PROGRESS IN HUNTINGTON'S DISEASE (HD) DRUG DEVELOPMENT - A REVIEW OF THE INDUSTRY PIPELINE

Kristine Dorward in Pullan's Pieces #219 Oct 2025

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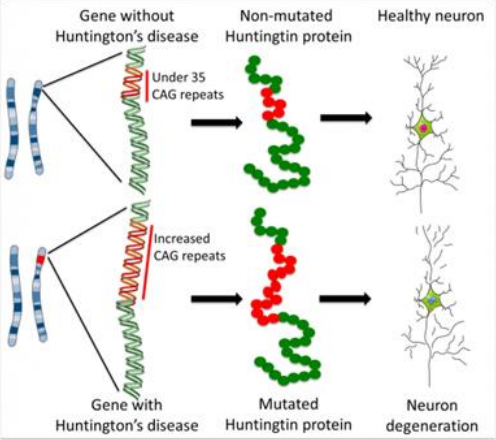
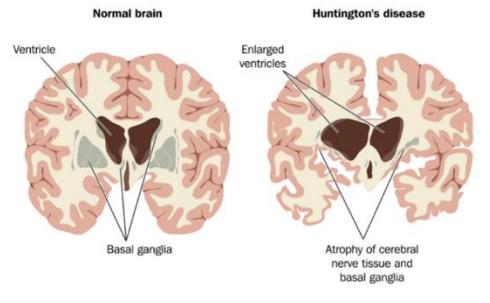
- Last month, the announcement that Huntington's disease was successfully treated for the first time brought inspiring new hope to patients and families afflicted by this deadly disease
- Huntington's Disease (HD) is a cruel, fatal hereditary neurodegenerative disorder caused by mutation(s) in the Huntington gene (HTT)
- Symptoms resemble a combination of dementia, Parkinson's and motor neuron disease, including loss of coordination (ataxia), twitching and jerking (chorea), dysphagia, slurred speech, cognitive difficulty, memory loss and depression
- Adult-onset HD typically occurs between 30 to 40 years of age and is fatal within 10 to 25 years; Juvenile-onset HD occurs before age 20 and follows a more rapid progression, with death in < 10 years
- As an autosomal dominant disease, parents have a 50% chance of passing the mHTT gene to their children
- Latest prevalence estimates indicate there are ~ 41,000 diagnosed patients in USA; with a slightly lower prevalence of 37 per 100,000 in EU; Asia and African regions are believed to be underrepresented due to low diagnostic rates

Developmental Defects & HD Pathology

Expanded repeat of CAG nucleotides, with 40 or more CAG repeats giving rise to HD

Enlarged ventricles and brain atrophy in Huntington's Disease





Therapeutic Candidates in Phase 3 or Phase 2 for Huntington's Disease

The table below outlines mid and late-stage therapies in development for HD, respective mechanisms of action and a note on upcoming events

Prilenia missed the primary endpoint in its Phase 3 (PROOF-HD) study, however, predopidine generated positive data on cUHDRS, SWR, and Q-motor scores in patients off antidopaminergic medications

Roche's Phase 3 (HD1) results failed to meet the primary endpoint but post-hoc analysis showed lower drug exposure may provide benefit in patients < 48 years; initiated Phase 2 (HD2) trial in prodromal and early manifest HD

Therapeutic Candidates in Phase 3 or Phase 2 for Huntington's Disease

Company	Drug Name	Route of Admin	Modality	Mechanism of Action	Phase	Upcoming Event
Prilenia	Predopidine	Oral	Small Molecule	Sigma 1 Receptor Agonist	3	Potential confirmatory Phase 3 initiation in H1 '26
PTC Novartis	Votoplam	Oral	Small Molecule	Total Huntington Gene splicing modifier	2	Potential Regulatory update post-FDA meeting Q4 '25
Medibiofarma	MBF-015	Oral	Small Molecule	Histone deacetylase 1/2 inhibitor	2	Potential R/O from Phase 2a trial, completed end of '24
Roche	Tominersen	IT	ASO	Total huntingtin mRNA ASO	2	Trial ongoing; R/O end of '26 or H1 '27
Skyhawk Tx	SKY-0515	Oral	Small Molecule	RNA splicing modifier targeting total huntingtin and PMS1	2	Potential trial results from Phase 2/3 ~ mid 2026
SOM Innovation Biotech	Bevantolol hydrochloride (SOM3355)	Oral	Small Molecule	Mild Beta 1-adrenergic antagonist & VMAT1/VMAT2 inhibitor	2	Potential Phase 3 initiation in late 2025
Vaccinex	Pepinemab (VX15/2503)	IV	Antibody	Anti-SEMA4D monoclonal antibody	2	Update on program progress in late '25
Cellavita	NestaCell	IV	Cell Therapy	Allogenic human dental pulp stem cells Antibody	2	Potential update on Phase 3 initiation late '26
Annexon	Tanruprubart (ANX005)	IV	Antibody	Anti-C1q monoclonal antibody	2	Potential update on program in late '25
Azevan Pharma	SRX-246	Oral	Small Molecule	Vasopressin 1a receptor antagonist	2	Potential update on Phase 3 program in late '25

