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Clinical Trials Corner

Huntington's Disease Clinical Trials Corner: November 2022

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Abstract. In this edition of the Huntington's Disease Clinical Trials Corner, we expand on the PIVOT HD (PTC518), and SIGNAL (pepinemab) trials, and list all currently registered and ongoing clinical trials in Huntington's disease.

We also introduce a 'breaking news' section highlighting recent updates about the SELECT HD, uniQure AMT-130, and VIBRANT HD clinical trials.

Keywords: Huntington's disease, clinical trials

INTRODUCTION

The Clinical Trials Corner is a regular feature 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 ongoing PIVOT HD (NCT05358717) [1] and the recently completed SIGNAL (NCT05358717) [2] clinical trials. 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 first edition of Huntington's Disease Clinical Trials Corner [3].

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

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In this edition we also introduce a 'breaking news' section where we will provide recent updates about the ongoing SELECT-HD (NCT05032196) [4], VIBRANT-HD (NCT05111249) [5], and uniQure AMT-130 (NCT05243017 and NCT04120493) [6, 7] trials.

ONGOING CLINICAL TRIALS

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

PIVOT HD (*NCT05358717*)

Study title: A Study to Evaluate the Safety and Efficacy of PTC518 in Participants With Huntington's Disease (HD) [1].

Intervention: Once daily oral PTC518, a small molecule *HTT* splicing modulator.

Description: The PIVOT HD study aims to evaluate the safety and efficacy of PTC518, a Huntingtin (HTT) lowering small molecule in patients with HD. Participants need to be fully independent with scores in the HD normalized prognostic index (PINHD)

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Table 1
Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Corner

	Trial name	Intervention	Edition
NCT02519036	IONIS-HTTRx	IONIS-HTT$_{Rx}$[a]	September 2017 [3]
NCT02215616	LEGATO-HD	Laquinimod	
NCT02197130	Amaryllis	PF-02545920	
NCT02006472	PRIDE-HD	Pridopidine	
NCT03225833	PRECISION-HD1	WVE-120101	February 2018 [18]
NCT03225846	PRECISION-HD2	WVE-120102	
NCT01795859	FIRST-HD	Deutetrabenazine	
NCT02481674	SIGNAL	VX15/2503	August 2018 [19]
NCT00712426	CREST-E	Creatine	
NCT03761849	GENERATION-HD1	RG6042[a]	January 2019 [20]
NCT03344601	PACE-HD	Physical activity	
NCT02535884	HD-DBS	Deep brain stimulation	June 2019 [21]
NCT02453061	TRIHEP3	Triheptanoin	
NCT04120493	AMT-130	AAV5-miHTT	April 2020 [22]
NCT04102579	KINECT-HD	Valbenazine	
NCT05111249	VIBRANT-HD	Branaplam	April 2022 [23]
NCT04514367	ANX005	ANX-005	
NCT04514367	SHIELD HD	Observational study	
NCT03761849	GENERATION-HD1	Tominersen[a]	
NCT05032196	SELECT-HD	WVE-003	
NCT03225833	PRECISION-HD1	WVE-120101	
NCT03225846	PRECISION-HD2	WVE-120102	
NCT02481674	SIGNAL	Pepinemab[b]	November 2022
NCT05358717	PIVOT HD	PTC518	

[a]IONIS-HTT$_{Rx}$, RG6042, and tominersen refer to the same molecule. [b]VX15/2503 and pepinemab refer to the same molecule.

between 0.18 and 4.93, encompassing from prodromal to early manifest participants.

PIVOT HD is a phase 2a randomized, multicentre, international, placebo-controlled, parallel assignment trial with a recruitment target of 162 participants. Participants will be randomized to receive 5 mg, 10 mg or 20 mg of PTC518 or placebo during 12 weeks. Recruitment is already open in the United States, Germany and the United Kingdom while sites in Australia, France and Netherlands are expected to start recruitment soon. The primary outcome will be safety and tolerability at 113 days while secondary outcomes include reduction in mutant HTT (mHTT) protein in cerebrospinal fluid (CSF) and total mHTT protein in blood, alongside effects in imaging biomarkers.

Sponsor/Funders: PTC Therapeutics.

