Huntington's Disease Clinical Trials Update: September 2024

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Abstract

In this edition of the Huntington's Disease Clinical Trials Update, we expand on the ongoing extension study of PTC518 from PTC Therapeutics, including 12-month interim results from the parent study. We also discuss 24-month interim results from uniQure's AMT-130 program and 28-week follow-up results from Wave Life Sciences' SELECT-HD clinical trial of WVE-003. Additionally, we provide a comprehensive listing of all currently registered and ongoing clinical trials in Huntington's disease.

Main text

Introduction

The Clinical Trials Update is a regular feature devoted to highlighting ongoing and recently completed clinical trials in Huntington's disease (HD). Clinical trials previously reviewed in this section are listed in Table 1.

We recently changed the title of this series from "Huntington's Disease Clinical Trials Corner" to "Huntington's Disease Clinical Trials Update". This reflects our commitment to delivering a comprehensive and scholarly exploration of the latest developments in HD research in a series that has been regularly published since 2017.

In this edition, we expand on the ongoing extension study of PTC518 (NCT06254482) from PTC Therapeutics,[1] including 12-month interim results from the parent study (NCT05358717).[2,3] In the "Breaking News" section, we discuss interim results from from uniQure's AMT-130 program (NCT04120493; NCT05243017),[4,5] which are based on 24-month follow-up data,[6] and interim results from Wave Life Sciences SELECT-HD clinical trial of WVE-003 (NCT05032196),[7] based on 28-week follow-up data.[8]

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 this series.[9]

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

Ongoing clinical trials

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

PTC518 (NCT06254482) Extension Study

Study Title: An Extension Study to Evaluate the Long-Term 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 aim of this extension study is to assess the long-term safety and pharmacodynamic effects of PTC518 in participants with HD. Participants who completed the treatment period in the parent study (NCT05358717),[2] meet the enrolment criteria, and opt in to participate in this extension study will first undergo baseline assessments, followed by 30 months of additional monitoring. In this extension study, all participants will receive active PTC518. Those who received PTC518 in the parent study will continue with the same blinded dose as before. Participants who were given a placebo in the parent study will be assigned a dose of PTC518 corresponding to their original randomization group. The primary outcomes are the number of participants with treatment-emergent adverse events (TEAEs) from baseline to month 30 and levels of blood total huntingtin protein (tHTT) from baseline to month 28. Secondary outcomes include changes from baseline in caudate volume, assessed by volumetric MRI at month 24; changes in composite Unified Huntington's Disease Rating Scale (cUHDRS) scores at month 24; cerebrospinal fluid (CSF) mutant huntingtin protein (mHTT) levels from baseline to month 24; and blood mHTT protein levels from baseline to month 28.

Sponsor/Funders: PTC Therapeutics

Comments: On 20th June 2024, PTC Therapeutics, Inc. released interim results from the phase IIa PIVOT-HD study of PTC518 (NCT05358717).[2,3] After 12 months of treatment of 32 participants during the parent study of PTC518 (NCT05358717),[2] PTC518 demonstrated a dose-dependent reduction in mHTT protein levels in both blood and cerebrospinal fluid (CSF), accompanied by positive trends in UHDRS Total Motor Score (UHDRS TMS) and cUHDRS, whilst also maintaining a favourable safety and tolerability profile.[3] The interim results showed that mHTT levels decreased by 22% and 43% in the blood and 21% and 43% in the CSF for the 5 mg and 10 mg doses, respectively. Additionally, at 12 months, treatment with PTC518 was associated with a trend of slowing of motor symptom progression, as assessed via UHDRS TMS, with TMS increasing by 2.0 points for the 5 mg dose and 1.3 points for the 10 mg dose, compared to a 4.9-point worsening in the placebo group.[3] Encouragingly, there was no increase in CSF neurofilament light (NfL) protein. NfL spikes were seen with branaplam and tominersen, but the absence of an increase with PTC518 demonstrates that neuroaxonal damage is neither an inevitable consequence of wild-type huntingtin protein lowering, nor a class effect of small-molecule HTT splice modulators. In addition to the 12-month interim results, the sponsor also announced that the Food and Drug Administration (FDA) has lifted the partial clinical hold on the program following a review of the PIVOT-HD data.

