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Clinical Trials Corner

Huntington's Disease Clinical Trials Corner: April 2022

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Abstract. In this edition of the Huntington's Disease Clinical Trials Corner we expand on GENERATION HD1, PRECISION-HD1 and PRECISION-HD2, SELECT-HD, and VIBRANT-HD trials, and list all currently registered and ongoing clinical trials in Huntington's disease.

Keywords: Huntington disease, clinical trials

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INTRODUCTION

The Huntington's Disease Clinical Trials Corner is a regular section devoted to highlighting ongoing and recently completed clinical trials in Huntington's disease (HD). We are pleased to return, after a longer pandemic-imposed hiatus than we had intended, with a refreshed and expanded regular authorship. Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Corner are listed in table 1.

In this edition, we highlight the ongoing trials VIBRANT-HD (NCT05111249) [1] and SELECT-HD (NCT05032196) [2]. We will also cover recently terminated clinical trials GENERATION HD1 (NCT03761849) [3], PRECISION-HD1 (NCT03225833) [4] and PRECISION-HD2 (NCT03225846) [5].

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 [6].

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 ongoing clinical trials is given in Tables 2, 3 and 4.

VIBRANT-HD (*NCT05111249*)

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) [1]

Intervention: Once weekly oral branaplam, a small molecule splicing modulator

Description: The VIBRANT-HD study, sponsored by Novartis Pharmaceuticals, aims to evaluate the dose of branaplam required to lower mutant huntingtin (mHTT) levels in the cerebrospinal fluid (CSF) of HD patients, to a degree expected to achieve disease modification.

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Table 1
Clinical trials previously reviewed by the Huntington's Disease Clinical Trials Corner *IONIS-HTT_{Rx}, RG6042, and tominersen refer to the same molecule

	Trial name	Intervention	Edition
NCT02519036	IONIS-HTTRx	IONIS-HTT_{Rx}*	September 2017 [21]
NCT02215616	LEGATO-HD	Laquinimod	
NCT02197130	Amaryllis	PF-02545920	
NCT02006472	PRIDE-HD	Pridopidine	
NCT03225833	PRECISION-HD1	WVE-120101	February 2018 [22]
NCT03225846	PRECISION-HD2	WVE-120102	
NCT01795859	FIRST-HD	Deutetrabenazine	
NCT02481674	SIGNAL	VX15/2503	August 2018 [23]
NCT00712426	CREST-E	Creatine	
NCT03761849	GENERATION-HD1	RG6042*	January 2019 [24]
NCT03344601	PACE-HD	Physical activity	
NCT02535884	HD-DBS	Deep brain stimulation	June 2019 [25]
NCT02453061	TRIHEP3	Triheptanoin	
NCT04120493	AMT-130	AAV5-miHTT	April 2020 [26]
NCT04102579	KINECT-HD	Valbenazine	
NCT05111249	VIBRANT-HD	Branaplam	April 2022
NCT03761849	GENERATION-HD1	Tominersen*	
NCT05032196	SELECT-HD	WVE-003	
NCT03225833	PRECISION-HD1	WVE-120101	
NCT03225846	PRECISION-HD2	WVE-120102	

VIBRANT-HD is a phase 2 multicentre study with a recruitment target of 75 early HD participants. It has a double-blind, placebo-controlled, multiple-dose design with three dose cohorts and 4:1 active to control randomization rate at each cohort. Participants will be followed up during a dose range finding period of 17 weeks followed by a blinded dose extension of 53 weeks. After the dose is determined, participants will roll over into an Open Label Extension (OLE) study during approximately 1 year that may be prolonged through an amendment or in a separate extension study.

The trial has already started recruiting in Canada, France, Germany, Hungary and Spain and more sites will open recruitment soon.

The primary outcomes will be the reduction of mHTT in CSF from baseline to week 17 and the safety and tolerability from baseline up to approximately two years.

Sponsor/Funders: Novartis Pharmaceuticals

Comments: Branaplam was initially investigated for the treatment of spinal muscular atrophy (SMA) (NCT02268552) where it has shown to stabilise *SMN2* pre-mRNA [7]. In the open-label SMA study most adverse events were disease-related with the drug showing a favourable safety profile. Subsequent analysis showed that branaplam also downregulated *HTT* expression through the enhanced inclusion of a 'poison exon' containing a premature stop codon. In consequence, there was a decrease in human *HTT* mRNA in SMA patients while studies with the BACHD mouse model have shown dose-dependent decreases in mHTT protein levels [8,9]. PTC Therapeutics has also announced another first-in-patient trial of an oral HTT-lowering splice modulator, PTC518, which will be covered in a future edition of Clinical Trials Corner [10].

