Clinical Trials Corner: September 2017

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Abstract. Clinical Trials Corner of Journal of Huntington’s Disease will regularly review ongoing and recently completed clinical trials in Huntington’s disease. In this inaugural issue, we list all currently registered and ongoing clinical trials, expand on LEGATO-HD and IONIS-HTTR\textsubscript{Rx}, and cover two recently finished trials: Amaryllis and Pride-HD.

Keywords: Clinical trials, Huntington’s disease

INTRODUCTION

Clinical Trials Corner of Journal of Huntington’s Disease is a new, regular, peer-reviewed section devoted to highlighting ongoing or recently completed clinical trials in Huntington’s disease (HD).

To do so, we will gather and curate data from the World Health Organization (WHO) International Clinical Trials Search Portal (ICTRP)—a central database that contains the trial registration datasets provided by 17 clinical trial registries [1], including the EU Clinical Trials Register (EU-CTR), the USA ClinicalTrials.gov, among others—using the keywords “Huntington’s” and “Huntington”. As trial registration has been settled as a condition for publication by the International Committee of Medical Journal Editors (ICMJE) since 2005 [2], and the following year the WHO supported this measure [3], we will use only publicly available information to describe the trials and their results.

There are only two drugs specifically approved for HD [4]: tetrabenazine [5] and deutetrabenazine [6], both with a moderate effect on involuntary movements. No intervention has shown to modify disease progression so far [7]. That being said, almost one hundred clinical trials and 50 different interventions have been or are currently being tested in HD [8]. It is clear that modifying the progression of HD is exceptionally difficult; that success in preclinical models so far has failed to anticipate the outcome of subsequent human trials; and that there is a need for not only better drugs, but better means of deciding which drugs we should test in patients.

In this inaugural Clinical Trials Corner, we will list all currently registered and ongoing clinical trials, expand on LEGATO-HD and IONIS-HTTR\textsubscript{Rx}, and cover two recently finished trials: Amaryllis (NCT02197130) and Pride-HD (NCT02006472). For future editions, we will summarize current efforts and recent developments as well as providing in-depth information on notable trials.

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

ONGOING CLINICAL TRIALS

A list of ongoing clinical trials is given in Tables 1, 2 and 3.
### Table 1
Ongoing pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington’s disease (HD). NINDS, National Institute of Neurological Disorders and Stroke; HSG, Huntington Study Group; N/S, not specified; PD, Parkinson’s disease; VMAT2, Vesicular Monoamine Transporter 2