The ongoing PTC518 extension study (NCT06254482),[1] with an estimated enrolment of 250 participants and monitoring up to 30 months, will be pivotal in evaluating the long-term safety and pharmacodynamic effects of PTC518 in HD.

Breaking News

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

The **uniQure AMT-130** program (NCT04120493; NCT05243017) investigates the effects of AMT-130, a gene therapy that uses a viral vector (AAV5-miHTT) to deliver a microRNA targeting the *HTT* gene.[4,5] This treatment is administered intracranially, with its effects anticipated to persist for several years.

On 9th July 2024, uniQure released encouraging interim results from the phase I/II clinical trials of AMT-130 for HD at 24 months.[6] In an exploratory analysis, participants receiving the high-dose AMT-130 showed an 80% reduction in disease progression at 24 months, as measured by cUHDRS, compared to a propensity score-weighted external historical control group generated from two observational studies (TRACK-HD and PREDICT-HD). Additionally, CSF NfL levels, a key biomarker of neuroaxonal damage, were significantly reduced, with both high- and low-dose groups showing NfL levels below baseline at 24 months. These interim and post-hoc findings, which are not placebo controlled, will likely require validation in appropriate studies designed with more patients and longer follow-up. This analysis suggests that AMT-130 has the potential for both clinical and efficacy biomarker improvements. Given the favorable results to date, uniQure plans to meet with the FDA later this year to discuss accelerated clinical development, following its achievement of the Agency's Regenerative Medicine Advanced Therapy (RMAT) designation. The ongoing phase I/II clinical trials will continue to assess the safety, tolerability, and efficacy of AMT-130, aiming to support further development and potential regulatory approval.

The **Wave Life Sciences SELECT-HD** phase Ib/IIa clinical trial (NCT05032196) evaluated WVE-003,[7] an allele-selective antisense oligonucleotide (ASO) designed to target the single-nucleotide polymorphism (SNP) SNP3, when allelic to the expanded CAG repeat in *HTT* pre-mRNA. This multicenter, randomized, double-blind, placebo-controlled trial aimed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of intrathecally administered WVE-003 in participants with early-stage HD who carry the SNP3 variant.

On 25th June 2024, Wave Life Sciences released interim results during the study period of 28 weeks.[8] WVE-003 was reported to be generally safe and well-tolerated, with no serious adverse events. Significant reductions in mHTT protein levels were observed throughout the 28-week study period. At 24 weeks, the mean reduction in CSF mHTT levels was 46% compared to placebo (p=0.0007), and at 28 weeks, this reduction was sustained at 44% (p=0.0002), supporting the potential for quarterly or less frequent dosing. Wild-type huntingtin protein levels, while harder to interpret, appeared broadly preserved during the study, supporting the allele-selective mechanism of WVE-003. While most participants treated with WVE-003 were said to show CSF NfL levels that were comparable to placebo, most patients exhibited NfL increases that only returned to baseline after cessation of study drug, and in many cases exceeded the ~50% increase seen on average with the highest dose of tominersen treatment (120mg every 8-weeks), which was an early biomarker finding associated with the adverse clinical outcomes that resulted in the early termination of the GENERATION-HD1 trial. The sponsor did not share information about CSF leukocyte count,

total protein, or other biomarkers that could help shed light on the mechanism for these NfL increases. In the absence of such information, it is tempting to speculate whether the NfL increases with WVE-003 are driven by the similar mechanisms as for GENERATION-HD1 with one possibility being neuroinflammation due to ASO backbone overexposure. Given the results from AMT-130, it is less likely that this is due to depletion of wild-type huntingtin. Although the clinical trial was not powered to detect clinical outcomes, there was a trend toward slower motor decline, as measured by the UHDRS TMS, with a mean difference of 4.25 at 24 weeks compared to placebo, though this was not statistically significant. These interim results suggest that WVE-003 is achieving better target engagement than its predecessors, and may offer the potential for therapeutic benefit, but the sponsor will need to give careful thought to the mechanism of NfL increases and how to explain and/or mitigate them in future trials.[8]

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Tables

Table 1

Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Update.

