Huntington’s Disease Clinical Trials Corner: June 2019

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Abstract. In this edition of the Huntington’s Disease Clinical Trials Corner we expand on the HD-DBS and on the TRIHEP3 trials, and we list all currently registered and ongoing clinical trials in Huntington’s disease.

Keywords: Huntington disease, clinical trials

INTRODUCTION

The Huntington’s Disease Clinical Trials Corner is a regular section devoted to highlighting ongoing and recently completed clinical trials in Huntington’s disease (HD). Clinical trials previously reviewed by the Huntington’s Disease Clinical Trials Corner are listed in Table 1.

In this edition, we highlight the HD-DBS trial (NCT02535884)(1), and the TRIHEP3 trial (NCT02453061)(2). We tabulate all currently registered and ongoing clinical trials in Tables 2 to 4. For further details on the methodology used, please refer to the first edition of Huntington’s Disease Clinical Trials Corner(3).

If you would like to draw attention to specific trials, please feel free to email us at: f.rodrigues@ucl.ac.uk and e.wild@ucl.ac.uk.

In addition to the above, the published report of the IONIS-HTT\textsubscript{Rx} trial (NCT02519036) is worthy of mention. The paper reports that monthly intrathecal IONIS-HTT\textsubscript{Rx}/RG6042 – an antisense oligonucleotide that signals wild-type and mutant huntingtin pre-mRNA to be degraded by RNase H1 – was safe and well-tolerated, and produced dose-dependent reductions in cerebrospinal fluid mutant huntingtin in early HD patients (4). This is an interesting signal but caution should be exercised as to whether this reduction translates into a clinically significant benefit for people with HD. Further investigation into the effects of this drug are expected from the currently ongoing phase 3 GENERATION-HD1 trial (NCT03761849)(5) and associated studies (6–10). These studies will help us better characterize the safety profile of this compound, define the most efficient posology, and understand if it is associated with a clinically relevant benefit, and towards which disease domain.

ONGOING CLINICAL TRIALS

A list of all ongoing clinical trials is given in Tables 2–4.

HD-DBS (NCT02535884)

Study title
Deep Brain Stimulation (DBS) of the Globus Pallidus (GP) in Huntington’s Disease (HD) (HD-DBS)(1).
Table 1
Clinical trials previously reviewed by the Huntington’s Disease Clinical Trials Corner

| Trial name               | Intervention          | Edition               |
|-------------------------|-----------------------|-----------------------|
| NCT02519036             | IONIS-HTTRx           | September 2017(3)     |
| NCT02215616             | LEGATO-HD             | Laquinimod            |
| NCT02197130             | Amaryllis             | PF-02545920           |
| NCT02006472             | PRIDE-HD              | Pridopidine           |
| NCT03225833             | PRECISION-HD1         | WVE-120101            |
| NCT03225846             | PRECISION-HD2         | WVE-120102            |
| NCT01795859             | FIRST-HD              | Deutetrabenazine      |
| NCT02481674             | SIGNAL                | VX15/2503             |
| NCT03761849             | GENERATION-HD1        | RG6042*               |
| NCT0344601              | PACE-HD               | Physical activity     |
| NCT02535884             | HD-DBS                | Deep brain stimulation|
| NCT02453061             | TRIHEP3               | Triheptanoin          |

*IONIS-HTTRx and RG6042 refer to the same molecule.

Intervention

DBS of the GP (11) with Medtronic ACTIVA® PC neurostimulator (Model 37601).

Description

The HD-DBS trial, sponsored by Heinrich-Heine University, aims to evaluate the efficacy and safety of pallidal DBS in adults (18 or more years of age) with manifest HD (i.e. clinically symptomatic and genetically confirmed [CAG ≥36]) and moderate disease stage (defined by the investigators as an Unified Huntington’s Disease Rating Scale [UHDRS] total motor score [TMS] ≥30), chorea (UHDRS chorea score ≥10) and a Mattis Dementia Rating Scale ≥120, comparing with sham stimulation, for motor function.

People with juvenile or predominantly bradykinetic forms of the disease, postural instability, unstable medication in the 6 weeks previous to inclusion, unstable medical or psychiatric comorbidities, coagulopathies and/or increased risk of haemorrhage, implanted pacemaker or defibrillator, pregnant or breast-feeding are not eligible for this study.

This trial is an international, multi-centre, randomized, sham-controlled, double-blind, parallel study. It has 2 study arms: the stimulation group, where participants have stimulation turned on immediately after implantation of the stimulator; and the sham stimulation group, where participants will have a stimulator implanted but it will not be switched on. The study lasts 12 weeks, and after that period all participants’ stimulators will be turned on.

