WELLS FARGO SECURITIES

IONS, SGMO, VYGR: Huntington's Disease Primer

Biotechnology

Positive on HTT Gene Silencing

$ Company Name	Rating	Price 01/31/18	FY EPS 2017E	FY EPS 2018E	FY P/E 2017	FY P/E 2018
Biotechnology, Overweight						
Ionis Pharmaceuticals, Inc. (IONS)	1 V	52.52	0.22	2.91	238.7x	18.1x
Sangamo Therapeutics (SGMO)	1 V	20.80	-0.75	-0.74	NM	NM
Voyager Therapeutics, Inc. (VYGR)	1 V	20.64	-2.74	-1.98	NM	NM

Source: Company data and Wells Fargo Securities, LLC estimates

1= Outperform, 2 = Market Perform, 3 = Underperform, V = Volatile, = Company is on the Priority Stock List
NA = Not Available, NC = No Change, NE = No Estimate, NM = Not Meaningful

- We are reiterating our OUTPERFORM rating on shares of Ionis Pharmaceuticals (IONS) following a "deep dive review" of Huntington's Disease (HD) and ahead of data expected for IONIS-HTT-Rx gene silencing at the CHDI meeting in late February and AAN meeting in mid April. We expect clinically relevant reductions in mutant Huntington protein and other markers of disease progression, with potential early signals of efficacy in more sensitive motor function measures. We believe that debate over safety of wild-type Huntingtin knockdown should be resolved favorably for IONS over the course of open-label extension experience in 2018, and see positive lateral benefits to earlier stage gene silencing efforts from Voyager (VYGR) and Sangamo (SGMO).
- The Wells Fargo Securities Biotechnology team has undertaken a detailed review of emerging therapeutics for Huntington's Disease (HD) with a detailed disease primer, review of disease biology, pre-clinical data, prior trial failures and ongoing programs targeted at Huntingtin gene silencing and disease-modifying therapy.
- With Ionis Pharmaceuticals (IONS) most advanced in clinical development with phase 1/2 data expected in February from a gene-silencing antisense oligonucleotide (ASO) therapeutic, IONIS-HTT-Rx, and with several other gene-silencing approaches moving into clinical development and toward data starting in 2019, the key focus of our report is on strength of data supporting the benefit of Huntingtin gene silencing, the debate between mutant Huntingtin knockdown vs. regular wide-type Huntingtin reduction, key trial endpoints and relative sensitivity to change and potential commercial opportunity.
- With Huntington's Disease (HD) caused by a trinucleotide repeat of C-A-G in the Huntingtin gene, and with disease severity driven by number of C-A-G repeats, above a threshold of 36, it is not surprising to us that pre-clinical models of Huntingtin gene silencing have produced consistent results in reducing mutant Huntingtin protein, improving motor function, reducing abnormal behaviors, and extending overall survival across animal models, including non-human primates. Prospective natural history studies confirm the key role of mutant Huntingtin protein in the disease pathology, with severity of disease and age of onset correlated with number of C-A-G repeats.
- (Continued on next page.)

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Please see page 28 for rating definitions, important disclosures and required analyst certifications. All estimates/forecasts are as of 02/01/18 unless otherwise stated. 01/31/18 17:57:17 ET

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Together we'll go far

- While debate exists in the literature regarding potential risks of non-selective targeting of C-A-G repeats and reduction in both mutant and wild-type Huntingtin protein, we believe that the most compelling data for adverse risk exists in neonatal and early development, and that significant evidence exists that normal wild-type Huntingtin protein can be reduced safely in mature animal models. With initial focus on the non-selective approach of IONIS-HTT-Rx on both mutant and wild-type Huntingtin knockdown, pre-clinical data suggest extended survival in a mouse model of Huntington's disease, with improvement in motor function and behavior and no adverse safety effects. Similar motor function benefits and safety have been observed in non-human primates (NPH), as well.
- Ultimately, clinical data is to be the arbiter of the optimal approach to gene silencing in Huntington's Disease; however, with 30,000 patients in the United States, alone, we would estimate a potential $20B global opportunity with room for multiple players. Of 8 most advanced gene-silencing programs, only 2 are mutant allele specific and the other 6 are non-selective across gene therapy, gene editing, and RNA therapeutic approaches.
- With initial focus on expectations for IONIS-HTT-Rx, we believe that with only 13 weeks of follow-up vs. 18-36 months for historical studies, the focus should be on the degree of mutant HTT reduction, neurofilament light chain (NfL) reduction, and safety, as opposed to clinical efficacy, although we note a full complement of motor and cognition measures being assessed, including finger-tapping, which appears to be a very sensitive measure of change.
- We believe that with initiation of an open-label extension (OLE) of the phase 1/2a study, and with opt-in from partner Roche, the likelihood of positive data emerging over the next 6-12 months is high. We understand that all patients completed 13 weeks of the phase 1/2a study and all are expected to roll into the open-label extension (OLE). We expect initial biomarker data for HTT and neurofilament reduction at the CHDI meeting, February 25 to March 1, with review of efficacy measures at the AAN meeting, April 21 to April 27, and potential open-label extension (OLE) data in 2H18. We would view reduction in mutant Huntingtin protein of greater than 25% as meaningful, based on pre-clinical data, and would view any trends in efficacy as highly positive given the short course of study.

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Molecular Biology Perspective of HD

- Huntington's disease (HD) is caused by a trinucleotide (CAG) repeat expansion in exon 1 of the huntingtin (HTT) gene.
    - HTT is a large cytoplasmic protein expressed in all mammalian cells. It consists of 3,144 amino acids, and the gene encoding HTT has a large number of exons (67 exons).
    - In normal individuals, the first exon of the HTT gene contains a stretch of 9-35 CAG trinucleotide repeats (median between 17 and 20). This stretch of CAG repeats is translated into a series of consecutive glutamine (Q) residues, called a polyQ tract, in the N-terminus of the HTT protein product.
    - A mutant HTT gene contains an expanded CAG repeat region, with 36 or more repeats. As a result, the mutant HTT protein contains an expanded polyQ tract.
    - The toxic effects of mutant HTT protein are positively correlated with the size of the CAG repeat expansion, with 36 CAG repeats considered the minimum size to confer pathological effects.
    - Most adult-onset cases of HD are associated with 40-50 repeats; juvenile-onset (i.e., younger than 20) disease is associated with more than 55 repeats; very early childhood onset disease is associated with 100-150 repeats. CAG repeat expansions between 36 and 39 may not lead to symptoms within a normal lifespan.
- The structure of the N-terminal region of a HTT protein containing 17Q has been solved. The 17Q stretch is a flexible region that can adopt several conformations, including alpha helix, random coil, and extended loop. A proline-rich domain (PRD) preceding the polyQ stretch contains a rigid structure called proline-proline (PP) helix, which may contribute to the stabilization of the polyQ structure, as well as the propensity of the mutant HTT to aggregate.
- The normal cellular function of HTT is not well understood. HTT is expressed in all mammalian cells. The highest expression of HTT is in the brain and testes. In neurons, HTT is associated with vesicle membranes and microtubules, as well as clathrin (a membrane protein that mediates endocytosis); and therefore, it is postulated that HTT may have a role in vesicle transport and synaptic function. In addition, some studies show that HTT may have anti-apoptotic function, mainly through inhibiting caspase 9 activation.
- Exon 1 of HTT with an expanded polyQ tract is sufficient to cause a progressive neurological phenotype in transgenic mice in the absence of the rest of the HTT protein.
- The mutant HTT protein is cleaved in cells, generating N-terminal fragments containing the polyQ tract. These fragments are traditionally believed to be the pathologic agent in HD.
- The N-terminal fragment translocates into the cell nucleus and form inclusion bodies. While some think inclusion bodies cause neuronal death (by interfering with transcription), others believe inclusion bodies are protective as they reduce the level of toxic soluble fragment.
- It has also been demonstrated that the N-terminal fragment can also be generated from aberrant splicing of the mutant HTT mRNA, and that the aberrant splice variant is found only in the brains of HD patients and not healthy controls.
- In addition, there is evidence that the CAG-expanded HTT RNA itself may be toxic because when the RNA code was altered from CAG repeats to CAA repeats, which is still code for a polyQ tract, the pathology was reduced.

Genetics Perspective of HD

- HD is an autosomal dominant neurodegenerative disorder. Most HD patients, therefore, are heterozygous (+/-) for the CAG expansion allele. In other words, HD patients have one mutant allele and one wild-type allele.
- The child of an affected parent has a 50% chance of inheriting the mutant HTT gene and the disease.
- Although most of HD cases run in family, roughly 3-5% of the cases may not have a family history.
- Besides HD, there are another 8 polyglutamine diseases caused by CAG repeat expansion. These are DRPLA (dentatorubropallidoluysian atrophy), SBMA (spinal and bulbar muscular atrophy), and SCA (spinocerebellar ataxia) Types 1, 2, 3, 6, 7, and 17. These diseases are caused by CAG repeats in different genes. All polyglutamine diseases share some common features, including midlife onset and a progressive course; nevertheless, each disease also displays a highly selective pattern of neurodegeneration, with little overlap between the brain regions affected. This suggests that although polyglutamine expansion is the causative event, the identity of the protein in which the expansion resides also contributes to the specificity of the disease.
- In a mouse study, insertion of 146 CAG repeats into an unrelated gene, hypoxathine phosphoribosyltransferase (HPRT), caused a late-onset neurological phenotype that progressed to premature death.
- In mice, deletion of both copies of the Hdh gene, the rodent analog of the HTT gene, was embryonic lethal. The study suggested that Hdh was involved in intracellular trafficking of nutrients, including ferric ions, which is important for embryonic development.
    - Somewhat surprisingly, the primary defect of the Hdh -/- mice appeared to lie in extraembryonic tissues – thus, injection of Hdh -/- embryonic stem (ES) cells into wild-type host blastocysts resulted in viable animals, whereas wild-type ES cells injected into Hdh -/- blastocysts resulted in chimeric embryos that die shortly after gastrulation.
- Studies of conditional inactivation of Hdh after birth demonstrated that Hdh is also required for postembryonic period. Inactivation of Hdh at postnatal day 5 led to neurological deficits, neurodegeneration, and impaired spermatogenesis.
- Heterozygous HTT knockout (+/-) mice, which contain only one copy of normal HTT, demonstrated impaired motor activity and cognitive deficits.
- HD patients homozygous for mutant HTT (i.e., having two copies of mutant HTT genes with expanded CAG repeats) have the same age of onset and symptoms as their heterozygous HD relatives, suggesting that the presence of polyQ does not interfere with HTT's function in early development
- Whether HTT is required for normal cellular function in adulthood is under debate. Some studies suggest that depletion of normal HTT in adult mouse brains has no consequences on survival, growth, or neuronal viability. Other studies find the opposite (more details on page 18).

