Journal of Huntington's Disease 12 (2023) 169–185
DOI 10.3233/JHD-239001
IOS Press

Clinical Trials Corner

Huntington's Disease Clinical Trials Corner: August 2023

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Accepted 4 July 2023
Pre-press 15 July 2023
Published 28 July 2023

Abstract. In this edition of the Huntington's Disease Clinical Trials Corner, we expand on the GENERATION HD2 (tominersen) and on the Asklepios Biopharmaceutical/BrainVectis trial with AB-1001. We also comment on the recent findings from the PROOF-HD trial, and list all currently registered and ongoing clinical trials in Huntington's disease.

Keywords: Huntington 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 clinical trials GENERATION HD2 (NCT05686551) [1] and the Asklepios Biopharmaceutical/BrainVectis trial with AB-1001 (NCT05541627) [2]. Finally, we discuss also results from the PROOF-HD (NCT04556656) [3] trial in the "Breaking news" section. 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 [4].

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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, 3 and 4.

GENERATION HD2 (NCT05686551) [1]

Study title: A Study to Evaluate the Safety, Biomarkers, and Efficacy of Tominersen Compared With Placebo in Participants With Prodromal and Early Manifest Huntington's Disease

Intervention: Intrathecally administered tominersen (120 mg) – formerly known as IONIS-HTTRx/ ISIS443139 / RG6042– is an antisense oligonucleotide that targets the Huntingtin (*HTT*) transcript non-allele-selectively lowering the production of mutant huntingtin protein.

Description: The GENERATION HD2 clinical trial aims to evaluate the safety, efficacy and biomarker effects of two doses of tominersen (60

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 [4]
NCT02215616	LEGATO-HD	Laquinimod	
NCT02197130	Amaryllis	PF-02545920	
NCT02006472	PRIDE-HD	Pridopidine	
NCT03225833	PRECISION-HD1	WVE-120101	February 2018 [27]
NCT03225846	PRECISION-HD2	WVE-120102	
NCT01795859	FIRST-HD	Deutetrabenazine	
NCT02481674	SIGNAL	VX15/2503	August 2018 [28]
NCT00712426	CREST-E	Creatine	
NCT03761849	GENERATION-HD1	RG6042[a]	January 2019 [29]
NCT03344601	PACE-HD	Physical activity	
NCT02535884	HD-DBS	Deep brain stimulation	June 2019 [30]
NCT02453061	TRIHEP3	Triheptanoin	
NCT04120493	AMT-130	AAV5-miHTT	April 2020 [31]
NCT04102579	KINECT-HD	Valbenazine	
NCT05111249	VIBRANT-HD	Branaplam	April 2022 [32]
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 [33]
NCT05358717	PIVOT HD	PTC518	
NCT05686551	GENERATION HD2	Tominersen[a]	July 2023
NCT05541627	AB-1001	AAVrh10.CAG.hCYP46A1[c]	

[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.

mg and 100 mg) administered to patients between 25 and 50 years of age with prodromal and early manifest HD (equivalent stages 2 and 3 of the Huntington's disease Integrated Staging System [5] (HD-ISS)) and a CAG-age product (CAP score) between 400 and 500.

GENERATION HD2 is a phase 2, international, multicentre, randomized, placebo-controlled, double-blind parallel study with the aim of selecting a safe dose of tominersen that lowers CSF mutant Huntingtin (mHTT) protein and shows a tendency towards efficacy. Participants will be randomized 1 : 1:1 to receive intrathecal infusions every 16 weeks with 60 mg or 100 mg of tominersen or placebo.

Participants will receive the study drug during 16 months followed a safety follow up period of 5 months and an optional OLE. After the 16-month double-blind treatment period concludes, participants will remain on blinded treatment until all study participants have completed 16 months of treatment

GENERATION HD2 plans to recruit 360 participants in 15 countries. The primary outcome will be safety. Other primary outcomes include change in cerebrospinal fluid (CSF) white cells, change in CSF total protein, change in CSF mHTT, change in structural brain MRI and clinical change measured through the Total Functional Capacity (TFC) and the composite Unified Huntington's Disease Rating Scale (cUHDRS) [6, 7].

