Huntington’s Disease Clinical Trials Corner: August 2018

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Abstract. In the third edition of the Huntington’s Disease Clinical Trials Corner we list all currently registered and ongoing clinical trials, expand on the SIGNAL trial (NCT02481674), and cover the recently finished CREST-E trial (NCT00712426).

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 SIGNAL trial (NCT02481674) \cite{1}, and summarise the results of the recently published CREST-E trial (NCT00712426) \cite{2, 3}. Finally 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 September 2017 edition of Huntington’s Disease Clinical Trials Corner \cite{4}.

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.

ONGOING CLINICAL TRIALS

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

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In this cohort participants received VX15/2503 or placebo for 6 months, and VX15/2503 for another 6 months in an open label extension, followed by a 3-month period of follow up. Enrolment in cohort B is completed. This cohort is underway and 53 participants will receive VX15/2503 or placebo for 36 months, followed by 3 or 6 months of follow up. The remainder of Cohort B’s participants will receive VX15/2503 or placebo for 18 months, followed by 6 months of follow up. The exact numbers and durations have not been confirmed publicly, to our knowledge. The trial has a recruitment target of 240 participants; recruitment is currently open at various sites in the United States of America and Canada.

VX15/2503 is humanized IgG4 monoclonal antibody against semaphorin 4D. Each participant’s involvement will last for at least 15 months and up to a maximum of 42 months.

The primary outcome is safety and tolerability. Secondary outcomes involve brain imaging with MRI, FDG-PET, 11C-PBR28 PET; clinical features; pharmacokinetics and pharmacodynamics. Exploratory analysis include cerebrospinal fluid biomarkers.

**Sponsors/funders**
Vaccinex Inc., and the Huntington Study Group.

**Comments**
Semaphorins are a family of proteins whose name derives from semaphore (from the Greek for sign-bearer). Initially described as signalling proteins for neuronal growth and regeneration, today they are known to be involved in many other processes such as the immune response. Semaphorin 4D, or CD100, is an axon-guiding molecule, and a B and T cell modulator.

In a YAC128 transgenic Huntington’s disease mouse model, targeting semaphorin 4D with monoclonal antibodies seemed to ameliorate striatal cortical and corpus callosum atrophy, and behavioural phenotype [6]. However, as of today, there is no published evidence supporting that the semaphorin family may be a therapeutic target in humans with HD.

Previous clinical trials involving 42 patients with advanced solid tumours (4 weekly doses up to 20 mg/kg per week) [7] and 50 patients with multiple sclerosis (single ascending dose up to 20 mg/kg) [8] showed VX15/2503 to be relatively well tolerated and safe, but were neither designed nor powered to assess clinical benefit.

Preliminary data from SIGNAL’s Cohort A have been presented at public meetings by Vaccinex, reporting interesting neuroimaging and neurometabolic results (PET imaging) in the VX15/2503 arm. Previous reports of atrophy slowing in HD have not ultimately been associated with clinical benefit or slowing of clinical progression [9–11], so such reports need to be treated with caution and interpreted in their full context.