Neurobiology Perspective of HD

- HD disease development involves neuropathology in both the striatum and cortex.
- The striatum demonstrates the most significant neuropathology in HD, with gross atrophy accompanied by selective neuronal loss and astrogliosis. Loss of 60% of cross-sectional area in the caudate nucleus and the putamen has been noted in typical postmortem samples.
    - The striatum (consisting of caudate nucleus and putamen) is part of the basal ganglia, a group of nerve cell clusters located in the center of the brain and strongly interconnected with the cerebral cortex, thalamus, and brainstem.
    - The function of the basal ganglia is to integrate all cortical activities into one behavioral output. The basal ganglia receive information from the cerebral cortex, process the information, and send the output back to the cerebral cortex via the thalamus, and to the brainstem. Parallel circuits in the basal ganglia regulate different aspects of behavior, including motor output (the most well-known function of basal ganglia), learning/cognition, and emotion.
- Certain areas of the cerebral cortex are also involved in HD development. Cortical thinning is observed in human patients prior to onset of symptoms, and by end stage, more than 30% of an HD patient's brain mass is lost.
- While ubiquitously expressed, mutant HTT affects certain cell types selectively. The medium spiny neurons in the striatum demonstrate the earliest cytotoxicity of mutant HTT.

Clinical Perspective of HD

- First symptoms typically appear between the ages of 30 and 50 years. About 10% of cases start before the age of 20 years, known as juvenile-onset HD.
- There is an inverse correlation between age of onset of HD symptoms and CAG repeat size.
- HD is a slowly progressing neurodegenerative disease. Most patients live for 15-20 years after diagnosis. The most common causes of death include pneumonia, choking, and suicide. The juvenile-onset form of HD progresses more quickly and patients live around 10 years.
- Symptoms of HD mainly consist of disturbances in three domains: motor, cognitive, and psychiatric symptoms. Key symptoms include unsteady gait, uncontrollable movements, difficulty speaking and swallowing, problems with memory and judgment, personality changes, mood swings, depression, and weight loss.
    - Motor symptoms
        - Involuntary, hyperkinetic, dance-like movements of limbs, face, and body, referred to as chorea. Unwanted movements are initially limited to distal extremities such as fingers and toes, but gradually spread to more proximal and axial muscles.
        - As the disease advances, uncontrollable movements and chorea initially increase in frequency and intensity. Then the unwanted movement becomes less prominent, giving way to dystonia. Dystonia refers to abnormal postures of limbs, trunk, and head that were a result of involuntary sustained contraction of agonist/antagonist muscles.
        - In a later stage of the disease, rigidity and bradykinesia (slow movements) supervene as the muscles become more rigid.
        - Other motor symptoms include dysarthria/dysphagia (slurred speech/difficulty swallowing), unsteady and awkward gait, poor balance, and falls.
        - In patients with juvenile-onset HD (onset before 20 years of age), rigidity and bradykinesia are the main motor symptoms, and chorea can be completely absent.
    - Cognitive decline can be variable: it may be present long before the first motor symptoms appear, but may also be very mild in patients with advanced disease. The cognitive decline is mainly related to executive functions. Patients lose the ability to plan or organize their life, or to distinguish what is relevant and what is not. Psychomotor processes (movements guided by with mental activity) are severely retarded. Flexibility of mind is lost (patients cannot make mental adjustments). Memory is also impaired. Language is relatively spared.

  - Psychiatric symptoms often precede the onset of motor symptoms. Estimates of the proportion of patients with psychiatric signs range between 33% and 76%. Depression and anxiety is common. HD is associated with an increased risk of suicide, which is a result of clinical depression. Research suggests that suicide often occurs before a diagnosis is made and in the middle stages of the disease when a patient begins to lose independence. Other psychiatric disturbances of HD include obsessions, compulsions, irritability, and aggression. Psychosis may appear in later stages of the disease.

- The progression of HD results in gradually increased dependency, and eventually patients require help with all activities of daily living. Patients in late stages are bed-bound and unable to speak (although they are generally able to understand language and are aware of family and friends).
- Although HD itself is not fatal, death is commonly caused by the complications of the disease, including pneumonia or other infections, injuries related to falls, and the inability to swallow.
- Diagnosis. Although HD is characterized by motor, cognitive, and behavioral symptoms, the clinical diagnosis is based on only the motor symptoms, which are measured by the motor assessment section of the UHDRS. More specifically, the most frequently used diagnosis criteria for clinical HD is a score of 4 in the Diagnostic Confidence-Level (DCL) sub-score in the UHDRS **scale** (see next section). A DCL subscore of 4 means that a movement disorder specialist is 99% sure that "unequivocal extrapyramidal signs" are present in a person with a family history of HD.
- **Stages of Diagnosed HD (i.e., Manifest HD)**
  - The Shoulson and Fahn Rating Scale utilizes the UHDRS **TFC score** to stage HD (the TFC score is described in details on page 10).
    - **Stage I: TFC score 11–13**. Typically from 0 to 8 years since motor diagnosis. Either (A) marginal engagement in occupation with part-time potential, and maintaining pre-disease levels of independence in finances, domestic chores, and activities of daily living, or (B) normal employment (perhaps at a lower level) and requiring only slight assistance in only one of the basic functions of finances, domestic chores, or activities of daily living.
    - **Stage II: TFC Total Score of 7–10**. Typically 3-13 years since motor diagnosis. Either (A) unable to work, requiring only slight assistance in all basic functions of finances, domestic chores, and daily activities, or (B) unable to work and requiring different levels of assistance with basic functions.
    - **Stage III: TFC Total Score of 3–6**. Typically 5-16 years since motor diagnosis. Unable to work and requiring major assistance in most basic functions.
    - **Stage IV: TFC Total Score of 1–2**. Typically 9-21 years since motor diagnosis. Requiring major assistance in most basic functions. Care may be provided at home, but needs may be better met at an extended care facility.
    - **Stage V: TFC Total Score of 0**. Typically 11-26 years since motor diagnosis. Requiring major assistance in all basic functions. Requiring full-time nursing care.
    - Progression on the TFC is about 1 point per year in Stage I and II, 0.38 point per year in State III, and 0.06 point per year in Stage IV.
  - Implications of baseline disease stage on clinical endpoint evaluation
    - Stage I and Stage II patients have the steepest natural decline and are most sensitive to currently available clinical measures.
    - Stage III and Stage IV patients have difficulty completing assessments, therefore resulting in floor and ceiling effects in clinical measures.
  - "Real world" staging – 3 stages
    - Early – patients continue to drive, manage their finances and work independently.
    - Middle – patients may lose some independence, but continue to perform activities of daily living..
  - Also note that individuals who carry the mutant HTT gene, but do not meet criteria for clinical diagnosis of HD are referred to as presymptomatic, preclinical, **premanifest**, or **prodromal HD**.

Clinical Endpoints Commonly Used in HD Trials

- **UHDRS (6 Components)**
  - **Motor Assessment** (Range 0-124)
    - The **Total Motor Score (TMS)**. A total of 31 items in 5 domains, with each item rated from 0 to 4 (0=normal, and 4=incapacitated). The 5 domains are as follows.
      - Eye movement
      - Chorea
      - Dystonia (muscle spasm and twisting)
      - Bradykinesia (slowness in movement)
      - Rigidity
  - **The Diagnostic Confidence Level (DCL)**
    - The examiner selects a response to the question: To what degree are you confident that this person meets the operational definition of the unequivocal presence of an otherwise unexplained extra-pyramidal movement disorder?"
      - 0 = normal
      - 1=nonspecific motor abnormalities (less than 50% confidence)
      - 2=motor abnormalities that may be signs of HD (50-89% confidence)
      - 3=motor abnormalities that are likely signs of HD (90-98% confidence)
      - 4=motor abnormalities that are unequivocal signs of HD (99% confidence)
  - **Cognitive Assessment**
    - Verbal fluency test
    - Symbol digit modalities test
      - Subject scans a coding key consisting of 9 abstract symbols, each paired with a number ranging from 1 to 9, and then the subject is asked to write down the number corresponding to each symbol as fast as possible.
    - Stroop color word test
      - Subject reads words of color names printed in color, with incongruence between the word's identity and the color in which it is printed. Subject must name the color in which the word is printed, and ignore the printed word. This test requires inhibition and response selection.
      - Particularly sensitive in cross-sectional and longitudinal studies of premanifest and early manifest HD.
  - **Behavioral Assessment** (Range 0-88)
    - Frequency and severity of 11 behavior signs and symptoms depression, irritability, and disruptive/inappropriate behavior.
  - **Functional Assessment** (Range 0-25)
    - 25 questions on ability to perform activities of daily living such as preparing a meal, walking around familiar places, or moving from one chair to another.
    - 1=Yes, 0=No
  - **Independence Assessment** (Range 0-100)
    - Level of independence, ranging from 0=tube fed, total bed care to 100=no special care needed.
  - **Total Functional Capacity (TFC)** (Range 0-13)

- The TFC is the most widely accepted and validated tool for assessing disease stage in HD. This scale rates a person's functional capacity and level of independence in 5 domains, with a score of 0–3 for each domain (lower score corresponding to more severe disease). The 5 domains are as follows.
  - Occupation (0=unable, 1=marginal work, 2=usual job, but with reduced capacity, 3=normal).
  - Finances (0=unable, 1=marginal assistance, 2=slight assistance, 3=normal).
  - Domestic chores (0=unable, 1=impaired, 2=normal).
  - Activities of daily living (0=total care, 1=gross tasks, 2=minimal impairment, 3=normal).
- Care level (0=full time nursing, 1=home of chronic care, 2=home).

- **Huntington's Disease Cognitive Assessment Battery (HD-CAB)**
  - Published in 2014, the HD-CAB is a cognitive assessment battery specifically designed for use in late premanifest and early HD clinical trials. The HD-CAB consists of 6 tests.
    - Symbol Digit Modalities Test
      - Subject scans a coding key consisting of 9 abstract symbols, each paired with a number ranging from 1 to 9, and then the subject is asked to write down the number corresponding to each symbol as fast as possible.
    - Paced Tapping
      - Subject asked to listen to a pacing tone, then begin tapping specified buttons on an input device using either the dominant index finger or alternating thumbs to produce the target pace, and to continue tapping at that same rate after the tone stops.
    - One Touch Stockings of Cambridge (abbreviated)
      - Stockings of Cambridge is a spatial planning test requiring subjects to match two sets of stimuli. The subject is shown two displays of colored balls in stockings. The subject must move the balls from the lower display to replicate the pattern shown in the upper display. One Touch Stockings of Cambridge is a variant of Stockings of Cambridge. Instead of moving the balls on the screen, subjects must work out the number of moves required to solve the problem, and then touch the number on the screen to indicate their response.
    - Emotion Recognition
      - Patients view Ekman and Friesen faces on a computer display, along with 7 emotion labels (anger, disgust, fear, happiness, neutral, sadness, surprise) and instructed to decide which emotion the person was feeling based on his/her facial expression.
    - Trail Making Test Part B
      - The Trail Making Test (TMT) has two parts, with Part B being more cognitively challenging. In Part A, subjects are required to rapidly sequence numbers from 1 through 25. In Part B, subjects are required to follow a sequential patter while shifting cognitive sets, sequencing from 1 to 13, while switching between numbers and letters (i.e., 1-A-2-B-3-C...). The score for this test is the time to complete the task.
    - The Hopkins Verbal Learning Test
      - Subject learns a list of 12 words and attempts to memorize them over the course of three learning trials. Roughly 20-25 minutes later, a delayed recall trial and a recognition trial are conducted. In the delayed recall trial, subject recalls any words remembered. In the recognition trial, subject provides yes/no response to 24 words, including the 12 target words and 12 false-positive words.