[a]IONIS-HTT_{Rx}, RG6042, and tominersen refer to the same molecule.

[b]VX15/2503 and pepinemab refer to the same molecule.

[c]AAVrh10.CAG.hCYP46A1, BV-101, and AB-1001 refer to the same molecule.

	Trial Name	Intervention	Edition
NCT02519036	IONIS-HTTRx	IONIS-HTT_{Rx}[a]	September 2017[9]
NCT02215616	LEGATO-HD	Laquinimod	
NCT02197130	Amaryllis	PF-02545920	
NCT02006472	PRIDE-HD	Pridopidine	
NCT03225833	PRECISION-HD1	WVE-120101	February 2018[10]
NCT03225846	PRECISION-HD2	WVE-120102	
NCT01795859	FIRST-HD	Deutetrabenazine	
NCT02481674	SIGNAL	VX15/2503	August 2018[11]
NCT00712426	CREST-E	Creatine	
NCT03761849	GENERATION-HD1	RG6042[a]	January 2019 [12]
NCT03344601	PACE-HD	Physical activity	
NCT02535884	HD-DBS	Deep brain stimulation	June 2019[13]
NCT02453061	TRIHEP3	Triheptanoin	
NCT04120493	AMT-130	AAV5-miHTT	April 2020[14]
NCT04102579	KINECT-HD	Valbenazine	
NCT05111249	VIBRANT-HD	Branaplam	April 2022[15]
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[16]
NCT05358717	PIVOT HD	PTC518	
NCT05686551	GENERATION HD2	Tominersen[a]	August 2023[17]
NCT05541627	AB-1001	AAVrh10.CAG.hCYP46A1[c]	
NCT05822908	VO659-CT01	VO659	March 2024[18]
NCT05111249	VIBRANT-HD	Branaplam	
NCT06254482*	**PIVOT HD**	**PTC518 (Extension Study)**	**September 2024**

Table 2

Table 2 – Pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington's disease (HD) since the first edition of the "Huntington's Disease Clinical Trials Corner". HTT, huntingtin; N/S, not specified; PD, Parkinson's disease; SCA1, spinocerebellar ataxia 1; SCA3, spinocerebellar ataxia 3; TD, tardive dyskinesia; TEAEs, treatment-emergent adverse events; VMAT2, Vesicular Monoamine Transporter 2. Note: IONIS-HTT$_{Rx}$, ISIS 443139, RG6042, and tominersen refer to the same molecule. **New trials added since the last Clinical Trials Update are indicated by *. Pharmacological trials terminated are indicated by †.**