**COMPLETED CLINICAL TRIALS**

**CREST-E (NCT00712426)**

**Study title**
Creatine Safety, Tolerability, & Efficacy in Huntington’s Disease [2, 3].

**Intervention**
Creatine monohydrate, a nutritional supplement.

**Description**
The goal of CREST-E trial was to assess the effects of up to 40 gm of oral creatine monohydrate daily compared with oral placebo on functional decline in adults with early manifest HD (i.e. motor signs
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 | Mechanism of Action | Population | Comparison | Main outcome                                              | Study design                                                                 | Estimated Enrolment | Sponsor                                      | Location                          |
|----------------|---------------|--------------|---------------------|------------|------------|----------------------------------------------------------|-----------------------------------------------------------------------------|---------------------|---------------------------------------------|-----------------------------------|
| NCT03342053    | IONIS-HTTRx OLE | ISIS 443139  | Allele-nonselective antisense oligonucleotide | HD         | None       | Safety and tolerability at 74 weeks                      | Open label extension                                                      | 46                   | Ionis Pharmaceuticals Inc.                  | Canada, Germany and UK (multi-centre) |
| NCT03225833    | PRECISION-HD1 | WVE-120102   | Allele-selective antisense oligonucleotide | Placebo    | Safety and tolerability at 1 and 120 days               | Randomized, double-blind, placebo-controlled, combined single ascending dose/multiple ascending dose trial | 48                   | Wave Life Sciences Ltd.                   | Canada and Poland (multi-centre)    |
| NCT03225846    | PRECISION-HD2 | WVE-120102   | Allele-selective antisense oligonucleotide | Placebo    | Safety and tolerability at 1 and 120 days               | Randomized, double-blind, placebo-controlled, combined single ascending dose/multiple ascending dose trial | 48                   | Wave Life Sciences Ltd.                   | Canada and Poland (multi-centre)    |
| NCT02453061    | TRIHEP 3      | Triheptanoin  | Anaplerotic therapy | 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 centre) |
| NCT02509793    | –             | Tetrabenazine | VMAT2 inhibitor     | HD with impulsivity | 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)               |
| NCT02507284    | STAIR         | SRX246       | Vasopressin 1a Receptor Antagonist | Placebo    | Feasibility at 12 weeks                                | Randomized, double-blind, placebo-controlled, parallel trials          | 108                  | Azevan Pharmaceuticals, National Institute of Neurological Disorders and Stroke (NINDS), and NeuroNEXT Network | USA (multi 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)                |

(Continued)
| Registration ID | Trial name | Intervention | Mechanism of Action | Population | Comparison | Main outcome | Study design | Estimated Enrollment | Sponsor | Location |
|----------------|------------|--------------|---------------------|------------|------------|--------------|--------------|----------------------|---------|----------|
| NCT02336633    | REVHD      | Resveratrol  | Dietary supplement  | HD         | Placebo    | Neuroimaging biomarkers at 1 year | Randomized, double-blind, placebo-controlled, parallel trial | 102      | Assistance Publique - Hopitaux de Paris | France (multi centre) |
| NCT02215616    | LEGATO-HD  | Laquinimod   | Immunomodulatory molecule | HD         | Placebo    | Efficacy at 1, 3, 6, and 12 months | Randomized, double-blind, placebo-controlled, parallel trial | 400      | Teva Branded Pharmaceutical Products, R&D Inc. | Canada, Czech Republic, France, Germany, India, Israel, Italy, Netherlands, Portugal, Russia, Spain, UK, USA (multi centre) |
| EUCTR2013-002545-10-SE | OSU6162 Open1309 | (~)-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 | 240 | A. Carlsson Research AB | Sweden (multi centre) |
| 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 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 |
| 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 centre) |

N/S, not specified; PD, Parkinson’s disease; VMAT2, Vesicular Monoamine Transporter 2. New trials since the last Clinical Trials Corner are indicated by *. 
### Table 3

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)

| Registration ID   | Trial name    | Intervention | Mechanism of Action | Population | Comparison | Main outcome                  | Study design                                   | Estimated Enrolment | Sponsor                                                                 | Location                  |
|------------------|---------------|--------------|---------------------|------------|------------|-------------------------------|-----------------------------------------------|----------------------|------------------------------------------------------------------------|----------------------------|
| 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 Heinrich-Heine University, KKS Netzwerk, Medtronic, The George Institute, EHDN, CHDI Foundation, Inc. | USA and Honduras (multi-centre) |
| 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 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)     |
| NCT02252380      | –             | 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. New trials since the last Clinical Trials Corner are indicated by *. 

