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Clinical Trials Update

Huntington's Disease Clinical Trials Update: February 2024

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Abstract. In this edition of the Huntington's Disease Clinical Trials Update, we expand on the ongoing program from VICO Therapeutics and on the recently terminated VIBRANT-HD clinical trials. We also discuss updates from uniQure's AMT-130 program and PTC therapeutics' trial of PTC518 and list all currently registered and ongoing clinical trials in Huntington's disease.

Keywords: Huntington disease, clinical trials

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 have 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 highlight the VO659-CT01 (NCT05822908) [1] and the VIBRANT-HD (NCT05111249) [2] clinical trials. Finally, in the "Breaking news" section, we discuss preliminary announcements from UniQure's AMT-130 program (NCT04120493 [3] and NCT05243017 [4]) and the PIVOT HD (NCT05358717) [5] trials.

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We tabulate all currently registered and ongoing clinical trials in Tables 2–4. For further details on the methodology used, please refer to the first edition of this series [18].

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.

ONGOING CLINICAL TRIALS

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

VO659-CT01 (NCT05822908) [1].

Study title: A Safety and Pharmacokinetics Trial of VO659 in SCA1, SCA3 and HD.

Intervention: Intrathecally administered VO659, an antisense oligonucleotide (ASO) targeting CAG repeats.

Description: The VO659 clinical trial, sponsored by VICO Therapeutics, aims to evaluate the safety and tolerability of four intrathecal doses of VO659 in adults ($\geq$25 and $\leq$60 years of age) with mild to moderate spinocerebellar ataxia 1 (SCA1) or

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Table 1
Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Corner. [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, AB-1001 refer to the same molecule

	Trial name	Intervention	Edition
NCT02519036	IONIS-HTTRx	IONIS-HTT$_{Rx}$[a]	September 2017 [6]
NCT02215616	LEGATO-HD	Laquinimod	
NCT02197130	Amaryllis	PF-02545920	
NCT02006472	PRIDE-HD	Pridopidine	
NCT03225833	PRECISION-HD1	WVE-120101	February 2018 [19]
NCT03225846	PRECISION-HD2	WVE-120102	
NCT01795859	FIRST-HD	Deutetrabenazine	
NCT02481674	SIGNAL	VX15/2503	August 2018 [20]
NCT00712426	CREST-E	Creatine	
NCT03761849	GENERATION-HD1	RG6042[a]	January 2019 [21]
NCT03344601	PACE-HD	Physical activity	
NCT02535884	HD-DBS	Deep brain stimulation	June 2019 [22]
NCT02453061	TRIHEP3	Triheptanoin	
NCT04120493	AMT-130	AAV5-miHTT	April 2020 [23]
NCT04102579	KINECT-HD	Valbenazine	
NCT05111249	VIBRANT-HD	Branaplam	April 2022 [24]
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 [14]
NCT05358717	PIVOT HD	PTC518	
NCT05686551	GENERATION HD2	Tominersen[a]	August 2023 [25]
NCT05541627	AB-1001	AAVrh10.CAG.hCYP46A1[c]	
NCT05822908	VO659-CT01	VO659	February 2024
NCT05111249	VIBRANT-HD	Branaplam	

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spinocerebellar ataxia 3 (SCA3) and in patients with early HD.

This study is a phase 1/2a clinical trial aiming to recruit 65 patients assigned to dose-ascending treatment cohorts. The first two cohorts will include only SCA1 and SCA3 participants while from cohort three onwards also HD patients will be included. Participants will be treated with four doses of VO659 every four weeks and will be followed up for additional 23 weeks after the last dose.

The primary outcome will be safety, determined through the proportion of adverse events, laboratory parameters in blood and cerebrospinal fluid (CSF), brain MRI and suicidal ideation. The main secondary outcomes are related to characterizing the pharmacokinetic data of VO659. Additional exploratory include assessing the pharmacodynamic profile and clinical effects of VO659.

Sponsor/Funders: VICO Therapeutics B. V.