Comments: PTC518 has been specifically developed for HD through a drug discovery platform to identify splicing modulators among > 300,000 compounds. PTC518 is an orally bioavailable small molecule that modulates the splicing of *HTT* pre-mRNA leading to the inclusion of a pseudoexon [8]. This inclusion results in a premature termination codon, leading to the degradation of *HTT* mRNA. Consequently, non-allele selective decreases in the HTT protein are expected. PTC518 is expected to decrease mHTT uniformly across the brain, including cortical and striatal areas and drug effects are potentially titratable and reversible. The sponsor claims that, in contrast to branaplam —— the other splicing modulator to have reached a clinical trial in HD – PTC518 is not effluxed from brain, permitting lower doses with less potential liability from systemic HTT lowering. The study drug has been already tested in healthy volunteers during a phase 1 clinical trial (PTC518-CNS-001-HD) showing a favourable safety profile, and leading to dose-dependent decreases in *HTT* mRNA in blood [9]. There is a plan for a longer open-label extension trial after the termination of the phase 2a study.

COMPLETED CLINICAL TRIALS

SIGNAL (*NCT02481674*)

Study title: A Study in Subjects with Late Prodromal and Early Manifest HD to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of Pepinemab (SIGNAL)

Intervention: Pepinemab (VX15/2503), an anti-semaphorin 4D antibody (SEMA4D) [2], administered as once monthly infusions

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. Note: IONIS-HTT_{Rx}, ISIS 443139, RG6042 and tominersen refer to the same molecule. 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
NCT05509153*	–	N-Acetyl Cysteine	Antioxidant	Premanifest HD	Placebo	Efficacy at 36 months	Randomized, double-blind,	160	Western Sydney Local Health District	Australia
ISRCTN56240656*	FELL-HD	Felodipine	Calcium channel blocker	Early HD	None	Safety at 62 weeks	Non-randomised, multiple dose	18	Cambridge University	United Kingdom
NCT05358821*	–	SAGE-718	Positive allosteric modulator of NMDA	Early and moderate HD	Placebo	Change in cognition at 28 days	Double-blind, placebo-controlled, single dose design	80	Sage Therapeutics	United States
NCT05358717*	PIVOT HD	PTC518	Small molecule splicing modulator	PreHD, prodromal and early HD	Placebo	Safety at 113 days	Randomized, double-blind, placebo controlled, parallel assignment, multiple dose.	162	PTC therapeutics	France, Germany, Netherlands, United Kingdom, United States
NCT05475483*	–	SOM-3355 (bevantolol hydrochlo-ride)	Beta-blocker	Early and moderate HD	Placebo	Efficacy at 8 weeks	Randomized, double-blind, placebo-controlled, parallel assignment multiple-dose,	129	SOM Biotech	France, Germany, Italy, Poland, Spain, Switzerland, United Kingdom
ACTRN12621001755820*	–	SLS-005 (Trehalose)	Disaccharide	Early HD, ALS, SCA3	None	Efficacy at 24 weeks	Non-randomized, open-label	15-18 (4 ALS, 10 HD, 4 SCA3)	Seelos Therapeutics	Australia

(*Continued*)

Table 2
(*Continued*)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
NCT05541627*	–	BV-101	AAV encoding for CYP46A1, enzyme converting cholesterol to 24-OH-cholesterol	Early HD	None	Safety at week 52	Non-randomized, open-label, sequential, single ascending dose	18	BrainVectis/AskBio	N/S
NCT05107128*	DIMENSION	SAGE-718	Positive allosteric modulator of NMDA	Early and moderate HD	Placebo	Change in cognition at 85 days	Double-blind, placebo-controlled, single dose design	178	Sage Therapeutics	Australia, Canada, United States
NCT05111249*	VIBRANT HD	Branaplam	Small molecule splicing modulator	Early HD	Placebo	Reduction of mHTT protein at week 17Safety at 104 weeks	Double-blind, placebo-controlled, multiple dose design	75	Novartis Pharmaceuti-cals	Belgium, Canada, France, Germany, Hungary, Italy, Spain, United Kingdom, United States
NCT05032196	SELECT-HD	WVE-003	Allele-selective antisense oligonu-cleotide	Early HD	Placebo	Safety at 36 weeks	Randomized, double-blind, placebo-controlled, combined single ascending dose/multiple ascending dose trial	36	Wave Life Sciences Ltd.	Australia, Canada, Denmark, France, Germany, Poland, Spain and United Kingdom