Therapeutic Candidates in Phase 1/2 or Phase 1 for HD

Ground-breaking news from Uniqure at the end of September detailed positive top-line results from their Phase 1/2 trial

Results encompassing 12 patients, treated for 36 months with AMT-130 showed statistically significant slowing of disease progression on cUHDRS and TFC versus a propensity-score–matched external control group (p=0.003 and p=0.033, respectively)

Uniqure plans H1 BLA filing under priority review.

Therapeutic Candidates in Phase 1/2 or Phase 1 for HD

Company	Drug Name	Route of Admin	Modality	Mechanism of Action	Phase	Upcoming Event
Wave Life Sciences	WVE-003	Oral	ASO	Mutant huntingtin mRNA antisense oligonucleotide targeting SNP3	1//2	IND submission for Phase 2/3 study expected in H2 '25
Uniqure	AMT-130	Brain Stem	Gene Therapy	AAV5 vector miRNA targeting total huntingtin and exon 1 protein fragment	1//2	Potential BLA Submission in H1 '26
Roche / Spark	RG6662 (SPK-10001)	IT	Gene Therapy	AAV vector miRNA targeting total huntingtin	1//2	Potential update on study progress late '25
Vico Therapeutics	VO659	IT	ASO	Pathogenic CAG repeat expansion antisense oligonucleotide	1//2	Potential update on study progress late '26
Alnylam	ALN-HTT02	IT	siRNA	siRNA targeting exon 1 of total huntingtin	1	Phase 1 data readout in 2026
ExoRNA Bioscience	ER2001	IV	siRNA	siRNA targeting mutant huntingtin via selfassembled exosomes	1	May initiate larger Phase 1 trial end of 2025
Luye Pharma	LPM3770164 (LY03015)	Oral	Small Molecule	VMAT2 inhibitor and Sigma-1 receptor agonist	1	Potential update on Phase 2 study design late 2025

Therapeutic Candidates in Preclinical Development for HD

Company	Drug Name	Route of Admin	Modality	Mechanism of Action	Phase	Upcoming Event
Acadia	ACP-271	Oral	Small Molecule	GPR88 Agonist	Preclinical	Initiate Phase 1 in Q4 2025
Roche	HTT SNP	IT	ASO	targeting SNP of mutant huntingtin for allele selective huntingtin	Preclinical	Potential Initation of Phase 1 late '25
Origami	ORI-113	Oral	Small Molecule	Protein degrader targeting mutant huntingtin	Preclinical	Potential IND approval in Q2 '26
Sarepta	SRP-1005	Sub-Q	siRNA	siRNA targeting total huntington	Preclinical	Potential Phase 1 Initiation in 2026
Harness Therapeutics	Undisclosed	Not disclosed	ASO	FAN1 nuclease upregulator	Preclinical	Potential Phase 1/ 2 trial initiation in 2026
LoQus 23 Therapeutics	Undisclosed	Not disclosed	Small Molecule	MSH3 Inhibitor	Preclinical	Potential Clinical Trial start in 2026
Elevate Bio	LETI-101	Intrastriatal	Gene Therapy	AAV5 vector containing CRISPR nuclease targeting mutant huntingtin	Preclinical	Seeking Licensing Partner for further development
T3D Therapeutics	T3D-959	Oral	Small Molecule	PPAR-delta/gamma agonist	Preclinical	Update on program late 2025
Vybion	INT-41	Intracerebral	Gene Therapy	rAAV6 containing mutant huntingtin intrabodies	Preclinical	Update on program late 2025
Takeda - Sangamo	Not Disclosed	IV	Gene Therapy	AAV containing zinc finger protein transcription factors targeting	Preclinical	Preclinical study updates in late 2025
Regenta Therapeutics	RGT-HD	Oral	Small Molecule	PMS1 pre-mRNA splicing modulator	Preclinical	Potential Update on program in late 2025
Rumi Scientific	Not Disclosed	Oral	siRNA	siRNA targeting BRD9	Preclinical	Potential Update on program in late 2025
Atlanta Therapeutics	ATL-101	Intrathecal	siRNA	Divalent siRNA targeting total huntington	Preclinical	IND filing late 2025
Sola Biosciences	SOL-175	Not disclosed	Gene Therapy	AAVrh10 vector containing JUMP70 protein to target polyQ stretch	Preclinical	Updates on preclinical studies late '25
Latus Bio	Not Disclosed	intraparenchymal infusion	Gene Therapy	AAV-DB-3 vector containing MSH3 miRNA	Preclinical	Update on program pending late '25
VectorY Therapeutics	VTx-003	Intrthecal	Gene Therapy	AAV5.2 vector containing transgene for mutant huntingtin antibodies	Preclinical	Update on program pending late '25
Alchemab	ATLX-1095	IV	Antibody	Total Ant-Huntington Antibody	Preclinical	Update on program pending late '25
Arvinas	Not Disclosed	Oral	Small Molecule	Mutant Huntington PROTAC degrader	Preclinical	Update on program pending late '25
ReviR Therapeutics	RTX-317	Oral	Small Molecule Targeting RNA Splicing	mHTT and PMS1 knockdown	Preclinical	Preclinical program progress

