivity estimators based on varying assumptions underlying the multiple imputation strategy. These sensitivity analyses will be described in the SAP.

Determination of Sample Size

The planned sample size is adequate to capture meaningful clinical decline on both the TFC and cUHDRS and was estimated on the basis of data available from non-interventional studies (TRACK-HD, COHORT, ENROLL-HD) and a randomized placebo-controlled study (2CARE). Based on these data, using the anticipated trial population, a meta-analysis for the change from baseline at 24 months in TFC score suggested a natural decline of 1.36 points and a corresponding pooled standard deviation of 1.78. A conservative treatment discontinuation rate at Week 101 for patients receiving placebo or active is assumed to be 20% and 15%, respectively. Using these assumptions, the simulation described in the protocol was performed to estimate the sample size.

It was estimated that 220 patients per arm will provide approximately 80% power, at a two-sided $\alpha = 0.05$ level, to detect a 40% slowing of clinical decline for RO7234292 as compared with placebo at 101 weeks. This treatment effect translates into an expected average decline of ~0.82 points at 101 weeks for the RO7234292 arms. The minimal detectable difference with these assumptions is ~0.38 points.

Optional Interim Analyses

The Sponsor may choose to conduct one or more interim analyses for efficacy. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an iDCC and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct an interim analysis, along with the rationale, specification of the endpoint (e.g., clinical and/or biomarker endpoint), number of patients, and statistical details for each analysis, will be *introduced via a future protocol amendment*, which will be submitted to

relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC Charter will document potential recommendations the iDMC can make to the Sponsor as a result of an interim analysis, and the iDMC Charter will be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of an interim analysis of efficacy data, the type I error rate will be controlled to ensure statistical validity is maintained. Additional criteria for recommending that the study be stopped for positive efficacy will be added to *a future protocol amendment*.

Appendix 2
Schedule of Assessments

	Screening [a]	BL		Treatment Period																								EoT [b]	EoT for ETT	ETT [b]	SFU
Month				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	25		29
Week	−4 to −1	1		5	9	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	73	77	81	85	89	93	97	101	101		117
Day (Window)	−28 to −2	−1	1		(±3) [dd]																										
Signed informed consent [c]	x																														
Review of inclusion and exclusion criteria	x																														
Demographic data	x																														
Medical history and baseline conditions [d]	x	x [e]																													
Blood sample for CAG repeat length	x																														
Viral serology [f]	x																														
Thyroid panel [g]	x																														
Vital signs [h]	x	x [e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Complete physical examination [i]	x	x [e]				x						x								x								x		x	x
Neurologic examination [j]	x	x [e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG [k]	x	x [e]				x						x								x								x	x	x	x
Hematology [l]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Chemistry [m]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x

Appendix 2
Schedule of Assessments (cont.)

	Screening [a]	BL		Treatment Period																								EoT [b]	EoT for ETT	ETT [b]	SFU
Month				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	25		29
Week	−4 to −1	1		5	9	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	73	77	81	85	89	93	97	101	101		117
Day (Window)	−28 to −2	−1	1		(±3) [dd]																										
Pregnancy test [n]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Local INR, aPTT, PTplatelet count [x]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Urinalysis [o]	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x
Plasma sample for PK			x			x		x				x [p]				x				x				x				x		x	
Plasma sample for immunogenicity testing			x			x		x				x				x				x				x				x		x	x
Plasma sample for biomarkers			x			x		x				x				x				x				x				x		x	x
Blood sample for clinical genotyping		x[e]																													
CSF sample for PK/safety/biomarkers			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[y]		x	
MRI [q]	x					x						x								x								x	x		
HD-DAS	x					x				x				x				x				x				x					
Independence Scale	x		x	x				x				x				x				x				x				x	x	x	
MoCA	x		x	x				x				x				x				x				x				x	x	x	
C-SSRS [r]	x	x[e]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
UHDRS FA			x	x				x				x				x				x				x				x	x	x	

Appendix 2
Schedule of Assessments (cont.)