NCT05243017	–	AMT-130	rAAV5-miHTT	Early HD	None	Safety at 6 months	Non-randomized, sequential ascending, multiple-dose trial	15	UniQure Biopharma B.V.	Germany, Poland, United Kingdom
NCT04713982	–	Deutetrabenazine	VMAT2 inhibitor	HD with chorea	None	Change in speech outcome at 10 weeks	Single-arm open label trial	30	Vanderbilt University Medical Center	USA (single centre)
NCT04826692	–	Metformin	Antihyperglycemic/ AMPK activator	Early and moderate HD	Placebo	Change in cognition at 52 weeks	Randomized, parallel assignment, double-blinded trial	60	Instituto de Investigacion Sanitaria La Fe	Spain (single centre)
NCT04514367	–	ANX005	C1q inhibitor	Early HD	None	Safety at 36 weeks	Single-dose open label trial	28	Annexon, Inc	USA (multi-centre)
NCT04421339	–	Melatonin	Melatonin receptor agonist	HD with sleep disturbance	Placebo	Sleep quality at 9 weeks	Randomised, cross-over, single-blinded (partici-pant/caregiver)	20	The University of Texas Health Science Center, Houston	USA (single centre)
NCT04400331	–	Valbenazine	VMAT2 inhibitor	Early and moderate HD	None	Safety at 104 weeks	Open label, single arm trial	150	Neurocrine Biosciences	USA and Canada
NCT04301726	–	Deutetrabenazine	VMAT2 inhibitor	HD with dysphagia	Placebo	Dysphagia at 18 months	Randomized, parallel assignment, triple blinded trial	48	Fundacion Huntington Puerto Rico	N/S

(*Continued*)

Table 2
(*Continued*)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
NCT04478734	HUNTIAM	Thiamine and biotin	B vitamins	HD	Moderate vs High doses of thiamine and biotin	Safety at 52 weeks	Randomized, parallel assignment, open-label trial	24	Fundación Pública Andaluza para la gestión de la Investigación en Sevilla	Spain (single centre)
NCT04201834	–	Risperidone	Dopamine antagonist	Early and moderate HD with chorea	None	Change in motor scales at 12 weeks	Non-randomized, open label (assessor-blind), uncontrolled trial	12	University of Rochester	USA (single centre)
NCT04071639	–	Haloperidol, risperidone, sertraline and coenzyme Q10	Multiple (dopamine antagonists, selective serotonin reuptake inhibitor, dietary supplement)	Early and moderate HD	Coenzyme Q10	Efficacy at 5 years	Randomized, open label, controlled, parallel trial	100	Second Affiliated Hospital, School of Medicine, Zhejiang University	China (single centre)
NCT04120493	AMT-130	rAAV5-miHTT	Nonselective miRNA	Early HD	Sham intervention	Safety at 18 months	Randomized, double-blind, sham-controlled, parallel trial	26	UniQure Biopharma B.V.	USA (multi-centre)
NCT04102579	KINECT-HD	Valbenazine	VMAT2 inhibitor	HD with chorea	Placebo	Efficacy at 12 weeks	Randomized, double-blind, placebo-controlled, parallel trial	120	Neurocrine Biosciences, Huntington Study Group	USA (multi-centre)

EUCTR2019-002178-30-DK	–	WVE-120102	Allele-selective antisense oligonucleotide	HD	None	Safety and tolerability at 97 weeks	Open-label extension	70	Wave Life Sciences Ltd.	Australia, Canada, Denmark, France, Poland and United Kingdom (multi-centre)
NCT04000594	GEN-PEAK	RG6042	Allele-nonselective antisense oligonucleotide	HD	None	Pharmacodynamics and pharmacokinetics at multiple timepoints until 6 months	Non-randomized. open-label, multiple-dose, parallel trial	20	Hoffmann-La Roche	The Netherlands and UK (multi-centre)
NCT03980938	–	Neflamapimod	p38α MAPK inhibitor	Early HD	Placebo	Change in cognitive scales at 10 weeks	Randomized, double-blind, placebo-controlled, cross-over trial	16	EIP Pharma Inc, Voisin Consulting, Inc.	UK (single centre)
NCT03842969	GEN-EXTEND	RG6042	Allele-nonselective antisense oligonucleotide	HD	None	Safety and tolerability at up to 5 years	Open-label extension	1050	Hoffmann-La Roche	USA, Canada, Europe (multi-centre)
NCT03761849	GENERATION-HD1	RG6042	Allele-nonselective antisense oligonucleotide	HD	Placebo	Clinical efficacy at 101 weeks	Randomized, double-blind, placebo-controlled, parallel trial	909	Hoffmann-La Roche	USA, Canada, Europe (multi-centre)
NCT03515213	–	Fenofibrate	PPARα agonist	HD	Placebo	Pharmacodynamics at 6 months	Randomized, double-blind, placebo-controlled, parallel trial	20	University of California, Irvine	USA (single centre)