Licensing & Co-Development Alliances Executed in '25 YTD

Key Take-Aways: Therapeutic Candidates in Development

Target Focus

A majority of companies are focusing on the root cause of HD:

~ 46% home in on mHTT/CAG repeats (allele selective approach)

~ 25% on wtHTT (non-selective, total HTT knockdown)

HDAC1/2, C1q, BDNF, SEMA4D, Sigma-1 and GPR88 are novel downstream targets with disease-modifying potential

Drug Modality

Small molecules represent ~ 37% of the industry pipeline

ASOs and siRNAs represent ~ 14% each

Gene therapy represents ~ 23%, with antibodies and cell therapy comprising ~ 9% and 3% respectively

Phases of Development

Prilenia's Pridopidine is in Phase 3 development and the most clinically advanced in the industry pipeline

Uniqure's remarkable Phase 1/ 2 trial results may chart a new regulatory course, as it plans to file its BLA in 2026 via accelerated approval and pursue subsequent confirmatory Phase 2/3 trials

A sizeable number of Phase 2 candidates focus on downstream targets while most Phase 1 and preclinical candidates involve gene therapy, ASOs and siRNAs

Encouraging Progress in Huntington's Disease:

Pridopidine has shown strong efficacy in patients taken off anti-dopaminergic medications, which is typically used to control chorea

This is the first clinical candidate to show a benefit on multiple clinical measures (cUHDRS, Q-Motor, and SWR)

A post-hoc analysis of Roche's Tominersen phase 3 study results showed improvement in younger patients (<48 yrs) with low CAP (CAP = product of excess CAG length and age)

PTC & Novartis' Votoplam, a total huntingtin splice modifier, has shown improvement in cUHDRS, TFC and TMS, with a positive safety profile from an interim analysis

Licensing Deals Involving Assets for Huntington's Disease

While few in number, these co-development and licensing deals in Huntington's Disease point to sizeable upfronts and total deal values.

Innovator Company	Licensing or Co-Development	Agreement Type & Asset(s)	Financial Terms	Territorial / Development Rights
Prilenia Therapeutics	Ferrer	Collaboration & license for pridopidine (HD, ALS)	Total up to ~€500 m (≈$535M) including ~€125M upfront & near-term milestones	Ferrer: commercialization & co-development in Europe & select markets; Prilenia retains NA, Japan, APAC rights
PTC Therapeutics	Novartis	License & collaboration for PTC518 (Votoplam)	$2.9B total deal value (upfront + milestones)	Novartis assumes development after Phase 2 and holds global commercial rights per agreement terms
Roche	Ionis Pharmaceuticals	Research, Option & License Agreement for Tominerson	$30M Upfront for Exclusive Option; $45M License Fee; Up to $395M in milestones + tiered royalties, mid-teens	Roche obtains global development and commercialization rights
Wave Life Sciences	Takeda	Research collaboration, Option Rights, Co-Dev. & License Agreement for HD and other	$110M up-front; $60M equity investment & $60M research funding; 50/50 co-development & profit split	Takeda allowed its Option to Expire unexercised in Oct '24

Given the remarkable scientific progress in HD recently, this devastating neurological disease most certainly deserves increased investment and accelerated licensing deal activity