- **Short Problem Behavior Assessment (PBA-s)**
  - A semi-structured clinical interview measuring the severity and frequency of 11 key behavioral symptoms. It has been noted to have excellent interrater reliability.
    - Depressed mood
    - Suicidal ideation
    - Anxiety
    - Irritability
    - Angry/aggressive behavior
    - Apathy (lack of initiative)
    - Perseverative thinking or behavior
    - Obsessive-compulsive behaviors
    - Delusions/paranoid thinking
    - Hallucinations
    - Disorientated behavior
- **Physical Performance Test**
  - Timed performance of standardized ADLs (activities of daily living), with item score of 0-4
    - Stairs
    - Picking up a penny from floor
    - 360 degree turn
    - 50-foot walk
    - Putting on/removing jacket
    - Book lift
    - Simulated eating
    - Writing a sentence

Biomarkers

- **Mutant HTT (mHTT) Levels in CSF**
  - mHTT levels in CSF have been shown to correlate with UHDRS scores (R=0.516, p<0.0001) and cognitive task scores, according to the HD-CLARITY study.
  - The HD-CLARITY study used an ultrasensitive single-molecule counting mHTT immunoassay to quantify mHTT in CSF.
  - CSF mHTT concentration was higher in manifest HD participants than in premanifest HD participants.
  - **CSF mHTT could potentially serve as a biomarker in clinical studies of mHTT-lowering therapies for HD.**
- **Neurofilament light chain (NfL) in the blood**
  - NfL is a structural component of nerve cells.
  - NfL was recently discovered by University College London (UCL) researchers as a protein that is released from sick brain cells into the CSF and then leaked into the blood.
  - The researchers used blood samples, brain images, and clinical exam data from the large observational study, TRACK-HD, and discovered that the more advanced disease stage a patient was in, the higher his/her blood NfL levels, and that higher blood NfL levels correlated with worse scores on movement and cognition tests. Therefore, blood NfL (or CSF NfL) could potentially be used as a biomarker to track HD progression and response to treatment.

Learnings from Natural History Studies in Premanifest HD

- The PREDICT-HD and TRACK HD studies were large multicenter prospective observational studies examining disease progression in individuals with premanifest HD and early-stage HD.
- Early motor abnormality can be observed and measured in premanifest HD (i.e., carriers of the HD gene).
- UHDRS total motor score (TMS) are increased in premanifest HD subjects who are closer to diagnosis compared with those further away from diagnosis.
- Quantitative measurements are much more sensitive than clinical diagnosis.
  - Finger tapping (inter-tap interval duration and variability) was one of the best motor indicators of progression from premanifest HD to manifest HD.
  - Changes in Q-motor measures can occur up to two decades before clinical diagnosis.
- Brain volume atrophy occurs 12-15 years before manifest HD.
- Cognitive and behavioral impairment occurs within the decade before motor manifest HD.

Epidemiology

- Estimates for the prevalence rate of HD in the United States range from 4.1 to 8.4 per 100,000 people. Thus, the U.S. HD prevalence population could be between 13,000 and 27,000 patients.
- Another widely quoted estimate of U.S. prevalence for HD is 30,000.
- Roughly 80% of patients are in early to mid stages of disease.
- Prevalence varies greatly between ethnic groups: while the prevalence in the United Kingdom is reported to be 10 in 100,000, the prevalence in Japanese and African populations is below 1 in 100,000.

Current Treatment Options

- Currently there is no disease-modifying therapy for HD. All therapeutic options are for treating symptoms, with a goal of improving quality of life.
- Chorea can be managed by dopamine depletors, including XENAZINE (tetrabenazine) and AUSTEDO (deutetrabenazine). Both drugs are FDA-approved for the treatment of chorea associated with HD. Side effects of XENAZINE include depression and suicidal thoughts. The recently approved AUSTEDO is a deuterated version of XENAZINE, and it demonstrates an improved tolerability profile.
- KLONOPIN (clonazepam), HALDOL (haloperidol), or CLORAZIL (clozapine) can be used to control movements, outbursts, and hallucinations.
- PROZAC (fluoxetine), ZOLOFT (sertraline), or PAMELOR (nortriptyline) can be used to manage depression and obsessive-compulsive behaviors.
- Extreme emotions and mood swings may be managed with lithium.
- Non-drug treatments may include psychotherapy, speech therapy, physical therapy, and occupational therapy.

Notable Recent HD Clinical Trial Failures

- **Dopaminergic stabilizer pridopidine (Teva)**
    - Pridopidine was developed by Danish biotech company NeuroSearch as an agent to target both the motor and behavior symptoms of HD.
    - Mechanism of action. Motor symptoms of HD are associated with abnormal dopamine and glutamate transmission within the corticostriatal pathways. In normal brain, the dopamine type 1 receptor (D1)-mediated direct pathway and the dopamine type 2 receptor (D2)-mediated indirect pathway act in balance, with the former ensruring performance of voluntary motor functions and the latter preventing involuntary movements. In HD brain, degeneration of striatal medium spiny neurons weakens output to the direct and indirect pathways, resulting in impaired voluntary movement and unwanted movement. Pridopidine is thought to inhibit the indirect pathway via D2 antagonization (preventing dopamine from binding to D2), thus attenuating involuntary movements.
    - Pridopidine is thought to act at dopamine 2 (D2) receptors and display state-dependent behavioral effects.
    - NeuroSearch ran two large trials, MermaiHD (n=437) and HART (n=227), and the primary endpoint of both studies was modified motor score (mMS), a 10-item subset of the UHDRS-TMS pertaining to voluntary motor function. Both trials failed to meet the primary endpoint, but an improvement was observed on the secondary endpoint of TMS with statistical significance in both studies: -3.0 points (p=0.004) in MermaiHD, and -2.8 points (p=0.039) in HART.
    - The pooled results from both trials were presented to FDA, and the FDA advised NeuroSearch that a third study is required for approval.

- Teva acquired pridopidine from NeuroSearch in 2012 and conducted a phase 2 study, PRIDE-HD, evaluating higher doses of pridopidine. The study randomized 408 patients with HD (age ≥21 years, ≥36 CAG repeats, UHDRS TMS ≥25 points, UHDRS Independence score of less than 90%) to pridopidine BID 45 mg, 67.5 mg, 90 mg, 112.5 mg or placebo for 26 weeks. The primary endpoint was initially designed as TMS at 26 weeks. While the study was ongoing, Teva discovered new mechanism of action for pridopidine, suggesting potential benefit beyond improving motor symptoms. As a result, Teva amended the study protocol to evaluate TMS and TFC (which assesses function and disease progression) at 52 weeks. **The study did not meet its primary endpoint on TMS**, with all pridopidine arms demonstrating similar or less improvement in TMS from baseline compared with the placebo arm at 26 weeks, as well as 52 weeks. **On the TFC endpoint**, the **lowest dose arm** (45 mg) **did demonstrate less decline from baseline at 52 weeks compared with placebo** (p=0.003). However, there was not a dose response because **the magnitude of benefit observed in higher dose arms** (67.5mg, 90 mg, and 112.5 mg) **was much smaller than that observed in the 45 mg dose arm**, **and the improvement in those arms did not reach statistical significance** (p=0.70, 0.51, and 0.41 respectively).
- Teva noted at the time of the top-line data release (September 2016) that these results were encouraging and could inform phase 3 development. To date, no phase 3 study has been initiated to date, and the current status of this program is unclear.

- **PDE-10A inhibitor PF-02545920 (Pfizer)**
  - PF-02545920 was a PDE-10A inhibitor developed by Pfizer for the treatment of motor impairment in HD. Phosphodiesterase 10A (PDE-10A) is an enzyme highly enriched in the striatal medium spiny neurons and is involved in the regulation of cytoplasmic levels of cAMP and cGMP and signaling within the basal ganglia.
  - In December 2016, Pfizer announced that the phase 2 Amaryllis trial of PF-02545920 in HD has produced negative results. Pfizer has since discontinued this program.
  - The Amaryllis study randomized 272 HD patients (with TMS ≥10, CAG repeats ≥36, and age between 30 and 65 years) to PF-02545920 20 mg BID, 5 mg BID, or placebo for 26 weeks. On the primary endpoint of TMS at 26 weeks, PF-02545920 failed to demonstrate any benefit over placebo, with a 0.8 point improvement from baseline in the 5 mg arm and a 0.4-point worsening from baseline in the 20 mg arm, vs. a 1.4-point improvement from baseline in the placebo arm (p=0.75 and p=0.20 respectively). In addition, PF-0254920 also failed to show significant benefit in cognition and behavior.
- **Antioxidant/BDNF PROCYSBI (Raptor)**
  - Cysteamine demonstrated neuroprotective mechanism of action and disease modulating effects in HD animal models.
  - Raptor conducted the phase 2/3 CYST-HD study of its PROCYSBI (cysteamine bitartrate) in 96 patients with HD (UHDRS TMS≥5, TFC≥11 [i.e., Stage I disease], CAG repeats >38, age between 18 and 65 years). The study has an 18-month double-blinded period, in which patients were randomized to PROCYSBI 600mg BID or placebo, and a subsequent open-label extension period, in which all patients received 600 mg BID for another 18 months. The primary endpoint is the difference between the two groups in mean changes from baseline at 36 months in TMS.
  - Data from the 36-month analysis were reported in December 2015. In the Intent-to-treat (ITT) population, the TMS change from baseline at 36 months is +10.0 in the PROCYSBI/PROCYSBI group vs. +13.3 in the placebo/PROCYSBI (i.e., delayed start) group. **The difference in TMS was not statistically significant (p=0.1825)**.
  - Other functional endpoints assessed included UHDRS TFC and UHDRS Independence Scale. On the TFC endpoint, all patients started as Stage I disease at baseline, and by 36 months, the number of patients (n=78 completors) in Stage I, II and III/IV was 15 (36%), 24 (57%), and 3 (7%) among the 42 completors in the PROCYSBI/PROCYSBI arm, vs. 13 (36%), 15 (42%), 8 (22%) among the 36 completors in the placebo/PROCYSBI arm. On the UHDRS Independence Scale, the number of patients with improvement (≥+5 point change), no worsening, and worsening (≤-5 point change) at 36 months was 4 (10%), 13 (31%), 25 (60%) among the 42 completors in the PROCYSBI/PROCYSBI arm, vs. 0, 5 (14%), 31 (86%) among the 36 completors in the placebo/PROCYSBI arm.

- There were **3 deaths due to suicide** during the open-label PROCYSBI treatment period, and Raptor noted that the deaths due to suicide were **generally consistent with background** rates, with more than 25% of HD patients attempting suicide at least once and resulting in **5-7% of deaths per published estimates**.
- Raptor noted an intention to advance PROCYSBI into registration study at the time of the CYST-HD data release. The company has since been acquired by Horizon Pharma, and the current status of the program is unclear.