| Registration ID | Trial name   | Intervention                      | Mechanism of Action                                                                 | Population          | Comparison   | Main outcome                                      | Study design                                         | Estimated Enrolment | Sponsor                                                                 | Location                        |
|-----------------|--------------|-----------------------------------|------------------------------------------------------------------------------------|---------------------|-------------|--------------------------------------------------|-----------------------------------------------------|----------------------|----------------------------------------------------------------------|---------------------------------|
| EUCTR2016-003730-25-NL | CHALLENGE-HD | SBT-020                           | Mitochondria-targeted cytoprotective peptide                                      | Early HD            | Placebo     | Safety and tolerability at 7 and 28 days         | Randomized, double-blind, placebo-controlled, parallel trial | 24                   | Stealth Biotherapeutics                                                | Netherlands (single center)     |
| NCT03019289     | –            | Pridopidine                       | Dopaminergic stabilizer                                                            | Healthy individuals and HD | –           | Pharmacodynamic at 1 day                         | Single dose, open-label, single group trial          | 38                   | Teva Branded Pharmaceutical Products, R&D Inc.                        | Germany (single center)         |
| NCT02453061     | TRIHEP 3     | Triheptanoin                       | Anaplerotic therapy                                                               | HD                  | Placebo     | Pharmacodynamic efficacy at 6 months            | Randomized, double-blind, placebo-controlled, parallel trial | 100                  | Institut National de la Santé Et de la Recherche Médicale, Ultragenyx Pharmaceutical Inc. | France, Netherlands (multi center) |
| NCT02519036     | IONIS-HTTRX  | IONIS-HTTRX                        | Antisense oligonucleotide                                                         | HD                  | Placebo     | Safety and tolerability at 29 weeks              | Randomized, double-blind, placebo-controlled, parallel trial | 46                   | Ionis Pharmaceuticals, Inc.                                           | Canada, Germany, UK (multi center) |
| NCT02509793     | –            | Tetrabenazine                      | VMAT2 inhibitor                                                                   | HD with impulsivity | –           | Cognitive and behavioral effects at 8 weeks     | Single group, open-label trial                      | 20                   | University of Texas Health Science Center, and H. Lundbeck A/S       | USA (single center)             |
| NCT02507284     | STAIR        | SRX246                             | Vasopressin 1a Receptor Antagonist                                                | Early and moderate HD with irritability | Placebo     | Feasibility at 12 weeks                         | Randomized, double-blind, placebo-controlled, parallel trials | 108                  | Azevan Pharmaceuticals, NINDS, & NeuroNEXXT Network                    | USA (multi center)              |
| NCT Number | Study Identifier | Intervention | Disease Area | Comparator | Comparator Details | Study Design | Sponsor | Country/Region |
|------------|------------------|--------------|--------------|------------|-------------------|-------------|---------|--------------|
| NCT02494778 | Open PRIDE-HD | Pridopidine Dopaminergic stabilizer | PRIDE-HD completers | – | Safety at 104 weeks | Single group, open label extension of PRIDE-HD | Teva Branded Pharmaceutical Products, R&D Inc. | Australia, Austria, Canada, Denmark, France, Germany, Italy, Netherlands, Poland, Russia, UK, USA (multicenter) |
| NCT02481674 | SIGNAL | 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 | Vaccinex Inc., HSG | USA (multicenter) |
| NCT02336633 | REVHD | Resveratrol Dietary supplement | HD | Placebo | Neuroimaging biomarkers at 1 year | Randomized, double-blind, placebo-controlled, parallel trial | Assistance Publique – Hôpitaux de Paris | France (multicenter) |
| NCT02215616 | LEGATO-HD | Laquinimod Immunomodulatory molecule | HD | Placebo | Efficacy at 1, 3, 6, and 12 months | Randomized, double-blind, placebo-controlled, parallel trial | Teva Branded Pharmaceutical Products, R&D Inc. | Canada, Czech Republic, France, Germany, India, Israel, Italy, Netherlands, Portugal, Russia, Spain, UK, USA (multicenter) |
| EUCTR2013-002545-10-SE | OSU6162 | (-)-OSU616 Monoaminergic stabilizer | HD, PD, brain trauma, stroke, myalgic encephalomyelitis and narcolepsy | – | Safety at 3, 6 and 12 months | Single group, open-label trial | A. Carlsson Research AB | Sweden (multicenter) |