	Screening [a]	BL		Treatment Period																								EoT [b]	EoT for ETT	ETT [b]	SFU
Month				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25		29	1
Week	−4 to −1	1		5	9	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	73	77	81	85	89	93	97	101		117	5
Day (Window)	−28 to −2	−1	1	(±3) [dd]																											
TFC [s]			x	x				x				x				x				x				x				x	x	x	
TMS [s, cc]	x		x	x				x				x				x				x				x				x	x	x	
CGI-S			x	x				x				x				x				x				x				x	x	x	
CGI-C				x				x				x				x				x				x				x	x	x	
SDMT [s]			x	x				x				x				x				x				x				x	x	x	
SWR [s]			x	x				x				x				x				x				x				x	x	x	
AES			x			x				x				x				x				x				x		x	x		
SMDDS			x			x				x				x				x				x				x		x	x		
NeuroQoL			x	x				x				x				x				x				x				x	x	x	
EQ-5D-5L (in-clinic)			x	x				x				x				x				x				x				x	x	x	
HUI® (in-clinic)			x	x				x				x				x				x				x				x	x	x	
PGI-S			x	x				x				x				x				x				x				x	x	x	
PGI-C				x				x				x				x				x				x				x	x	x	
Roche HD mobile app in-clinic assessments	x		x						x						x						x							x	x	x	
Roche HD mobile app remote data collection	Continuous remote data collection [t]																														
Optional exit interview [u]																												x	x		

Appendix 2
Schedule of Assessments (cont.)

	Screening [a]	BL		Treatment Period																								EoT [b]	EoT for ETT	ETT [b]	SFU
Month				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	25		29
Week	−4 to −1	1		5	9	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	73	77	81	85	89	93	97	101	101		117
Day (Window)	−28 to −2	−1	1	(±3) [dd]																											
Blood sample for RBR DNA (optional) [v]			x																												
Blood sample for RBR RNA (optional) [v]			x									x								x								x		x	
Serum sample for RBR (optional) [v]			x									x								x								x		x	
Change in medical information since previous visit [w]				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Lumbar puncture [x]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [y]		x [y]	
Study drug administration			x	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x	x [z]	x				
Concomitant medications [aa]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [bb]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

ADA = anti-drug antibody; AES = Apathy Evaluation Scale; BL = baseline; CGI-C = Clinical Global Impression, Change; CGI-S = Clinical Global Impression, Severity; CSF = cerebrospinal fluid; C−SSRS = Columbia-Suicide Severity Rating Scale; cUHDRS = composite Unified Huntington's Disease Rating Scale; DCL = diagnostic confidence level; eCRF = electronic Case Report Form; EoT = end of treatment; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; ETT = early treatment termination; FA = Functional Assessment; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HD = Huntington disease; HD-DAS = HD Daily Activities Scale; HUI = Health Utilities Index; MoCA = Montreal Cognitive Assessment; MRI = magnetic resonance imaging; Neuro-Qol = Quality of Life in Neurological Disorders; PGI-C = Patient Global Impression,

Appendix 2
Schedule of Assessments (cont.)

Change; PGI-S = Patient Global Impression, Severity; PK = pharmacokinetic; Q8W = every 8 weeks; RBR = Research Biosample Repository; SDMT = Symbol Digit Modalities Test; SFU = safety follow-up; SMDDS = Symptoms of Major Depressive Disorder Scale; SWR = Stroop Word Reading; TFC = Total Functional Capacity Scale; TMS = Total Motor Score; UHDRS = Unified Huntington's Disease Rating Scale.

Notes: All assessments should be performed at the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] A maximum of one re-screening will be allowed within 8 weeks of the initial screening failure for patients who fail the initial screening (e.g., as a consequence of abnormal laboratory values or general medical status not meeting inclusion or exclusion criteria). If re-screening is required, CAG repeat length testing does not need to be repeated and the screening MRI and viral serology from the initial screening may be acceptable as part of the re-screening assessments, if performed within 12 weeks of the baseline visit.