- **Copper and zinc ion homeostasis modulator PBT2 (Prana Biotechnology)**
  - Australia-based Prana Biotechnology's (PRAN) is developing PBT2 for the treatment of HD as well as Alzheimer's disease. PBT2 is a metal protein-attenuating compound that might reduce metal-induced aggregation of mutant HTT. In a mouse model of HD, PBT2 prolonged survival.
  - Prana conducted a phase 2a study Reach2HD and reported final data in late 2014. The study enrolled 109 patients with early to mild stage HD (age ≥25 years, CAG repeats ≥ 36, TFC between 6 and 13, inclusive, cognitive impairment demonstrated by a MoCA score ≥12). Patients were randomized to PBT2 100 mg QD, 250 mg QD, or placebo for 26 weeks. The primary endpoint was safety. Key secondary endpoints included change in the main composite Z score of 5 cognitive tests (Category Fluency Test, Trail Making Test Part B, Map Search, Symbol Digit Modalities Test, and Stroop Word Reading Test) and scores on 8 individual cognitive tests (the above five plus the Trail Making Test Part A, Montreal Cognitive Assessment, and the Speeded Tapping Test). Other secondary endpoints included UHDRS TMS, UHDRS TFC, UHDRS total behavioral score, brain iron concentration, left caudate volume, and blood concentration of mutant HTT and selenium.
  - The results of the study were published in Lancet Neurology in November 2014. Patients enrolled had a mean of 43.9 CAG repeats. Baseline characteristics related to UHDRS included mean TMS of 32.2, TFC of 9.2, total behavioral score of 10.5, and total independence score of 81.6. Baseline cognitive measures included Category Fluency Test score of 12.6, Trail Making Test Part A of 56.7, Part B of 144.3, Map Search scores of 18.5 (number correct in 1 min) and 34.0 (number correct in 2 min), Symbol Digit Modalities Test score of 25.6, Stroop Word Reading Test score of 66.7, Montreal Cognitive Assessment score of 23.0, Speeded Tapping Test score of 517.1.
  - **PBT2 failed to significantly improve the main cognition measure, a composite score that summarizes 5 cognitive tests, compared with placebo** at 26 weeks. In terms individual cognitive measures, **7 of the 8 cognitive measures tested demonstrated no difference between PBT2 and placebo**. One of the 8 cognitive tests, the Trail Making Test Part B, demonstrated a benefit for PBT2 250 mg vs. placebo (p=0.042), but not for PBT2 100 mg group vs. placebo (p=0.925). **PBT2 also demonstrated no significant differences vs. placebo in motor, behavioral, functional, or global assessments**.
  - Following an end-of-phase 2 meeting, FDA has issued a partial clinical hold in February 2015 requiring Prana to conduct additional animal neurotoxicity studies before moving to doses the company considers clinically relevant and plans to use in a phase 3 study.
  - European regulators have advised Prana in December 2016 to conduct further non-clinical work to evaluate the neurotoxicity seen in a dog study before pursuing a phase 3 study.

Summary of Gene-Silencing HD Therapies in Development

- Gene silencing is considered the most attractive approach for the treatment of HD because it can potentially **address to the root cause of HD.**
- Multiple HTT gene-silencing approaches are currently being developed; some programs target both wild-type and mutant HTT (non-selective), while others target only the mutant HTT (allele specific).
    - Antisense oligonucleotide (ASOs)
        - Ionis Pharmaceuticals (IONS) – IONIS-HTT-Rx in phase 2 (non-selective).
        - WAVE Life Sciences (WVE) - WVE-120101 and WVE-120102 in phase 1b/2a (mutant allele specific).
    - Gene therapy with virally encoded microRNAs (miRNAs)
        - Voyager Therapeutics (VYGR) and Sanofi - VY-HTT01 in preclinical stage (non-selective).
        - uniQure (QURE) – AMT-130 in preclinical stage (non-selective).
        - Spark Therapeutics (ONCE) – gene therapy candidate in preclinical stage.
    - Zinc finger protein fused with transcription repressor (ZFP-TF)
        - Sangamo Therapeutics (SGMO) and Shire – ZFP-TF program in research stage (mutant allele specific).
    - Small interfering RNAs (siRNAs)
        - Alnylam (ALNY) – ALN-HTT (this program appears to be inactive since 2012).
        - Academic program at UT Southwestern utilizing single-strand RNA (ssRNA) (allele specific).
- Gene editing using CRISPR-Cas9 has also been explored in animal models of HD in an academic study conducted by Emory University researchers (non-selective).

Debate on the Safety of Non-Selective Silencing of HTT (both Wild-type and Mutant)

- Normal and mutant HTT differ only in the length of the polyQ tract. Therefore, normal HTT may be targeted along with mutant HTT in a therapeutic approach that does not distinguish between wild-type and mutant HTT alleles.
- Although deletion of HTT in embryonic stages has been clearly established as deleterious, there are different opinions regarding whether deletion of HTT in adulthood is harmful.
- Some studies have suggested that deletion of HTT in adult animals has no deleterious effects.
    - Researchers from the University of Kentucky published a paper in 2012, demonstrating that 6-month partial suppression of HTT in adult monkey striatum was well tolerated. The authors infused an AAV2 (adeno-associated virus serotype 2) vector encoding a short hairpin RNA targeting HTT mRNA into the striatum of adult rhesus monkeys. The average reduction in HTT mRNA levels in the striatum was 30% at 6 months post injection, and the average reduction in HTT protein levels in the putamen was 45%. No adverse events were observed behaviorally, and no neurodegeneration was observed on histological examination.
    - Researchers from the Emory University published a paper in Proceedings of the National Academy of Sciences (PNAS) in 2016, demonstrating that deletion of HTT in adult mice had no detectable deleterious effects.
    - The Emory researchers used a genetic system known as the tamoxifen-inducible Cre-loxP system to inactivate the mouse HTT gene homolog, Hdh, in adult mice. The tamoxifen-inducible Cre-loxP system is widely used in mouse genetic studies to achieve gene knock-out in adult animals. The system consists of genetic modifications that insert a pair of special sites (loxP sites) in the HTT gene. The system also has transgenic expression of a special enzyme (called Cre) that, when activated, can cut out the sequence flanked by the loxP sites and inactivate the HTT gene. The special enzyme is expressed in the animal in an inactive form, but can be activated by a small molecule compound (tamoxifen), which can be administered to the animal at desired time points.

- The Emory researchers deleted HTT in mice at 2, 4, and 8 months of age. Systemic deletion of HTT at 2 months of age, but not at 4 or 8 months of age, was lethal in 10 days, and the underlying cause of death was acute pancreatitis. The Emory researchers subsequently discovered that HTT interacts with a serine protease inhibitor (Spink3) to inhibit trypsin activity in pancreatic cells in an age-dependent manner. To avoid this deleterious non-neuronal effect, the Emory researchers then conditionally deleted HTT specifically in the brain. When neuronal HTT was depleted in mice at 2, 4, and 8 months of age, there was no detectable difference between the HTT knockout mice and controls in terms of brain size, brain volume, brain morphology on histological examination, or biomarker expressions in the brain. There was a slight detriment to survival in the 2-month group (death in 10% of animals in 5 days). The death was postulated to be a result of leaky expression of Cre enzyme in the pancreas, although this possibility was not formally investigated. Survival in the 4- and 8-month groups was not affected by neuronal HTT depletion. All mice in the 2-, 4-, and 8-month groups demonstrated normal motor function as measured by rotarod performance (rotarod is a rotating cylinder to test coordination and motor planning).
- Finally, an argument for humans' tolerance of reduced normal HTT can be made based on genetic findings that individuals who have only one copy of the HTT gene (i.e., hemizygous loss of one of the two HTT genes) are phenotypically normal.

- Other studies, however, have suggested that deletion of HTT in adult brain results in deleterious effects.
  - Researchers from the University of Tennessee (UT) published a paper in PLoS Genetics in 2017, suggesting that elimination of HTT in adult mice resulted in behavioral and motor deficits, as well as widespread neuropathy. These changes were postulated to be a result of altered brain iron homeostasis.
  - The UT researchers also used the tamoxifen-inducible Cre-loxP system to achieve conditional deletion of HTT, similar to the approach used by Emory University researchers. At various stages in adulthood (3, 6, or 9 months of age), the engineered mice were given the small molecule compound, resulting in near complete elimination of HTT gene from all tissues after 5 days.
  - The UT researchers reported that upon HTT inactivation, mice developed progressive gait abnormalities, resting tremors, and, by end-stage, pronounced weakness in hind limbs and decreased locomotor activity. Mice with inactivated HTT also demonstrated impaired rotarod performance. The severity of these impairment depended on the age at which HTT was inactivated. Mice inactivated at 3 months of age had the most severe phenotype.
  - Survival was also affected in HTT-inactivated mice in the UT study. The median survival of mice that had their HTT inactivated in early adulthood (3 months of age) was approximately 17 months. The median survival of mice that had their HTT inactivated at a later stage (9 months of age) was approximately 19 months. In contrast, median survival of engineered mice that did not receive the small molecule compound treatment was 22 months.
  - Impacts of HTT loss on brain regions were closely analyzed in the UT study. Long-term HTT elimination did not result in overt neuronal death in either the cortex, or the striatum. However, there was a gradual reduction in brain mass (brain atrophy). Extensive reactive gliosis was noted in various regions of the brain, including thalamus, granular cell layer of the cerebellum, and striatum. In addition, thalamic calcifications containing iron was seen in HTT-inactivated mice as early as 13 months of age, and consistently between 15 and 18 months. Such calcification was also seen in normal mice, but rarely before 18 months of age. The researchers believed that the calcification was a result of chronic iron depletion in the brain. The researchers were able to show reduced ferric iron content in the brain of HTT-inactivated mice, as well as altered expression of iron transport and storage proteins in the brain, including ferritin and transferrin receptor. The researchers cited work by others that implicated HTT in iron transport in mouse embryos. Other abnormalities noted in HTT-inactivated mice included corneal opacity, thickening of the cornea, prolapsed rectum, urinary retention resulting in distended bladder, and as expected, testicular atrophy.

- Regarding the discrepancy between the results of the Emory study and the UT study, despite the similar approaches used, the following two possibilities were offered by the authors of the UT study, although neither was particularly convincing. First, the Emory study eliminated HTT in mice on an Hdh +/+ background (i.e., starting with 100% HTT levels), whereas the UT study eliminated HTT on an Hdh +/- background (i.e., starting with 50% HTT levels). Thus, one possibility is that HTT elimination in adult mice on a +/- background might be more deleterious than HTT elimination on a +/+ background, although it is difficult to rationalize why this is the case. Second, the differences in the genetic backgrounds of the two study's models might underlie the different results.
- In a 2013, PLoS ONE paper, researchers from Institut Curie, France reported that selective depletion of HTT in the cortex and hippocampus in adult mice 2 months of age (using a Cre-loxP system, on a Hdh +/+ background) resulted in behavioral abnormalities (alteration of anxiety-related behavior), and reduced survival and abnormal arborization of newborn neurons in the hippocampus, which was postulated to be a result of altered BDNF signaling, as HTT is a major regulator of the transport of the neurotrophic factor BDNF in cortical neurons.
- Other studies have demonstrated that HTT has general anti-apoptotic function. More interestingly, overexpression of wild-type HTT can reduce the cellular toxicity of mutant HTT exon 1 fragments in both neuronal and non-neuronal cell lines. Wild-type HTT can also protect against apoptosis in the testis of mice expressing mutant HTT transgene.

Ionis Pharmaceuticals and Roche's ASO Candidate IONIS-HTT-Rx

- IONIS-HTT-Rx is a generation 2.0+ antisense drug designed to reduces the production of all forms of the huntingtin (HTT) protein.
- IONS recently completed **a randomized phase 1/2a study of IONIS-HTT-Rx in 46 early** manifest **HD patients**. The phase 1/2a study was conducted at 6 clinical sites in Canada, Germany, and the United Kingdom between August 2015 and November 2017.
- Ionis reported in December 2017 that the phase 1/2a study has demonstrated **dose-dependent reductions of mutant HTT**, and that the dose-dependent reductions of mutant HTT **substantially exceeded the company's expectations**. **Detailed data** from the phase 1/2 study are expected at **a medical meeting in 1H18**.
- The study enrolled 46 patients (aged 25-65 years) with **early manifest**, **Stage I HD**, defined as TFC between 11 and 13. Note that the TFC scale ranges from 0 to 13, with greater scores indicating higher functioning. (See page 8 for more details.) Baseline characteristics of the enrolled patients are as follows. The mean age was 47 years (range 26-65). The mean number of CAG repeats was 44, with a range of 40-55. The proportion of patients with a total functional capacity (TFC) score of 11, 12, or 13 was 33%, 41%, and 26%, respectively.