Sponsor/Funders: Hoffman-La Roche

Comments: Tominersen has been tested in the phase 1b/2a IONIS-HTT_{RX} (NCT02519036) [8], its OLE (NCT03342053) [9], and the phase 3 GENERATION HD1 [10] (NCT03761849) clinical trials, showing dose dependent decreases in CSF mHTT. In GENERATION HD1 (NCT03761849), following two loading doses of 120 mg with an interval of 4 weeks, early and moderate HD participants received placebo or tominersen at a dose of 120 mg every eight (Q8) or every 16 (Q16) weeks. In 2021 the trial was prematurely stopped following an unblinded review, showing that participants in the Q8 cohort had worse scores in clinical scales compared to participants on placebo, while there were no significant differences between the Q16 group and placebo [11]. There were

also dose-dependent increases in ventricular volume over the study period, above 25% over 69 weeks in patients on the Q8 dose regime and above 15% increases among participants in the Q16 cohort [11]. These ventricular increases receded after tominersen administration was paused [11].

More recently, a *post-hoc* subgroup analysis of GENERATION HD1 by the study sponsor showed a non-statistically significant beneficial tendency among Q16 participants that were below the median for the age and disease burden, measured through the CAP score (a product of age and CAG repeat length). In this subgroup, point estimates for the cUHDRS as well as its functional, cognitive, and motor subscales, were in the favourable direction at 69 weeks. These effects were more marked in participants with lower exposure to the drug [7].

Based on these results the sponsor has developed the GENERATION HD2 trial, where younger participants with lower disease burden will receive lower doses of the drug with a 16-weeks interval without loading doses. GENERATION HD2 will evaluate whether there is potential benefit for Q16 administration of the lower 60 mg and 100mg doses in this study population.

AB-1001 (NCT05541627) [2]

Study title: A Study to Evaluate AB-1001 Striatal Administration in Adults With Early Manifest Huntington's Disease

Intervention: AB-1001 (also known as BV-101 and AAVrh10.CAG.hCYP46A1) is an adeno-associated viral vector serotype Rh10 containing the human cholesterol 24-hydroxylase gene administered through one-off intrastriatal bilateral injections

Description: The goal of the AB-1001 trial is to evaluate the safety of the intrastriatal administration of AAVrh10.CAG.hCYP46A1 in adults (18–65 years) with early manifest HD. It will evaluate two doses of the gene therapy construct administered through bilateral injections into the caudate and putamen.

The study plans to recruit between 12 and 18 participants in France and consists of a dose-finding and a dose expansion periods with participants being followed up total of 5 years following screening [12].

Eligible participants need to have stable HD and striatal volumes in the screening MRI, being larger than 2.3 cm per side for the putamen and larger than 1.7 cm per side for the caudate. Exclusion criteria include unstable or serious medical conditions other than HD, previous gene therapy or administration experimental agents through brain surgery or inability to undergo the study procedures.

Secondary outcomes include change from baseline in volumetric MRI, cUHDRS, CSF mHTT, neurofilament light chain (NfL) and 24-OH-cholesterol as well as changes in magnetic resonance spectroscopy and in the positron emission tomography (PET) fluorodeoxyglucose (FDG) striatal profile.

Sponsor/Funders: Asklepios Biopharmaceutical (AskBio) / BrainVectis

Comments: Changes in cellular cholesterol metabolism are associated with neurodegeneration in HD [13]. The cholesterol 24-hydroxylase (CYP46A1) enzyme converts cholesterol to 24S-hydroxycholesterol which can cross the blood-brain barrier and be degraded in the periphery [14]. However, the concentrations of CYP46A1 are decreased in the striatum of HD patients and animal models of HD [15]. Consistently, there is increased accumulation of cholesterol in striatal neurons [15]. Administration of *CYP46A1* gene therapy to the zQ175 knock-in HD mice restored cholesterol homeostasis and prevents neuronal dysfunction decreasing mHTT aggregates, improving axonal transport of BDNF and endosomal trafficking [16].

AB-1001 has shown to improve motor behaviour, decrease mHTT aggregates and NfL concentrations in the R6/2 mouse model of HD [17]. MRI-guided striatal infusions of AB-1001 are also well tolerated in non-human primates [17]. However, the complex cholesterol pathways have not been well studied in human HD patients. Any intraparenchymal gene therapy approach to HD is permanent and high-risk by definition, and it remains to be seen whether any potential benefits will justify the risk.