Comments: There are nine neurodegenerative disorders caused by expanded CAG repeats, leading to elongated polyglutamine (polyQ) stretches in the encoded proteins. These enlarged polyQ proteins are believed to trigger neuronal death partially or substantially through gain-of-function mechanisms [7]. In these conditions, decreasing the concentrations of the mutant proteins could modify disease course.

VO659 is an antisense oligonucleotide (ASO) that targets the RNA produced from CAG repeats in DNA, having the potential to treat all polyQ disorders with a single compound. Its *HTT* mechanism acts through steric blocking of protein translation, leading to decreased concentrations of polyQ proteins without degrading the mRNA transcript. In SCA3 it induces exon skipping of the exon containing the CAG repeat, leading to a premature stop codon. VO659 has a preference to bind larger CAG repeats, being expected to lower the mutant proteins to a larger extent than the wild-type isoforms. Its RNA target implies it should act on exon-1-containing RNA *HTT* species, potentially including misspliced exon 1 variants.

VO659 produced dose-dependent reductions in mutant polyQ proteins in different mouse mod-

els of polyQ diseases. In the R6/2 HD mice, intracerebroventricular dosing led to decreased mutant Huntingtin (mHTT) concentrations alongside increased brain volumes and improved motor performance [8].

A study with intrathecal dosing of VO659 in non-human primates showed good drug distribution, with larger concentrations in the spinal cord, cerebellum and cortical regions compared with deep subcortical structures. There were no increases in neurofilament light (NfL) protein in the cerebrospinal fluid (CSF) of treated animals. VO659 has a long half-life after intrathecal administration, supporting infrequent dosing regimes [9].

The main drawback of this approach is its lack selectivity against other wild-type CAG-repeat containing genes, requiring close monitoring particularly prior to dose increases. This trial is already recruiting and the first participant with SCA3 was dosed in April 2023 [10].

COMPLETED CLINICAL TRIALS

VIBRANT-HD (NCT05111249) [2].

Study title: A Dose Range Finding Study With Open-Label Extension to Evaluate the Safety of Oral LMI070/Branaplam in Early Manifest Huntington's Disease (VIBRANT-HD).

Intervention: Oral branaplam, a small molecule splicing modulator lowering the production of the Huntingtin (HTT) protein.

Description: The VIBRANT-HD clinical trial, sponsored by Novartis, aimed to select a safe and tolerable dose of branaplam that lowered mHTT in CSF to a degree sufficient to achieve disease modification.

It was a phase 2 clinical trial including adults ($\geq$25 and $\leq$75 years of age) with early manifest HD. This double-blind, placebo-controlled study evaluated the effects of multiple doses of branaplam in three dose cohorts. The study drug was planned to be administered during a period of 17 weeks followed by a blinded extension of 53 additional weeks.

The primary outcome of VIBRANT-HD was to determine the dose-response relationship of branaplam on mHTT protein change from baseline to week 17 as well as the safety during the study period.

The recruitment target was 75 participants. However, the trial was stopped after 26 participants were enrolled in the first study cohort, due to the identification of findings suggestive of peripheral neuropathy in treated participants.

Sponsor/Funders: Novartis Pharmaceuticals

Comments: Branaplam was initially developed for the treatment of spinal muscular atrophy as it restores the full-length SMN2 transcript [11]. However, it also lowers *HTT* expression through the inclusion of a pseudoexon leading to premature stop codons in the mature HTT transcript. Branaplam rescued motor phenotypes in the BACHD mice and has wide distribution after oral administration, including good penetration into the basal ganglia [11].

Preclinical studies also found peripheral axonal damage in dogs treated with branaplam. In consequence, the study protocol of VIBRANT-HD included detailed assessments to detect peripheral neuropathy [12]. Soon after the recruitment of the first cohort there were signals suggestive of peripheral neuropathy in two participants, with 78% of study participants eventually developing at least one sign or symptom of peripheral neuropathy during the study period. These findings led initially to the temporary suspension of the drug and eventually the termination of the study.

