Huntington’s Disease Clinical Trials Corner: February 2018

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Abstract. In the second edition of the Huntington’s Disease Clinical Trials Corner we list all currently registered and ongoing clinical trials, summarise the top-line results of the recently-announced IONIS-HTTRx trial (NCT02519036), expand on Wave Life Sciences’ PRECISION-HD1 (NCT03225833) and PRECISION-HD2 (NCT03225846), and cover one recently finished trial: the FIRST-HD deutetrabenazine trial (NCT01795859).

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.

Table 1

| Registration ID | Trial name    | Intervention   | Edition |
|-----------------|---------------|----------------|---------|
| NCT02519036     | IONIS-HTTRx   | IONIS-HTTRx    | September |
| NCT02215616     | LEGATO-HD     | Laquinimod     | 2017(6) |
| NCT02197130     | Amaryllis     | PF-02545920    |         |
| NCT02006472     | Pride-HD      | Pridopidine    |         |

In this edition, we summarise the recently-announced top-line results from the phase 1b/2a IONIS-HTTRx huntingtin-lowering antisense oligonucleotide (ASO) trial (NCT02519036) [1]; highlight the new Wave Life Sciences allele-selective ASO trials, PRECISION-HD1 (NCT03225833) [2] and PRECISION-HD2 (NCT03225846) [3], and summarise the results of the FIRST-HD (NCT01795859) [4, 5] trial of deutetrabenazine.

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 [6].

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

BREAKING NEWS

December 11th 2017 saw the initial announcement of top-line results from the first-in-human phase 1b/2a trial of IONIS-HTTRx, the first ASO designed to lower huntingtin protein (HTT) to be tested in people with HD (NCT02519036) [1]. The announcement came in the form of a press release from the sponsor, Ionis Pharmaceuticals [7], and was followed by substantial media coverage [8, 9]. As we detailed in the previous Clinical Trials Corner [6], the trial had safety as its primary endpoint. Encouragingly, the release reported that “the safety and tolerability profile . . .
| 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 | HD | 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 | HD | 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) |
| 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 centre) |
| NCT03019289   | – | Pridopidine | Dopaminergic stabilizer | Healthy individuals and HD | None | Pharmacodynamic efficacy at 1 day | Single dose, open-label, single group trial | 38 | Teva Branded Pharmaceutical Products, R&D Inc. | Germany (single centre) |
| 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 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 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 | Early and moderate HD with irritability | 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)      |
| NCT02494778      | Open PRIDE-HD | Pridopidine                          | Dopaminergic stabilizer | PRIDE-HD completers        | None             | Safety at 104 weeks                                                           | Single group, open label extension of PRIDE-HD                              | 300                 | Teva Branded Pharmaceutical Products, R&D Inc.                           | Australia, Austria, Canada, Denmark, France, Germany, Italy, Netherlands, Poland, Russia, UK, 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               | 116                 | 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)   |
| NCT Identifier | Trial Name | Drug | Primary Outcomes | Study Design | Sponsor | Principal Investigator | Country/Centres |
|---------------|------------|------|------------------|-------------|---------|------------------------|-----------------|
| NCT0215616    | 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 (multicentre) |
| 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 (multicentre) |
| 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 (multicentre) |
| NCT00632645   | NEUROHD    | Olanzapine Dopamine agonist | HD with motor or behavioural symptoms | Tetrabenazine or tiapride | Efficacy at 12 months | Randomized, open-label, controlled, parallel trial | 180 | Assistance Publique – Hôpitaux de Paris, Teva Branded Pharmaceutical Products, R&D Inc | France (single centre) |
| NCT01306929   | OPEN-HART  | Pridopidine Dopaminergic stabilizer | HART or PRIDE-HD completers | None | Safety at 2 years | Single group, open label extension of HART | 235 | Teva Branded Pharmaceutical Products, R&D Inc | Canada, USA (multicentre) |
| 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 |
| ACTRN12616001-611415 | 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) |
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). 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 ∗

| Registration ID | Trial name | Intervention | Mechanism of Action | Population | Comparison | Main outcome | Study design | Estimated Enrollment | 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 | 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) |
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). 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 *.

| Registration ID | Trial name | Intervention | Mechanism of Action | Population | Comparison | Main outcome | Study design | Estimated Enrolment | Sponsor | Location |
|----------------|------------|--------------|---------------------|------------|------------|--------------|--------------|---------------------|---------|----------|
| 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 (multicentre) |
| 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) |
| NCT01879267  | –          | Endurance exercise training | Physiotherapy | HD and healthy controls | None | Motor effects 6 months | Single group, open-label trial with parallel healthy controls arm | 40      | University of Zurich | Switzerland (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) |