SELECT-HD (*NCT05032196*)

Study title: A Multicenter, Randomized, Double-blind, Placebo Controlled, Phase 1b/2a Study of WVE-003 Administered Intrathecally in Patients With Huntington's Disease [2]

Intervention: WVE-003, an allele-selective antisense oligonucleotide (ASO)

Description: WVE-003 is an ASO that targets the single-nucleotide polymorphism (SNP) SNP3, an

Table 2
Ongoing pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington's disease (HD). N/S, not specified; PD, Parkinson's disease; VMAT2, Vesicular Monoamine Transporter 2. Note: IONIS-HTT$_{Rx}$, ISIS 443139, RG6042 and tominersen refer to the same molecule. New trials since the last Clinical Trials Corner are indicated by *

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
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	rAAV-miHTT	Non allele selective miRNA	Early HD	None	Safety at 6 months	Non-randomized, sequential ascending, multiple-dose trial	15	UniQure Biopharma B.V.	Germany, Poland, United Kingdom
NCT04713982*	-	Deutetrabenazine	VMAT2 inhibitor	HD with chorea	None	Change in speech outcome at 10 weeks	Single-arm open label trial	30	Vanderbilt University Medical Center	USA (single centre)
NCT04826692*	-	Metformin	Antihyperglycemic/ AMPK activator	Early and moderate HD	Placebo	Change in cognition at 52 weeks	Randomized, parallel assignment, double-blinded trial	60	Instituto de Investigacion Sanitaria La Fe	Spain (single centre)
NCT04514367*	-	ANX005	C1q inhibitor	Early HD	None	Safety at 36 weeks	Single-dose open label trial	28	Annexon, Inc	USA (multi-centre)
NCT04421339*	-	Melatonin	Melatonin receptor agonist	HD with sleep disturbance	Placebo	Sleep quality at 9 weeks	Randomised, cross-over, single-blinded (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 and Canada
NCT04301726*	-	Deutetrabenazine	VMAT2 inhibitor	HD with dysphagia	Placebo	Dysphagia at 18 months	Randomized, parallel assignment, triple blinded trial	48	Fundacion Huntington Puerto Rico	N/S

(*Continued*)

Table 2
(*Continued*).

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
NCT04478734*	HUNTIAM	Thiamine and biotin	B vitamins	HD	Moderate vs High doses of thiamine and biotin	Safety at 52 weeks	Randomized, parallel assignment, open-label trial	24	Fundación Pública Andaluza para la gestión de la Investigación en Sevilla	Spain (single centre)
NCT04201834	-	Risperidone	Dopamine antagonist	Early and moderate HD with chorea	None	Change in motor scales at 12 weeks	Non-randomized, open label (assessor-blind), uncontrolled trial	12	University of Rochester	USA (single centre)
NCT04071639	-	Haloperidol, risperidone, sertraline and coenzyme Q10	Multiple (dopamine antagonists, selective serotonin reuptake inhibitor, dietary supplement)	Early and moderate HD	Coenzyme Q10	Efficacy at 5 years	Randomized, open label, controlled, parallel trial	100	Second Affiliated Hospital, School of Medicine, Zhejiang University	China (single centre)
NCT04120493	AMT-130	rAAV5-miHTT	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 and United Kingdom (multi-centre)
NCT04000594	GEN-PEAK	RG6042	Allele-nonselective antisense oligonucleotide	HD	None	Pharmacodynamics and pharmacokinetics at multiple timepoints until 6 months	Non-randomized. open-label, multiple-dose, parallel trial	20	Hoffmann-La Roche	The Netherlands and UK (multi-centre)

NCT03980938	-	Neflamapimod	p38 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	PPAR agonist	HD	Placebo	Pharmacodynamics 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 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 and United Kingdom (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 and United Kingdom (multi-centre)

(*Continued*)

Table 2
(*Continued*).