(*Continued*)

Table 2
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Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
NCT03764215	Tasigna HD	Nilotinib	Selective Bcr-Abl tyrosine kinase inihbitor	HD	None	Safety, tolerability and pharma-codynamics at 3 months	Open label, multiple ascending dose	20	Georgetown University	USA (single centre)
NCT03225833	PRECISION-HD1	WVE-120101	Allele-selective antisense oligonu-cleotide	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.	Australia, Canada, Denmark, France, Poland and United Kingdom (multi-centre)
NCT03225846	PRECISION-HD2	WVE-120102	Allele-selective antisense oligonu-cleotide	HD	Placebo	Safety and tolerability at 1 and 120 days	Randomized, double-blind, placebo-controlled, combined single ascending dose/multiple ascending dose trial	60	Wave Life Sciences Ltd.	Australia, Canada, Denmark, France, Poland and United Kingdom (multi-centre)
NCT02453061	TRIHEP 3	Triheptanoin	Anaplerotic therapy	HD	Safflower oil	Pharmacodynamic efficacy at 6 months	Randomized, double-blind, controlled, parallel trial	100	Institut National de la Santé Et de la Recherche Médicale, Ultragenyx Pharmaceuti-cal 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)
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)
EUCTR2013-002545-10-SE	OSU6162Open1309	(-)-OSU616	Monoaminergic stabilizer	HD, PD, brain trauma, stroke, myalgic encephalomyeli-tis and narcolepsy	None	Safety at 3, 6 and 12 months	Single group, open-label trial	240	A. Carlsson Research AB	Sweden (multi-centre)
NCT00514774	UDCA-HD	Ursodiol	Bile acid	HD	Placebo	Safety, tolerability and pharma-cokinetics 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

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	Esimated Enrolment	Sponsor	Location
NCT04244513	–	GPi DBS	Deep brain stimulation	HD with chorea	Sham intervention	Efficacy at 3 and 6 months	Randomized, double-blind, sham-controlled, cross-over trial	40	Beijing Municipal Administration of Hospitals, Medtronic	China (multi-centre)
NCT04219241	ADORE-EXT	Cellavita	Stem cell therapy	HD	None	Efficacy and safety at 2 years	Open label extension	35	Azidus Brasil, Cellavita Pesquisa Científica Ltda	Brazil (single centre)
ISRCTN52651778	TRIDENT	Foetal stem cell transplant	Stem cell therapy	Early stage HD	Usual care	Safety at 4 weeks	Randomized, open label, controlled, parallel trial	30	Cardiff University	UK (single centre)
NCT02728115	SAVE-DH	Cellavita	Stem cell therapy	HD	None	Safety at 5 years	Non-randomized, open label, uncontrolled, parallel trial	6	Azidus Brasil	Brazil (single centre)
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, France 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)
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; N/S, not specified, 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
RBR-463yhb3*	–	Multimodal physiotherapy	Balance intervention with rhythmic cues	HD	Educational program	Balance	Randomized, double-blinded, parallel assignment trial	36	São Paulo University	Brazil
ACTRN12622000908730*	–	Online platform	Computerised cognitive training	Premanifest and early HD	Lifestyle education	Change in cognition at 12 weeks	Randomized, blinded (investigator, statistician) parallel assignment trial	50	Monash University, Australia	Australia
ISRCTN11906973*	HD-DRUM	Training app	Drumming	Premanifest, early and moderate HD	Standard medical care	Feasibility	Randomized, parallel assignment trial	50	Cardiff University, UK	UK
NCT05326451*	–	Transcranial Direct Current Stimulation	Transcranial electrical stimulation	Early and moderate HD	None	Treatment completion, acceptability and safety	Non-randomized, open label, single group trial	10	The University of Texas Health Science Center, Houston, USA	USA (single centre)
ACTRN12622000345785*	–	Multidisciplinary therapy coaching program	Education	Premanifest and early HD	Lifestyle guidance	Barriers and motivators to engagement in telehealth interventions and digital health literacy	Randomized, single blind, parallel assignment trial	84	Perpetual limited	Australia