(Continued)
| Registration ID | Trial name | Intervention | Mechanism of Action | Population | Comparison | Main outcome | Study design | Estimated Enrolment | Sponsor | Location |
|----------------|------------|--------------|---------------------|------------|------------|--------------|--------------|-------------------|---------|----------|
| NCT00652457    | MEM-HD     | Memantine    | NMDA receptor antagonist | HD and memory or concentration difficulties | Placebo | Efficacy at 3 and 6 months | Randomized, double-blind, placebo-controlled, cross-over trial | 60 | University of California, San Diego, Forest Laboratories | USA (multi center) |
| NCT00632645    | NEUROHD    | Olanzapine   | Dopamine agonist    | HD with motor or behavioral symptoms | Tetrabenazine, or tiapride | Efficacy at 12 months | Randomized, open-label, controlled, parallel trial | 180 | Assistance Publique – Hôpitaux de Paris, | France (single center) |
| NCT01306929    | OPEN-HART  | Pridopidine  | Dopaminergic stabilizer | HART or PRIDE-HD completers | – | Safety at 2 years | Single group, open label extension of HART | 235 | Teva Branded Pharmaceutical Products, R&D Inc. | Canada, USA (multi center) |
| 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, HSG, Huntington Society of Canada | N/S |
| NCT01897896    | ARC-HD     | Deutetabenazine | VMAT2 inhibitor | Early and moderate HD with chorea on tetrabenazine or FIRST-HD completers | – | Safety at 54 weeks | Single group, open-label, drug-switching trial | 238 | Auspex Pharmaceuticals, Inc., Teva Pharmaceutical Industries | Australia, Canada, USA (multi center) |
| ACTRN1261-6001611415 | VCAS-HD | Varenicline | Nicotinic acid receptor partial agonist | HD | Placebo | Efficacy at 10 weeks | Randomized, double-blind, placebo-controlled, parallel trial | 40 | University of Auckland | New Zealand (single center) |
Table 2
Ongoing 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). DBS, deep brain stimulation; EHDN, European Huntington’s Disease Network; ET, Essential Tremor; GP, Globus pallidus; HT, Holmes Tremor; MNC, mononuclear cells; PD, Parkinson’s disease; TD, Tardive dyskinesia; WD, Wilson’s disease

| Registration ID | Trial name | Intervention | Mechanism of Action | Population | Comparison | Main outcome | Study design | Estimated Enrolment | Sponsor | Location |
|----------------|------------|--------------|---------------------|------------|------------|--------------|--------------|---------------------|--------|----------|
| NCT02535884    | 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, Germany, Switzerland (multi center) |
| NCT01834053    | BMACHC     | Bone Marrow Derived MNC transplant | Bone marrow transplant | HD with chorea | – | Cognitive and behavioral effects at 6 months | Single group, open-label trial | 50      | Chaitanya Hospital, Pune | India (single center) |
| 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 center) |
| NCT02252380    | –          | Magnetic Resonance Guided Focused Ultrasound | Extracranial stereotactic radioablation | HD, ET, HT, PD, WD, dystonia, TD, or orofacial dyskinesias | – | Adverse events after the procedure | Single group, open-label trial | 10      | InSightec | Canada (single center) |
| Registration ID | Trial name | Intervention | Mechanism of Action | Population | Comparison | Main outcome | Study design | Estimated Enrollment | Sponsor | Location |
|----------------|------------|--------------|---------------------|------------|------------|--------------|--------------|----------------------|---------|----------|
| NCT02990676    | CogTrainHD | Computerized Cognitive Training | Cognitive training | HD         | No intervention | Feasibility at 4 years | Open-label, controlled, parallel trial | 50       | Cardiff University | UK (single center) |
| NCT01879267    | –          | Endurance exercise training | Physiotherapy | HD and healthy controls | –          | Motor effects 6 months | Single group, open-label trial with parallel healthy controls arm | 40       | University of Zurich | Switzerland (single center) |
| NCT02464293    | –          | Mindfulness-based Cognitive Therapy | Cognitive therapy | Premanifest and early HD with behavioral symptoms | –          | Behavioral effect at 2 weeks, 3 months and 1 year | Single group, open-label trial | 16       | Lancaster University, Central Manchester University Hospitals NHS Foundation Trust | UK (single center) |
| 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 center) |
| NCT02750982    | –          | Laughter Therapy | Cognitive therapy | HD, AD, ALS, brain injury, MS, PD, post/stroke or spinal cord injury | –          | Behavioral effects at 8 weeks | Single group, open-label trial | 24       | Brown, Theodore R., M.D., MPH | USA (single center) |
| NCT01602276    | –          | tDCS | Transcranial magnetic stimulation | Subcortical brain damage, including HD | Sham stimulation | Efficacy at 1 month | Randomized, single-blind, placebo-controlled, cross-over trial with parallel healthy control arm | 150      | Johns Hopkins University | USA (single center) |
LEGATO-HD (NCT02215616)

**Study title:** A Clinical Study in Subjects With Huntington’s Disease to Assess the Efficacy and Safety of Three Oral Doses of Laquinimod [9].