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)
Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Estimated Enrolment	Sponsor	Location
NCT02509793	-	Tetrabenazine	VMAT2 inhibitor	HD with impulsivity	None	Cognitive and behavioural effects at 8 weeks	Single group, open-label trial	20	University of Texas Health Science Center, and H. Lundbeck A/S	USA (single centre)
NCT02481674	SIGNAL	VX15/2503	Anti-semaphorin 4D monoclonal antibody	Late premanifest or early HD	Placebo	Safety and tolerability at 15 and 21 months	Randomized, double-blind, placebo-controlled, parallel trial	240	Vaccinex Inc., Huntington Study Group	USA (multi-centre)
EUCTR2013-002545-10-SE	OSU6162Open1309	(-)-OSU616	Monoaminergic stabilizer	HD, PD, brain trauma, stroke, myalgic encephalomyelitis 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 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 – Ongoing invasive non-pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington's disease (HD). AD, Alzheimer's disease, CBD; Corticobasal Degeneration; DBS, deep brain stimulation; ET, Essential Tremor; GP, Globus pallidus; HT, Holmes Tremor; MNC, mononuclear cells; MS, Multiple Sclerosis; PD, Parkinson's disease; TD, Tardive dyskinesia; WD, Wilson's disease. New trials since the last Clinical Trials Corner are indicated by *

Registration ID	Trial name	Intervention	Mechanism of Action	Population	Comparison	Main outcome	Study design	Esimated Enrolment	Sponsor	Location
NCT04244513	-	GPi DBS	Deep brain stimulation	HD with chorea	Sham intervention	Efficacy at 3 and 6 months	Randomized, double-blind, sham-controlled, cross-over trial	40	Beijing Municipal Administration of Hospitals, Medtronic	China (multi-centre)
NCT04219241	ADORE-EXT	Cellavita	Stem cell therapy	HD	None	Efficacy and safety at 2 years	Open label extension	35	Azidus Brasil, Cellavita Pesquisa Científica Ltda	Brazil (single centre)
ISRCTN52651778	TRIDENT	Foetal stem cell transplant	Stem cell therapy	Early stage HD	Usual care	Safety at 4 weeks	Randomized, open label, controlled, parallel trial	30	Cardiff University	UK (single centre)
NCT02728115	SAVE-DH	Cellavita	Stem cell therapy	HD	None	Safety at 5 years	Non-randomized, open label, uncontrolled, parallel trial	6	Azidus Brasil	Brazil (single centre)
NCT03252535	ADORE-HD	Cellavita	Stem cell therapy	HD	Placebo	Efficacy at 120 days	Randomized, double-blind, placebo-controlled, parallel trial	35	Azidus Brasil	Brazil (single centre)
NCT03297177	-	Autologous stem/stromal cells	Autologous stem/stromal cell injection	HD, AD, PD, CBD, MS	None	Safety at 5 years	Single group, open-label trial	300	Healeon Medical Inc, Global Alliance for Regenerative Medicine, Regeneris Medical	USA and Honduras (multi-centre)
NCT02535884	HD-DBS	GP DBS	Deep brain stimulation	Moderate HD with chorea	Sham intervention	Efficacy at 12 months	Randomized, double-blind, sham-controlled, parallel trial	50	Heinrich-Heine University, KKS Netzwerk, Medtronic, The George Institute, EHDN, CHDI Foundation, Inc.	Austria, France Germany, Switzerland (multi-centre)
NCT01834053	BMACHC	Bone Marrow Derived MNC transplant	Bone marrow transplant	HD with chorea	None	Cognitive and behavioural effects at 6 months	Single group, open-label trial	50	Chaitanya Hospital, Pune	India (single centre)
NCT02252380	-	Magnetic Resonance Guided Focused Ultrasound	Extracranial stereotactic radioablation	HD, ET, HT, PD, WD, dystonia, TD, or orofacial dyskinesias	None	Adverse events after the procedure	Single group, open-label trial	10	InSightec	Canada (single centre)

Table 4
Ongoing non-invasive non-pharmacological clinical trials registered at the World Health Organization (WHO) International Clinical Trials Research Platform (ICTRP) for people with Huntington's disease (HD). AD, Alzheimer's disease; ALS, Amyotrophic Lateral Sclerosis; ET, Essential Tremor; HT, Holmes Tremor; MS, Multiple Sclerosis; N/S, not specified, PD, Parkinson's disease; TD, Tardive dyskinesia. New trials since the last Clinical Trials Corner are indicated by *

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

allelic variant linked to the expanded CAG repeat tract in *HTT* pre-mRNA. The SELECT-HD trial aims to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of WVE-003 administered intrathecally. The active drug will be compared with intrathecal placebo in participants with stage 1 HD who carry SNP3 variant and are aged between 25 and 60 years.

This trial is a phase 1b/2a, multicentre, international, placebo-controlled, double-blind study. SELECT-HD has a single and multiple-ascending dose design. In each cohort, participants will be assigned to receive the active ASO or placebo. The trial has a recruitment target of 36 participants that will be followed up during a minimum of 36 weeks. Recruitment is already open in Canada, France, Poland, Germany, Spain and the United Kingdom.

