Official Title: A Multi-Site, Prospective, Longitudinal, Cohort Study Measuring Cerebrospinal Fluid-Mutant Huntingtin Protein in Patients With Huntington's Disease

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PROTOCOL

TITLE:	**A MULTI-SITE, PROSPECTIVE, LONGITUDINAL, COHORT STUDY MEASURING CEREBROSPINAL FLUID-MUTANT HUNTINGTIN PROTEIN IN PATIENTS WITH HUNTINGTON'S DISEASE**
PROTOCOL NUMBER:	BN40422
VERSION NUMBER:	3
TEST PRODUCT	None
MEDICAL MONITOR:	[redacted], M.D., M.Sc.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	*See electronic data stamp below*

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
18-Dec-2019 13:36:49	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
1	3 July 2018
1 (Germany)	2 August 2018
2 (Germany)	18 October 2018

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Changes to the protocol are summarized below. Please note that version 1 (Germany) and version 2 (Germany) of the protocol were specific to Germany, and changes in those versions relative to version 1 (global) are noted below. This version 3 (global) of the protocol replaces the current version 1 (global) and all German-specific versions.

- The EudraCT number has been removed from the main cover page, from the protocol amendment acceptance form, and from the protocol synopsis cover page as it is not required in studies without an investigational medicinal product (the EudraCT number was removed previously in the Germany-specific protocol version 2).
- The protocol has been updated to included additional information that is applicable to the open-label extension study (Sections 3.1 and 4.3).
- The protocol has been updated to provide clarification as to when a second lumbar puncture/cerebrospinal fluid (CSF) collection attempt is permitted and now specifies that all mandatory assessments should be completed and reviewed prior to the second attempt (Sections 3.1, 4.5.6, and Appendix 1); this will ensure that the primary endpoints are evaluated in the majority of the patients at this visit.
- The protocol has been updated to allow the use of local CAG results for enrollment-matching purposes, although centrally-assessed CAG results will be used for the final analysis (Section 4.2).
- The protocol has been updated to allow a maximum of one re-screening for each patient and to clarify when this is permitted; it now notes the assessments that may be exempted at re-screening (CAG repeat length testing, screening MRI, and viral serology) (Section 4.5.2 and Appendix 1).
- The protocol has been updated to allow for the collection of each patient's Huntington's Disease Identification Number (HDID) so that data from this study can be linked to data from other studies and registries (Sections 4.5.3 and 8.4).
- The guidance for lumbar puncture has been updated in Section 4.5.6 to state that fluoroscopy is allowed if it is required by local/institutional standards and to clarify that sedation must not be used; references to fluoroscopy were removed previously in the Germany-specific protocol version 1.
- Section 4.5.7 has been updated to reflect local or central laboratory practices and to require the assessment of red blood cell (RBC) count and white blood cell (WBC) count in CSF samples.
- Because knowledge about biomarkers and biomarker assays continues to evolve, Section 4.5.7 now states that blood samples for clinical genotyping, CSF, and plasma samples collected for biomarker research will be destroyed no later than 10 years (rather than 5 years) after the final Clinical Study Report has been completed.

- Section 4.5.8 has been updated to state that if an MRI scan is unusable, re-scanning should be conducted more than 3 days after the lumbar puncture and within one week of the original scan if at all possible.
- Section 4.5.9 has been updated to state that ECGs should not be obtained within 30 minutes (rather than not within 3 hours) after a meal.
- Section 4.5.10 has been updated to prohibit the use of paper scales to capture Clinical Outcomes except for performance outcome measures (e.g., SWR, SDMT, and MoCA).
- Section 4.5.10.16 has been updated to clarify which visits will require the use of the full Columbia-Suicide Severity Rating Scale and which visits will require the use of the follow-up scale; the protocol now states that this scale must be administered by a study-qualified physician.
- The primary and secondary medical monitor information has been updated (Section 5.4.1).
- Section 8.2 has been updated to mandate a signature on the companion informed consent form (when applicable).
- Appendix 4 has been updated to specify the study site personnel who are responsible for each assessment at clinic visits.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A MULTI-SITE, PROSPECTIVE, LONGITUDINAL, COHORT STUDY MEASURING CEREBROSPINAL FLUID-MUTANT HUNTINGTIN PROTEIN IN PATIENTS WITH HUNTINGTON'S DISEASE**
PROTOCOL NUMBER:	BN40422
VERSION NUMBER:	3
TEST PRODUCT	None
MEDICAL MONITOR:	[redacted], M.D., M.Sc.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the CRO.

PROTOCOL SYNOPSIS

TITLE:	**A MULTI-SITE, PROSPECTIVE, LONGITUDINAL, COHORT STUDY MEASURING CEREBROSPINAL FLUID-MUTANT HUNTINGTIN PROTEIN IN PATIENTS WITH HUNTINGTON'S DISEASE**
PROTOCOL NUMBER:	BN40422
VERSION NUMBER:	3
TEST PRODUCT:	None
INDICATION:	Huntington's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This longitudinal study in patients with early Huntington's disease (HD) will explore the prognostic value of baseline cerebrospinal fluid (CSF) mutant huntingtin protein (mHTT); the relationship of CSF mHTT to other key biological markers in the putative causal pathway; rate and variability of CSF mHTT increase in untreated patients; and the utility of recording clinical outcome measures via sensors contained in the Roche HD mobile app. Since no study medication will be given to the patients, safety assessments will consist of monitoring and recording adverse events, including serious adverse events, related to study procedures. Specific objectives are outlined below.

Primary Objective

The primary objective of this study is to examine the predictive value of baseline CSF mHTT levels on measures of disease progression using the following endpoints:

- Change from baseline in the following clinical endpoints at 3, 9, and 15 months: composite Unified Huntington's Disease Rating Scale (cUHDRS), Total Functional Capacity Scale (TFC), Total Motor Scale (TMS), Symbol Digit Modalities Test (SDMT), Stroop Word Reading (SWR) Test, and Independence Scale (IS)
- Change from baseline in biomarkers of neuronal injury (e.g., CSF NfL and tau) at 3, 9, and 15 months
- Change from baseline in brain atrophy endpoints (e.g., whole brain volume decline, caudate volume decline) as determined by brain MRI, at 3, 9, and 15 months

Secondary Objective

The secondary objective of this study is to investigate the temporal profile of longitudinal CSF mHTT changes within patient, and the association of these changes with corresponding changes in biomarkers of neuronal injury (e.g., CSF NfL and tau) and clinical outcomes using the following endpoints:

- Within-patient change from baseline in CSF mHTT levels at 3, 9, and 15 months
- Association of change from baseline in CSF mHTT levels at 3, 9, and 15 months and:
  - Change from baseline in clinical measures (cUHDRS, TFC, TMS, SDMT, SWR, and IS) at 3, 9, and 15 months
  - Change from baseline in biomarkers of neuronal injury (e.g., CSF NfL and tau) at 3, 9, and 15 months
  - Change from baseline in brain atrophy endpoints, as determined by brain MRI at 3, 9, and 15 months

Exploratory Objectives

The exploratory objectives of this study are:

- To examine the association of the Roche HD mobile app and standard clinical assessments at baseline and at 3, 9, and 15 months
- To examine the association of the Roche HD mobile app and biological markers under study at baseline and at 3, 9, and 15 months
- To examine the utility of Roche HD mobile app and patient-reported outcomes (PROs) in monitoring disease progression in early HD
- To examine the association of potential prognostic biomarkers and genetic modifiers with disease status and disease progression

Study Design

Description of Study

The study is designed as a multi-site, prospective, 15-month longitudinal, cohort study measuring CSF mHTT in patients with early manifest Stage I or Stage II HD. After completion *of the observational period*, participants will *have the option of receiving the active compound RO7234292 in an* OLE study *(Study BN40955, ClincalTrials.gov Identifier NCT03842969), provided they meet eligibility criteria, the data from the ongoing RO7234292 program supports continued development,* and subject to approval by the relevant competent authorities and *Institutional Review Boards/*Ethics Committees (*IRBs*/ECs).

This study will enroll up to approximately 100 patients at approximately 20 sites. After a 28-day screening period, patients will return to the clinic at baseline and at Months 3, 9, and 15. During these visits, patients will receive clinical, MRI, and Roche HD mobile app assessments; they will also provide CSF and blood samples. *Patients who will not enter the OLE study (Study BN40955, ClinicalTrials.gov Identifier NCT03842969) will have a* post-observational follow-up visit 2 weeks after the 15-month longitudinal period *that* may occur by telephone or in the clinic. Early termination visits should take place via clinic visit, where possible. *If there is the occurrence of a failed CSF collection procedure due to inadequate establishment of access to the IT space, there may be a second attempt up to 14 days after the original attempt. For this additional visit, local laboratory analysis of coagulation factors (INR and/or PT, aPTT) and platelets must be conducted and the results reviewed within 72 hours prior to performing the LP. In addition, neurological examination, vital signs, and a review of AEs and concomitant medication should occur as part of the safety and tolerability evaluations on the day of LP.*

The final study visit will be Study Day 421 (Month 15) for patients who enter the OLE Study (Study BN40955, ClinicalTrials.gov Identifier NCT03842969), and the follow-up visit will be the final study visit for those patients who do not enter the OLE.

Number of Patients

The study will enroll up to approximately 100 patients with early manifest Stage I or II HD.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Capacity to consent to participate in the study as assessed using the Evaluation to Sign Consent tool and investigator judgment
- Age 25 to 65 years, inclusive, at the time of signing Informed Consent Form
- Early manifest, Stage I or Stage II HD (defined as TFC of 7–13, inclusive)
- Genetically confirmed disease (CAG repeat length $\geq$ 36 in huntingtin gene by direct DNA testing)
- Body mass index $\geq$ 18 and $\leq$ 32 kg/m^2; total body weight $>$ 50 kg

- Ability to undergo and tolerate MRI scans (e.g., no claustrophobia, no metal implants including MRI-incompatible intrauterine devices or metal dental braces, chorea of a severity that precludes MRI scans, or any condition that renders testing intolerable for the patient)
- Ability to tolerate blood draws and lumbar puncture
- Ability and willingness to comply with all aspects of the protocol, including completion of interviews and questionnaires and carrying/wearing of a digital monitoring device
- Stable medical, psychiatric, and neurological status for at least 12 weeks prior to screening and at the time of enrollment

  Patients may be managed according to clinical judgment during study observational period.
- Signed study companion consent for participation, <u>if a study companion is available</u>

  A study companion should be reliable, competent, and at least 18 years of age; willing to accompany the patient to clinic visits and to be available to the study site by telephone if needed; and (in the opinion of the investigator) a person who is and will remain sufficiently knowledgeable of the patient's ongoing condition to respond to study site enquiries about the patient. The study companion will complete study companion assessments and will provide demographic and social status data (e.g, relationship to patient and employment status).
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods during the observational period.