[b] Patients who complete the treatment period will return to the clinic for a treatment completion visit at Week 101 (i.e., the EoT visit). All patients who discontinue study treatment prematurely but do not withdraw consent for continued participation in the study will return to the clinic for study visits at Weeks 53 and 69 (if not already completed) and at Week 101 (i.e., the EoT for ETT visit) for collection of at least the data for the primary and secondary endpoints (see Sections2.1.1, 2.1.2, and 2.2 of the Protocol v3). If the ETT visit falls within ±30 days of either scheduled visits at Week 53 or Week 69, then only ETT will be considered. The ETT visit should be performed 28 days (±3 days) after the last dose. Patients will also attend the scheduled EoT for ETT visit at Week 101 for limited assessments including the collection of the primary and secondary endpoints (see Sections 2.1.1, 2.1.2, and 2.2 of the Protocol v3). Study visits should be planned as per the study schedule, however under exceptional circumstances, time window of ±3 days can be utilized.

[c] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[d] Medical history, including clinically significant diseases, surgeries, HD history (including past hospitalizations [i.e., number, duration, and reason]), over the last 2 years, reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at baseline.

[e] Assessments may take place on Day −1 or Day 1.

[f] Viral serology: HBsAg and HCV antibody

[g] Thyroid panel: thyroid-stimulating hormone and free thyroxine (also known as T4) levels.

[h] Vital signs include respiratory rate, pulse, temperature, and systolic and diastolic blood pressure while the patient is in a seated position after resting for approximately 5 minutes. Record abnormalities observed at baseline (Day -1 or Day 1) on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Appendix 2
Schedule of Assessments (cont.)

[i] A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems (including fundoscopy); genitourinary examinations may be performed if clinically indicated. The physical examinations should be conducted in the same manner on each occasion to ensure comparability to previous examinations. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities (i.e., beyond expected variation or normal age-related change) should be recorded as adverse events on the Adverse Event eCRF. Height will be measured at baseline only.

[j] A neurologic examination, performed at screening and at every clinical visit, should include assessment of mental status, level of consciousness, cranial nerve function, motor function, sensory function, reflexes, and coordination. The neurologic examinations should be conducted in the same manner on each occasion to ensure comparability to previous examinations. Neurologic examinations should be performed before and after treatment on each dosing day. Weight should also be measured at each visit. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities (i.e., beyond expected variation or normal age-related change) should be recorded as adverse events on the Adverse Event eCRF.

[k] Triplicate ECG are to be performed after the patient has been in a supine position for approximately 10 minutes. ECGs for each patient should be obtained from the same machine whenever possible. At screening, baseline (Day −1 or Day 1) and other visits, pre-dose ECG should be performed prior to any blood draws and where applicable before the lumbar puncture.

[l] Hematology includes WBC count, RBC count, platelet count, hemoglobin, hematocrit, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

[m] Serum chemistry panel: includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, gamma-glutamyl transferase, and CPK.

[n] All women of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[o] Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[p] At the Week 37 visit, PK samples will be collected prior to dosing and at 1, 2, and 4 hours post-dose. All patients will remain in clinic at least 4 hours after lumbar puncture.

[q] At Weeks 13, 37, and 69 and at the EoT visit, the MRI should be scheduled to occur before the lumbar puncture. It can be scheduled in the days prior to the lumbar puncture (provided it occurs within the visit window). After patient enrollment, the MRI scan should be performed 7–14 days prior to the lumbar puncture to allow time for re-scanning if the quality of the initial MRI is inadequate. MRI should take place as early as

possible within the screening window but may take place at any time during screening. Results must be available before the patient can be enrolled in the study.

[r] The C-SSRS will be used to assess eligibility for the study (full version at baseline, requiring approximately 20 minutes to administer) and to monitor the patients throughout the study at clinic visits (follow-up version, requiring approximately 5 minutes to administer, assuming absence of suicidal ideation and no change in clinical status from previous administration).