The trial has already started recruitment, and has a recruitment target of 50 participants, over 4 countries (Austria, France, Germany and Switzerland) and 12 sites.

The primary outcome is the UHDRS TMS at 12 weeks, measured as the difference in the mean change from baseline between the stimulation arm and the sham-stimulation arm. The secondary outcomes include the UHDRS chorea score and the bradykinesias items, the Burke-Fahn-Marsden Dystonia Rating Scale, the Q-Motor choreomotography task, the Mattis Dementia Rating Scale, the Verbal Fluency Test, the Symbol Digits Modalities Test, the Stroop Test, the Hospital Anxiety and Depression Scales and the Snaith Irritability Scale, the Problem Behaviours Assessment Short Form, the Short Form 36 Health Survey, the Clinical Global Impression Scale, and safety.

Sponsors/funders

Heinrich-Heine University, KKS Netzwerk, Medtronic, the George Huntington Institute, EHDN and CHDI Foundation.

Comments

DBS is a relatively well-studied intervention for some manifestations of Parkinson’s disease, tremor and dystonia. DBS involves the surgical implantation of electrical electrodes in the deep brain structures, connected via a wire to an implantable pulse generator (i.e. stimulator) usually positioned subcutaneously in the pectoral region. Although the precise mechanisms of action are still not completely understood, this intervention is aimed at interrupting certain neuronal circuits.

In Parkinson’s disease DBS is frequently used to minimize levodopa-induced dyskinesia, which has a similar phenomenology to chorea in HD, but a different aetiology. This is accomplished by bet-
Table 2
Ongoing pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington’s disease (HD)

| Registration ID   | Trial name          | Intervention                          | Population                        | Comparison | Main outcome                                      | Study design                                                                 | Estimated Enrolment | Sponsor                                      | Location                      |
|------------------|---------------------|---------------------------------------|-----------------------------------|------------|--------------------------------------------------|-------------------------------------------------------------------------------|---------------------|---------------------------------------------|--------------------------------|
| NCT03854019*     | –                   | Dextromethorphan/quinidine            | HD with irritability              | Placebo    | Clinical efficacy at 6 and 13 weeks              | Randomized, double-blind, placebo-controlled, cross-over trial               | 22                  | University of Texas Health Science Center, Cures Within Reach | USA (single centre)         |
| NCT03842969*     | GEN-EXTEND          | RG6042                                | Allele- nonselective antisense oligonucleotide | HD         | None                                             | Safety and tolerability at up to 5 years                                     | 950                 | Hoffmann-La Roche                          | USA, Canada, Europe (multi centre) |
| NCT037618-49     | GENERATION-HD1      | RG6042                                | Allele- nonselective antisense oligonucleotide | HD         | Placebo                                          | Clinical efficacy at 101 weeks                                               | 660                 | Hoffmann-La Roche                          | USA, Canada, Europe (multi centre) |
| NCT03787758      | –                   | SAGE-718                              | NMDA positive allosteric modulator | Placebo    | Safety at 21 days                                | Randomized, double-blind, placebo-controlled, multiple ascending dose trial | 10                  | Sage Therapeutics                          | N/S                            |
| NCT03575676      | –                   | SOM3355                               | VMAT2 inhibitor and β1 antagonist  | Early and moderate HD with chorea | Placebo | Chorea at 6 months                               | Randomized, double-blind, placebo-controlled, cross-over trial              | 30                  | SOM Biotech SL                              | Spain (multi centre)          |
| NCT03515213      | –                   | Fenofibrate                           | PPARx agonist                      | HD         | Placebo                                          | Pharmacodynamics at 6 months                                                 | 20                  | University of California, Irvine            | USA (single centre)          |
| NCT03764215      | Tasigna HD          | Nilotinib                             | Selective Bcr-Abl tyrosine kinase inhibitor | HD         | None                                             | Safety, tolerability and pharmacodynamics at 3 months                        | 20                  | Georgetown University                       | USA (single centre)          |
| NCT03342053      | IONIS-HTTxx OLE     | ISIS 443139                           | Allele- nonselective antisense oligonucleotide | HD         | None                                             | Safety and tolerability at 74 weeks                                           | 46                  | Ionis Pharmaceuticals Inc.                  | Canada, Germany and UK (multi-centre) |
| NCT03225833      | PRECISION-HD1       | WVE-120102                            | Allele-selective antisense oligonucleotide | HD         | Placebo                                          | Safety and tolerability at 1 and 120 days                                    | 48                  | Wave Life Sciences Ltd.                     | Canada and Poland (multi-centre) |
| NCT03225846      | PRECISION-HD2       | WVE-120102                            | Allele-selective antisense oligonucleotide | HD         | Placebo                                          | Safety and tolerability at 1 and 120 days                                    | 48                  | Wave Life Sciences Ltd.                     | Canada and Poland (multi-centre) |