Registration ID	Trial Name	Intervention	Mechanism of Action	Population	Comparison	Main Outcome	Study Design	Estimated Enrolment	Sponsor	Location
NCT06474650*	-	LPM3770164	VMAT2 inhibitor	Healthy controls	None	Pharmacokinetics pre-dose and up to 240 hours post-dose	Randomized, open-label, two-period, double-crossover (phase I) study	16	Luye Pharma Group Ltd.	China (single centre)
NCT06469853*	-	MBF-015	Histone deacetylase 1/2 (HDAC 1/2) inhibitor	Early and moderate HD	None	Safety and tolerability at 43 days	Open-label, single centre (phase IIa) study	10	Medibiofarma S.L.	Spain (single centre)
NCT06312189*	-	Valbenazine	VMAT2 inhibitor	HD with chorea; participated in study NBI-98854-HD3006 (NCT04400331)	None	Number of participants with TEAEs up to week 106	Non-randomized, open-label	7	Neurocrine Biosciences	Canada (multi-centre)
NCT06254482*	-	PTC518	Small molecule splicing modulator	Participants who completed the treatment period in PTC518-CNS-002-HD	None	Number of participants with TEAEs up to month 30; blood total HTT levels up to month 28	Randomized, double-blind, parallel assignment, extension (phase IIb) study	250	PTC Therapeutics	Australia, Austria, Canada, France, Germany, Italy, Netherlands, New Zealand, Spain, UK (multi-centre)
NCT06097780	-	Nestacell	Dental pulp stem cell	Early and moderate HD	Placebo	Efficacy at 1 year	Randomized, double-blind, parallel assignment, multiple dose	120	Azidus Brasil	N/S
NCT06024265	-	ER2001	Small interfering RNA	Early HD	None	Safety at 6.5 months	Multiple dose, open-label trial	15	ExoRNA Bioscience	China (single centre)
2022-001565-12	-	PTC518	Small molecule splicing modulator	Premanifest, prodromal, and early HD	None	Safety at 24 months, blood total HTT levels at 24 months	Randomized, double-blind, parallel assignment,	250	PTC Therapeutics	France, Germany, Netherlands, UK, USA (multi-centre)

							multiple dose			
NCT05822908	-	VO659	CAG-targeting antisense oligonucleotide	Early HD, mild-moderate SCA1, mild-moderate SCA3	None	Safety at 253 days	Open-label, non-randomized, sequential assignment, multiple ascending dose	65 (19 HD, 19 SCA1 and 27 SCA3)	VICO Therapeutics B.V.	France, Germany, Italy, Poland, the Netherlands, UK (multi-centre)
NCT04556656†	PROOF-HD	Pridopidine	Sigma-1 receptor activation	Early HD	Placebo	Change in function at 65 weeks	Randomized, double-blind, parallel assignment, single dose trial	499	Prilenia Therapeutics	Austria, Canada, Czechia, France, Germany, Italy, Netherlands, Poland, Spain, UK, USA (multi-centre)
NCT05686551	GENERATION HD2	Tominersen	Non-allele-selective antisense oligonucleotide	Prodromal and early HD	Placebo	Safety at 24 months	Randomized, double-blind, dose-finding trial	360	Hoffmann-La Roche	USA, Spain, more sites to be confirmed (multi-centre)
NCT05655520	-	SAGE-718	Positive allosteric modulator of NMDA	Premanifest, early, and moderate HD	None	Safety at 13 months	Single-dose open-label trial	300	Sage Therapeutics	Canada, USA (multi-centre)
NCT03019289†	-	Pridopidine	Sigma-1 receptor activation	Healthy controls, early and moderate HD	None	Sigma-1 receptor occupancy	Multiple dose, open-label trial	23	Prilenia Therapeutics / Teva	Germany (single centre)
NCT02494778†	Open PRIDE HD	Pridopidine	Sigma-1 receptor activation	Early and moderate HD	Placebo	Efficacy at 106 weeks	Open-label extension	400	Prilenia Therapeutics / Teva	Australia, Austria, Canada, France, Germany, Italy, Netherlands, Poland, Russia, UK, USA (multi-centre)
NCT02006472†	PRIDE HD	Pridopidine	Sigma-1 receptor activation	Early and moderate HD	Placebo	Efficacy at 26 weeks	Randomized, double-blind, parallel assignment, dose-finding trial	408	Prilenia Therapeutics / Teva	Australia, Austria, Canada, Denmark, France, Germany, Italy, Poland, Russia, Netherlands, UK, USA (multi-centre)
NCT01306929†	OPEN-HART	Pridopidine	Sigma-1 receptor activation	HD	None	Safety up to 72 months	Randomized, placebo-controlled, dose-ranging, parallel-group study.	134	Prilenia Therapeutics / Teva	Canada, USA (multi-centre)