  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 following are acceptable contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the observational study 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.

<u>Exclusion Criteria</u>

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

- Any condition, including severe chorea, that would prevent either writing or performing pen-and-paper or smartphone-based tasks
- 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 active suicidal ideation is demonstrated by the Columbia-Suicide Severity Rating Scale. If suicidal ideation is generally 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 appropriately qualified mental health professional per judgment of the investigator.
- Current active psychosis, confusional state, or violent behavior
- Any serious medical condition or clinically significant laboratory, vital sign, or electrocardiogram abnormalities at screening that, in the investigator's judgement, precludes the patient's safe participation in and completion of the study

- Pregnant or breastfeeding, or intending to become pregnant during the study
- Positive for hepatitis C virus antibody or hepatitis B surface antigen at screening
- Known HIV infection
- Current or previous use of an antisense oligonucleotide (including small interfering RNA)
- Current use of antipsychotics prescribed for psychosis, cholinesterase inhibitors, memantine, amantadine, or riluzole including use within 12 weeks of enrollment

  Use of antipsychotics for motor symptoms and/or tetrabenazine or deutetrabenazine is not permitted unless on stable dose for at least 12 weeks prior to screening.

- Treatment with an investigational drug within 30 days prior to screening or 5 half-lives of the investigational drug, whichever is longer
- Antiplatelet or anticoagulant therapy within the 14 days prior to screening or anticipated use during the study, including, but not limited, to aspirin (unless $\leq$81mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban, and apixaban
- History of bleeding diathesis or coagulopathy; platelet count $<$ lower limit of normal unless stable and assessed by the Investigator and Sponsor Medical Monitor to be not clinically significant
- 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
- History of gene therapy or cell transplantation or any other experimental brain surgery
- Concurrent or planned concurrent participation in any clinical study without approval of the Medical Monitor
- Presence of implanted shunt for the drainage of CSF or an implanted CNS catheter
- Prexisting structural brain lesion (e.g., tumor, arterio-venous malformation) as assessed by MRI scan

End of Study

The end of the study will be the date from which the last patient, last visit is recorded in the study database. The end of the study is expected to occur 15.5 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 27 months.

Statistical Methods

Primary Analysis

The primary objective of this study is to investigate whether baseline CSF mHTT is a predictor of the change from baseline to 15 months for the following variables:

- Clinical endpoints (cUHDRS, TFC, TMS, SDMT, SWR, and IS)
- CSF and blood biomarkers
- Brain imaging (MRI)

Initially, a linear model will be used to evaluate the association between each response variable (e.g., change from baseline to 15 months in cUHDRS) and baseline CSF mHTT without adjustment for any baseline characteristics.

The same model will then be considered again, adjusting for baseline level of the response variable (e.g., baseline cUHDRS), baseline CSF mHTT levels, CAG, and baseline CAP (the latter defined as the product of age at baseline by [CAG—33.66]. A sensitivity analysis to evaluate the impact of additional baseline characteristics (e.g., gender, education level) may be performed.

Other approaches may be used in the case of severe multicollinearity, which would results in model instability.

Determination of Sample Size

In this study, up to approximately 100 patients are expected to be enrolled across approximately 20 sites.

Interim Analyses

The Sponsor may choose to conduct one or more interim analyses. The decision to conduct such an optional interim analysis and the timing of the analysis will be documented in the Sponsor's study master file prior to the conduct of the interim analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AES	Apathy Evaluation Scale
CGI-C	Clinical Global Impression–Change
CGI-S	Clinical Global Impression–Severity
ClinRO	clinician-reported outcome
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
cUHDRS	composite Unified Huntington's Disease Rating Scale
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
FDA	Food and Drug Administration
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HD	Huntington's disease
HDID	*Huntington's Disease Identification Number*
HD-SDI	Huntington's Disease–Speaking Difficulty Item
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IS	Independence Scale
IxRS	interactive voice or web-based response system
mHTT	mutant huntingtin protein
MRI	magnetic resonance imaging
Neuro-Qol	Quality of Life in Neurological Disorders
NfL	neurofilament light chain
NRS	numeric rating scale
ObsRO	observer-reported outcome
OLE	open-label extension
PerfO	performance outcome
PGI-C	Patient Global Impression–Change
PGI-S	Patient Global Impression–Severity

Abbreviation	Definition
PRO	patient-reported outcome
RBR	Research Biosample Repository
SDMT	Symbol Digit Modalities Test
SMDDS	Symptoms of Major Depressive Disorder Scale
SWR	Stroop Word Reading
TFC	Total Functional Capacity Scale
TMS	Total Motor Scale
UHDRS	Unified Huntington's Disease Rating Scale
VAS	visual analog scale
WES	whole exome sequencing
WGS	whole genome sequencing
WHODAS 2.0	WHO Disability Assessment Schedule 2.0
WPAI	Work Productivity and Activity Impairment

1. BACKGROUND

1.1 BACKGROUND ON HUNTINGTON'S DISEASE

Huntington's disease (HD) is an autosomal dominant genetic disease, with onset typically in adulthood, caused by expansion of CAG repeats on exon 1 of chromosome 4. This mutation produces a toxic form of huntingtin protein (mHTT), which is, based upon preclinical and clinical evidence, the assumed primary disease-causing protein (Wild and Tabrizi 2017). Individuals who carry at least 40 CAG repeats experience progressive motor, cognitive, and functional decline usually in adult life, typically age 40–45 years, with an end stage of profound physical wasting. Common causes of death include pneumonia, heart failure, and starvation (Sorensen and Fenger 1992). Currently, the only approved therapies (i.e., tetrabenazine and deutetrabenazine) target abnormal involuntary movements (i.e., chorea) associated with HD, and these symptomatic therapies have a challenging benefit–risk profile.

1.2 STUDY RATIONALE

With the advent of huntingtin protein–lowering therapies and the ability to measure the mutant protein in cerebrospinal fluid (CSF), there is a need to better understand the potential of CSF mHTT to serve as a biomarker for drug development and for predicting and measuring disease progression in HD. In cross-sectional studies, CSF mHTT protein levels are specific to HD; correlate with severity of disease burden, motor, and cognitive symptoms; and are associated with markers of neuronal damage (e.g., neurofilament light chain [NfL]) (Wild et al. 2015). Yet, the relationship between baseline mHTT levels and subsequent clinical progression and to longitudinal changes in other biomarkers is unknown. Longitudinal collection of CSF mHTT will allow evaluation of the prognostic value of mHTT protein levels; provide information on the rate and variability of increased levels over time in untreated patients; evaluate the relationship of this biomarker to other key putative biological markers over time (e.g., NfL levels in CSF or plasma, progressive brain atrophy as assessed by magnetic resonance imaging [MRI]); and help determine the role played by mHTT in the causal pathway.

Findings from this study will inform drug development and will aid in the interpretation of ongoing therapeutic studies, which use mHTT as a biomarker of disease state, an exploratory pharmacodynamic measure, a potential prognostic biomarker for likely disease progression, and a potential biomarker of progression and treatment efficacy. The study will also explore the utility of clinical outcome measures collected via sensors in smartphones and wrist-worn wearables ("the Roche HD mobile app"). The data generated by the digital approach will be correlated with standard clinical assessments and with the other biological markers under study.

Study BN40422 is part of a broader development plan for RO7234292, an anti-sense oligonucleotide (originally developed by Ionis Pharmaceuticals, Inc. and formerly referred to as ISIS 443139 or IONIS-HTTRx). A Phase I/IIa study has been completed (Study ISIS 443139-CS1), and RO7234292 is now being investigated in an open-label

extension (OLE) study (*BN40697*; Clinicaltrials.gov Identifier NCT03342053) as the first potential therapy in clinical development to target the underlying cause of HD.

2. OBJECTIVES AND ENDPOINTS

This longitudinal study in patients with early HD will explore the prognostic value of baseline CSF mHTT; the relationship of CSF mHTT to other key biological markers in the putative causal pathway; rate and variability of CSF mHTT increase in untreated patients; and the utility of recording clinical outcome measures via sensors contained in the Roche HD mobile app. Since no study medication will be given to the patients, safety assessments will consist of monitoring and recording adverse events, including serious adverse events, related to study procedures. Specific objectives are outlined below.