(Continued)
| Registration ID     | Trial name    | Intervention          | Mechanism of Action       | Population | Comparison | Main outcome                             | Study design                       | Estimated Enrolment | Sponsor                                                                 | Location                        |
|-------------------|--------------|-----------------------|---------------------------|------------|------------|------------------------------------------|------------------------------------|-------------------|-------------------------------------------------------------------------|----------------------------------|
| NCT02509793       | –            | Tetrabenazine         | VMAT2 inhibitor           | HD         | None       | Cognitive and behavioural effects at 8 weeks | Single group, open-label trial    | 20                | University of Texas Health Science Center, and H. Lundbeck A/S          | USA (single centre)              |
| NCT02481674       | SIGNAL       | VX15/2503             | Anti-semaphorin 4D monoclonal antibody | Late premanifest or early HD | Placebo   | Safety and tolerability at 15 and 21 months | Randomized, double-blind, placebo-controlled, parallel trial | 240               | Vaccinex Inc.; Huntington Study Group                                   | USA (multi centre)               |
| NCT02336633       | REVHD        | Resveratrol           | Dietary supplement        | HD         | Placebo    | Neuroimaging biomarkers at 1 year         | Randomized, double-blind, placebo-controlled, parallel trial | 102               | Assistance Publique - Hôpitaux de Paris                                | France (multi centre)            |
| EUTR2013-002545-10-SE | OSU6162Open1309 (-)-OSU616 | Monoaminergic stabilizer | HD, PD, brain trauma, stroke, myalgic encephalomyelitis and narcolepsy | None      | Safety at 3, 6 and 12 months | Single group, open-label trial | Randomized, double-blind, placebo-controlled, parallel trial | 240               | A. Carlsson Research AB                                                  | Sweden (multi centre)            |
| NCT00514774       | UDCA-HD      | Ursodiol              | Bile acid                | HD         | Placebo    | Safety, tolerability and pharmacokinetics at 35 days | Randomized, double-blind, placebo-controlled, parallel trial | 21                | Oregon Health and Science University, Huntington Study Group, Huntington Society of Canada | N/S                              |

N/S, not specified; PD, Parkinson’s disease; VMAT2, Vesicular Monoamine Transporter 2. Note: IONIS-HTTRx, ISIS 443139 and RG6042 refer to the same molecule. New trials since the last Clinical Trials Corner are indicated by *.
| Registration ID | Trial name | Intervention | Mechanism of Action | Population | Comparison | Main outcome | Study design | Estimated Enrolment | Sponsor | Location |
|----------------|------------|--------------|---------------------|------------|-----------|-------------|-------------|---------------------|---------|----------|
| ISRCTN52651778 | TRIDENT    | Foetal stem cell transplant | Stem cell therapy | Early stage HD | Usual care | Safety at 4 weeks | Randomized, open label, controlled, parallel trial | 30 | Cardiff University | UK (single centre) |
| NCT02728115    | SAVE-DH    | Cellavita    | Stem cell therapy   | HD         | None      | Safety at 5 years  | Non-randomized, open label, uncontrolled, parallel trial | 6  | Azidus Brasil   | Brazil (single centre) |
| NCT03252535    | ADORE-HD   | Cellavita    | Stem cell therapy   | HD         | Placebo   | Efficacy at 120 days | Randomized, double-blind, placebo-controlled, parallel trial | 35 | Azidus Brasil   | Brazil (single centre) |
| NCT03297177    | –          | Autologous stem/stromal cells | Autologous stem/stromal cell injection | HD, AD, PD, CBD, MS | None      | Safety at 5 years  | Single group, open-label trial | 300 | Healeon Medical Inc, Global Alliance for Regenerative Medicine, Regeneris Medical | USA and Honduras (multi-centre) |
| NCT0253584     | HD-DBS     | GP DBS       | Deep brain stimulation | Moderate HD with chorea | Sham intervention | Efficacy at 12 months | Randomized, double-blind, sham-controlled, parallel trial | 50 | Heinrich-Heine University, KKS Netzwerk, Medtronic, The George Institute, EHDN, CHDI Foundation, Inc. | Austria, France (multi-centre) |
| NCT01834053    | BMACHC     | Bone Marrow Derived MNC transplant | Bone marrow transplant | HD with chorea | None      | Cognitive and behavioural effects at 6 months | Single group, open-label trial | 50 | Chaitanya Hospital, Pune | India (single centre) |
| NCT02263430    | –          | GP DBS       | Deep brain stimulation | HD with chorea | Sham stimulation | Efficacy at 12 months | Randomized, double-blind, placebo-controlled, parallel trial | 8  | Beijing Pins Medical Co., Ltd, Beijing Tiantan Hospital | China (single centre) |
| NCT02252300    | –          | Magnetic Resonance Guided Focused Ultrasound | Extracranial stereotactic radioablation | HD, ET, HT, PD, WD, dystonia, TD, or orofacial dyskinesias | None      | Adverse events after the procedure | Single group, open-label trial | 10 | InSightec | Canada (single centre) |