Preliminary analysis presented in 2023 showed that there were decreases of CSF mHTT up to 26.6% in treated patients at 17 weeks. However, there were also NfL increases in serum after 9 weeks of treatment although these tended to decrease thereafter, even in patients that continued dosing longer than 9 weeks. There were also increases in ventricular volume up to 9.5% at 17 weeks in patients on branaplam compared to 1.6% volume increases in participants on placebo. Following termination of the study, adverse findings in volumetric MRI and peripheral neuropathy showed evidence of reversal. Similar adverse events were reported in GENERATION HD1 (NCT03761849), testing tominersen, a non-allele selective ASO targeting HTT [13].

While disappointing, these findings affirm the value of NfL as a reactive potential marker of safety and undesirable neuroaxonal damage for clinical trials in HD. As discussed below, another small-molecule splicing modulator has since been reported as not showing any such early increases in NfL, suggesting these untoward reactions are neither a class effect of HTT-lowering splice modulators, nor of HTT lowering in general.

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BREAKING NEWS

AMT130 is a modified viral vector engineered to express a microRNA targeting exon 1 *HTT* mRNA (rAAV5-miHTT). Intracranial administration of AMT130 at two different doses is being tested in two clinical trials including early HD participants (NCT04120493 [3] and NCT05243017 [4]). Following a pause in recruitment [14] the trial was restarted in 2023. Two updates from the sponsor in 2023 showed that following an expected initial increase in CSF NfL shortly after the surgical procedure, the concentrations of the biofluid biomarker returned to baseline concentrations. There were no persistent serious adverse events. The sponsor also reported favorable trends in clinical scales compared with matched natural history cohorts, although only six participants had follow up periods longer than 18 months [15, 16].

PTC518 is an orally bioavailable small-molecule splicing modulator that targets *HTT* mRNA. It is being tested in early HD patients participating in the PIVOT-HD (NCT05358717) [5] clinical trial. An interim data analysis in June 2023 showed that at 12 weeks there was dose-dependent lowering of HTT in blood cells. There were high concentrations of PTC518 in CSF. Importantly, there were no increases in CSF NfL and no treatment-related adverse events despite intense monitoring for peripheral neuropathy [17].

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FUNDING

CEF has received speaking honoraria from Roche España. SJT receives research grant funding from the CHDI Foundation, Vertex Pharmaceuticals, the UK Medical Research Council, the Wellcome Trust and the UK Dementia Research Institute that receives its funding from DRI Ltd., funded by the UK MRC, Alzheimer's Society, and Alzheimer's Research UK. EJW is supported by CHDI Foundation, Inc. EJW reports grants from CHDI Foundation, and F. Hoffmann-La Roche Ltd.

CONFLICT OF INTEREST

CEF was an investigator in the LEGATO-HD (NCT02215616), IONIS HTTRx OLE (NCT03342053), 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 analogues licensed to Adrestia Therapeutics. SJT was an investigator on IONIS HTTRx (NCT02519036), IONIS HTTRx 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 HTTRx (NCT02519036), IONIS HTTRx 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.

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 Update". N/S, not specified; HTT, Huntingtin; PD, Parkinson's disease; SCA1, spinocerebellar ataxia 1; SCA3, spinocerebellar ataxia 3; 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*

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
NCT06024265*	–	ER2001	Small interfering RNA	Early HD	None	Safety at 6.5 months	Multiple dose, open label trial	15	ExoRNA Bioscience	China
2022-001565-12*	–	PTC518	Small molecule splicing modulator	PreHD, prodromal and early HD	None	Safety at 24 months, blood total HTT levels at 24 months	Randomized, double-blind, parallel assignment, multiple dose	250	PTC therapeutics	France, Germany, Netherlands, United Kingdom, United States
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, United Kingdom
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, United Kingdom, USA
NCT05686551	GENERATION HD2	Tominersen	Non allele-selective antisense oligonucleotide	Prodromal and early manifest HD	Placebo	Safety at 24 months	Randomized, double-blind, dose-finding trial	360	Hoffmann-La Roche	USA, Spain, more sites to be confirmed
NCT05655520	–	SAGE-718	Positive allosteric modulator of NMDA	PreHD, early and moderate HD	None	Safety at 13 months	Single-dose open label trial	300	Sage Therapeutics	United States
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
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, United Kingdom, USA