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to examine the predictive value of baseline CSF mHTT levels on measures of disease progression using the following endpoints:

- Change from baseline in the following clinical endpoints at 3, 9, and 15 months: composite Unified Huntington's Disease Rating Scale (cUHDRS), Total Functional Capacity Scale (TFC), Total Motor Scale (TMS), Symbol Digit Modalities Test (SDMT), Stroop Word Reading (SWR) Test, and Independence Scale (IS)
- Change from baseline in biomarkers of neuronal injury (e.g., CSF NfL and tau) at 3, 9, and 15 months
- Change from baseline in brain atrophy endpoints (e.g., whole brain volume decline, caudate volume decline) as determined by brain MRI, at 3, 9, and 15 months

2.2 SECONDARY OBJECTIVE

The secondary objective of this study is to investigate the temporal profile of longitudinal CSF mHTT changes within patient, and the association of these changes with corresponding changes in biomarkers of neuronal injury (e.g., CSF NfL and tau) and clinical outcomes using the following endpoints:

- Within-patient change from baseline in CSF mHTT levels at 3, 9, and 15 months
- Association of change from baseline in CSF mHTT levels at 3, 9, and 15 months and:
  - Change from baseline in clinical measures (cUHDRS, TFC, TMS, SDMT, SWR, and IS) at 3, 9, and 15 months
  - Change from baseline in biomarkers of neuronal injury (e.g., CSF NfL and tau) at 3, 9, and 15 months
  - Change from baseline in brain atrophy endpoints, as determined by brain MRI at 3, 9, and 15 months

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are:

- To examine the association of the Roche HD mobile app and standard clinical assessments at baseline and at 3, 9, and 15 months
- To examine the association of the Roche HD mobile app and biological markers under study at baseline and at 3, 9, and 15 months
- To examine the utility of Roche HD mobile app and patient-reported outcomes (PROs) in monitoring disease progression in early HD
- To examine the association of potential prognostic biomarkers and genetic modifiers with disease status and disease progression

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

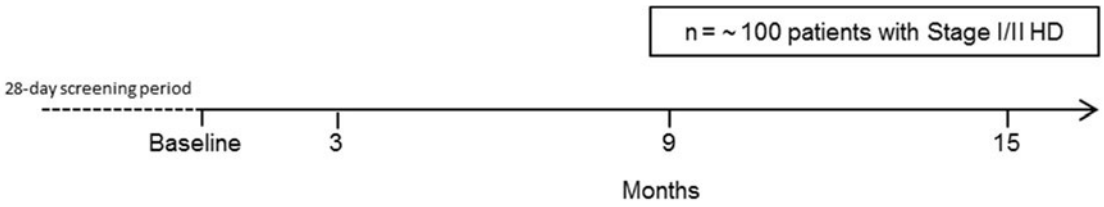
The study is designed as a multi-site, prospective, 15-month longitudinal, cohort study measuring CSF mHTT in patients with early manifest Stage I or Stage II HD. After completion *of the observational period*, participants will *have the option of receiving the active compound RO7234292 in an* OLE study *(Study BN40955, ClinicalTrials.gov Identifier NCT03842969), provided they meet eligibility criteria, the data from the ongoing RO7234292 program supports continued development,* and subject to approval by the relevant competent authorities and *Institutional Review Boards/*Ethics Committees (*IRBs*/ECs).

This study will enroll up to approximately 100 patients at approximately 20 sites. After a 28-day screening period, patients will return to the clinic at baseline and at Months 3, 9, and 15. During these visits, patients will receive clinical, MRI, and Roche HD mobile app assessments; they will also provide CSF and blood samples. *Patients who will not enter the OLE study (Study BN40955, ClinicalTrials.gov Identifier NCT03842969) will have a* post-observational follow-up visit 2 weeks after the 15-month longitudinal period *that* may occur by telephone or in the clinic. Early termination visits should take place via clinic visit, where possible. *If there is the occurrence of a failed CSF collection procedure due to inadequate establishment of access to the IT space, there may be a second attempt up to 14 days after the original attempt. For this additional visit, local laboratory analysis of coagulation factors (INR and/or PT, aPTT) and platelets must be conducted and the results reviewed within 72 hours prior to performing the LP. In addition, neurological examination, vital signs, and a review of AEs and concomitant medication should occur as part of the safety and tolerability evaluations on the day of LP.*

The final study visit will be Study Day 421 (Month 15) for patients who enter the OLE Study (Study BN40955, ClinicalTrials.gov Identifier NCT03842969), and the follow-up visit will be the final study visit for those patients who do not enter the OLE.

Figure 1 presents an overview of the study design, with 1 month defined as one 28-day period. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



HD = Huntington's disease.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study will be the date from which the last patient, last visit is recorded in the study database. The end of the study is expected to occur 15.5 months after the last patient is enrolled.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 27 months. In addition, the Sponsor may decide to terminate the study at any time.

3.3 RATIONALE FOR STUDY DESIGN

There are currently no longitudinal CSF mHTT data in patients with HD. This study has been designed to collect data for CSF mHTT, other biomarkers, clinical assessments, and the Roche HD mobile app assessments at four timepoints over 15 months.

3.3.1 Rationale for Patient Population

Patients with early-stage HD, defined as Stage I or II by Shoulson and Fahn (1979), will be included in this study, as they are expected to show progressive decline in clinical parameters measurable over a ≥12-month timeframe (Huntington Study Group 1996; Schobel et al. 2017), and because they have measurable abnormalities in the key biomarkers in cross-sectional studies compared to controls and prodromal individuals (e.g., for CSF mHTT [Southwell et al. 2015; Wild et al. 2015]) as well as longitudinal differences on other outcomes (e.g., for NfL, brain atrophy, and clinical endpoints [Byrne et al. 2017]). The population also represents the stage of manifest HD that might be more plausibly reversed or slowed in response to a therapeutic intervention versus more advanced patients with more neurodegeneration present at baseline who experience less longitudinal decline in clinical parameters such as the TFC score (Penney et al. 1990). Since this population overlaps with the population targeted for the upcoming clinical efficacy studies of the RO7234292 development program, the natural history study will provide useful comparative data.

3.3.2 Rationale for Clinical Assessments

3.3.2.1 Patient-Reported, Clinician-Reported, Observer-Reported, and Performance Outcome Questionnaires

Individuals with HD exhibit a triad of motor, cognitive, and behavioral/psychiatric symptoms that contribute to clinical progression and/or morbidity and quality of life. A recent survey of patients and caregivers/companions reported executive function/cognitive decline, chorea movement/balance, and depression/apathy as the most impactful symptoms (Simpson et al. 2016).

A comprehensive battery of patient-, clinician-, observer-reported, and performance outcome assessments (PRO, ClinRO, ObsRO, and PerfO, respectively) will be used to document changes over time. The proposed endpoint strategy captures measures known to be sensitive to clinical progression from a clinician and patient perspective, as well as assessments solicited by companion/caregiver report.

The Unified Huntington's Disease Rating Scale (UHDRS) is a collection of assessments commonly used to assess disease status (including symptoms and their impact) and progression in patients with HD (Huntington Study Group 1996). The individual scales of the UHDRS include the TFC score; the highly correlated Independence and Functional Assessment Scales; the TMS; SDMT; SWR; verbal fluency test; and a behavioral assessment. The cUHDRS is a composite of weighted subcomponents of the UHDRS, which also covers multiple domains (motor, cognitive, and functional) and possesses greater sensitivity to detect longitudinal change compared to the UHDRS or its individual subtests (Schobel et al. 2017).

Apathy, depression, anxiety, and irritability are core behavioral symptoms associated with HD (Simpson et al. 2016). The Apathy Evaluation Scale (AES) is a widely used and valid measure of apathy. To assess change in other behavioral symptoms, a newly developed scale, the Symptoms of Major Depressive Disorder Scale (SMDDS), will be used to capture depressive symptoms as well as irritability and anxiety. This scale was selected for its excellent coverage of these core symptoms.

To complement the PerfO measures of cognition (SDMT and SWR), the Quality of Life in Neurological Disorders (Neuro-Qol) Cognition Function Short Form assesses self-reported issues with cognition, such as slow thinking or difficulty learning new tasks.

Speech difficulty is a common issue (with both cognitive and motor deficits impacting ability) and will be measured by a novel single-item measure, the Huntington’s Disease–Speaking Difficulty Item (HD-SDI).

The clinician will complete a Clinical Global Impression of Severity (CGI-S) at baseline and a Clinical Global Impression of Change (CGI-C), and the patient will complete the Patient Global Impression of Severity (PGI-S) and the Patient Global Impression of Change (PGI-C).

Concepts such as health-related quality of life (HRQoL), health state utilities, and societal impacts (e.g., work productivity) are of particular interest to European Health Technology Assessment agencies. The WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) and the EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire will assess HRQoL and health state utilities, respectively. The Work Productivity and Activity Impairment (WPAI) Scale will capture changes in employment status, including a reduction of work hours or loss of productivity.

Further details on these assessments are included in Section 4.5.10.

3.3.2.2 Roche Huntington's Disease Mobile App

The Roche HD mobile app collects sensor data from smartphones and wrist-worn wearables. Smartphones and wrist-worn wearables have high-quality sensors that enable remote, non-invasive, frequent, and precise measurement of motor and non-motor symptoms. Such technology has been used previously in Parkinson disease (Maetzler et al. 2013; Arora et al. 2015; Ossig et al. 2016) and HD (Andrzejewski et al. 2016; Dinesh et al. 2016).

Several cognitive and motor measures sensitive to symptom progression in early HD (Tabrizi et al. 2012) lend themselves to sensor-based measurement. Fine motor impairments can be measured using touch sensors (e.g., circle tracing [Say et al. 2011] and speeded tapping [Tabrizi et al. 2012]). Gait and balance have previously been successfully captured using wearable sensors (Dalton et al. 2013; Andrzejewski et al. 2016; Dinesh et al. 2016), as has choreatic movement in HD patients (Reilmann et al. 2011; Kegelmeyer et al. 2017).

Patients will be asked to complete daily "active" tests and then carry the devices with them as they go about their daily routines (i.e., "passive monitoring"). The collected sensor data will be correlated with traditional clinical assessments as mentioned above and will be used to track the longitudinal trajectory of motor, cognitive, behavioral, and functional parameters.

3.3.3 Rationale for Biomarker Assessments

3.3.3.1 Cerebrospinal Fluid Biomarkers

Measurement of protein levels in the CSF offers the potential to monitor molecular changes that take place in the CNS. A toxic gain-of-function mechanism of mHTT is widely considered to be the primary driver of disease pathophysiology in HD (Wild and Tabrizi 2017). mHTT protein in human CSF is associated with disease stage and severity and with markers of neuronal damage, including CSF NfL and CSF tau levels (Wild et al. 2015). NfL levels in CSF predict progressive MRI measures of brain atrophy, as well as progressive clinical decline in patients (Wild and Tabrizi 2017). Longitudinal analysis of CSF mHTT, NfL, and other biomarkers related to HD, neurodegeneration, and inflammation will facilitate understanding of HD pathophysiology and progression.