AD, Alzheimer's disease; CBD, Corticobasal Degeneration; DBS, deep brain stimulation; ET, Essential Tremor; GP, Globus pallidus; HT, Holmes Tremor; MNC, mononuclear cells; MS, Multiple Sclerosis; PD, Parkinson's disease; TD, Tardive dyskinesia; WD, Wilson's disease.
Table 4
Ongoing non-invasive non-pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington’s disease (HD)

| Registration ID | Trial name                  | Intervention                                      | Mechanism of Action | Population               | Comparison     | Main outcome                                      | Study design                                      | Estimated Enrolment | Sponsor                                                                 | Location                  |
|-----------------|-----------------------------|---------------------------------------------------|---------------------|--------------------------|----------------|--------------------------------------------------|--------------------------------------------------|---------------------|------------------------------------------------------------------------|---------------------------|
| ACTRN12618001717246 | –                           | Multidisciplinary therapy program                 | Exercise, cognitive training, lifestyle guidance and social activities | Premanifest HD | Standard of care | Feasability and safety | Clustered, non-randomized, open label, parallel trial | 40                  | Edith Cowan University, Deakin University and Lotterywest              | Australia (two centres) |
| NCT03417583     | –                           | Neuropsychiatric treatment protocol               | Multidisciplinary intervention | HD with neuropsychiatric symptoms | Standard of care | Change in quality of life at 18 months          | Non-randomized, assessor-blinded, parallel trial | 100                 | Vanderbilt University Medical Center and Teva Pharmaceuticals USA      | USA (single centre)       |
| CTRI/2018/01/011359 | –                           | Repetitive transcranial magnetic stimulation       | Transcranial magnetic stimulation | Early to moderate HD and PD | Sham stimulation | Efficacy at 5 days                          | Randomized, single-blind, placebo-controlled, parallel trial | 40                  | Vinay Goyal India (single centre)                                      | India (single centre)    |
| NCT03344601     | PACE-HD                     | Supported structured aerobic exercise training program | Physiotherapy | HD                      | Activity as usual | Data completeness, recruitment, retention, safety, adherence, likeliness and acceptability at 12 months | Nested open-label, randomized controlled parallel trial | 120                 | Cardiff University and CHDI Foundation, Inc USA (multi centre)        | Germany, Spain and USA |
| ACTRN12617001269325 | –                           | Swallowing skill training                          | Speech and language therapy | HD and ALS | None | Swallowing function and quality of life at 2 weeks | Single group, open-label trial | 54                  | University of Canterbury New Zealand (single centre)                   |                           |
| NCT02216474     | –                           | tDCS                                              | Transcranial magnetic stimulation | HD or Tourette Syndrome | Sham stimulation | Efficacy at 2 weeks                           | Randomized, double-blind, placebo-controlled, cross-over trial | 100                 | Birmingham and Solihull Mental Health NHS Foundation Trust, University of Birmingham | UK (single centre)       |

AD, Alzheimer’s disease; ALS, Amyotrophic Lateral Sclerosis; ET, Essential Tremor; HT, Holmes Tremor; MS, Multiple Sclerosis; PD, Parkinson’s disease; TD, Tardive dyskinesia.
ter controlling the cardinal features of PD, hence reducing the levodopa dose equivalents. There is still uncertainty about whether there is a direct effect of DBS over dyskinesia. In HD, chorea is thought to be caused by the loss of striatal projections to the indirect basal ganglia pathway and consequent thalamic overactivity (11), and although there is a shortage of good-quality evidence, some pilot studies have shown interesting preliminary results when manipulating these circuits with DBS in HD (12, 13).

The scarcity of data so far accumulated precludes drawing conclusions on the safety and efficacy profile of this intervention in HD, but it seems sensible to assume that this population may be susceptible to the same intervention-related adverse events as other tested populations. Disease-specific side effects may be more difficult to predict.

Only large well-controlled prospective controlled studies will allow us to fully understand the efficacy and safety profile of DBS in HD.