During this trial, participants will be recruited first into a dose-finding cohort receiving either a low dose ($4x10^8$ vg/ μ L) or a high dose ($1.1x10^9$ vg/ μL) of the study construct. The data will be reviewed for dose-limiting toxicities after each cohort is fully recruited and the dose expansion cohort will receive the dose selected after the initial phase. This study is already recruiting participants in France and presents a different approach for disease modification compared to HTT-lowering therapies.

BREAKING NEWS

Sigma-1-regulated pathways are altered in different neurodegenerative disorders, including HD [18]. Activation of the sigma-1-receptor positively influences these pathways in model systems [19]. The PROOF-HD (NCT04556656) [3] clinical trial investigated pridopidine, a sigma-1-receptor agonist at a dose of 45 mg twice a day versus placebo. Pridopidine was previously tested as a dopaminergic stabiliser in the HART (NCT00724048 [20], NCT01306929 [21]), MermaiHD (NCT00665223 [22, 23]), and PRIDE-HD (NCT02006472 [24], NCT02494778 [25]) but failed to meet primary endpoints.

In the PROOF-HD trial, the primary (TFC) and the key secondary (cUHDRS) endpoints were not met at 65 weeks [26]. The drug was again well tolerated without significant side effects. A planned subgroup analysis showed possible benefit in treated participants compared with placebo, when participants on antidopaminergics were excluded [26]. The significance of these findings is unclear, and antidopaminergic medications are widely used in HD to treat motor and behavioural symptoms. Based on these findings the company is now considering its options for the future of the compound.

ACKNOWLEDGMENTS

CE-F 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.

CONFLICTS OF INTEREST

CEF was an investigator in the LEGATO-HD (NCT02215616), IONIS HTT_{Rx} OLE (NCT033 42053), 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), GENERA TION-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 Corner". 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 added 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
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, United States
NCT05686551*	GENERATION HD2	Tominersen	Non allele selective antisense oligonu-cleotide	Prodromal and early manifest HD	Placebo	Safety at 24 months	Randomized, double-blind, dose-finding trial	360	Hoffmann-La Roche	United States, Spain, more sites to be condirmed
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, United States

(*Continued*)

Table 2
(*Continued*)

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, United States
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, Inited States
NCT05509153	–	N-Acetyl Cysteine	Antioxidant	Premanifest HD	Placebo	Efficacy at 36 months	Randomized, double-blind trial	160	Western Sydney Local Health District	Australia
ISRCTN5 6240656	FELL-HD	Felodipine	Calcium channel blocker	Early HD	None	Safety at 62 weeks	Non-randomised, 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	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 trial	162	PTC therapeutics	France, Germany, Netherlands, United Kingdom, United States

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
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, United States
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, United States
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

(*Continued*)

Table 2
(*Continued*)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
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	–	Deutetra-benazine	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	Antihyper-glycemic/ 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 dis-turbance	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	–	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 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	Non allele selective miRNA	Early HD	Sham interven-tion	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 oligonu-cleotide	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 oligonu-cleotide	HD	None	Pharmaco-dynamics and pharma-cokinetics at multiple timepoints until 6 months	Non-randomized. open-label, multiple-dose, parallel trial	20	Hoffmann-La Roche	The Netherlands and UK (multi-centre)

(*Continued*)

Table 2
(*Continued*)

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
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 oligonu-cleotide	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 oligonu-cleotide	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	Pharmaco-dynamics at 6 months	Randomized, double-blind, placebo-controlled, parallel trial	20	University of California, Irvine	USA (single centre)
NCT03764215	Tasigna HD	Nilotinib	Selective Bcr-Abl tyrosine kinase inihbitor	HD	None	Safety, tolerability and pharmaco-dynamics 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	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-centre)
NCT02509793	–	Tetrabenazine	VMAT2 inhibitor	HD with impulsiv-ity	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 pre-manifest 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
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 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 radioabla-tion	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
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 Corner 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	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
ISRCTN119069*73	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 - Hôpitaux 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)

(*Continued*)

Table 4
(*Continued*)

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

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