3.3.3.2 Blood-Derived Biomarkers

NfL levels in blood correlate with NfL levels in CSF and could serve as prognostic blood biomarkers of disease onset and progression in HD (Wild and Tabrizi 2017; Johnson et al. 2018). Longitudinal analysis of NfL and other biomarkers related to HD and neuronal degeneration or inflammation in blood will facilitate understanding of HD pathophysiology and progression.

3.3.3.3 Genetic Testing to Determine CAG Repeat Length

HD is caused by a CAG repeat expansion in the first exon of the *HTT* gene located on chromosome 4 resulting in a polyglutamine expansion in the huntingtin protein. Above 35 CAG repeats, the age of HD onset is inversely correlated with the length of the expansion (Duyao et al. 1993). CAG repeat length will be determined by direct DNA testing.

3.3.3.4 Clinical Genotyping

Although CAG repeat length is inversely correlated to age of onset in HD, it only accounts for approximately 50% of the variance. Identification of other genetic modifiers of disease severity and disease progression in HD could provide important insights, as has been recently shown in the Genetic Modifiers of Huntington's Disease Consortium (2015), where relatively common single nucleotide polymorphisms in the HD population were found to be associated with either an accelerated or delayed age of motor onset. A blood sample will be collected to detect individual single nucleotide polymorphisms previously described to explore, for example, their influence on progression rates.

3.3.3.5 Magnetic Resonance Imaging

MRI is a non-invasive method to assess structure and function of the human brain and can provide insights into pathophysiological mechanisms of neurologic and neuropsychiatric disease. Several MRI techniques have shown sensitivity to detect abnormal structure and function within brains of individuals suffering from HD.

Structural Magnetic Resonance Imaging

Numerous structural MRI studies have demonstrated wide-spread brain atrophy, including neocortex, striatum, white matter, and cerebellum in patients with premanifest and manifest HD (Douaud et al. 2006; Harrington et al. 2016). Brain volume correlates with cognitive function (Peinemann et al. 2005). Further, the whole brain, caudate, and ventricular volumes can predict and track progressive clinical decline in patients with HD and also associate with molecular markers of neurodegeneration, such as NfL (Tabrizi et al. 2012).

Diffusion Magnetic Resonance Imaging

Widespread changes of basal ganglia–cortical structural connectivity have also been observed in patients with early manifest HD (Novak et al. 2015), including associations between striatum-sensorimotor cortex connections and UHDRS motor scale

(Bohanna et al. 2011), suggesting that the clinical phenotype in manifest HD may be a result of altered structural connectivity.

Resting-State Functional Magnetic Resonance Imaging

Resting-state functional MRI studies have generated solid evidence for functional connectivity alterations and their correlation to several clinical and cognitive measures in patients with HD (Werner et al. 2014; Dogan et al. 2015; Liu et al. 2016; Espinoza et al. 2018), implying that disrupted functional integrity of distinct brain networks may underlie clinical progression in HD.

Structural MRI will be used to assess brain volume, diffusion MRI will be used to examine structural brain connectivity, and resting-state functional MRI will be employed to identify functional connectivity. All of the measures will be assessed at the whole-brain and regional levels. The acquisition parameters of each sequence, structure, and length of each MRI session and image processing algorithms will be outlined in a separate MRI manual.

4. MATERIALS AND METHODS

4.1 PATIENTS

The study will enroll up to approximately 100 patients with early manifest Stage I or II HD.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Capacity to consent to participate in the study as assessed using the Evaluation to Sign Consent tool and investigator judgment
- Age 25 to 65 years, inclusive, at the time of signing Informed Consent Form
- Early manifest, Stage I or Stage II HD (defined as TFC of 7–13, inclusive)
- Genetically confirmed disease (CAG repeat length $\geq$36 in huntingtin gene by direct DNA testing)
- Body mass index $\geq$18 and $\leq$32 kg/m^2; total body weight $>$50 kg
- Ability to undergo and tolerate MRI scans (e.g., no claustrophobia, no metal implants including MRI-incompatible intrauterine devices or metal dental braces, chorea of a severity that precludes MRI scans, or any condition that renders testing intolerable for the patient)
- Ability to tolerate blood draws and lumbar puncture
- Ability and willingness to comply with all aspects of the protocol, including completion of interviews and questionnaires and carrying/wearing of a digital monitoring device
- Stable medical, psychiatric, and neurological status for at least 12 weeks prior to screening and at the time of enrollment

Patients may be managed according to clinical judgment during study observational period.

- Signed study companion consent for participation, <u>if a study companion is available</u>

  A study companion should be reliable, competent, and at least 18 years of age; willing to accompany the patient to clinic visits and to be available to the study site by telephone if needed; and (in the opinion of the investigator) a person who is and will remain sufficiently knowledgeable of the patient's ongoing condition to respond to study site enquiries about the patient. The study companion will complete study companion assessments and will provide demographic and social status data (e.g., relationship to patient and employment status).

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods during the observational period.

  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 following are acceptable contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the observational study 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.

4.1.2 <u>Exclusion Criteria</u>

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

- Any condition, including severe chorea, that would prevent either writing or performing pen-and-paper or smartphone-based tasks
- 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 active suicidal ideation is demonstrated by the Columbia-Suicide Severity Rating Scale (C-SSRS). If suicidal ideation is generally 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 appropriately qualified mental health professional per judgment of the investigator.

- Current active psychosis, confusional state, or violent behavior
- Any serious medical condition or clinically significant laboratory, vital sign, or electrocardiogram abnormalities at screening that, in the investigator's judgement, precludes the patient's safe participation in and completion of the study
- Pregnant or breastfeeding, or intending to become pregnant during the study
- 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 use of antipsychotics prescribed for psychosis, cholinesterase inhibitors, memantine, amantadine, or riluzole including use within 12 weeks of enrollment

  Use of antipsychotics for motor symptoms and/or tetrabenazine or deutetrabenazine is not permitted unless on stable dose for at least 12 weeks prior to screening.

- Treatment with an investigational drug within 30 days prior to screening or 5 half-lives of the investigational drug, whichever is longer
- Antiplatelet or anticoagulant therapy within the 14 days prior to screening or anticipated use during the study, including, but not limited, to aspirin (unless $\leq$81mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban, and apixaban
- History of bleeding diathesis or coagulopathy; platelet count $<$lower limit of normal unless stable and assessed by the investigator and Sponsor Medical Monitor to be not clinically significant
- 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
- History of gene therapy or cell transplantation or any other experimental brain surgery
- Concurrent or planned concurrent participation in any clinical study without approval of the Medical Monitor
- Presence of implanted shunt for the drainage of CSF or an implanted CNS catheter
- Preexisting structural brain lesion (e.g., tumor, arterio-venous malformation) as assessed by MRI scan

4.2 METHOD AND STRATEGY OF ENROLLMENT

Enrollment in the study will be competitive, and an interactive voice or web-based response system (IxRS) system will be used to manage enrollment of patients across different sites.

A patient will be enrolled after written informed consent has been obtained, all screening assessments have been completed, and the investigator has verified that the patient is eligible per criteria in Sections 4.1.1 and 4.1.2. Further, for a patient to be enrolled in this study, the patient must match a participant from the ongoing OLE study (Clinicaltrials.gov Identifier NCT03342053*, BN40697*). The matching criteria are defined as follows:

- Disease stage (Stage I or II)
- Sex
- Age (± 5 years)
- CAG repeats (± 2)

Of note, due to the characteristics of the baseline multiple-ascending dose (MAD) sample (i.e., all participants had Stage I HD, TFC 11–13), it is anticipated that only a small proportion of patients from the MAD study *(Clinicaltrials.gov Identifier NCT02519036, ISIS 433139-CS1)* who enroll in the MAD OLE study *(Clinicaltrials.gov Identifier NCT03342053, BN40697)* will have progressed to Stage II HD (defined as TFC 7–10). Accordingly, the majority of participants in this study are anticipated to have Stage I HD, TFC 11–13.

The matching algorithm will be implemented through an IxRS system, allowing only the enrollment of "matched" patients and constantly updating the list of OLE *study (BN40697)* participants still remaining to be matched. Further details on the matching procedure (e.g., what to do if a patient matches multiple OLE participants) will be provided in a separate IxRS document. *To facilitate enrolment, CAG matching is based on local CAG results. The study analysis will utilize the centrally assessed CAG result.*

The Sponsor will attempt to find matches for at least 40 OLE *study (BN40697)* participants and will thereafter find a second match based on the aforementioned criteria. However, if this proves more difficult than predicted and extends timelines beyond what is acceptable, the Sponsor may change the enrollment strategy (i.e., amending the IxRS specification as needed) and could eventually continue recruiting patients in Stages I and II of manifest HD without all or some of the matching constraints. This decision will be communicated to the study investigators in a timely manner.

4.3 ACCESS TO TREATMENT AFTER STUDY COMPLETION

After completing this study, the patient will be eligible to enroll in an OLE study *(Study BN40955, ClinicalTrials.gov Identifier NCT03842969)* with active RO7234292 compound for a period of approximately 15 months (may be adjusted based on

emerging data), provided the data from the ongoing RO7234292 program support continued development, the patient meets the inclusion and exclusion criteria for the OLE, and subject to approval by the relevant competent authorities and *Institutional Review Boards/*Ethics Committees (*IRBs/*ECs).

Following the OLE, the Sponsor will offer continued access to Roche Investigational Medicinal Product (IMP) (RO7234292) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP (RO7234292) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMP (RO7234292) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for HD
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for HD
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from the screening visit to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

4.4.1 Permitted Therapy

Throughout the study, investigators or treating physicians may prescribe concomitant medications or treatment deemed necessary to provide adequate supportive care or for treatment of adverse events.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice.

4.4.2 Prohibited Therapy

Patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental doses that are being tested for the treatment of HD. The following agents are also specifically prohibited:

- Antiplatelet or anticoagulant therapy, including, but not limited to, aspirin (unless $\leq$81 mg/day), clopidogrel, dipyridamole, warfarin, dabigatran, rivaroxaban, and apixaban
- Sedation for any procedures in the study

  Depending on institutional guidelines, local anesthesia may be used for the lumbar puncture procedure.
- Anti-anxiety medication for imaging-related anxiety during the screening scan

  Anti-anxiety medication is strongly discouraged during scheduled scans at postbaseline clinic visits. If anti-anxiety medication is used for a postbaseline scan, the scan must be performed at the end of the assessment day or preferably on a different day, to avoid impacting other assessments.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All mandatory activities must be performed and documented for each patient.