(Continued)
| Registration ID | Trial name | Intervention | Mechanism of Action | Population | Comparison | Main outcome | Study design | Estimated Enrolment | Sponsor | Location |
|----------------|------------|--------------|---------------------|------------|------------|--------------|--------------|-------------------|---------|----------|
| 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) |
| 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) |
supports continued development”. More excitingly, dose-dependent reductions in cerebrospinal fluid mutant huntingtin concentration were seen in patients who received IONIS-HTTRx. C. Frank Bennett, Ionis’ Senior Vice President of Research, noted that the mutant huntingtin reduction “substantially exceeded our expectations”. As a result, Roche has exercised its option to license the drug and will now be responsible for future development of the program. In a separate statement for the HD community, Ionis confirmed that an efficacy trial was planned and that “future studies for the program will be conducted globally, including in the US” [10]. Meanwhile, an open-label extension is underway for the 46 participants who took part in the original study (Table 2, NCT03342053) [11].

This is a significant positive announcement in a therapeutic program with substantial promise for disease-modification in HD. Naturally, it will need to be supported by release of more detailed data from the trial, and peer-reviewed publication of the results. The sponsor has committed to supplying these updates in the first half of 2018 [10].

**ONGOING CLINICAL TRIALS**

A list of all ongoing clinical trials is given in Tables 2, 3 and 4.

**PRECISION-HD1 (NCT03225833) and PRECISION-HD2 (NCT03225846)**

**Study titles:** A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 1b/2a Study of WVE-120101 Administered Intrathecally in Patients With Huntington’s Disease [2] and A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 1b/2a Study of WVE-120102 Administered Intrathecally in Patients With Huntington’s Disease [3].

**Intervention:** Respectively WVE-120101 and WVE-120102, two distinct allele-selective ASOs [12].

**Description:** The PRECISION-HD trials aim to compare the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple ascending doses of WVE-120101 and WVE-120102, respectively, administered intrathecally, comparing with intrathecal placebo, for disease modification in people with HD (i.e. clinical diagnostic motor features of HD, a Unified Huntington’s Disease Rating Scale (UHDRS) Diagnostic Confidence Level of 4, and a UHDRS Total Functional Capacity (TFC) between 13 and 7, inclusively) who carry a targeted single nucleotide polymorphism (SNP) rs362307 or rs362331, respectively, and are aged between 25 and 65 years old.

These trials are phase 1b/2a, multi-centre, international, randomized, placebo controlled, double-blind, parallel studies. They have a combined single ascending dose/multiple ascending dose design, comprising four cohorts of progressively higher ASO doses. In each cohort, participants will be allocated to receive a single dosage or three dosages of the ASO or a placebo. Each trial has the recruitment target of 48 participants; currently recruitment is open in Canada and Poland. The WVE-120101 and WVE-120102 compounds are ASOs targeting the pre-mRNA transcript of two allelic variants linked to the expanded CAG repeat tract in the HTT gene, with the aim of selectively reducing the production of mutant huntingtin protein while leaving the level of wild-type huntingtin protein relatively unaltered. Each participant’s involvement will last for 210 days.

The primary outcome is safety and tolerability at 210 days. The secondary outcomes involve pharmacokinetic measurements in plasma; pharmacodynamic measures in cerebrospinal fluid, including mutant huntingtin; and the UHDRS TFC.

**Sponsors/funders:** Wave Life Sciences Ltd.

**Comments:** The CAG expansion in the HTT gene is frequently allelically linked to three different SNPs that collectively are thought to be present in at least 80% of the gene expansion carriers of European ancestry [13]. These two trials are running in parallel and will target two of these SNPs. Participants’ DNA samples will first be screened for the presence of one of both SNPs, and then further tested to establish whether either SNP is allelic to the HTT CAG expansion.

While the molecule tested in the IONIS-HTTRx trial and its open-label extension (NCT02519036) [1] is expected to reduce the translation of both wild-type and mutant pre-mRNA, the PRECISION-HD ASOs were designed to target selectively the mutant pre-mRNA and mark it for degradation by RNase H. This selectivity is attained by means of targeting the most frequent SNPs associated with mutant HTT. The theoretical advantage is that this may reduce the potential long-term risk stemming from lowering of wild-type huntingtin and associated loss-of-function [14].