Exhibit 1. Baseline Characteristics of the Phase 1/2a Study

	Baseline Values
Age (yr)	Mean = 47 Range = 26 - 65
Gender	Male: 28 (61%) Female: 18 (39%)
Total Functional Capacity (TFC)*	11: N=15 (33%) 12: N=19 (41%) 13: N=12 (26%)
CAG repeats	Mean = 44 Range = 40 - 55

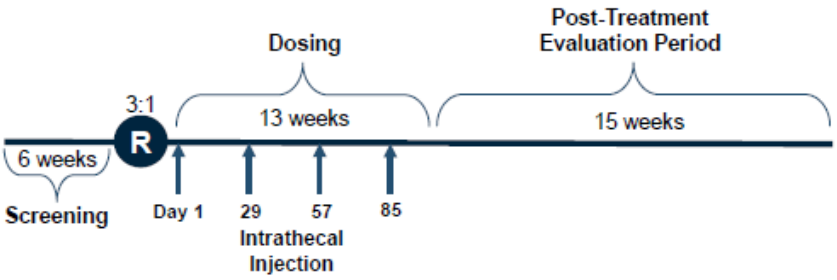
Source: Ionis Presentation

- In the phase 1/2a study, patients were randomized to **5 dose levels** of **IONIS-HTT-Rx** or placebo administered **intrathecally once every 4 weeks** for 13 weeks. The objectives of the study include evaluating the safety and tolerability of ascending doses of IONIS-HTT-Rx administered intrathecally, and evaluating the pharmacokinetics profile of INOIS-HTT-Rx in the cerebrospinal fluid (CSF).

- The primary outcome measures are safety and tolerability. The secondary outcome measure is drug concentration in the CSF. Other outcome measures include drug pharmacokinetic (PK) properties, and **CSF concentration of HTT**, **CSF concentration of neurofilament light chain**, **ventricular volume**, and the **Huntington's disease cognitive assessment battery (HD-CAB) composite score**.

Exhibit 2. Design of the Phase 1/2a Study of IONIS-HTT-Rx

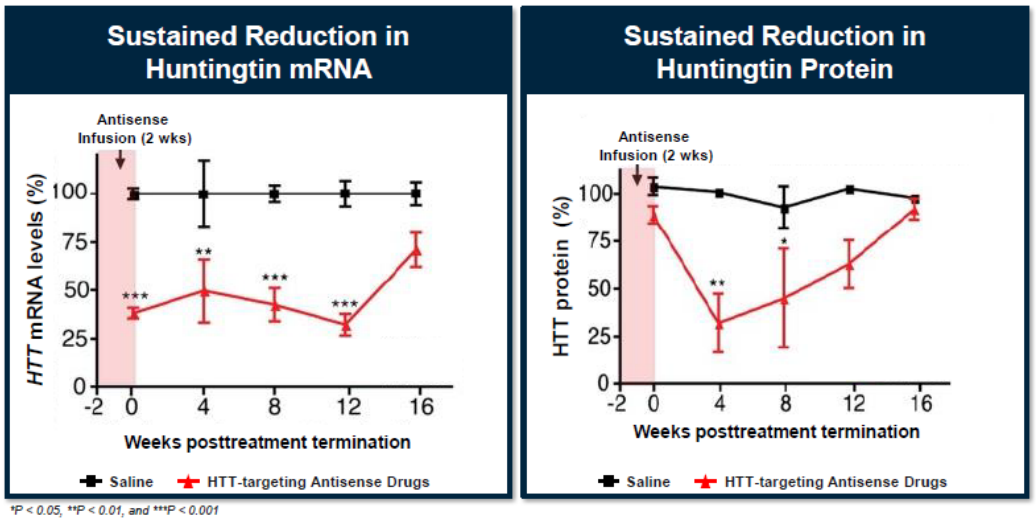
Cohorts	PBO (n)	IONIS-HTT$_{Rx}$ (n)
A	~1	~3
B	~2	~6
C	~2	~6
D	~3	~9
E	~3	~9



Source: Ionis Presentation

- IONIS-HTT-Rx was described as safe and well tolerated in the phase 1/2a study, supporting continued development of this drug candidate.
- Partner **Roche has recently exercised its option to license IONIS-HTT-Rx**, following completion of the phase 1/2a study. Roche is now responsible for all development, regulatory, and commercialization activities of IONIS-HTT-Rx. Ionis earned a $45MM license fee and is to receive royalties on future product sales.
- IONS and partner Roche recently initiated an open-label extension (OLE) study for patients who completed the phase 1/2 a study. Roche is now responsible for all development, regulatory, and commercialization activities of the IONIS-HTT-Rx program, including the ongoing OLE study and all future studies.
- **Preclinical data.** In 2012, Ionis and its academic collaborators at the University of California San Diego (UCSD) published a paper in Neuron describing the activity of ASOs in mouse models of HD.
- One of the mouse models used in the study is the BACHD mice (bacterial artificial chromosome-mediated transgenic mouse model for HD), which express a transgene encoding full-length mutant human huntingtin with an expansion of 97 mixed CAA-CAG repeats, under the control of the human HTT promoter. In the BACHD mice, the mutant human HTT protein is expressed at 1.5x the level of endogenous mouse HTT. The BACHD model recapitulates characteristics of human HD, with development of progressive motor incoordination, hypokinetic motor activity and brain atrophy. Significant symptoms develop by 6 months of age.
- The BACHD mice were administered an ASO (20-mer gapmer, referred to in the paper as HuASO) specific for human HTT (and not mouse HTT) by **continuous infusion into the right lateral ventricle**, for 2 weeks. By the end of the 2 week infusion, there was a **62% reduction in mutant human HTT mRNA** levels in brain tissues. The HTT protein levels did not decrease to a similar extent, presumably because the half-live of HTT protein is longer than that of the mRNA; nevertheless, by 4 weeks after termination of infusion, **the HTT protein levels were reduced by 66%.** ASO accumulation was detected in most brain regions, including frontal cortex, striatum, thalamus, midbrain, brainstem and cerebellum. ASO was present in both neuronal cells and non-neuronal cells, such as astrocytes. The extent of mRNA expression reduction varied in different brain regions, ranging from 81% in the ipsilateral (same side) striatum to 46% in midbrain and brainstem. **The suppression of HTT mRNA and protein expression was durable**, and the levels of HTT mRNA and protein did not return to baseline levels until 16 weeks after the termination of infusion.

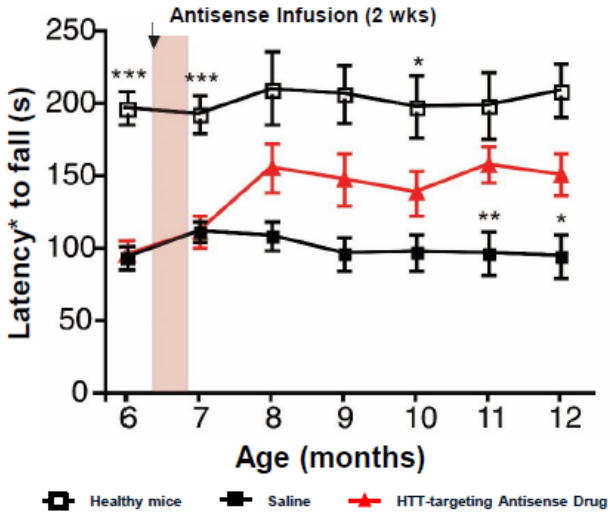
Exhibit 3. HTT-Targeting ASO Reduced HTT mRNA and Protein Levels in Brain Tissues in a Mouse Model of HD



Source: Ionis Presentation

- To evaluate the efficacy of ASO, 6-month old (already symptomatic) BACHD mice were infused for 2 weeks with HuASO and then followed for 6 months. At 8 weeks after treatment initiation, the **motor function of the HuASO treated mice improved** compared with baseline or with mice treated with control ASO. The motor function was measured by the latency to fall on rotarod (a rotating cylinder to test coordination and motor planning). Wild-type mice (no disease) demonstrated an average latency of ~200 seconds in this task. At 8 weeks after treatment initiation, BACHD mice treated with HuASO demonstrated an average latency of ~150 seconds, compared with ~110 seconds for BACHD mice treated with saline or ~70 seconds for BACHD mice treated with control ASO. The improvement in motor function persisted for 6 months after the treatment had ended and more than 2 months after restoration of mutant HTT protein production to pre-treatment levels. There was also a **reversal in behavior** after treatment, as measured by an open-field mobility assay. The reversal in behavior was not seen until 6 months after initiation of treatment. There was also a **reversal in anxiety** after treatment, as measured by a light/dark area choice assay (time in light area ~90 seconds for saline treated BACHD mice, vs. ~260 seconds for HuASO treated animals, which was similar to healthy, wile-type mice).

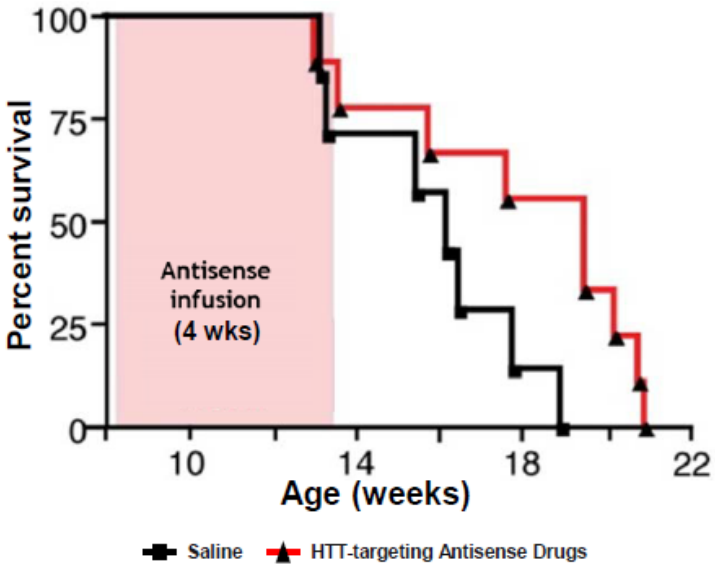
Exhibit 4. Improvement in Motor Function (Rotarod Test) in Mouse HD Model



Source: Ionis Presentation

- At 9 months after treatment initiation, in control ASO-treated BACHD mice, mutant HTT was present in a diffused cytoplasmic pattern, as well as in aggregates (mutant HTT was detected by an antibody specific for the polyglutamine tract). In contrast, in BACHD mice treated with HuASO, there was only diffused cytoplasmic staining, with very few aggregates. Thus, although the soluble mutant protein was restored at 9 months post the 2-week HuASO treatment, the transient suppression of mutant HTT was sufficient to delay the formation of polyglutamine aggregates.
- To determine if suppression of endogenous wild-type HTT represented a safety risk in adult animals, BACHD and non-transgenic mice were treated at 2 months of age with vehicle, HuASO (same as above), or MoHuASO, an ASO that reduces mutant HTT to the same level as HuASO, but also reduces mouse HTT to 25% normal levels. Motor function was improved to a similar degree and duration in mice treated with MoHuASO compared with mice treated with HuASO. Behavior (hypoactivity) was also improved to a similar degree in mice treated with MoHuASO compared with mice treated with HuASO. Thus, **transient suppression of normal HTT (to 25% of normal levels) in adult mice did not pose a safety risk**, nor did it attenuate the therapeutic benefit of targeted suppression of mutant HTT.
- **ASO therapy also prevented brain loss and extended survival in an acute, fatal model of HD.** The R6/2 mice express a fragment of the human HTT gene with an expanded CAG repeat and exhibit progressive motor phenotype, dramatic loss of brain mass, and a lifespan of roughly 16 weeks. Infusion of an ASO targeting the mutant R6/2 transgene into the right lateral ventricle of 8-week old R6/2 mice (symptomatic, with brain loss already evident) for 4 weeks reduced the human HTT mRNA expression by 43%, and prevented brain mass loss, with a brain mass of ~400 mg at 4 weeks after treatment initiation (a level similar to baseline) vs. 364 mg for vehicle-treated R6/2 mice at the same time point. The median lifespan of R6/2 mice was extended to 136 days in mice treated with ASO compared with 113 days in vehicle-treated mice. In this model, ASO was not able to impact the level of mutant HTT aggregates during the time course of the treatment.