4.5.1 Capacity to Consent

Patients' capacity to consent to participate in the study will be assessed using the Evaluation to Sign Consent tool (DeRenzo et al. 1998). This is a brief, five-item questionnaire utilized by study site personnel during a targeted interview with the patient. Patient responses to the questionnaire will not be collected by the Sponsor and are intended only to guide study site personnel in their evaluation of each potential patient's capacity to consent.

4.5.2 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients/study companions and for patients/study companions who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

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, central CAG repeat length testing from the initial screening 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. Participants are not required to re-sign the consent form if they are re-screened.

4.5.3 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient from screening to the study completion/discontinuation visit will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications, smoking, use of alcohol or drugs of abuse, any major procedures or hospitalizations, and any physician visits for HD or general medical care should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity and education level based upon International Standard Classification of Education scale. Demographic data and social status data (e.g., relationship to patient and employment status) will also be collected for the study companion.

A unique HD identification number (HDID) will be collected from patients who already have an HDID. For patients without an HDID who are willing to be assigned one, the number will be created via a web portal (see Section 8.4).

4.5.4 Physical/Neurological Examinations

A complete physical examination will be performed at screening, baseline, Months 3, 9, 15, and as clinically indicated. The examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Neurological examination includes assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes. 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 associated with a study procedure should be recorded as adverse events on the Adverse Event eCRF.

4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position after resting for approximately 5 minutes, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

4.5.6 Collection of Cerebrospinal Fluid (Lumbar Puncture Procedure)

Patients will have CSF collected at baseline and at Months 3, 9, and 15. Prior to performing each scheduled lumbar puncture, local laboratory analysis of coagulation factors (INR *and/or PT*, aPTT) and platelets must be conducted and results reviewed. Collection for these local labs 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 08:00 and 12:00 hours) to minimize potential diurnal variation of CSF parameters. CSF fluid (20 mL) is to be collected for analyses using a standard lumbar puncture collection kit. If there are difficulties in collecting 20 mL of CSF fluid, a minimum of 15 mL should be collected. A 24G Whitacre (atraumatic) needle should be used. Depending on institutional guidelines, local anesthesia may be used for the procedure. Sedation *is not allowed*. 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. *Fluoroscopy guidance can also be used, if local institutional guidelines dictate and if locally required approvals of the technique are obtained, but it is not required. Where fluoroscopy is used, patients should also be informed and consent obtained.*

If there is the occurrence of a failed CSF collection procedure due to inadequate establishment of access to the IT space, a second attempt may occur up to 14 days after the original attempt. For this additional visit, local laboratory analysis of coagulation factors (INR and/or PT, aPTT) and platelets must be conducted and the results reviewed, within 72 hours prior to performing the LP. In addition, neurological examination, vital signs and a review of AEs and concomitant medication should occur as part of the safety and tolerability evaluations on the day of LP.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory *or to a central laboratory* for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit *and* platelet count *are required;* differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells) *as per local practice*
- Serum chemistry panel: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, GGT, CPK, *as per local standard practice*
- Coagulation: INR *and/or PT*, aPTT
- Thyroid panel: thyroid-stimulating hormone
- Viral serology: HBsAg, HCV antibody
- Pregnancy test

  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.
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) *as per local standard practice* and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) *as per local standard practice, if indicated. Microscopic examination is only required in case of an abnormal dipstick result (for example, blood in urine or high protein value).*
- CSF: *RBC count, WBC count*, glucose, and protein

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Whole blood sample for determination of CAG repeat length in huntingtin gene (*HTT*) by direct DNA testing, for patient eligibility into the study
- Whole blood sample for clinical genotyping for DNA extraction to enable exploratory analysis and assay development with respect to genes related to *HTT* function and severity of the disease
- CSF samples to perform biomarker analysis, including mHTT and NfL, and other exploratory biomarkers related to HD, neurodegeneration, and inflammation

  Samples may also be used to support the development of additional biomarker assays to detect huntingtin protein or other proteins related to HD pathophysiology.
- Plasma samples, which may be used to evaluate biomarkers such as NfL and tau, as well as other exploratory blood-based biomarkers related to HD, neurodegeneration, and inflammation

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exception:

- Blood samples for clinical genotyping, CSF, and plasma samples collected for biomarker research will be destroyed no later than *10* years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.8 Neuroimaging Assessments

The MRI should be performed using a 3-Tesla (3T) magnet. If a 3T magnet is not available in reasonable proximity to the study site, in exceptional circumstance, with prior agreement from the Medical Monitor, a 1.5T magnet may be used. The acquisition parameters of each sequence, structure, and length of each MRI session, as well as image processing algorithms, will be outlined in a separate MRI manual. MRI scans will be managed by a central laboratory to monitor and ensure the integrity and quality of the acquired data. Local neuroradiologists will assess MRI-related study eligibility criteria at screening and for safety monitoring. For MRI scans at Months 3, 9, and 15, 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), or it can be scheduled to occur on the same day as the lumbar puncture (provided it is prior to the lumbar puncture). *If re-scanning at a post-screening visit is necessary due to a non-usable original scan, the re-scanning should be conducted more than 3 days after the lumbar puncture and within one week of the original scan, if at all possible. If the rescan falls outside of the study visit window, this should be reported as a minor deviation.*

4.5.9 Electrocardiograms

A single ECG recording will be obtained at screening.

The ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recording must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within *30 minutes* after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

The investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.5.10 Patient-Reported, Clinician-Reported, Observer-Reported, and Performance Outcomes

PRO, ClinRO, ObsRO, and PerfO data will be collected in clinic to document the change from baseline over time. Additionally PRO, ObsRO and PerfO data will be collected remotely. The assessments, translated into the local language as appropriate, will be completed in their entirety at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, questionnaires will be self-administered or administered by a trained rater (as appropriate). In-clinic data should be collected prior to the performance of the lumbar puncture procedure.

Patients, clinicians, and study companions (if participating) will use an electronic device to capture outcome data during clinic visits *and scoring of ClinRO and PerfO measures will be supervised during acquisition and entry into a tablet to ensure instructions are given and appropriately followed. Paper must not be used to capture clinical outcome data unless it is for performance outcome measures (e.g., SWR, SDMT, and MoCA). Performance measure outcomes must be completed in ink and not pencil.*

Study companions will use an electronic device to capture data remotely. Patients will use a smartphone or wrist-worn wearable to capture outcome data (see Section 4.5.11). The electronic device and/or instructions for completing the questionnaires electronically will be provided by site staff. Electronic device data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel. See Appendix 2 and Appendix 3 for a summary of timing and duration of each PRO, ClinRO, ObsRO, and PerfO assessment. Appendix 4 shows the order and approximate timing of assessments at each clinic visit.

4.5.10.1 Total Functional Capacity Scale

The TFC represents the investigator's assessment of the patient's capacity to perform a range of activities of basic daily living, including working, chores, managing finances, eating, dressing, and bathing. The 5-item assessment is based on a brief interview with the patient and the study companion (if available). The TFC score ranges from 0 to 13, with a higher score representing better functioning. The TFC takes approximately 10 minutes to administer and will be completed at clinic visits.

4.5.10.2 Total Motor Scale

The TMS score is the sum of the individual motor ratings obtained from administration of the 31-item motor assessment portion of the UHDRS by the investigator. The score ranges from 0 to 124, with a higher score representing more severe impairment. The TMS takes approximately 15 minutes to administer and will be completed at clinic visits.

4.5.10.3 Symbol Digit Modalities Test

The 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 pairs abstract symbols with specific numbers according to a translation key. The test measures the number of items correctly paired (maximum of 110 correct pairs) in 90 seconds. The SDMT will be administered at clinic visits and can be completed in under 5 minutes. It will also be administered remotely on the Roche HD mobile app (via electronic SDMT) and at clinic visits after clinical assessments are complete.

4.5.10.4 Stroop Word Reading Test

The SWR Test is a measure of processing and psychomotor speed. Patients are presented with a page of color names (i.e., "blue," "red," or "green") printed in black ink and are asked to read aloud as many words as possible within a given amount of time (in 45 seconds). The number of words read correctly is counted, with a higher score indicating better cognitive performance. The SWR will be administered at clinic visits and an electronic adaptation will be administered remotely on the Roche HD mobile app and at clinic visits after clinical assessments are complete.

4.5.10.5 Independence Scale

A patient's IS score is a measure of disease progression in functional disability. The IS evaluates a patient's degree of independence, as assessed by the investigator, and is a subscale of the UHDRS. The scale consists of 19 discrete levels ranging from 10 to 100 (by 5), in which a score of 100 indicates no special care is needed and a score of 10 indicates the patients is fed by tube and requires total bed care.

4.5.10.6 Clinical Global Impression—Severity and Clinical Global Impression–Change

The CGI-S is a single-item measure of current global severity and is completed by the clinician at clinic visits. Several variations exist, with minor adaptations made to ensure

the scale is specific to the study/disease area of interest. The CGI-S is assessed using an 11-point numeric rating scale (NRS), where higher scores indicate greater severity. The CGI-S can be completed in approximately 3 minutes.

The CGI-C is a single-item measure of change in global status (from baseline) and is completed by the clinician at postbaseline visits. As with the CGI-S, several variations exist. The CGI-C has seven response options: "very much worse," "much worse," "minimally worse," "no change," "minimally improved," "much improved," and "very much improved." The CGI-C can be completed in approximately 3 minutes. To assess the relevance of this change, a follow-up question with dichotomous response options ("yes" or "no") asks if the change has had a meaningful impact on the patient's wellbeing.

4.5.10.7 Patient Global Impression–Severity and Patient Global Impression–Change

The PGI-S is a single-item measure of current global severity and is completed by the patient at clinic visits. Several variations exist, with minor adaptations made to ensure the scale is specific to the study/disease area of interest. The PGI-S is assessed using an 11-point NRS, where higher scores indicate greater severity.