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Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
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, United Kingdom, USA
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
NCT05509153	–	N-Acetyl Cysteine	Antioxidant	Premanifest HD	Placebo	Efficacy at 36 months	Randomized, double-blind trial	160	Western Sydney Local Health District	Australia
ISRCTN5624-0656	FELL-HD	Felodipine	Calcium channel blocker	Early HD	None	Safety at 62 weeks	Non-randomized, multiple dose trial	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 trial	80	Sage Therapeutics	USA
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 trial	162	PTC therapeutics	France, Germany, Netherlands, United Kingdom, USA
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, United Kingdom
ACTRN126210 01755820	–	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

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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
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
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 multiple dose design	75	Novartis Pharmaceuticals	Belgium, Canada, France, Germany, Hungary, Italy, Spain, United Kingdom, USA
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 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 center)
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 center)
NCT04514367	–	ANX005	C1q inhibitor	Early HD	None	Safety at 36 weeks	Single-dose open label trial	28	Annexon, Inc	USA (multi-center)
NCT04421339	–	Melatonin	Melatonin receptor agonist	HD with sleep disturbance	Placebo	Sleep quality at 9 weeks	Randomized, cross-over, single-blinded (participant/caregiver)	20	The University of Texas Health Science Center, Houston	USA (single center)

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Table 2
(*Continued*)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
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	–	Deutetra-benazine	VMAT2 inhibitor	HD with dysphagia	Placebo	Dysphagia at 18 months	Randomized, parallel assignment, triple blinded trial	48	Fundacion Huntington Puerto Rico	N/S
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 center)
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 center)
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 center)
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-center)
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-center)
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-center)

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NCT04000594	GEN-PEAK	RG6042	Allele-nonselective antisense oligonucleotide	HD	None	Pharmaco-dynamics and pharmacokinet-ics at multiple timepoints until 6 months	Non-randomized. open-label, multiple-dose, parallel trial	20	Hoffmann-La Roche	The Netherlands and UK (multi-center)
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 center)
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-center)
NCT03761849	GENERA-TION-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-center)
NCT03515213	–	Fenofibrate	PPARα agonist	HD	Placebo	Pharmaco-dynamics at 6 months	Randomized, double-blind, placebo-controlled, parallel trial	20	University of California, Irvine	USA (single center)
NCT03764215	Tasigna HD	Nilotinib	Selective Bcr-Abl tyrosine kinase inhibitor	HD	None	Safety, tolerability and pharmacody-namics at 3 months	Open label, multiple ascending dose	20	Georgetown University	USA (single center)
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 and United Kingdom (multi-center)

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Table 2
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Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
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 and United Kingdom (multi-center)
NCT02453061	TRIHEP 3	Triheptanoin	Anaplerotic therapy	HD	Safflower oil	Pharmaco-dynamic 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-center)
NCT02509793	-	Tetrabenazine	VMAT2 inhibitor	HD with impulsivity	None	Cognitive and behavioral effects at 8 weeks	Single group, open-label trial	20	University of Texas Health Science Center, and H. Lundbeck A/S	USA (single center)
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-center)
EUCTR2013-002545-10-SE	OSU6162 Open1309	(–)-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-center)
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

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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 Update". 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	Esimated Enrolment	Sponsor	Location
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-center)
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 center)
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 center)
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 center)
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-center)
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-center)
NCT01834053	BMACHC	Bone Marrow Derived MNC transplant	Bone marrow transplant	HD with chorea	None	Cognitive and behavioral effects at 6 months	Single group, open-label trial	50	Chaitanya Hospital, Pune	India (single center)
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 center)

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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 Update". 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
ChiCTR2300069844	–	Repetitive transcranial magnetic stimulation	Transcranial magnetic stimulation	HD	None	EEG	Non-randomized, open label, single group trial	20	Shenzhen People's Hospital	China
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
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
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
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 center)
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 – Hôpitaux de Paris	France (single center)

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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	–	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 center)
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 centers)
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 center)
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 center)
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-center)
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 center)

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