Exhibit 5. Improvement in Survival in Mouse Model of HD

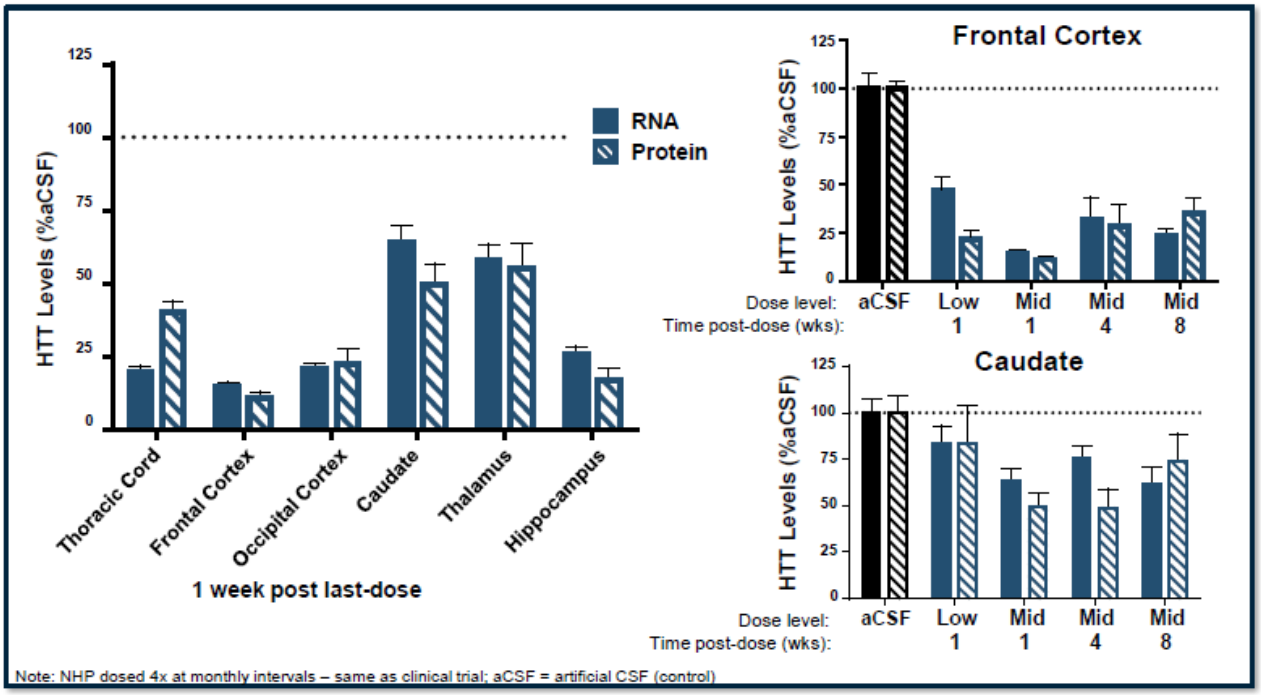


Source: Ionis Presentation

- **Continuous intrathecal (IT) administration** of ASO in **non-human primates (NHPs)** produced sustained reduction in HTT mRNA in most brain and spinal cord regions, including the regions of interest to HD pathology – the striatum and the cortex. An ASO that targets both monkey and human HTT mRNA (referred to as MkHuASO) was continuously infused intrathecally at a dose of 4 mg per day into Rhesus monkeys for 21 days. The infused MkHuASO was detected in most regions of the cortex (pyramidal neurons and surrounding tissue), caudate nucleus of the striatum (periventricular medium spiny neurons), hippocampus, pons, and cerebellum. HTT mRNA was reduced in anterior cortex (by 53%), posterior cortex (37%), caudate (25%), cervical spinal cord (~65%), midbrain (~25%), hippocampus (~23%), pons (~25%), and cerebellum (~15%). The mRNA levels remained reduced in the anterior (by 50%) and posterior cortex (by 70%) and spinal cord (by 50%) for 4 weeks after the termination of treatment, and only began to increase after 8 weeks. Thus, in both rodents and NHPs, the ASO suppression of HTT mRNA levels was long lived (2 or 3 months).

- **NHPs dosed with a similar regimen as in the clinical trial demonstrated sustained HTT mRNA and protein reduction with cortical predominance.** IONS has presented additional preclinical data from a study in which NHPs were dosed 4 times at monthly intervals – the same regimen as used in the clinical trial. At 1 week post the last dose, HTT mRNA and protein levels were reduced in various brain tissues, including thoracic cord, frontal cortex, occipital cortex, caudate, thalamus, and hippocampus. The levels of reduction were variable, with the greatest reduction observed in the frontal cortex. At the low dose, the HTT mRNA reduction was roughly 50% in the frontal cortex and 20% in the caudate at 1 week post last dose. At the mid dose, the HTT mRNA reduction was roughly 80% in the frontal cortex and 40% in the caudate at 1 week post dose. The suppression of HTT mRNA and protein levels was maintained for at least 8 weeks after the last dose.

Exhibit 6. HTT-Targeting ASO Produced Sustained HTT mRNA and Protein Reduction in NHP CNS



- Cortical-predominate pharmacodynamic effect lasts approximately eight weeks
- Measurable effect in caudate is approximately 15-20% when cortical effect is around 50%

1. *Tabrizi, S. (2017). Antisense Oligonucleotide Therapy for Huntington's Disease: A Clinical Trials Perspective. Presented at the ANA Annual Meeting, San Diego, CA.*

Source: Ionis presentation

WAVE Life Sciences' (WVE) ASO Candidates WVE-120101 and WVE-120102

- WVE-120101 and WVE-120102 are allele-specific agents specifically targeting the mutant HTT gene and not the wild-type HTT gene
- Allele specificity is achieved by exploiting single nucleotide polymorphisms (SNPs) that distinguish mutant HTT alleles from the wild-type allele. These SNPs are genetic mutations (beyond CAG repeats) found only in mutant HTT genes and not in wild-type HTT genes.
    - According to a study conducted in European Caucasian patients, 86% of HD patients shared 26 different SNPs, with only 5 of these SNPs needed to cover 75% of patients.
- The SNP targeted by WVE-120101 (SNP1) is found in ~50% of HD patients.
- The SNP targeted by WVE-120102 (SNP2) is found in ~50% of HD patients.
- ~70% of HD patients have either SNP1 or SNP2.
- The WVE ASO compounds are so-called stereopure ASOs.
    - Stereopure ASOs are ASOs synthesized with a proprietary process such that the chirality at each phosphorothioate linkages is pre-determined and non-random. WVE believes that controlling stereochemistry of ASOs may have effects on stability and RNase H1 activity of ASOs, resulting in better in vivo potency and durability of responses.
- WVE is conducting two simultaneous phase 1b/2a studies, one for WVE-120101 (PRECISION-HD1) and one for WVE-120102 (PRECISION-HD2).
- The PRECISION studies are randomized, double-blind, placebo-controlled studies evaluating single and multiple doses of WVE-120101 or WVE-120102 administered intrathecally (IT) in adult patients with early manifest HD who carry the target SNP on the same allele as the pathogenic CAG expansion.
- Each of the PRECISION studies is to enroll 48 patients into 4 dose cohorts (12 per cohort). In each dose cohort, the first 2 patients are "sentinel patients", and are randomized to a single dose of drug or placebo, with 48-hour in-patient observation followed by an 8 week washout. If no serious adverse events (SAEs) are observed, the remaining 10 patients are randomized 4:1 to the same single dose of drug or placebo, with 24-hour in-patient observation followed by an 8-week washout. Upon Data Monitoring Board review, all 12 patients in the dose cohort are randomized 3:1 to 3 doses of the drug or placebo at the same dose level – the 3 doses are administered at weeks 8, 12, and 16. In the meanwhile, the next dose cohort is initiated, again starting with the single-dose sentinel patients.
- The key inclusion criteria of the PRECISION trials include age between 25 and 65 years, Stage I or II disease as defined by UHDRS (Unified Huntington's Disease Rating Scale) Total Functional Capacity Scores between 7 and 13 (inclusive), and clinical diagnostic motor features of HD defined as UHDRS diagnostic confidence score of 4.
- The primary endpoint of the study is safety, and secondary endpoints include PK, PD (i.e., **concentration of mutant HTT in CSF**), and clinical effects as measured by the **Total Functional Capacity** (from day 1 to day 140). Other outcome measures include changes from baseline to day 140 in **UHDRS**, short problems behavior assessment (**PBA-s**), and **brain MRI** (magnetic resonance imaging).
- The studies were initiated in mid-2017 and are expected to report **data in 1H19**.
- **Preclinical data.**
    - WVE have reported that WVE-120101 reduces the levels of mutant HTT mRNA and protein, but not the levels of wild-type HTT mRNA and protein, in a reporter cell line. More specifically, when the reporter cell line was treated with 3 nM, 10 nM, and 30 nM WVE-120101, mutant HTT mRNA demonstrated a change of roughly -70%, -80%, and -95%, while wild-type HTT mRNA demonstrated a change of +30%, +20%, and -10%, respectively. In addition, the mutant HTT protein demonstrated a change of -80%, -95%, and -90%, while wild-type HTT protein demonstrated a change of roughly -5%, -5%, and -20%, at the three doses respectively. WVE noted that similar results have been replicated in a HD patient-derived cell line.
        - WVE also demonstrated that intrathecal injection of WVE-120101 and WVE-120102 achieved distribution in non-human primate brain, including in the cingulate cortex and caudate nucleus.