**Intervention:** Laquinimod, an immunomodulatory molecule [10].

**Description:** The LEGATO-HD trial aims to compare the efficacy and safety of laquinimod 0.5 mg qd, 1 mg qd, 1.5 mg qd, and placebo qd, for disease modification in people with HD (CAG repeat number ≥ 36 plus Unified Huntington’s Disease Rating Scale (UHDRS) Total Motor Score (TMS) >5), aged between 21 and 55 years old.

Participant involvement will last for 12 months of treatment. The trial is a phase 2, international, multicenter, randomized, placebo controlled, double blind, parallel study. The recruitment aim is 400 participants in Canada, Czech Republic, France, Germany, India, Israel, Italy, Netherlands, Portugal, Russia, Spain, United Kingdom, and United States of America.

The primary outcome is change from baseline in the UHDRS TMS after 1, 3, 6, and 12 months of treatment. The secondary outcomes involve the UHDRS Total Functional Capacity (TFC), the Clinician’s Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) global score, the Huntington’s Disease Cognitive Assessment Battery (HD-CAB), and caudate volume.

**Sponsors/funders:** Teva Branded Pharmaceutical Products, R&D Inc.

**Comments:** Along the course of this study, due to safety concerns derived from a study of laquinimod in multiple sclerosis, the sponsor opted to stop the 1.5 mg qd dosage but maintain the others. This study is now fully recruited [11] with an expected completion date of August 2018.

IONS-HTTRx (NCT02519036)

**Study title:** Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of IONIS-HTTRx in Patients With Early Manifest Huntington’s Disease [12]

**Intervention:** IONIS-HTTRx, an antisense oligonucleotide against the huntingtin pre-mRNA transcript of the HTT gene in an allelenoselective manner, with the aim of reducing the production of mutant huntingtin protein. The intervention is administered 4 times at 4 week intervals over the course of 13 weeks. The dose has ascended consecutively throughout the study.

Each participant’s involvement will last for 29 weeks. It is a phase 1b/2a, international multi-center, randomized, placebo controlled, double blind, parallel, dose-ascending study, taking place in Canada, Germany and the United Kingdom. The recruitment goal of 46 participants was reached in June 2017 [14].

The primary outcome is safety and tolerability at 29 weeks. The secondary outcomes involve pharmacokinetic and pharmacodynamic measures in the cerebrospinal fluid, such as peak drug concentrations, time to peak dose concentrations, huntingtin concentration, neurofilament light concentration, and also ventricular volume and performance on the HD Cognitive Assessment Battery (HD-CAB).

**Sponsors/funders:** Ionis Pharmaceuticals, Inc.

**Comments:** This trial is currently fully recruited and an open-label extension was announced in June 2017 for the participants in the original trial.

COMPLETED CLINICAL TRIALS

Amaryllis (NCT02197130)

**Study title:** Randomized, Placebo Controlled Study Of The Efficacy And Safety Of PF-02545920 In Subjects With Huntington’s Disease [15].

**Intervention:** PF-02545920, a phosphodiesterase 10a inhibitor [16].

**Description:** The goal of the Amaryllis trial was to compare the efficacy and safety of PF-02545920 5 mg bid, PF-02545920 20 mg bid, and placebo bid, for symptomatic relief of motor impairment in people with early HD (CAG repeat number ≥ 36 plus UHDRS TFC ≥ 7) and chorea (UHDRS TMS ≥ 10), aged between 30 and 65 years old.

Participant involvement lasted for 26 weeks. It was a phase 2, international, multi-center, randomized, placebo controlled, double blind, parallel study conducted in Canada, Germany, Poland, United Kingdom, and United States of America. 272 participants were recruited.

The primary outcome was change from baseline in the UHDRS TMS after 26 weeks of treatment.
The secondary outcomes involved the UHDRS TFC, the Clinical Global Impression-Improvement, the Columbia Suicide Severity Rating Scale (C-SSRS), extrapyramidal symptoms, and white cell counts and neutrophil counts.