The PGI-C is a single-item measure of change in global status (from baseline) and is completed by the patient at postbaseline visits. As with the PGI-S, several variations exist. The PGI-C has seven response options: "very much worse," "much worse," "minimally worse," "no change," "minimally improved," "much improved," and "very much improved." To assess the relevance of this change, a follow-up question with dichotomous response options ("yes" or "no") asks if the change has had a meaningful impact on the patient's wellbeing.

4.5.10.8 Montreal Cognitive Assessment

The Montreal Cognitive Assessment 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. It will be used in this study to characterize patients at screening and takes approximately 10 minutes to administer.

4.5.10.9 WHO Disability Assessment Schedule 2.0

The WHODAS 2.0 (12-item version) assesses disability and aspects of HRQoL. It is intended for use in any disease population, and it is linked to the concepts in the International Classification of Functioning, Disability, and Health. The 12-item version contains 15 items, 12 of which produce a total score, with 3 additional questions administered to assess overall difficulty and activity impairment. All items are scored on a 0–4 Likert-type scale. The total raw score is converted onto a 0–100 point scale, where higher scores indicate greater difficulty. The WHODAS 2.0 will be completed by both the patient and study companion (if available, about the patient) at baseline and postbaseline clinic visits on an electronic device. In addition, it will be completed

monthly by the patient remotely on the Roche HD mobile app and by the study companion remotely on an electronic device. The WHODAS 2.0 will take approximately 10 minutes to complete.

4.5.10.10 Work Productivity and Activity Impairment

The WPAI contains 6 items assessing the impact of disease on employment status (yes/no), hours missed due to disease, hours missed due to other reasons, hours worked, and impact on productivity and on daily activities (both using an 11-point NRS, where higher scores indicate greater impact). The WPAI takes approximately 5 minutes to complete. The WPAI will be completed by the patient and study companion (if available, about the patient and him/herself). It will be completed monthly by the patient remotely on the Roche HD mobile app and by the study companion remotely on an electronic device.

4.5.10.11 Apathy Evaluation Scale

The AES is an 18-item assessment of apathy, including overt behavior, cognitive aspects of motivation, and emotional responsivity. Each item is scored on a 4-point Likert scale, from 1 ("Not at all") to 4 ("A lot"). A total score is created by summing the 18 items (scores range from 18 to 72; 3 items are reverse scored), with higher scores indicating greater apathy. The AES takes approximately 10 minutes to complete and will be completed by the patient and study companion (if available) at clinic visits.

4.5.10.12 Neuro-Qol Cognition Function Short Form, Version 2

The Neuro-Qol Cognition Function Short Form contains 8 items (including "trouble concentrating" and difficulty "learning new tasks or instructions"), each assessed using a 5-point Likert scale, where lower scores indicate greater difficulty (4 items) or greater frequency (4 items). The raw sum score is converted to a T-score distribution (mean = 50, SD = 10). The Neuro-Qol Cognition Function Short Form takes approximately 5 minutes to complete and will be completed by the patient at clinic visits.

4.5.10.13 Huntington's Disease—Speaking Difficulty Item

The HD-SDI is a single question assessing difficulty speaking over the past 7 days. It is assessed using a 5-point Likert scale, where higher scores indicate a greater frequency of difficulty. The HD-SDI can be completed in less than 1 minute and will be completed by the patient weekly remotely on the Roche HD mobile app.

4.5.10.14 Symptoms of Major Depressive Disorder Scale

The SMDDS is a newly developed, valid, and reliable self-report assessment of depression (McCarrier et al. 2016). It contains 16 items, measuring concepts such as sadness, irritability, worry, and sleep disturbance. Each item is assessed on a 5-point Likert scale, from "Not at all" to "Extremely" (9 items) and from "Never" to "Always" (7 items). Item scores from 15 of the items (the least severe of the two eating items is dropped) are summed to create a 0–60 score, where higher scores indicate more severe

depressive symptomatology. The SMDDS takes approximately 10 minutes to complete and will be completed by the patient at clinic visits.

4.5.10.15 EuroQol 5-Dimension, 5-Level Questionnaire

The EQ-5D-5L is a validated self-report health status questionnaire used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a 5-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) that measures health state. Published weighting systems allow for creation of a single composite score of the patient's health status (Index score) from the 5-item scores (i.e., does not include the VAS). The EQ-5D-5L takes approximately 5 minutes to complete. The Index score will be used in this study for informing pharmacoeconomic evaluations. The VAS score will be used to assess HRQoL. The EQ-5D-5L will be completed both by the patient (about him/herself) and by the study companion (if available, about him/herself) at baseline and postbaseline clinic visits on an electronic device. In addition, it will be completed weekly by the patient remotely on the Roche HD mobile app and weekly by the study companion remotely on an electronic device.

4.5.10.16 Columbia-Suicide Severity Rating Scale

The C-SSRS is a structured tool to assess suicidal ideation and behavior *and should be performed by a study qualified physician.* Four constructs are measured: severity of ideation, intensity of ideation, behavior, and lethality of actual suicide attempts. Binary (yes/no) data are collected for 10 categories, and composite endpoints based on the categories are followed over time to monitor patient safety (Posner et al. 2011). It maps to the Columbia-Classification Algorithm for Suicide Assessment and meets the criteria listed in the U.S. Food and Drug Administration (FDA) draft guidance for assessment of suicidality in clinical trials (FDA 2012). The C-SSRS will be used to assess eligibility for the study (full version at *screening*, requiring approximately 20 minutes to administer) and to monitor the patients *from baseline* 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).

The patient should be referred for immediate psychiatric evaluation in any event of suspected active suicidal intent, significant suicidal behavior, or clinical finding suggesting that the patient is dangerous to himself or herself.

4.5.11 Roche HD Mobile App (Smartphone and Wrist-Worn Wearable)

Each patient will receive a preconfigured smartphone and wrist-worn wearable with installed software for the Roche HD Mobile App assessments. Patients will use the devices and software to continuously assess motor and non-motor symptoms, as well as activities associated with routine daily living. Additional details are available in the "Roche HD Mobile App (Smartphone) Manual."

4.5.11.1 Roche HD Mobile App Remote Monitoring

Patients will be provided devices and trained on their use during screening. During the study, patients will be instructed to conduct an "active test" every day at approximately the same time (ideally in the morning, after breakfast). The active test consists of a short, preconfigured schedule of tasks that assess motor symptoms (upper and lower body movements, upper limb dexterity, voice) and non-motor symptoms (processing speed/voice). For "passive monitoring," patients will be instructed to carry the smartphone and wear the wrist-worn wearable throughout the day as they go about their daily routine.

Device sensor data will be recorded continuously, throughout the active tests and passive monitoring. Sound will only be recorded during selected active test tasks. Data are encrypted and uploaded to secure servers when the smartphone is connected to WiFi.

Patients will be asked to charge the devices overnight. If patients have a WiFi network at home, they will be encouraged to connect their smartphone to enable data transfer. If no WiFi network is available, the sensor data will be transferred during site visits or after the devices have been returned.

4.5.11.2 Roche HD Mobile App In-Clinic Assessments

Patients will be instructed to bring the smartphone and wearable to every clinic visit to check adherence and technical status of the devices. At clinic visits, patients will be asked to conduct the "active test" tasks under the supervision of trained site staff.

The smartphone and wearable must be returned to the clinic in cases where the patient does not meet eligibility criteria, at the end of the study, and upon early termination. At the end of the study or at the time when the patient has completed the study, patients will be asked to complete a pen-and-paper satisfaction survey about their experience using the smartphone and wrist-worn wearable during the study.

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with adverse events or disease progression

- To increase knowledge and understanding of disease biology
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board (IRB) or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to target or diseases:

- Leftover CSF and plasma biomarker samples, and any derivatives thereof (e.g., proteins, peptides)
- Blood (for RBR DNA and RBR RNA) and serum samples collected at baseline and at 15-month visits

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.12.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.12.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. However, if RBR specimens have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study BN40422

does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study BN40422.

4.5.12.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study may be replaced, particularly if withdrawal is early-on (e.g., within first 6 months).

4.6.2 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Patient enrollment is unsatisfactory
- Program termination

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.3 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice or any other pertinent local law or guideline
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

After informed consent has been obtained and after the initiation of study procedures, both adverse events and serious adverse events related to a study procedure will be reported until the last clinic visit.

5.2 SAFETY PARAMETERS

Since no study medication will be given to the patients, safety assessments will consist of monitoring and recording adverse events, including serious adverse events related to study procedures.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution.

In the case of this non-drug study, any untoward medical occurrence in a clinical investigation subject that is related to a protocol-mandated intervention is considered an adverse event (e.g., invasive procedures such as *lumbar punctures*).

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.8)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a pre-defined grading criteria (see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions)

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

In the case of this non-drug study, this section is not applicable.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that adverse events related to a protocol-mandated intervention (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality to study procedure (see Section 5.3.4).

In the case of this non-drug study, investigators and patients are reminded to report any adverse reactions (for which they suspect a causal role of a medicinal product [e.g., concomitant medication]) that come to their attention, either to the marketing authorization holder of the suspected medicinal product or to the concerned competent authorities, via the national spontaneous reporting system.

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events related to a protocol-mandated intervention at each patient contact. All adverse events related to a protocol-mandated intervention, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF *until the patient's last visit or withdrawal*.

After informed consent has been obtained, serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as *lumbar punctures*) should be reported (see Sections 5.4–5.6 for instructions for reporting serious adverse events) until the patient's last visit or withdrawal.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 1 provides guidance for assessing adverse event severity.

Table 1 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to a study procedure, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study procedure
- Known association of the event with the procedure under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–procedure-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events related to a protocol-mandated intervention on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events related to a protocol-mandated intervention based on signs and symptoms should be nullified and replaced by one adverse event related to a protocol-mandated intervention report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events related to a protocol-mandated intervention (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All adverse events related to a protocol-mandated intervention should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event related to a protocol-mandated intervention is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event related to a protocol-mandated intervention is one that resolves between patient evaluation timepoints and subsequently recurs. Each

recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event related to a protocol-mandated intervention.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Liver Function Tests

In the case of this non-drug study, this section is not applicable.