Sangamo's ZFP-TF Program for HD

- Partnered with Shire. Shire is responsible for all development activities including filing the IND application. According to SGMO's most recent presentation, this program is still in "research" stage and not yet in the preclinical stage.
- ZFP-TF consists of a zinc finger protein (ZFP) fused to a transcription factor (TF). The ZFP targets the mutant HTT gene, while the TF represses the transcription of the gene. The ZFP is designed to recognize longer CAG repeats, and therefore, targets only the mutant HTT allele, but not the wild-type allele.
- ZFP-TF is delivered into the striatum using AAV vector.
- **Preclinical data.**
    - In fibroblast cell lines and neurons derived from multiple HD patients, a ZFP-TF product candidate drove roughly 90% repression of mutant HTT alleles (40-69 CAG repeats), while minimally affecting the normal HTT alleles (15-21 CAG repeats).
    - In R6/2 mice, a mouse model mimicking the motor symptoms of human HD, Injection of AAV vectors containing the ZFP-TF transgene into the striatum of the brain demonstrated reduction in mutant HTT mRNA without affecting wild-type HTT levels, and increased expression of markers of medium spiny neurons, a type of nerve cell in the striatum primarily lost in HD. In addition, ZFP-TF treatment also reversed the "clasping behavior," a manifestation of motor defects in this animal model.
    - In another HD model, the Q175 mice, early administration of ZFP at two months of age prevented mutant HTT aggregation, and administration at six months of age resulted in clearance of existing HTT aggregates.
    - Genome-wide expression analysis confirmed an exquisite specificity for mutant HTT.

Voyager Therapeutics' (VYGR) Gene Therapy Candidate VY-HTT01

- Partnered with Sanofi, with co-promotion rights in the United States.
- Knock-down approach through expressing siRNAs from an microRNA (miRNA) scaffold delivered with adeno-associated viral (AAV) vectors.
- VYGR expects to utilize the same surgical approach as used in its lead program VY-AADC01 for Parkinson's disease to deliver the vector directly into the brain, although it may also be possible for the company to explore alternative delivery routes through the use of novel AAV capsids.
- **Preclinical data.** In a mouse model of HD, treatment with an AAV vector encoding HTT-targeting miRNA reduced HTT gene expression by more than 50% and achieved functional benefit.
    - The mouse model used in this study, the YAC128 transgenic mouse, harbors a yeast artificial chromosome (YAC) encoding the mutant human HTT gene bearing 128 CAG repeats and exhibits characteristic HD pathology and age-dependent, progressive motor defects.
    - In the study, the AAV vector was delivered directly into the CNS using bilateral intrastriatal injections. The miRNA sequence used was not selective, and therefore, targets both mutant (human) HTT and wild-type (mouse) HTT.
    - Mice treated with AAV vector encoding HTT-targeting miRNA (AAV2/1-miRNA-Htt) demonstrated greater than 50% reduction in HTT gene expression.
    - Significant benefit was observed in motor function as measured by rotarod test and in behavioral function as measured by the Porsolt Swim Test. In these tests, AAV2/1-miRNA-Htt treatment restored function in HD mice to near normal levels as seen in wild-type mice.
        - In the Porsolt swim test, mice are placed in water for a period of 7 minutes, and the predominant behavior, either swimming, or immobility, were recorded in 10-second intervals, in the last 4 minutes of the test. The percentage of time spent in the immobile state was calculated, with higher percentages indicating depressive behavior. In this test, mice treated with AAV2/1-miRNA-Htt demonstrated a nearly 40% reduction in time spent immobile.
    - There were no overt toxicity signals in the brains of treated animals in this study, suggesting that the adult mouse brain can tolerate reduced levels of wild-type HTT.

- Currently in lead candidate selection in non-human primates, with **potential IND filing in 2019**
    - At its R&D Day in November 2017, VYGR showed data on 4 candidates, with 60-75% HTT gene knockdown at high doses and 45-65% knockdown at lose doses in the putamen of non-human primates (NHP).
    - The lead candidate, VY-HTT01, demonstrated ~60% knockdown at high dose and ~45% knockdown at low dose in NHP putamen.
    - VY-HTT01 also demonstrated the highest precision and efficiency of pri-miRNA processing, with preliminary safety data in NHPs supporting tolerability.
    - VYGR is conducting additional IND-enabling studies, and expects to make two IND filings in 2019 from the company's three preclinical programs including the Huntington's program, the amyotrophic lateral sclerosis (ALS) program, and the Friedreich's ataxia program.

uniQure's (QURE) HD Gene Therapy Candidate AMT-130

- AMT-130 consists of an AAV5 vector carrying a DNA cassette encoding an engineered microRNA (miRNA) that silences the human HTT expression.
- **Non-selective knockdown of both wildtype and mutant HTT**
- The AAV vector is delivered into the striatum using MRI-guided stereotactic administration.
- QURE is conducting IND-enabling studies and expects to make IND filings in the United States and European Union (CTA filing) to **initiate a phase 1/2 study in 2018.**
- **Preclinical Data**
    - QURE presented preclinical data at the European Society of Gene and Cell Therapy (ESGCT) meeting in October 2017. The study was based on data from two mouse models of HD: the Q175 knock-in (KI) (heterozygous) mice and the R6/2 mice. AMT-130 was administered as a one-time treatment into the striatum of mice. The Q175 KI mice were treated at 3 months of age, and the R6/2 mice were treated at 1 month of age.
    - In the Q175 KI mice, AMT-130 demonstrated sustained reduction of soluble mutant HTT in the striatum (up to 39%) and in the cortex (up to 13%) at 12 months post-administration. AMT-130 also demonstrated strong reduction of mutant HTT aggregates in the striatum (up to 30%) and in the cortex (up to 40%) at 12 months.
    - In the R6/2 mice, a model characterized by early onset of motor symptoms and greatly reduced life-span, AMT-130 demonstrated significant improvement of motor symptoms at 3 months of age, with improved performance on rotarod (**latency to fall: ~60 seconds vs. ~39 seconds for vehicle treated mice, for an increase of 21 seconds**), and with longer time until touching hindlegs (~16 seconds vs. 8 seconds for vehicle) or clasping (~22 seconds vs. ~15 seconds for vehicle). In addition, **AMT-130 also increased the median survival of R6/2 mice by 4 weeks**, from 120 days (for vehicle treated mice) to 149 days (for AMT-130 treated mice) (p=0.027).
    - Previously, QURE has reported data in a minipig model of HD. In this model, the distribution of the vector was widespread upon MRI-guided, convection-enhanced delivery of the vector into the striatum. Injection of 3E13 genome copy (gc) AMT-130 into the striatum and thalamus resulted in reductions in mutant HTT mRNA and protein levels in the brain. The reduction in mutant HTT mRNA was ~50% in the putamen, caudate, and cortex, and ~80% in the thalamus. The reduction in mutant HTT protein was ~50% in the putamen, caudate and thalamus, and ~25% in the cortex. There was also a trend for reduced mutant HTT protein in the CSF.
    - QURE and collaborators at UCSF also reported that injection of AAV5 into the putamen and/or thalamus (5E11 gc per hemisphere for putamen and 2E13 gc per hemisphere for thalamus) of non-human primates resulted in robust transduction in the infusion site and in other distal nuclei.

Spark's (ONCE) HD Gene Therapy Program

- Spark's AAV gene therapy program for HD is in preclinical stage.
- Initial studies likely involve focal delivery to the CNS, with global delivery to the CNS a potential direction in the future.

Academic Efforts - Allele-Selective RNAi Approach by UT Southwestern Researchers

- Researchers at **UT Southwestern Medical Center** evaluated mechanisms for allele-selective inhibition of HTT without involving SNPs. Their mechanism directly targets the CAG repeats, with an miRNA-like RNAi mechanism that promotes suppression of translation, rather than RNA degradation. Selectivity for mutant HTT was achieved by virtue of the greater number of CAG repeats present in the mutant HTT mRNA compared with the wild-type HTT mRNA.
- A 2012 Cell paper published by the UT Southwestern group described the use of single-strand RNA (ssRNA) to achieve a 50-70% reduction in mutant HTT protein in relevant brain regions, with the wild-type HTT protein unaffected.
    - The sequence of the ssRNA is complementary to six CAG repeats, but with central mismatches.
    - The mismatches were placed at positions predicted to disrupt cleavage of the mRNA target by argonaute 2 (AGO2), an essential protein mediating mRNA degradation.
    - The ssRNA contain chemical modifications to increase stability (note: unmodified ssRNA has a serum half-life of merely seconds to minutes).
    - Utilized the HdhQ150/Q7 heterozygous mouse model of HD, which carries one wild-type mouse huntingtin gene (Q7) and one mouse huntintin allele, with 150 CAG repeats knocked into exon 1 (Q150)
    - The ssRNA was introduced into the lateral ventricle to achieve distribution throughout the CNS via cerebral spinal fluid.
    - Treatment with ssRNA resulted in roughly 40-75% reduction in mutant HTT protein in frontal cortex, striatum, thalamus, cerebellum, and brain stem, while wild-type HTT protein levels in these brain regions were not affected. The ssRNA treatment also did not affect HTT mRNA levels, consistent with the postulated mechanism of protein translation inhibition, but not RNA degradation.
    - In contrast, an antisense oligonucleotide (ASO) targeting outside the region of CAG repeats resulted in 60% reduction in overall HTT mRNA, 80% reduction in wild-type HTT protein, and 90% reduction in mutant HTT protein levels.
- A 2010 Cell Chemical Biology paper published by the UT Southwestern group described a similar strategy to the one discussed above, but was achieved through double-strand siRNA molecules.

Academic Efforts - CRISPR/Cas9 Gene Editing Approach by Emory University Researchers

- Researchers at the Emory University published a paper in January 2018 describing a CRISPR/Cas9 mediated gene-editing approach that ameliorated neurotoxicity in a mouse model of HD.
- HTT-specific CRISPR/Cas9 was delivered using an adenovirus vector into the striatum of adult HD mice.
- The approach was not allele specific, so both the mutant and the wild-type alleles are inactivated. The authors observed no side effect of neurodegeneration for the duration of the study (several months).
- In an interview with the Huntington Study Group, the authors suggested that they plan to do long-term observation to see if there are any side effects of removing HTT expression in adult brain tissue.