Sponsors/funders: Pfizer

Results: The trial was completed on September 2016. Although the results have not been released in a peer-reviewed publication, Pfizer has officially announced that the phosphodiesterase 10a inhibitor did not meet its goals in improving motor impairment in people with HD. Indeed several other secondary outcomes remained unchanged, such as functional ability [17]. As a consequence, the ongoing 12 month-long open-label extension (NCT02342548) of PF-02545920 20 mg bid was discontinued in February 2017 [18].

Pride-HD (NCT02006472)

Study title: A Phase 2, to Evaluating the Safety and Efficacy of Pridopidine Versus Placebo for Symptomatic Treatment in Patients With Huntington’s Disease [19].

Intervention: Pridopidine, a dopaminergic stabilizer [20].

Description: Pride-HD trial aimed to compare the efficacy and safety of pridopidine 45 mg bid, 67.5 mg bid, 90 mg bid, 112.5 mg bid, and placebo bid, for symptomatic relief of motor impairment in people with HD (CAG repeat number ≥ 36 plus UHDRS Independence Score < 90%) and chorea (UHDRS TMS ≥ 25), aged ≥ 21 years old.

It lasted for 52 weeks, was a phase 2, international, multi-center, randomized, placebo controlled, double blind, parallel study taking place in Australia, Austria, Canada, Czech Republic, Denmark, France, Germany, Italy, Netherlands, Poland, Russia, United Kingdom, and United States of America. It recruited 408 participants.

The primary outcome was change from baseline in the UHDRS TMS after 26 weeks of treatment. The secondary outcomes involved the modified Physical Performance Test, and adverse events. Early in the course of the study, the sponsors instituted a change in the study design, from a 26-week study focused primarily on changes in motor symptoms as measured by the TMS, to a longer 52-week study to explore pridopidine’s potential impact on functional endpoints.

Sponsors/funders: Teva Branded Pharmaceutical Products, R&D Inc., European Huntington’s Disease Network (EHDN) and Huntington’s Study Group (HSG).

Results: The trial was completed on July 2016. On September 2016 Teva announced on its website that “pridopidine demonstrates slowing of progression of Huntington disease in Pride-HD study as measured by total functional capacity” [21]. This announcement sparked some controversy [22], since the data presented by Teva at the 9th EHDN Plenary Meeting 2016 The Hague showed that Pride-HD failed to meet its primary endpoint – change in UHDRS TMS at 26 weeks [21]. The interpretation of potential benefit hinged upon a lack of decline in the UHDRS TFC at the extended 52-week timepoint. The effect was only significant in patients taking the lowest dose of pridopidine. The sponsor also pointed out “an unusually high placebo effect” that complicated interpretation of the findings. The Chairs of the EHDN Executive Committee issued a statement responding to Teva’s announcement, saying “there has been discussion over the statement in the press release that these results indicate that pridopidine slows down disease progression in HD. This statement needs to be read in the context of the whole document, which clearly speaks about slowing decline in functional capacity. This should not be misunderstood as a demonstration of disease modification or of neuroprotection” [23].

Still, the final results of this study have not yet been published, and we look forward to seeing them after peer review. The open label extension of this trial—Open PRIDE-HD (NCT02494778)—is still ongoing, according to the latest public information.

ACKNOWLEDGMENTS

The authors are supported by CHDI Foundation, Inc. (salary support to FBR for conduct of the HDClarity study) and Medical Research Council UK (salary support to EJW).

CONFLICTS OF INTEREST

FBR and EJW are sub-investigators on LEGATO-HD (NCT02215616) and IONIS-HTTRx (NCT02519036), and EJW was a sub-investigator on Amaryllis (NCT02197130). The authors did not make use of confidential or privileged information: all materials included in this manuscript were collected from publicly available sources. EJW has participated in scientific advisory boards with
Hoffmann-La Roche Ltd, Ionis, Shire, GSK and Wave Life Sciences. 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.

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