

# 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) [1], and summarise the results of the recently published CREST-E trial (NCT00712426) [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 [4].

If you would like to draw attention to specific trials, please feel free to email us at: [f.rodriques@ucl.ac.uk](mailto:f.rodriques@ucl.ac.uk) and [e.wild@ucl.ac.uk](mailto: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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## SIGNAL (NCT02481674)

### Study title

VX15/2503 Treatment for Huntington's Disease (SIGNAL) [1].

### Intervention

VX15/2503 (20 mg/kg), an anti-semaphorin 4D antibody [5].

### Description

The SIGNAL trial, sponsored by Vaccinex (Rochester, NY, USA), aims to evaluate the safety, tolerability, pharmacokinetics and efficacy of monthly intra-venous VX15/2503 in adults ( $\geq 21$  years of age) with late prodromal (i.e. a CAG-age Product superior to 200 and a Unified Huntington's Disease Rating Scale [UHDRS] Diagnostic Confidence Level of 2 or 3) and early manifest HD (i.e. a UHDRS Diagnostic Confidence Level of 4 and a UHDRS Total Functional Capacity [TFC] above or equal to 11), comparing with intra-venous placebo, for disease modification.

This trial is phase 2, multi-centre, national, randomized, placebo controlled, double-blind, parallel study. It is divided into cohort A and cohort B, and will involve 240 participants. Cohort A recruited 36 participants and was completed in December 2015.

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 <sub>Rx</sub>	September 2017 [4]
NCT02215616	LEGATO-HD	Laquinimod	
NCT02197130	Amaryllis	PF-02545920	
NCT02006472	Pride-HD	Pridopidine	
NCT03225833	PRECISION-HD1	WVE-120101	February 2018 [15]
NCT03225846	PRECISION-HD2	WVE-120102	
NCT01795859	FIRST-HD	Deutetrabenazine	
NCT02481674	SIGNAL	VX15/2503	August 2018
NCT00712426	CREST-E	Creatine	

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-HTT <sub>RX</sub> OLE	ISIS 443139	Allele-nonspecific 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)
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)
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)
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)

Table 2  
(Continued)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
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 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
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)

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	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 \*.

Table 4

Ongoing non-invasive non-pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington's disease (HD)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
CTRI/2018/01/011359*	–	Repetitive transcranial magnetic stimulation	Transcranial magnetic stimulation	Early to moderate HD and PD	HD 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	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)

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  $\geq 36$  plus a UHDRS Total Functional Capacity  $\geq 7$ ).

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 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 *HTT*<sub>Rx</sub> (NCT02519036) and IONIS *HTT*<sub>Rx</sub> 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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