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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-HTT$_{RX}$ 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
Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Corner

Registration ID	Trial name	Intervention	Edition
NCT02519036	IONIS-HTTRx	IONIS-HTT$_{Rx}$	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-HTT$_{RX}$ 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-HTT$_{RX}$, 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 …

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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). N/S, not specified; PD, Parkinson's disease; VMAT2, Vesicular Monoamine Transporter 2. 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
NCT03342053*	IONIS-HTT_{RX} 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 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*)

Table 2
(*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)

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 encephalo-myelitis 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)
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,	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 (multi centre)
NCT00514774	UDCA-HD	Ursodiol	Bile acid	HD	Placebo	Safety, tolerability and pharmacokinet-ics 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
ACTRN12616001611415	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 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	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	Esimated Enrolment	Sponsor	Location
NCT03344601*	PACE-HD	Supported structured aerobic exercise training program	Physiotherapy	HD	Activity as usual	Data completeness, recruitment, retention, asfety, adherence, fidelity and acceptability at 12 months	Nested open-label, randomized controlled parallell 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)
ACTRN12617 001269325*	–	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*)

Table 4
(*Continued*)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Esimated 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-HTT_{Rx}. 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-HTT_{Rx} 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-HTT_{Rx} 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 $\geq$36 plus a UHDRS TFC $\geq$ 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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HDClarity study) and Medical Research Council UK (salary support to EJW).

CONFLICTS OF INTEREST

FBR and EJW are sub-investigators on LEGATO-HD (NCT02215616), IONIS HTT_{Rx} (NCT02519036) and IONIS HTT_{Rx} 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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