The primary outcome will be safety and tolerability. Secondary outcomes include pharmacokinetic and pharmacodynamic measurements in plasma and CSF as well as fluid biomarkers and the composite UHDRS (cUHDRS) [2,11,12].

Sponsor/Funders: Wave Life Sciences Ltd

Comments: The CAG expansion in the *HTT* gene is allelically linked to different SNPs enriched in the mutant allele. SNP3 is estimated to be present in the expanded allele of approximately 40% of adults with HD [13]. WVE-003 incorporates a modified phosphoryl guanidine-containing (PN) backbone that has shown to increase the tissue exposure, half-life in the central nervous system and potency of the ASO compared to first generation molecules used in previous HD trials by Wave Life Sciences Ltd[4,5]. WVE-003 has shown to selectively decrease mHTT mRNA *in vitro*, as well as in the cortex and striatum in the BACHD transgenic mice. In addition, the presence of SNP3 on the CAG-expanded *HTT* allele can be identified with 1-2 weeks turnaround time through a novel investigational assay[12].

Results from the PRECISION HD1/2 trials (NCT03225833 and NCT03225846)[4,5] did not support further development of WVE-120102 and WVE-120101 (see below). Wave Life Sciences has modified the design of SELECT-HD to incorporate learnings from previous trials including a new ASO chemistry, different doses, new methods for rapid patient identification and an adaptative study design.

Completed clinical trials

GENERATION HD1 (*NCT03761849*)

Study title: A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase 3 Clinical Study to Evaluate the Efficacy and Safety of Intrathecally Administered RO7234292 (RG6042) in Patients With Manifest Huntington's Disease[3].

Intervention: Tominersen (120 mg) – formerly known as IONIS-HTT_{Rx} / ISIS443139 / RG6042 – is an antisense oligonucleotide that targets the *HTT* transcript non-allele-selectively with the aim of lowering the production of mutant huntingtin protein.

Description: The GENERATION-HD1 trial, sponsored by Hoffmann-La Roche, aimed to evaluate the efficacy and safety of intrathecal tominersen in adults (25 to 65 years of age) with manifest HD (i.e. a Unified Huntington's Disease Rating Scale (UHDRS) Diagnostic Confidence Level (DCL) of 4, a UHDRS Independence Score above or equal to 70, and a CAG-age Product (CAP) score equal or greater than 400) and functional independence at baseline to maintain self-care and core activities of daily living, comparing with intrathecal placebo, for disease modification. Initially it was planned to be administered every four (Q4) or every eight (Q8) weeks. However, following the results from the OLE study (NCT03342053) showing increased frequency of adverse events in the four-weekly group [14] the phase 3 protocol was amended to two less frequent dosing frequencies: 120mg tominersen every eight or every 16 weeks.

This trial was a phase 3, international, multi-centre, randomized, placebo controlled, double-blind, parallel study. It had three study arms. The intervention was planned to be administered for 101 weeks, and participants were planned to be followed up for 29 months.

This trial recruited 791 participants over 97 study sites. It started enrolment in 2019. This pivotal trial had two primary clinical outcomes for regulatory purposes, the UHDRS Total Functional Capacity (TFC) for the FDA, and the cUHDRS for the EMA [15]. Secondary outcomes included other components of the UHDRS, clinical global impression, adverse events, the Montreal Cognitive Assessment (MoCA), the Columbia-Suicide Severity Rating

Scale (C-SSRS), pharmacokinetic markers, CSF mHTT, CSF neurofilament light chain (NfL), and MRI brain volumes.

Sponsor/Funders: Hoffman-La Roche

Comments: In 2021, following unblinded review of the data by an Independent Data Monitoring Committee the trial was prematurely terminated [16]. Although there were significant decreases in CSF mHTT, preliminary analysis showed that the Q8 cohort had performed worse in clinical scales compared to placebo, whereas the Q16 group did not show significant differences. These changes affected cognitive, motor, functional scales and the cUHDRS [17].

Participants in the eight-weekly group had transient increases in CSF NfL of approximately 30% above baseline at week 21; these were present but lesser (approximately 10%) in the Q16 cohort. There was an increased frequency of serious adverse events in the Q8 cohort together with dose-dependent increases in ventricular volume and three cases of hydrocephalus[16]. Multiple reasons may be accountable for the results in GENERATION HD1. It is possible that a toxic effect was mediated by excessive dosing. Increased CSF proteins and CSF white cell counts found in the study suggest the possibility of dose-dependent inflammatory reactions against the ASO [18] leading to neuronal death and CSF NfL increases. Subsequently, inflammation could also mediate ventricular increases through increased CSF viscosity as reported in a previous case with tominersen [19] and in patients with SMA receiving the ASO nusinersen [20]. An adverse effect of lowering wild-type huntingtin cannot be excluded, but is impossible to deconvolve from drug exposure which is inevitably in close relationship to huntingtin lowering.

