

# Design of a prospective, longitudinal, natural history study in Huntington's disease (HD)



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## Summary

mHTT is a protein thought to cause HD, and can be measured in collected spinal fluid.<sup>1</sup> This study will provide valuable information on the relationship between levels of mHTT and a wide range of assessments that measure HD-related symptoms and their impact on daily function. Spinal fluid will be collected when patients begin the study and at 3, 9 and 15 months. Progression of the disease will be followed closely over 15 months and the results are expected to aid interpretation of clinical trials.

## Study Objectives

- Primary** To examine the predictive value of baseline CSF mHTT levels on measures of HD progression assessed by measuring change from baseline at 3, 9 and 15 months in the following endpoints:
- clinical: cUHDRS, TFC, TMS, SDMT, SWR Test and IS.
  - biomarkers of neuronal injury:<sup>1</sup> CSF NfL, Tau.
  - brain atrophy (by MRI); decline in whole brain volume, caudate volume.
- Secondary** To investigate the temporal profile of longitudinal changes in CSF mHTT levels within the patient, and the association of these changes with clinical measures, markers of neuronal injury and clinical outcomes from the primary endpoint at baseline, and 3, 9 and 15 months.
- Exploratory**
- To examine the association of the Roche HD app with standard HD clinical assessments, biomarkers and patient-reported outcomes.
  - To examine the association of potential prognostic biomarkers and genetic modifiers with HD disease status and disease progression.

As no medication will be given to the patients during the study, safety assessments will consist of monitoring and recording AEs and SAEs related to study procedures.

## Patient Eligibility Criteria

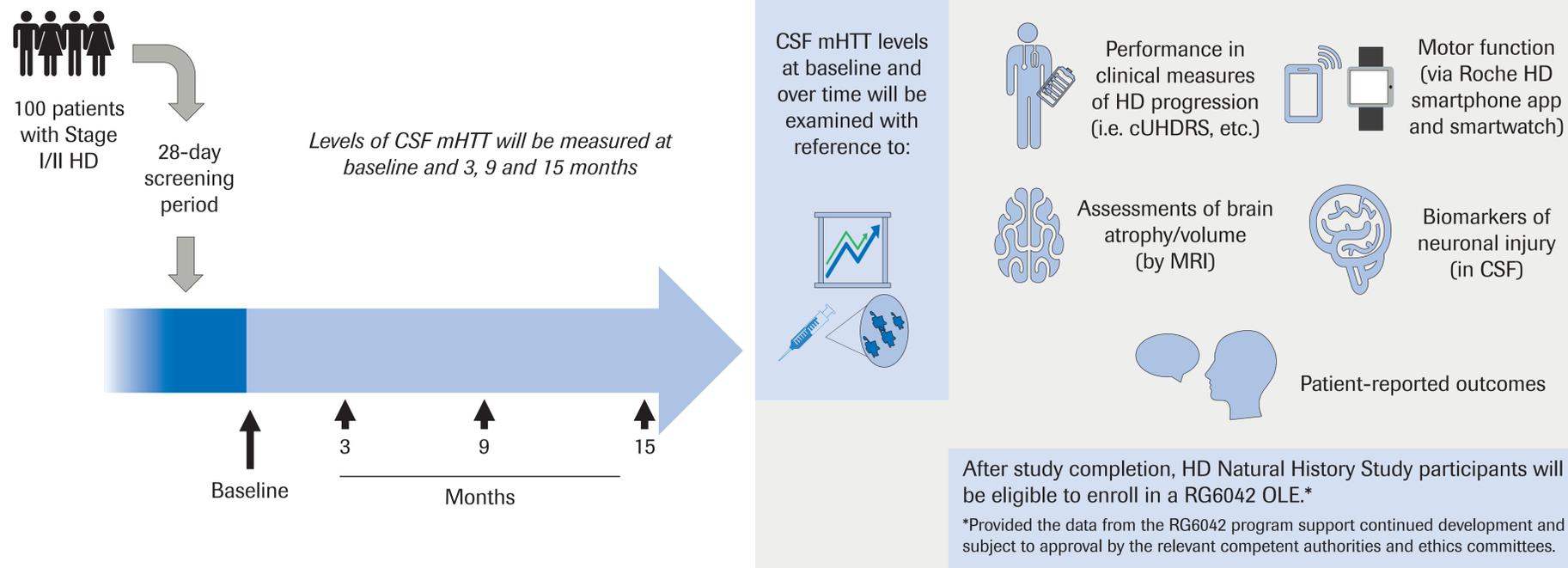
### Select Inclusion Criteria

- Aged 25–65 years.
- Early manifest, Stage I or Stage II HD (defined as TFC of 7–13, inclusive).
- Genetically confirmed disease (CAG repeat length  $\geq 36$  in *HTT* by direct DNA testing).
- Be capable of undergoing MRI scans, lumbar puncture and blood draws.
- Stable medical, psychiatric and neurologic status for 12 weeks prior to screening and at the time of enrollment.

### Select Exclusion Criteria

- 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 that required hospital visit and/or change in level of care within 12 months prior to screening.
- Current active psychosis, confusional state or violent behaviour.
- Treatment with an investigational drug within 30 days prior to screening or 5 half-lives of the investigational drug, whichever is longer.
- Any serious medical condition or clinically significant laboratory, vital sign, or electrocardiogram abnormalities at screening that, precludes the patient's safe participation in and completion of the study.
- Antiplatelet or anticoagulant therapy within the 14 days prior to screening.
- History of bleeding diathesis or coagulopathy.
- History of gene therapy or cell transplantation or any other experimental brain surgery.
- Presence of implanted shunt for the drainage of CSF or an implanted CNS catheter.

## HD Natural History Study Design



## Conclusions

This study will provide valuable information on the relationship between putative biomarkers, including CSF mHTT, and clinical outcomes in HD. It is expected to aid interpretation of current and future clinical trials.

## Abbreviations

AE, adverse event; CNS, central nervous system; CSF, cerebrospinal fluid; cUHDRS, composite Unified Huntington's Disease Rating Scale; HD, Huntington's disease; IS, independence scale; *htt*, huntingtin gene; mHTT, mutant huntingtin protein; MRI, magnetic resonance imaging; NfL, neurofilament light chain; OLE, open-label extension; SAE, serious adverse event; SDMT, Symbol Digit Modalities Test; SWR, Stroop Word Reading; TFC, Total Functional Capacity; TMS, Total Motor Score.

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## References

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