**TRIHEP3 (NCT02453061)**

**Study title**
A Comparative Phase 2 Study Assessing the Efficacy of Triheptanoin, an Anaplerotic Therapy in Huntington’s Disease (TRIHEP3)(2).

**Intervention**
Triheptanoin oil 1 g/kg/day (14).

**Description**
The TRIHEP3 trial, sponsored by the Institut National de la Santé et de la Recherche Médicale and Ultragenyx Pharmaceutical Inc., aims to evaluate the effects of daily triheptanoin in adults (≥18 years of age) with genetically confirmed manifest HD (i.e. UHDRS TMS between 5 and 40), compared with daily safflower oil. People with a BMI <18 or >30, hypersensitivity to triheptanoin, major co-morbidities, history of severe head injury, pregnant or breastfeeding, or on tetrabenazine are not eligible.

TRIHEP3 is an international, multi-centre, randomized, double-blind, controlled, parallel phase 2 trial. It has 2 study arms: the active group, where participants receive triheptanoin oil 1 g/kg/day for 12 months; and the comparator group, where participants receive safflower oil 1 g/kg/day for 6 months and triheptanoin oil 1 g/kg/day for the following 6 months.

The study lasts 12 months, the first half over double-blinded conditions, and the second half as an open-label extension. Recruitment is currently closed and the study is being performed at one centre in France and one centre in the Netherlands. One hundred participants were recruited.

The primary outcomes are pharmacodynamics neuroimaging markers at 3 and 6 months - $^{31}$P-MRS and volumetric MRI. Secondary outcomes include the UHDRS, comprising the motor, functional and cognitive components, the Problem Behaviours Assessment Short Form, the Short Form 36 Health Survey, adverse events, tolerance and other neuroimaging biomarkers.

**Comments**

Albeit with a low success rate (15), several dietary nutrients with possible effects over metabolic processes have been tested in HD over the years, including d-α-tocopherol (16), idebenone (17), coenzyme Q10 (18), ethyl-eicosapentaenoate (19–21), and creatine (22–24).

Triheptanoin is an odd-chain triglyceride with anaplerotic properties (i.e. it replenishes biochemical cycles with intermediate metabolites), providing the Krebs cycle with both acetyl-CoA and propionyl-CoA. So far, triheptanoin has been tested for several disorders of the brain metabolism, including pyruvate decarboxylase deficiency, and GLUT1 deficiency where a significant symptomatic effect was demonstrated in a small open-label study (25).

In HD, several lines of evidence support the existence of a dysfunction of the energy metabolism, including the Krebs cycle, oxidative phosphorylation and glycolysis. Two small open-label studies in HD showed that triheptanoin may have the potential to bring peripheral (26) and central nervous system metabolic biomarkers (27) to levels observed in healthy controls. They also anticipate triheptanoin to be well tolerated (26, 27), and overall the cumulative evidence suggests a good safety profile for doses between 1 to 2.5 g/kg/day(14).

The TRIHEP3 trial will be completed by the end of 2019 and the results are expected in mid-2020.

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CONFLICTS OF INTEREST

FBR and EJW were sub-investigators on LEGA TO-HD (NCT02215616), IONIS HTT Rx (NCT02519036) and IONIS HTT Rx OLE (NCT03342053), and are sub-investigators on the Roche GENERATION-HD (NCT03761849), Roche Natural History Study (NCT03664804) and Roche GEN-EXTEND (NCT03842969) trials, and EJW was a sub-investigator on the Amaryllis (NCT02197130). EJW is the chief investigator of the Roche GEN-PEAK trial (NCT04000594) and FBR is a sub-investigator. JJF was principal investigator on LEGATO-HD and on a trial of ethyl-eicosapentanoate in Huntington’s disease. The authors did not make use of confidential or privileged information: all materials included in this manuscript were collected from publicly available sources. FBR has provided consultancy services to GLG. EJW has participated in scientific advisory boards with Hoffmann-La Roche Ltd, Ionis, Shire, GSK, Wave Life Sciences, PTC Therapeutics, Takeda and Mitoconix. All honoraria were paid through UCL Consultants Ltd, a wholly owned subsidiary of UCL. Their Host Institution, University College London Hospitals NHS Foundation Trust, has received funds as compensation for conducting clinical trials for Ionis Pharmaceuticals, Pfizer and Teva Pharmaceuticals. Hoffman La Roche Ltd has supported UCL with research funding for EJW. In view of the support to both regular authors from Hoffman-La Roche Ltd, JJF was invited to be a co-author to ensure the sections on the Ionis/Roche program were suitably balanced.

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