5.3.5.6 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study procedure, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

5.3.5.7 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.8 Hospitalization or Prolonged Hospitalization

Any adverse event related to a protocol-mandated intervention that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.6 Patient-Reported or Observer-Reported Outcome Data

Adverse event reports will not be derived from PRO or ObsRO data by the Sponsor, and safety analyses will not be performed using PRO or ObsRO data. Sites are not expected to review the PRO or ObsRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in this non-drug study. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event:

- Serious adverse events caused by a protocol-mandated intervention (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], *M.D., Ph.D.* (Primary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Medical Monitor: [redacted], *M.D., M.Sc.* (Secondary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events

After informed consent has been obtained, serious adverse events (see Section 5.2.2) caused by a protocol-mandated intervention should be reported until the patient's last visit or withdrawal. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system. In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study. The investigator should then withdraw the patient from the study in the case of pregnancy. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient and make referral to appropriate medical professional.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event related to a protocol-mandated intervention until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient’s medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

5.5.2 Sponsor Follow-Up

For serious adverse events related to a protocol-mandated intervention and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as Section 5.3.1) if the event is believed to be related to a protocol-mandated intervention. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events related to a protocol-mandated intervention against cumulative procedure experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATION AND ANALYSIS PLAN

This is a non-interventional study and is exploratory in nature. As such, there is no predefined hypothesis testing, and all analyses will be regarded as exploratory. Where applicable, parameter estimates will be reported together with 90% CI. P-values may still be reported.

Basic assumptions of the proposed analyses will be checked, and data transformation (e.g., logarithm transformation) or other analyses could be carried out, if appropriate.

The fact that patients in this study are matched to the OLE study (Clinicaltrials.gov Identifier NCT03342053) may offer the future opportunity to compare the current observational study against the OLE study. Details of this analysis are not in the scope of this protocol and may be described in a separate document not related to Study BN40422.

6.1 DETERMINATION OF SAMPLE SIZE

In this study, up to approximately 100 patients are expected to be enrolled across approximately 20 sites. This number is driven by the objective of having a 2:1 match, based on baseline characteristics, to patients from the OLE study.

6.2 ANALYSIS POPULATION

All patients who fulfill the entry criteria at screening and have been enrolled in the study will be included in the analysis.

6.3 PRIMARY ANALYSES

The primary objective of this study is to investigate whether baseline CSF mHTT is a predictor of the change from baseline to 15 months for the following variables:

- Clinical endpoints (cUHDRS, TFC, TMS, SDMT, SWR, and IS)
- CSF and blood biomarkers
- Brain imaging (MRI)

Initially, a linear model will be used to evaluate the association between each response variable (e.g., change from baseline to 15 months in cUHDRS) and baseline CSF mHTT without adjustment for any baseline characteristics.

The same model will then be considered again, adjusting for baseline level of the response variable (e.g., baseline cUHDRS), baseline CSF mHTT levels, CAG, and baseline CAP (the latter defined as the product of age at baseline by [CAG—33.66] (Zhang et al. 2011). A sensitivity analysis to evaluate the impact of additional baseline characteristics (e.g., gender, education level) may be performed.

Other approaches may be used in the case of severe multicollinearity, which would result in model instability.

6.4 SECONDARY ANALYSES

The secondary objective for this study is to investigate the within-patient change from baseline in CSF mHTT levels and the association between changes from baseline in CSF mHTT levels at 3, 9, and 15 months and changes in clinical measures (cUHDRS, TFC, TMS, SDMT, SWR, and IS), biomarkers of neuronal injury, and brain atrophy endpoints.

Initially, a linear model will be used to evaluate the association between each response variable (e.g., change from baseline to 15 months in CSF NfL levels) and the change in CSF mHTT level, without adjustment for any baseline characteristics. A similar model will then be considered, adjusting for baseline level of the response variable, CAG, and baseline CAP. A sensitivity analysis to evaluate the impact of additional baseline characteristics (e.g., baseline mHTT, gender, education level) may be performed.

6.5 SAFETY ANALYSES

The safety analysis population will consist of all patients who underwent study-specific procedures. Given the non-drug nature of this study, limited safety analyses will be reported.

The number of unique patients who experience and report an adverse event, each adverse event, and the number of adverse events themselves will be tabulated by MedDRA System Organ Class and Preferred Term. Adverse events will also be summarized by severity (see Section 5.3.3).

Laboratory absolute values at screening will be listed and summarized descriptively. Values outside the normal range will be listed and summarized.

6.6 EXPLORATORY ANALYSES

The association between standard clinical endpoints and Roche HD mobile app versions (e.g., SWR and eSWR, SDMT, and eSDMT) will be evaluated.

Finally, longitudinal changes over time will be described, adjusted on baseline characteristics, for most variables. Signal-to-noise ratio, defined as the change in the endpoint divided by the corresponding variability, will be derived where applicable.

Additional exploratory analyses may be performed as appropriate. Data from this study may be combined with data from other studies to inform disease and causal models.

6.7 INTERIM ANALYSES

The Sponsor may choose to conduct one or more interim analyses. The decision to conduct such an optional interim analysis and the timing of the analysis will be documented in the Sponsor's study master file prior to the conduct of the interim analysis.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data, electronic data from clinic visits (see Section 7.3), and electronic data obtained from the Roche HD mobile app (see Section 7.4) will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED, CLINICIAN-REPORTED, OBSERVER-REPORTED, AND PERFORMANCE OUTCOME DATA

Patients, clinicians, and study companions (if available) will use an electronic device to capture PRO, ClinRO, ObsRO, and PerfO data, as applicable. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure vendor web portal. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor’s standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format on a compact disc.

7.4 ELECTRONIC DATA OBTAINED BY THE ROCHE HD MOBILE APP

During “Active Tests” and “Passive Monitoring,” the smartphone and wrist-worn wearable record movement and location data. Data on the technical status of the devices is also recorded. Patients can choose to pause location data recording.

No patient identifiable information is stored on the devices. For selected "Active Test" tasks, touch and sound is also recorded. Video is not recorded.

HD Mobile App data are encrypted and uploaded to secure servers whenever the smartphone is connected to WiFi. All HD Mobile App data will be managed by the Sponsor who will monitor and ensure the integrity and quality of the acquired data. This includes, but is not limited, to the analysis of sensor data together with protocol-specified assessments and activities associated with routine daily living.

7.5 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.7.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.6 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.7 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study, including eCRFs, electronic PRO, ClinRO, ObsRO (if applicable), and PerfO data, Informed Consent Forms, and laboratory test results, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form, Mobile Nursing Informed Consent Form, or Study Companion ICF, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. *If a study companion is available, the study companion must also sign and date a consent form prior to participation in the study.* The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker and Roche HD Mobile App analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate. *Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. Linking of data will be facilitated by the HDID number (see Section 4.5.3). The HDID is not specific to Study BN40422 but is a unique coded identifier for persons participating in studies in HD. This HDID will stay the same for a person throughout all trials. The use of the unique identifier will assure that people are only enrolled once in large observational studies like Enroll-HD, REGISTRY, COHORT, PREDICT, and TRACK-HD and will also allow approved comparison and combination of data between studies. The HDID is a 9 digit number created by a secure one-way algorithm, based on unchanging information (date of birth, birth name, place of birth and mother's maiden name). The identifying data are used for the split second*

needed by the algorithm needed to generate the HDID and are never stored electronically on the web portal or in the study database. For patients without a preexisting HDID number in the source notes, the investigator should store the original data and the newly generated HDID in the patient's source documents and in the investigator file. The HDID can be generated within the web portals of the observational studies or in the specially defined portal for the HDID generation at: https://hdid.enroll-hd.org. In addition, redacted clinical study reports and other summary reports will be provided upon request.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor and contract research organization will provide clinical operations management, and the Sponsor will provide data management and medical monitoring.

Approximately 20 sites globally will participate to enroll up to approximately 100 patients. Additional countries and sites may be added or substituted if underperforming. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, neuroimaging, electrophysiological assessment, and biomarker analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the physician must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the physician.

In accordance with standard editorial and ethical practice, Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating physician will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of the Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate Sponsor's personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1 Schedule of Activities

	Screening Period	Observational Period						Follow-Up (or Early Termination) [a]
Study Day	Days −29 to −2	Day −1 to 1 (Baseline)	Day 85 (Month 3)	Day 169 (Month 6)	Day 253 (Month 9)	Day 337 (Month 12)	Day 421 (Month 15)	
Visit Window (days)			±7	±10	±7	±10	±7	
Type of visit	CL	CL	CL	PH	CL	PH	CL	CL or PH
Capacity to consent assessment and informed consent [b]	x							
Demographic data	x							
Medical history and baseline conditions	x	x						
Vital signs [c]	x	x	x		x		x	
Height [d]	x							
Weight [e]	x	x	x		x		x	
Physical examination [f]	x	x	x		x		x	
Neurological examination [g]	x	x	x		x		x	
CAG repeat length [h]	x							
Chemistry, hematology, urinalysis [i]	x	x	x		x		x	
Viral serology [j]	x							
Pregnancy test [k]	x		x		x		x	
Coagulation [l]	x	x	x		x		x	
Thyroid panel	x							
ECG (12-lead)	x							

Appendix 1 Schedule of Activities (cont.)

	Screening Period	Observational Period						Follow-Up (or Early Termination) [a]
Study Day	Days −29 to −2	Day −1 to 1 (Baseline)	Day 85 (Month 3)	Day 169 (Month 6)	Day 253 (Month 9)	Day 337 (Month 12)	Day 421 (Month 15)	
Visit Window (days)			±7	±10	±7	±10	±7	
Type of visit	CL	CL	CL	PH	CL	PH	CL	CL or PH
Lumbar puncture and CSF sample [m]		x	x		x		x	
MRI [n]	x		x		x		x	
ClinROs, ObsROs, PerfOs, and PROs conducted in clinic [o]	x	x	x		x		x	
C-SSRS [p]	x	x	x		x		x	
Roche HD mobile app equipment training	x							
Roche HD mobile app in-clinic assessment [q]	x	x	x		x		x	
Roche HD mobile app remote data collection [q]	Continuous remote data collection							
Whole blood sample for clinical genotyping		x						
Plasma samples for biomarkers		x	x		x		x	
RBR DNA (optional) [r]		x						
RBR RNA (optional) [r]		x					x	
RBR serum (optional) [r]		x					x	
Change in medical information since last visit [s]			x	x	x	x	x	

Appendix 1 Schedule of Activities (cont.)