Post-hoc exploratory analysis of GENERATION-HD1 suggested that younger participants with lower CAP scores performed better compared to the remaining subgroups. Consequently, Roche is developing a new phase 2 clinical trial in this subgroup of patients[17] with lower doses, in the hope of identifying a therapeutic window for the compound.

PRECISION-HD1 (*NCT03225833*) and PRECISION-HD2 (*NCT03225846*)

Study title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 1b/2a Study of WVE-120101 Administered Intrathecally in Patients With Huntington's Disease[4] and A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 1b/2a Study of WVE-120102 Administered Intrathecally in Patients With Huntington's Disease[5].

Intervention: Respectively WVE-120101 and WVE-120102, two distinct allele-selective ASOs.

Description: The PRECISION-HD trials aimed to compare the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple ascending doses of WVE-120101 and WVE-120102, respectively, administered intrathecally, comparing with intrathecal placebo, for disease modification in people with HD (i.e. clinical diagnostic motor features of HD, a UHDRS DCL of 4, and a UHDRS TFC between 13 and 7, inclusively) who carried SNPs rs362307 or rs362331, respectively, and were aged between 25 and 65 years old. These trials were phase 1b/2a, multi-centre, international, randomized, placebo controlled, double-blind, parallel studies. They had a combined single ascending dose/multiple ascending dose design, comprising five cohorts with progressively higher ASO doses (2 mg, 4 mg, 8 mg, 16 mg and 32 mg).

In each cohort, participants were allocated to receive a single dose or three doses of the ASO or a placebo. These trials finally recruited 61 participants (PRECISION-HD1) and 88 participants (PRECISION-HD2)

The WVE-120101 and WVE-120102 compounds are ASOs targeting the pre-mRNA *HTT* transcript of two allelic variants linked to the expanded CAG repeat tract in the *HTT* gene, with the aim of selectively reducing the production of mHTT protein while leaving the concentration of wild-type huntingtin protein relatively unaltered. Each participant's involvement lasted for 210 days. The primary outcome was safety and tolerability at 210 days. The secondary outcomes involve pharmacokinetic measurements in plasma; pharmacodynamic measures in CSF, including mHTT; and the UHDRS TFC.

Sponsor/Funders: Wave Life Sciences Ltd.

Comments: Preliminary results of the PRECISION-

HD1 and PRECISION-HD2 did not show significant decreases in mHTT or total HTT at the doses tested. There was no dose-responsiveness, suggesting that higher doses would be unlikely to show decreases in the concentration of CSF mHTT. There was no increase in CSF NfL. Overall, the ASOs were well tolerated at lower doses. However, 40% of the participants receiving the 32 mg dose in PRECISION-HD1 and 46% in PRECISION-HD had serious adverse events at higher doses[4,5].

Following these findings both trials were terminated in March 2021, however, Wave Life Sciences has developed SELECT-HD with WVE-003 (as described above), a new ASO with improved chemical structure targeting a third SNP[2].

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CONFLICTS OF INTEREST

CEF was an investigator in the LEGATO-HD (NCT02215616), IONIS HTT_{Rx} OLE (NCT03342053), GENERATION-HD1 (NCT03761849), Roche Natural History Study (NCT03664804), Roche GEN-EXTEND (NCT03842969), Roche GEN-PEAK (NCT04000594), uniQure AMT-130 (NCT05243017) and Triplet Therapeutics SHIELD-HD (NCT04406636) trials.

FBR is a full-time Medpace UK Ltd employee. FBR was an investigator on LEGATO-HD (NCT02215616), IONIS HTT_{Rx} (NCT02519036), IONIS HTT_{Rx} OLE (NCT03342053), GENERATION-HD1 (NCT03761849), Roche Natural History Study (NCT03664804), Roche GEN-EXTEND (NCT03842969), Roche GEN-PEAK (NCT04000594), Triplet Therapeutics SHIELD-HD (NCT04406636) and Novartis VIBRANT-HD (NCT05111249) studies. FBR has provided consultancy services to GLG, Hoffman La Roche Ltd, Evigrade, and Enroll-HD Clinical Trials Committee.

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) and Roche GEN-EXTEND (NCT03842969) trials.

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

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

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