NCT05509153	NAC-preHD	N-Acetyl Cysteine	Antioxidant	Premanifest HD	Placebo	Efficacy at 36 months	Randomized, double-blind trial	160	Western Sydney Local Health District	Australia (multi-centre)
ISRCTN56240656†	FELL-HD	Felodipine	Calcium channel blocker	Early HD	None	Safety at 62 weeks	Non-randomised, multiple dose trial	18	Cambridge University	UK (single centre)
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 trial	80	Sage Therapeutics	USA (multi-centre)
NCT05358717	PIVOT HD	PTC518	Small molecule splicing modulator	Premanifest, prodromal, and early HD	Placebo	Safety at 113 days	Randomized, double-blind, placebo controlled, parallel assignment, multiple dose trial	162	PTC Therapeutics	France, Germany, Netherlands, UK, USA (multi-centre)
NCT05475483	-	SOM-3355 (bevantolol hydrochloride)	Beta-blocker	Early and moderate HD	Placebo	Efficacy at 8 weeks	Randomized, double-blind, placebo-controlled, parallel assignment multiple-dose trial	129	SOM Biotech	France, Germany, Italy, Poland, Spain, Switzerland, UK (multi-centre)
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 (two centres)
NCT05541627	-	AB-1001 (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	AskBio/ BrainVectis	France (single centre)
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, USA (multi-centre)
NCT05111249†	VIBRANT HD	Branaplam	Small molecule splicing modulator	Early HD	Placebo	Reduction of mHTT protein at week 17 Safety at 104 weeks	Double-blind, placebo-controlled	75	Novartis Pharmaceuticals	Belgium, Canada, France, Germany, Hungary, Italy,

							multiple dose design			Spain, UK, USA (multi-centre)
NCT05032196†	SELECT-HD	WVE-003	Allele-selective antisense oligonucleotide	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, UK (multi-centre)
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, UK (multi-centre)
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 Investigación 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 (participant/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, Canada (multi-centre)
NCT04301726	-	Deutetrabenazine	VMAT2 inhibitor	HD with dysphagia	Placebo	Dysphagia at 18 months	Randomized, parallel assignment, triple blinded trial	48	Fundación Huntington Puerto Rico	N/S
NCT04478734; CTIS2023-508637-14-00	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	Spain (single centre)

									Sevilla	
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	Non allele selective 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, UK (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	Netherlands, 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	Randomized,	20	University of	USA

						6 months	double-blind, placebo-controlled, parallel trial		California, Irvine	(single centre)
NCT03764215	Tasigna HD	Nilotinib	Selective Bcr-Abl tyrosine kinase inhibitor	HD	None	Safety, tolerability and pharmacodynamics at 3 months	Open-label, multiple ascending dose	20	Georgetown University	USA (single centre)
NCT03225833†	PRECISION-HD1	WVE-120101	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.	Australia, Canada, Denmark, France, Poland, UK (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	60	Wave Life Sciences Ltd.	Australia, Canada, Denmark, France, Poland, UK (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 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)
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,	None	Safety at 3, 6, and 12 months	Single group, open-label trial	240	A. Carlsson Research AB	Sweden (multi-centre)

				myalgic encephalomyelitis, and narcolepsy						
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

Table 3

Table 3 – 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) since the first edition of the "Huntington's Disease Clinical Trials Corner". 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 Update are indicated by *.**

Registration ID	Trial Name	Intervention	Mechanism of Action	Population	Comparison	Main Outcome	Study Design	Estimated Enrolment	Sponsor	Location
NCT06444217*	FibroTG-HD	Skin biopsy	Skin biopsy	Individuals with a CAG ≥36 allele (with reduced or full penetrance)	None	In vitro validation of a RNA trans-splicing gene therapy for the correction of supernumerary CAG repeats into fibroblasts derived from skin biopsies	Open-label, single group assignment	20	University Hospital, Angers	France (single centre)
NCT06097780	-	Nestacell	Dental pulp stem cell	Early and moderate HD	Placebo	Efficacy at 1 year	Randomized, double-blind, parallel assignment, multiple dose	120	Azidus Brasil	N/S
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	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,	35	Azidus Brasil	Brazil (single centre)

							placebo-controlled, parallel trial			
NCT03297177	-	Autologous stem/stromal cell injection	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	Honduras, USA (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