	Screening Period	Observational Period						
Study Day	Days −29 to −2	Day −1 to 1 (Baseline)	Day 85 (Month 3)	Day 169 (Month 6)	Day 253 (Month 9)	Day 337 (Month 12)	Day 421 (Month 15)	Follow-Up (or Early Termination) [a]
Visit Window (days)			±7	±10	±7	±10	±7	
Type of visit	CL	CL	CL	PH	CL	PH	CL	CL or PH
Adverse events [t]	x	x	x	x	x	x	x	x
Concomitant medications [u]	x	x	x	x	x	x	x	x

CL = clinic; ClinROs = clinician-reported outcomes; CSF = cerebrospinal fluid; C-SSRS = Columbia-Suicide Severity Rating Scale; eCRF = electronic Case Report Form; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HD = Huntington disease; MRI = magnetic resonance imaging; ObsROs = observer-reported outcomes; PerfOs = performance outcomes; PH = phone; PROs = patient-reported outcomes; RBR = Research Biosample Repository.

[a] Post-observational follow-up visit will take place 2 weeks after end of observational period and will occur via clinic visit or by telephone call. Early termination visit should occur via clinic visit where possible.

[b] Capacity to consent assessment (patient only) and informed consent (for both the patient and study companion [if available]).must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before baseline visit. *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, central CAG repeat length testing from the initial screening 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.*

[c] Includes measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position after resting for approximately 5 minutes, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF.

[d] Height in meters.

[e] Weight in kilograms.

[f] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. 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 associated with a study procedure should be recorded as adverse events on the Adverse Event eCFR.

Appendix 1 Schedule of Activities (cont.)

[g] Neurological examination includes assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function and reflexes. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities associated with a study procedure should be recorded as adverse events on the Adverse Event eCRF.

[h] At screening, a mandatory whole blood sample will be obtained for DNA extraction for analysis of CAG repeat length.

[i] Screening laboratory assessments include hematology (WBC count, RBC count, hemoglobin, hematocrit*, platelet count, all required;* differential count including neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells *as per local practice*); serum chemistry (sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, ALP, ALT, AST, uric acid, GGT, CPK*, as per local standard practice*); and urinalysis (dipstick including pH, specific gravity, glucose, protein, ketones, blood and microscopic examination, including sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria*, as per local standard practice*). *Microscopic examination is only required in case of an abnormal dipstick result (for example, blood in urine or high protein value).*

[j] Viral serology: HBsAg and HCV antibody.

[k] 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.

[l] Coagulation: INR *and/or PT*, aPTT.

[m] Patients will have CSF collected at baseline and at Months 3, 9, and 15 *for the assessment of RBC count, WBC count, glucose, and protein.* Prior to performing each scheduled lumbar puncture, local laboratory analysis of coagulation factors (INR *and/or PT*, aPTT) and platelets must be conducted and results reviewed. Collection for these local labs 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 08:00 and 12:00 hours) to minimize potential diurnal variation of CSF parameters. CSF fluid (20 mL) is to be collected for analyses using a standard lumbar puncture collection kit. If there are difficulties in collecting 20 mL of CSF fluid, a minimum of 15 mL should be collected. A 24G Whitacre (atraumatic) needle should be used. Depending on institutional guidelines, local anesthesia may be used for the procedure. Sedation *is not allowed*. 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. In the case of a failed CSF collection procedure due to inadequate establishment of access to the IT space, a second attempt may occur up to 14 days after the originally attempt. For this additional visit, local laboratory analysis of coagulation factors (INR and/or PT, aPTT) and platelets must be conducted and the results reviewed, within 72 hours prior to performing the LP. In addition, neurological examination, vital signs and a review of AEs and concomitant medication should occur as part of the safety and tolerability evaluations on the day of LP.*

Appendix 1 Schedule of Activities (cont.)

[n] For MRI scans at Months 3, 9, and 15, 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), or it can be scheduled to occur on the same day as the lumbar puncture (provided it is prior to the lumbar puncture). *If re-scanning at a post-screening visit is necessary due to a non-usable original scan, the re-scanning should be conducted more than 3 days after the lumbar puncture and within one week of the original scan, if at all possible. If the rescan falls outside of the study visit window, this should be reported as a minor deviation.*

[o] Questionnaires will be self-administered or administered by trained rater (as appropriate) at screening and at each clinic visit prior to the lumbar puncture. See Appendix 2 and Appendix 3 for details.

[p] The C-SSRS must be administered on scheduled timepoints and may be performed at other timepoints per investigator's discretion.

[q] The Roche HD mobile app includes a short, preconfigured schedule of daily tasks ("active test") that assess motor symptoms (upper and lower body movements, upper limb dexterity, voice) and non-motor symptoms (processing speed/voice). In addition, passive monitoring data is collected. During the in-clinic assessment, the entire suite of active tests should be performed.

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

[s] At the time of each follow-up physical examination, 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.

[t] After informed consent has been obtained, adverse events caused by a protocol-mandated intervention should be reported until the patient's last visit or withdrawal. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to protocol-related procedures until a final outcome can be reported.

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

Appendix 2 Clinician-Reported Outcomes

Assessment	Name	Items	Concepts	Approx. Duration	Timing
CGI-C	Clinical Global Impression–Change	1	Overall change in patient status	3 min	Postbaseline clinic visits
CGI-S	Clinical Global Impression–Severity	1	Overall severity of patient status	3 min	Baseline and postbaseline clinic visits
C-SSRS	Columbia-Suicide Severity Scale	5	Suicidal ideation and behavior	20 min full version; 5 min follow-up version	Full version at screening in clinic; follow-up version at baseline and all postbaseline clinic visits
TFC	Total Functional Capacity Scale	5	Overall function	10 min	All clinic visits
TMS	Total Motor Score	31	Motor function	15 min	All clinic visits
IS	Independence Scale	1	Functional disability	3 min	All clinic visits

Appendix 3 Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing
AES	Apathy Evaluation Scale	18	Apathy	10	PRO + ObsRO	Baseline and postbaseline clinic visits
Roche HD mobile app	Roche HD mobile app with daily Active Test and Passive Monitoring	NA	Tasks ("active test") that assess motor symptoms (upper and lower body movements, upper limb dexterity, voice) and non-motor symptoms (processing speed/voice); continuous passive monitoring	4–7	Sensor data, PRO, PerfO	Daily + at clinic visits on Roche HD mobile app
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire	6	Health utilities	5	PRO + ObsRO	Baseline and postbaseline clinic visits and weekly on Roche HD mobile app and electronic device
HD-SDI	Huntington's Disease–Speaking Difficulty Item	1	Speech	1	PRO	Weekly on Roche HD mobile app
MoCA	Montreal Cognitive Assessment	11	Overall cognitive status	10	PerfO	Screening
Neuro-Qol Cog Func	Neuro-Qol Cognitive Function Short Form	8	Cognition	5	PRO	Baseline and postbaseline clinic visits

Appendix 3 Patient-Reported, Observer-Reported, and Performance Outcomes and Roche HD Mobile Application (cont.)

Assessment	Name	Items	Concepts	Approx. Duration (min)	PRO, ObsRO, PerfO, Behavior	Timing
PGI-C	Patient Global Impression–Change	1	Overall change in patient status	3	PRO	Postbaseline clinic visits
PGI-S	Patient Global Impression–Severity	1	Overall severity of patient status	3	PRO	Baseline and postbaseline clinic visits
SDMT/ eSDMT	Symbol Digit Modalities Test	Max no. in 90 sec	Cognitive	5	PerfO	All clinic visits (SDMT/eSDMT); weekly on Roche HD mobile app (eSDMT)
SMDDS	Symptoms of Major Depressive Disorder Scale	16	Depression, anxiety, irritability, sleep	10	PRO	Baseline and postbaseline clinic visits
SWR/eSWR	Stroop Word Reading Test	Max no. in 45 sec	Cognitive	5	PerfO	All clinic visits (SWR/eSWR); weekly on Roche HD mobile app (eSWR)
WHODAS 2.0	WHO Disability Assessment Schedule 2.0 (12-item scale)	15	Broad coverage	10	PRO + ObsRO	Baseline and postbaseline clinic visits and monthly on Roche HD mobile app and electronic device
WPAI	Work Productivity and Activity Impairment	6	Work productivity	5	PRO + ObsRO	Monthly on Roche HD mobile app and electronic device

ADL = activities of daily living; min = minute; ObsRO = observer-reported outcome; PRO = patient-reported outcome; PerfO = performance outcome.

Appendix 4 Order and Approximate Timing of Assessments at Clinic Visits

Block	Assessments	Total Duration (minutes)	*Site Staff Responsible*
1	Total Functional Capacity Scale[1] Independence Scale[1] Total Motor Score[1] Symbol Digit Modalities Test[2] Stroop Word Reading Test[2] Montreal Cognitive Assessment (screening only) [2] Columbia-Suicide Severity Rating Scale[1] Clinical Global Impression–Severity[1] Clinical Global Impression–Change (postbaseline visits only)[1]	~45–60	*1: Qualified study physician* *2: Qualified study personnel*
Break		20	
2	Apathy Evaluation Scale Neuro-Qol Cognition Function Short Form WHO Disability Assessment Schedule 2.0 EuroQol 5-Dimension, 5-Level Questionnaire	~30	*Qualified study personnel*
Break		10	
3	Symptoms of Major Depressive Disorder Scale Patient Global Impression–Severity Patient Global Impression–Change (postbaseline visits only)	~15	*Qualified study personnel*
Break		10	
4	Roche HD mobile application	~20	*Qualified study personnel*

Note: Not all assessments will be completed at all visits. Consult Appendix 3 for timing.