NCT04917133	HUNT'ACTIV	Adapted physical workshops plus classic 4-week rehabilitation program	Physical activity, cycling, horse riding, situation tests, cultural outings	Mid-stage HD	Classic 4-week rehabilitation program	Motor function at 1 month	Randomized, parallel assignment trial	32	Assistance Publique - Hopitaux de Paris	France (single centre)
NCT04429230	–	Transcranial pulsed current stimulation	Transcranial electrical stimulation	HD	Sham intervention	Feasibility at one year	Randomised, crossover double-blinded trial	15	Western University, Canada	N/S
ACTRN12620000281998	–	Ketogenic diet	–	HD	None	Change in cognition and motor scores at 12 weeks	Non-randomized, open label, single group trial	10	Waikato Hospital	New Zealand (-)
ACTRN12619000870156	–	Transcranial alternating current stimulation	Transcranial magnetic stimulation	Premanifest and early HD	Sham intervention	Biomarkers	Randomized, open-label, cross-over trials	60	Monash University, Epworth Centre for Innovation in Mental Health	Australia (single centre)
ACTRN12618001717246	–	Multidisciplinary therapy program	Exercise, cognitive training, lifestyle guidance and social activities	Premanifest HD	Standard of care	Feasibility and safety	Clustered, non-randomized, open label, parallel trial	40	Edith Cowan University, Deakin University and Lotterywest	Australia (two centres)
NCT03417583	–	Neuropsychiatric treatment protocol	Multidisciplinary intervention	HD with neuropsychiatric symptoms	Standard of care	Change in quality of life at 18 months	Non-randomized, assessor-blinded, parallel trial	100	Vanderbilt University Medical Center and Teva Pharmaceuticals USA	USA (single centre)

(*Continued*)

Table 4
(*Continued*)

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	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 (multicentre)
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)

Description: The SIGNAL trial aimed to investigate the effects of pepinemab in participants with early manifest or late prodromal HD. It was divided into two cohorts. Cohort A included 36 participants receiving placebo or pepinemab during 6 months, followed by 6 months where the drug was administered to all study participants.

In cohort B early manifest ($n = 179$) and late prodromal ($n = 86$) HD participants received four-weekly intravenous administrations of pepinemab at a dose of 20 mg/kg. Participants were treated during 18 months followed by 3 months safety follow up. The primary outcome for this study was safety and tolerability. Coprimary efficacy outcomes included the clinical global impression of change (CGIC) and two subitems from the HD cognitive assessment battery (HD CAB): the one-touch stockings of Cambridge (OTS) and paced tapping (PTAP).

Sponsor/Funders: Vaccinex Inc.

Comments: Neuroinflammation is one of the core pathogenic mechanisms in HD [10]. SEMA4D is a protein of the semaphorin family involved in immune regulation [11]. In the brain, it regulates the transition to reactive states in glial cells [2]. Blockade of SEMA4D with immunotherapy improved pathology and clinical phenotypes in the YAC128 mice [12].

The safety profile showed similar tolerability and adverse events between participants in the active drug and participants in the placebo group. Efficacy outcomes for early manifest participants did not show significant differences in the CGIC scale, although there were statistically significant changes favouring the active arm in the OTS, while findings in the PTAP were not significant. In contrast, clinical scales including the UHDRS-Total Motor Score, UHDRS-Total Functional Capacity; or the quantitative Q-motor assessment tool did not differ between groups.

Structural imaging findings showed statistically significantly reduced rates of caudate atrophy treatment and increased FDG-PET signal in patients on active treatment. The sponsor has interpreted these as supportive of a therapeutic effect, but it is also possible that other explanations such as inflammation or oedema could produce these outcomes.

There were no significant differences in efficacy outcomes among late prodromal participants. A *post hoc* analysis of early manifest participants showed that participants with more advanced disease tended to show better clinical outcomes. In consequence, a future phase 3 clinical trial with pepinemab could include participants with moderate stage HD. It has not yet been announced whether a larger trial will be run or what form it may take.

BREAKING NEWS

In this new section we will provide brief updates about ongoing or recently terminated clinical trials.

The SELECT-HD (NCT05032196) [4] clinical trial investigates WVE-003, an allele selective antisense oligonucleotide targeting *HTT* pre-mRNA at different doses versus placebo. A recent press release from Wave Life Sciences Ltd. reported that participants receiving a single administration of WVE-003 (combined data for 30 mg and 60 mg groups) had decreased CSF mHTT concentrations compared to baseline, while the concentrations of the wild-type Huntingtin (wtHTT) protein remained unchanged. There was no dose-dependent effect found and nor did these results reach statistical significance. Additional subjects are now being recruited to these dosing cohorts. Adverse events were well balanced between groups, but there were increases in the concentrations of CSF neurofilament light protein (NfL) -a marker of axonal damage- from baseline in some patients. The trial is currently ongoing and a higher dose cohort is expected to be recruited soon [13].