However, it is also worth noting that no safety concerns have so far been identified in the ongoing, allele-nonselective IONIS-HTTRx programme [6].
Wave’s platform is also distinguished by the ability to specify the chirality of each phosphorothioate bond in the ASO backbone, which has the potential to improve characteristics such as stability and target mRNA degradation [15]. Each approach – both in terms of chiral purity and allele-selectivity – has potential advantages and disadvantages [12]. Each SNP-selective compound will have to go through independent testing and approval; the testing process to establish suitability is novel and time-consuming; and some mutation-carriers will be ineligible by virtue of possessing no suitable SNPs.

Together, the Wave and IONIS platforms will be informative and provide safety and efficacy information relating to different HTT lowering approaches.

COMPLETED CLINICAL TRIALS

FIRST-HD (NCT01795859)

Study title: A Randomized Double-Blind, Placebo-Controlled Study of SD-809 Extended Release for the Treatment of Chorea Associated With Huntington Disease [4, 16].

Intervention: Deutetrabenazine or SD-809, a vesicular monoamine transporter type 2 (VMAT2) selective inhibitor.

Description: The goal of FIRST-HD trial was to compare the efficacy and safety of oral deutetrabenazine against an oral placebo, both taken twice daily and titrated to optimal dosage, for symptomatic relief of chorea in adults with stage 1 to 3 manifest HD (i.e. motor signs characteristic of HD plus HTT CAG repeat length ≥ 36 plus a UHDRS TFC ≥ 5) and with significant chorea (i.e. a UHDRS total maximum chorea score (TMC) of 8 or higher).

This trial was a phase 3, multi-centre, international, randomized, placebo controlled, double blind, parallel study. It recruited 90 participants from Canada and the United States. Participant involvement lasted for 13 weeks.

The primary outcome was change from baseline in the UHDRS TMC at weeks 9 and 12. The UHDRS TMC is a subscore of UHDRS total motor score (TMS) that only includes the chorea-related items, and ranges from 0 to 28. The secondary outcomes were the Patient Global Impression of Change (PGIC), the Clinician Global Impression Change (CGIC), the Short Form 36 Health Survey (SF-36), the Berg Balance Test (BBT), and adverse events.

Sponsors/funders: Teva Pharmaceutical Industries

Results: The trial was completed on December 2014 and the results published in July 2016 [16]. It showed deutetrabenazine to be superior to placebo in decreasing chorea associated with HD, objectively and subjectively, and to improve quality of life, but not balance. Interestingly, in a post-hoc analysis, dystonia subscores on TMS also lessened with deutetrabenazine. In regards to safety, deutetrabenazine was comparable with placebo, with the exception of weight gain that was more prevalent in the active treatment arm. It is noteworthy that this study was not powered to investigate adverse events and further information is required to draw definitive conclusions about safety.

In April 2017, the FDA approved this drug for the treatment of chorea associated with HD. Like tetrabenazine, its label includes a contraindication for patients who are suicidal, or who have untreated or inadequately treated depression.

Deutetrabenazine is a modified version of tetrabenazine containing deuterium (i.e. a stable isotope of hydrogen with mass number of 2) in strategic positions. This modification is intended to provide better pharmacokinetic properties (i.e. slower enzymatic degradation) to this otherwise chemically-identical compound, due to stronger bonds between carbon and deuterium.

Still, little is known about how deutetrabenazine compares with tetrabenazine, an older VMAT2 inhibitor also approved by FDA. In ARC-HD—a multicentre, international, single arm, open label study – the Huntington Study Group explored the safety of switching overnight from a stable and efficacious dosage of tetrabenazine to deutetrabenazine (NCT01897896) [17]. In a preliminary report, about 50% of the sample had at least one adverse event, but the drug was well tolerated with low rates of neuropsychiatric adverse events [18].

Unfortunately no head-to-head blinded comparison has been made between these compounds or is planned. Indirect treatment comparisons showed no apparent efficacy difference [19]. The safety results are contradictory [19, 20], possibly due to a statistical artefact [21]. Overall these results call for close post-licensing surveillance to guide informed prescribing decisions.

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CONFLICTS OF INTEREST

FBR and EJW are sub-investigators on LEGATO-HD (NCT02215616), IONIS HTTRx (NCT02519036) and IONIS HTTRx OLE (NCT03342053), 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 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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