Table 4 – 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) since the first edition of the "Huntington's Disease Clinical Trials Corner". 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 Update are indicated by *.**

Registration ID	Trial Name	Intervention	Mechanism of Action	Population	Comparison	Main Outcome	Study Design	Estimated Enrolment	Sponsor	Location
NCT06490367*	TREHD	Time-restricted eating (TRE) diet	TRE diet, specifically maintaining a 6-8-hour eating window every day for 12 weeks	Premanifest, prodromal, and early HD	None	Change from baseline in the daily eating period at week 13	Prospective interventional, open-label, single-arm trial	25	Oregon Health and Science University	USA (single centre)
NCT06414967*	MUSIC-HD	Music therapy	Music therapy using a digital music therapy tool combined with conventional management	Early HD	None	Change in irritability after 3 months	Single group, open-label	15	Poitiers University Hospital	France (single centre)
RBR-75ys4s9*	-	Dance therapy	Dance sessions offered by physiotherapists using auditory and visual stimuli	HD, PD, dystonia	Standard medical treatment	Quality of life improvement	Two-arm randomized controlled trial with a blinded examiner	100	Universidade Federal de Juiz de Fora	Brazil (single centre)
ChiCTR2300069844	-	Repetitive transcranial magnetic stimulation	Transcranial magnetic stimulation	HD	None	EEG	Non-randomized, open-label, single group trial	20	Shenzhen People's Hospital	China (single centre)
ISRCTN47330596	-	Psychological intervention	Guided self help	Premanifest and manifest HD	Usual treatment	Feasibility at 3 and 6 months	Interventional randomized controlled trial	30	Leicestershire Partnership NHS Trust, UK	UK (single centre)
RBR-463yhb3	-	Multimodal physiotherapy	Balance intervention with rhythmic cues	HD	Educational program	Balance	Randomized, double-blinded, parallel assignment trial	36	São Paulo University, Brazil	Brazil (single centre)

ACTRN12622000908730	-	Online platform	Computerized 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 (two centres)
ISRCTN11906973	HD-DRUM	Training app	Drumming	Premanifest, early, and moderate HD	Standard medical care	Feasibility	Randomized, parallel assignment trial	50	Cardiff University, UK	UK (single centre)
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 (two centres)
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 - Hôpitaux de Paris	France (single centre)
NCT04429230	-	Transcranial pulsed current stimulation	Transcranial electrical stimulation	HD	Sham intervention	Feasibility at one year	Randomized, crossover double-blinded trial	15	Western University, Canada	N/S
ACTRN12620000281998	-	Ketogenic diet	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	Premanifest HD	Standard of care	Feasibility and safety	Clustered, non-randomized, open-label,	40	Edith Cowan University, Deakin University and	Australia (two centres)

			guidance and social activities				parallel trial		Lotterywest	
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)
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, USA (multi-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)

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Conflict of Interest

MF was a sub-investigator in the GENERATION-HD2 (NCT05686551), PTC518 (NCT05358717; NCT06254482), and uniQure AMT-130 (NCT05243017) clinical 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 analogues 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, Remix Therapeutics and Skyhawk Therapeutics. All honoraria for these consultancies were paid through the offices of UCL Consultants Ltd., a wholly owned subsidiary of University College London. 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 (NCT04000594) and uniQure AMT-130 (NCT05243017).

SJT and EJW are Editorial Board Members of this journal but were not involved in the peer-review process of this article nor had access to any information regarding its peer-review.

Data Availability

Data sharing not applicable as no datasets generated and/or analysed for this study.