[s] The cUHDRS is a composite motor, cognitive, and global functional clinical outcome measure in patients with HD comprised of the TFC, the TMS, the SDMT, and the SWR scores.

[t] The electronic devices for remote data collection will be supplied to patients at screening and must be returned to the clinic in cases where the patient does not meet eligibility criteria, at the end of the study, or upon early termination from the study.

[u] Optional exit interviews will be conducted within approximately 1 week after the EoT visit; these interviews can be conducted by telephone.

[v] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate.

[w] At the time of each study drug administration, an interval medical history should be obtained and any changes in medications, any major procedures or hospitalizations, and any physician visits for HD or general medical care should be recorded.

[x] Prior to performing each scheduled lumbar puncture, local laboratory analysis of coagulation factors (INR, aPTT, PT) and platelets must be conducted and the results reviewed. Collection for these local laboratory tests may occur at any time in the 72 hours prior to the lumbar puncture. The lumbar puncture should be performed at approximately the same time at each visit (ideally in the morning between 8:00 a.m. and 12:00 noon or in the early afternoon between 12:00 noon and 3:00 p.m.) to minimize potential diurnal variation of CSF parameters. CSF fluid (20 mL) is to be collected for analyses using a lumbar puncture collection kit. If there are difficulties in collecting 20 mL of CSF fluid, a minimum of 5 mL should be collected over a maximum of 60 minutes. If only 5 mL is collected after 60 minutes, the operator must confirm CSF flow is present prior to injecting drug at 60 minutes. A 24G Whitacre (atraumatic) needle should be used. Depending on institutional guidelines, local anesthesia should be used for the procedure. Sedation may not be used. Spinal ultrasound may be used for the lumbar puncture procedure if deemed necessary, but is not required. Ultrasound guidance may be used if attempts at lumbar puncture without imaging are unsuccessful, if it is local practice to use ultrasound, or if institutional guidelines dictate use of ultrasound with each lumbar puncture. Patients will be discouraged from resting supine after the lumbar puncture procedure and will be encouraged to mobilize immediately by walking around at a minimum and, if feasible, walking briskly.

[y] The last CSF sample will be obtained at the Week 101 EoT visit, but no study drug will be administered.

[z] Patients in Q8W arm will receive placebo at these visits.

[aa] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from screening to the study completion/discontinuation visit.

Appendix 2
Schedule of Assessments (cont.)

[bb] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 5 months after the final dose of study drug. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment.

[cc] The DCL will be assessed at screening only (i.e., without the full TMS assessment). The TMS scale will be assessed (excluding the DCL) at all other timepoints.

[dd] Excluding MRIs, which have a visit window of −14 days.

Appendix 3 Mixed-Model Repeated Measures Technical Details

The advantage of mixed-model repeated measures (MMRM) analysis is that it takes into account the fact that measurements from the same patients are correlated and also that all available data are used without eliminating individuals without complete information. The following points will be considered during MMRM model fitting;

- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

  In the event the model fails to run using the KR method, then the residual method will be used instead.

- For modelling change from baseline, an Unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED statement.

  In the event that this model fails to converge, alternative correlation structures will be applied in the following pre-specified order: Heterogeneous Toeplitz (TOEPH), Antedependence (ANTE[1]) and Heterogeneous Compound Symmetry (CSH).

- Distributional assumptions underlying the model used for analysis will be examined to gain confidence that the model assumptions are reasonable and where needed, sensitivity analyses will be performed.

The sample SAS code for fitting the MMRM will be as the following:

```
proc mixed data=DATANAME method=REML;
class USUBJID TREATMENT VISIT;
model CHANGE=BASELINE  CAP BAGE CAG TREATMENT TREATMENT*VISIT / ddfm=KR;
repeated VISIT / subject=USUBJID type=UN
lsmeans TREATMENT*VISIT/ pdiff cl;
ods output LSMeans=LSMeans diffs=diff;
run;
```