In contrast, the VIBRANT-HD (NCT05111249) [5] clinical trial evaluates branaplam, an orally available small molecule repurposed from spinal muscular atrophy (SMA) trials. Branaplam decreases the concentrations of mHTT and wtHTT through pseudoexon inclusion [14]. Dosing in VIBRANT-HD has been suspended in August based on findings suggesting incipient peripheral neuropathy in some patients, including clinical manifestations, neurophysiological abnormalities and increases in blood NfL [15].

Finally, the uniQure AMT-130 clinical trials (NCT05243017 and NCT04120493) [6, 7] investigates the effects of AMT-130. AMT-130 consists of a viral vector containing a microRNA targeting the *HTT* gene (AAV5-miHTT). This gene therapy is administered intracranially and its effects are expected to last for years. AMT-130 has been administered to 10 patients with early HD at a low dose, showing decreases of CSF mHTT of 53.8% compared to baseline in the treated group [16]. However, in July three suspected unexpected adverse reactions (SUSARs) were reported among participants in the higher-dose cohort. These participants showed inflammatory responses and severe

headaches in the weeks after drug administration and have recovered since then. Enrolment in the lower dose cohort continued but recruitment was paused in the higher dose cohort waiting for further safety review, being restarted only recently [17].

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CONFLICTS OF INTEREST

CEF was an investigator in the LEGATO-HD (NCT02215616), IONIS HTT_{Rx} OLE (NCT-03342053), GENERATION-HD1 (NCT03761849), Roche Natural History Study (NCT03664804), Roche GEN-EXTEND (NCT03842969), Roche GEN-PEAK (NCT04000594), uniQure AMT-130 (NCT05243017), Triplet Therapeutics SHIELD-HD (NCT04406636), VIBRANT-HD (NCT05111249), PIVOT HD (NCT05358717) trials.

SJT has undertaken consultancy services for Annexon, Alphasights, Alnylam Pharmaceuticals Inc., Atalanta Pharmaceuticals (SAB), F. Hoffmann-La Roche Ltd/ Genentech, Guidepoint, Horama, Locanobio, LoQus23 Therapeutics Ltd (SAB), Novartis Pharma, PTC Therapeutics, Sanofi, Spark Therapeutics, Takeda Pharmaceuticals Ltd, Triplet Therapeutics (SAB), University College Irvine and Vertex Pharmaceuticals Incorporated. All honoraria for these consultancies were paid through the offices of UCL Consultants Ltd., a wholly owned subsidiary of University College London. SJT has a patent Application number 2105484.6 on the FAN1-MLH1 interaction and structural analogs licensed to Adrestia Therapeutics. SJT was an investigator on IONIS HTT_{Rx} (NCT02519036), IONIS HTT_{Rx} OLE (NCT03342053), GENERATION-HD1 (NCT03761849), Roche Natural History Study (NCT03664804), uniQure AMT-130 (NCT05243017), SHIELD-HD (NCT04406636), PIVOT HD (NCT05358717) and Roche GEN-EXTEND (NCT03842969) trials.

EJW has undertaken consultancy/advisory board work with Hoffman La Roche Ltd, Triplet Therapeutics, Takeda, Vico Therapeutics, Voyager, Huntington Study Group, Teitur Trophics, EcoR1 Capital, PTC Therapeutics, Alnylam, Annexon Biosciences and Remix Therapeutics. He has participated in advisory boards for Hoffmann La Roche, Triplet therapeutics and PTC therapeutics. All honoraria for these consultancies were paid through the offices of UCL Consultants Ltd., a wholly owned subsidiary of University College London. He holds a stock option for Triplet Therapeutics in part compensation for advisory board membership. EJW was an investigator in the Amaryllis (NCT02197130), LEGATO-HD (NCT02215616), IONIS HTT_{Rx} (NCT02519036), IONIS HTT_{Rx} OLE (NCT03342053), GENERATION-HD1 (NCT03761849), Roche Natural History Study (NCT03664804), Roche GEN-EXTEND (NCT03842969), VIBRANT-HD (NCT05111249), PIVOT HD (NCT05358717), Roche GEN-PEAK trial (NCT04000594) and uniQure AMT-130 (NCT05243017).

The authors did not make use of confidential or privileged information: all materials included in this manuscript were collected from publicly available sources.

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