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| Registration ID      | Trial name                                 | Intervention                                           | Mechanism of Action                  | Population                        | Comparison          | Main outcome                  | Study design                      | Estimated Enrollment | Sponsor                                      | Location                        |
|---------------------|--------------------------------------------|--------------------------------------------------------|--------------------------------------|------------------------------------|----------------------|-----------------------------|-------------------------------|-------------------------|--------------------------------------------|---------------------------------|
| 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)            |
| NCT03344601         | PACE-HD                                    | Supported structured aerobic exercise training program | Physiotherapy                        | HD                                 | Activity as usual    | Data completeness, recruitment, retention, safety, adherence, fidelity and acceptability at 12 months | Nested open-label, randomized controlled parallel trial | 120                     | Cardiff University and CHDI Foundation, Inc | Germany, Spain and USA (multi centre) |
| NCT03306888         | –                                          | Physical Activity Coaching Intervention               | Physiotherapy                        | Premanifest and early HD           | None                 | Change in physical activity at 4 months | Single group, open-label trial | 14                      | Columbia University                        | USA (single centre)              |
| 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)     |
| NCT02990676         | CogTrainHD                                 | Computerised Cognitive Training                       | Cognitive training                  | HD                                 | No intervention      | Feasibility at 4 years      | Open-label, controlled, parallel trial | 50                      | Cardiff University                          | UK (single centre)              |
| NCT02464293         | –                                          | Mindfulness-based Cognitive Therapy                  | Cognitive therapy                   | Premanifest and early HD with behavioural symptoms | None                 | Behavioural 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 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                     | UK (single centre)                         | Birmingham and Solihull Mental Health NHS Foundation Trust | |
| NCT02750982         | –                                          | Laughter Therapy                                     | Cognitive therapy                   | HD, AD, ALS, brain injury, MS, PD, post/stroke or spinal cord injury | None                 | Behavioural effects at 8 weeks | Single group, open-label trial | 24                      | Brown, Theodore R., M.D., MPH              | USA (single centre)              |
| 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 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. New trials since the last Clinical Trials Corner are indicated by *.
characteristic of HD plus a positive family history for HD or a HTT CAG repeat length ≥36 plus a UHDRS Total Functional Capacity ≥7).

This trial was a phase 3, multi-centre, international, randomized, placebo-controlled, double-blind, parallel study. Although designed to recruit 650 participants from Australia, Canada, New Zealand, and the United States, the trial only recruited 553 participants before being halted for futility after an interim analysis. Participant involvement lasted for up to 48 months.

The primary outcome was rate of change from baseline in the UHDRS TFC at weeks 12 to 48 depending on each participant’s date of enrolment. The secondary outcomes included changes in other UHDRS scores, adverse events, tolerability, quality of life, and several biofluid and imaging biomarkers.

Sponsors/funders
Massachusetts General Hospital, University of Rochester, National Center for Complementary and Integrative Health.

Results
The trial was completed on December 2014 and the results published in July 2017 [2]. CREST-E was the largest clinical trial undertaken in HD. The results showed that although no major safety concerns were noted apart from an increased risk of diarrhoea. Creatine did not have an effect on functional decline in HD, nor on any other outcome studied.

Creatine has previously been studied in pre-symptomatic and symptomatic individuals. In PRECREST (NCT00592995) [9, 12] 64 premanifest and at-risk individuals were enrolled in a 6-month randomized placebo-controlled double-blinded study of up to 15 gm of oral creatine monohydrate bid, followed by a 12-months open-label extension period. In CREST-HD (NCT00026988) [13, 14] 69 people with manifest HD were enrolled in a 16-week randomized placebo-controlled double-blinded study of 4 gm of oral creatine monohydrate bid.

As in CREST-E, no safety concerns emerged in PRECREST apart from an increased risk of nausea and diarrhoea, but there was no change in clinical measures.

Further creatine clinical trials have been registered and the recruitment is completed (Pre-CREST-X [NCT01411150], Pre-CREST-X2 [NCT01411163], CREST-X [NCT01412151]) but to our knowledge, their results are not public yet.

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CONFLICTS OF INTEREST
FBR and EJW were sub-investigators on LEGATO-HD (NCT02215616), and are sub-investigators on the IONIS HTTRx (NCT02519036) and IONIS HTTRx OLE (NCT03342053) trials, and EJW was a sub-investigator on the Amaryllis study (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, Wave Life Sciences, PTC Therapeutics 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.

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