Notable Non-Gene-Targeted HD Therapy Candidates in Development

- **NFkB inhibitor/neuroninflammation modulator laquinimod (Teva)**
  - Teva is conducting a phase 2 study, LEGATO-HD, of laquinimod in HD. The study randomizes 351 patients with HD (age 21 to 55 years, 36-49 CAG repeats, TMS ≥5 points) to laquinimod 0.5 mg, 1.0 mg, 1.5 mg (this arm was discontinued in 2015), or placebo. The primary endpoint of the study is change in TMS from baseline to Months 1, 3, 6, and 12. Secondary endpoints included percent change in caudate volume, change in HD-CAB (Huntington's disease cognitive assessment battery) total score, change in UHDRS TFC, and CIBIC-Plus (Clinician's interview based impression of change) global score. The study was initiated in October 2014, and is expected to **complete in June 2018**. Note that two trials of laquinimod in multiple sclerosis – phase 3 CONCERTO in relapsing remitting multiple sclerosis and phase 2 APPEGGIO in primary progressive multiple sclerosis – have recently reported negative results.
- **Vasopressin receptor inhibitor SRX-246 (Azevan Pharmaceuticals)**
  - Vasopressin 1a (V1a) receptor, when bound by the hormone vasopressin, mediates signaling that plays a role in social and emotional behaviors. High levels of vasopressin, which may occur in HD patients, can be associated with irritable or aggressive behaviors. Irritability is a major problem for HD patients, affecting caregiver burden and quality of life, and interfering with nursing home placement.
  - The Pennsylvania-based Azevan Pharmaceuticals is studying its V1a receptor inhibitor SRX-246 in the phase 1/2 STAIR study for the treatment of neuropsychiatric symptoms of HD. The study plans to enroll 108 irritable subjects with HD. The primary endpoint of the study is tolerability, and secondary endpoints included those that measure the drug's effect on irritability, including the UHDRS, UHDRS Irritability and Aggression scale, Aberrant Behavior Checklist (ABC-I) Irritability Scale, Cohen-Mansfield Agitation Inventory (CMAI), Clinical Global Impression Scale (CGI), Caregiver Burden Assessment, and a novel eDiary. The study is expected to complete in June 2018.
- **Anti-Semaphorin 4D antibody VX15/2503 (Vaccinex)**
  - Semaphorin 4D (SEMA4D) has been shown to regulate the activation and migration of inflammatory cells and to inhibit differentiation of oligodendrocyte precursors in the brain
  - Vaccinex is conducting a randomized phase 2 study, SIGNAL, to evaluate VX15/2503 monthly infusion vs. placebo in 240 patients with late prodromal HD (defined as CAG-age product score, or CAP score, >200 and Diagnostic Confidence Level, or DCL, of 2 or 3) or early manifest HD (defined as TFC ≥11 and DCL of 4). Other inclusion criteria include CAG repeats ≥36 and age ≥21 years. The primary endpoint of the study is safety, and secondary endpoints include HD-CAB composite score, UHDRS motor scale, Q-motor scale, behavior (PBA questionnaire), UHDRS core functional assessments, brain volumes by MRI, brain metabolic activity by FDG-PET (fluorodeoxyglucose-PET) and TSPO-PET (translocator protein-targeted-PET), SEMA4D levels on T cells, and soluble SEMA4D levels. The study is expected to complete in mid-2020.
- **Stem cell therapy Cellavita HD (Azidus Brasil)**
  - A randomized phase 2 dose response study of stem cell therapy Cellavita HD is expected to begin in April 2018. The study plans to enroll 35 patients (40-50 CAG repeats, TMS≥5, and TFC of 8-11) primary endpoint is effective dose, and secondary endpoints included various UHDRS domains, body mass index (BMI), risk of suicidal ideation, and brain MRI measures for cortical thickness, and volume of various brain structures especially the basal ganglia, with special attention to caudate and metabolic changes. The study is expected to complete in 2020.
- **Deep brain stimulation (DBS) (Investigator sponsored, in collaboration with Medtronic)**
  - An investigator sponsored randomized study is evaluating DBS of the globus pallidus (GP) using Medtronic's ACTIVA PC device in HD patients for improvement of motor function. The study plans to enroll 50 patients, with an expected completion date in 2020.
  - The primary endpoint of the study is UHDRS TMS at 12 weeks between the stimulation group (device turned on) vs. the non-stimulation group (device turned off). Secondary endpoints include UHDRS chorea subscore, UHDRS bradykinesia subscore, the BFMDRS (Burke-Fahn-Marsden dystonia rating scale), the Q-motor choreomotography test (Reilmann Battery), MDRS (Mattis dementia rating scale), the verbal fluency test (formal lexical, categorical, category change), the symbol digit modalities test, the Stroop word color test, HADS-SIS (hospital anxiety and depression scale combined with Snaith irritability scale), PBA-s, SF36 (short form health survey), and CGI (clinical global impression scale).

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Rating Basis Information:

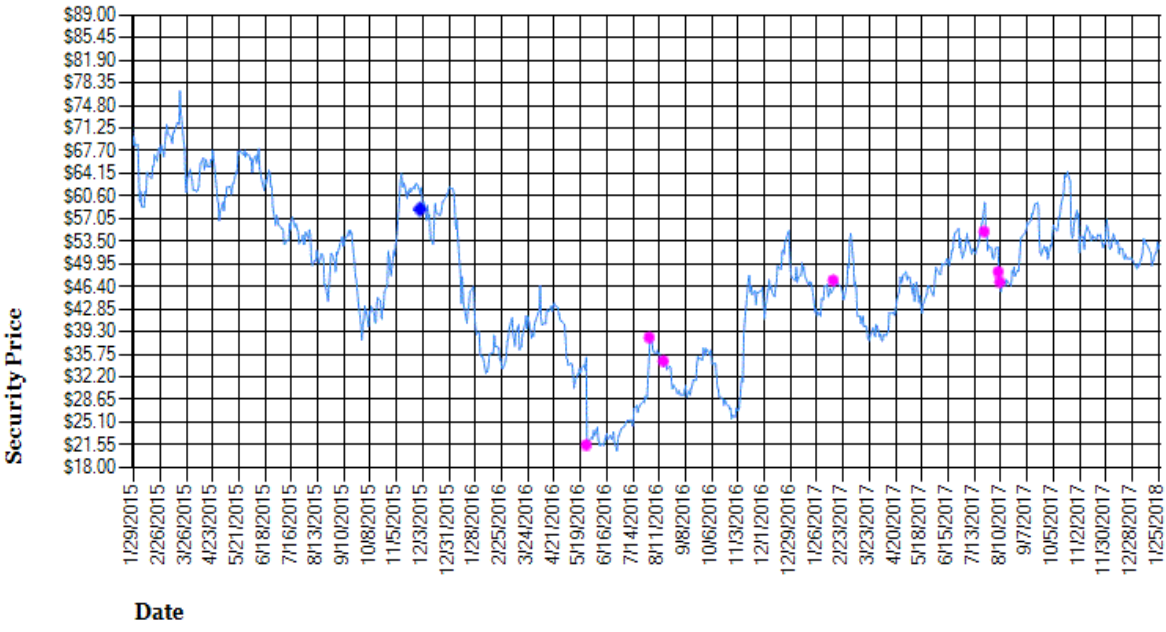
IONS Thesis: Leadership in RNA therapeutics has produced a pipeline of about 40 drug candidates with unprecedented predictability and potency of effect, and with high likelihood of clinical, regulatory and commercial success, in our view.

SGMO Thesis: Competitive advantage in gene-editing, stemming from years of experience with single loci targeting, should be maintained and translated into clinical success as multiple programs enter clinical development, including Hurler's disease and Hemophilia A.

VYGR Thesis: We believe that VY-AADC01 represents a transformational opportunity in the treatment of Parkinson's with sustained production of the missing enzyme AADC to generate needed dopamine in the brain. Reproducibility of gene therapy coverage in the brain and related improvement in symptoms supports an opportunity not reflected in current valuation.

Required Disclosures

Ionis Pharmaceuticals, Inc. (IONS) 3-yr. Price Performance



Date	Published Price ($)	Rating Code	Price Target	Val. Rng. Low	Val. Rng. High	Close Price ($)
1/27/2015		Hausner				
1/27/2015	NA	NR	NE			72.40
12/3/2015		Birchenough, MD				
12/3/2015	58.00	1	NE	90.00	97.00	58.00
5/26/2016	23.12	1	NE	42.00	55.00	21.36
8/1/2016	29.19	1	NE	61.00	64.00	38.01
8/17/2016	33.96	1	NE	63.00	68.00	34.34
2/14/2017	46.09	1	NE	68.00	73.00	46.99
7/25/2017	53.25	1	75	NE	NE	54.71
8/8/2017	49.25	1	94	NE	NE	48.31
8/11/2017	46.43	1	113	NE	NE	46.76

Source: Wells Fargo Securities, LLC estimates and Reuters data

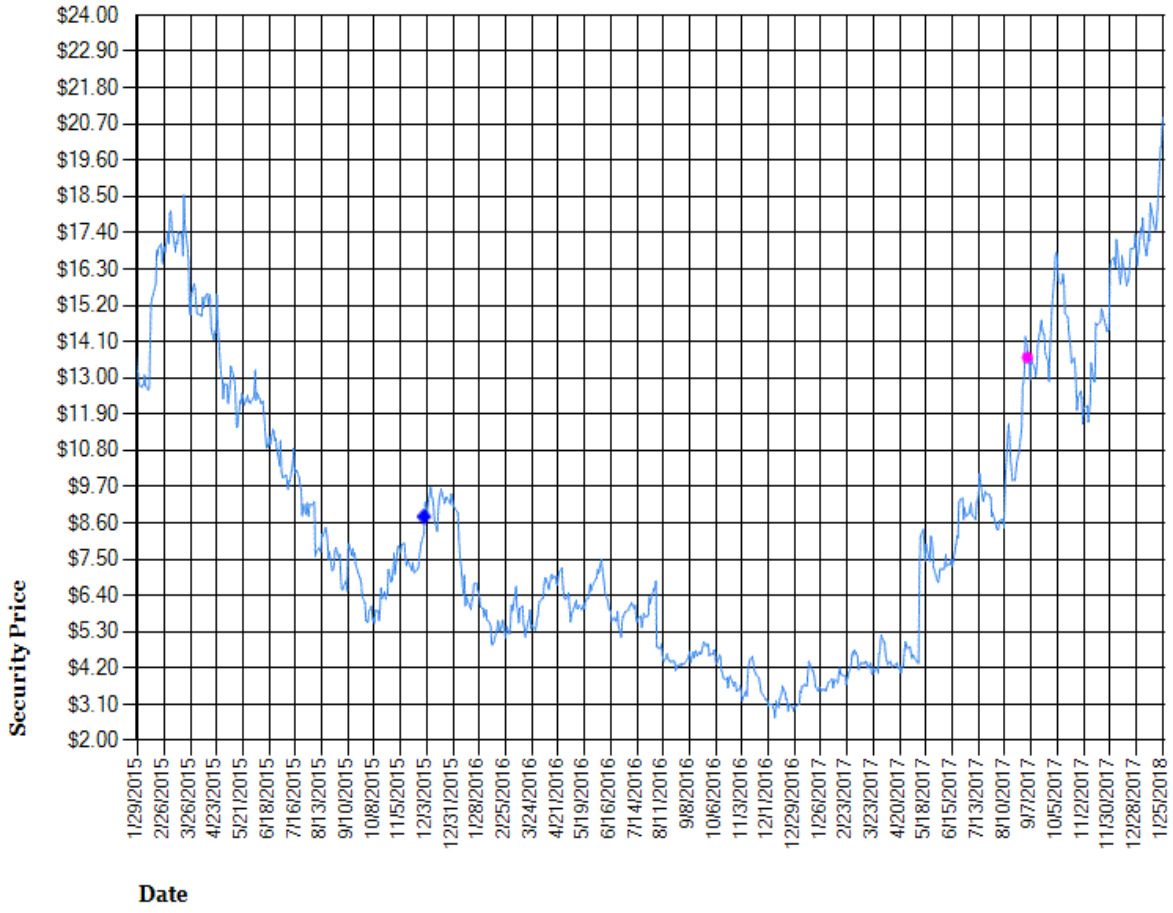
Symbol Key

- ▼ Rating Downgrade
- ▲ Rating Upgrade
- ● Price Target/Val Range Change
- ◆ Initiation, Resumption, Drop or Suspend
- ■ Analyst Change
- ◨ Split Adjustment

Rating Code Key

1	Outperform/Buy	SR	Suspended
2	Market Perform/Hold	NR	Not Rated
3	Underperform/Sell	NE	No Estimate

Sangamo Therapeutics (SGMO) 3-yr. Price Performance



Date	Published Price ($)	Rating Code	Price Target	Val. Rng. Low	Val. Rng. High	Close Price ($)
12/3/2015		Birchenough, MD				
12/3/2015	8.72	1	NE	16.00	24.00	8.72
● 9/5/2017	14.25	1	30	NE	NE	13.55

Source: Wells Fargo Securities, LLC estimates and Reuters data

Symbol Key

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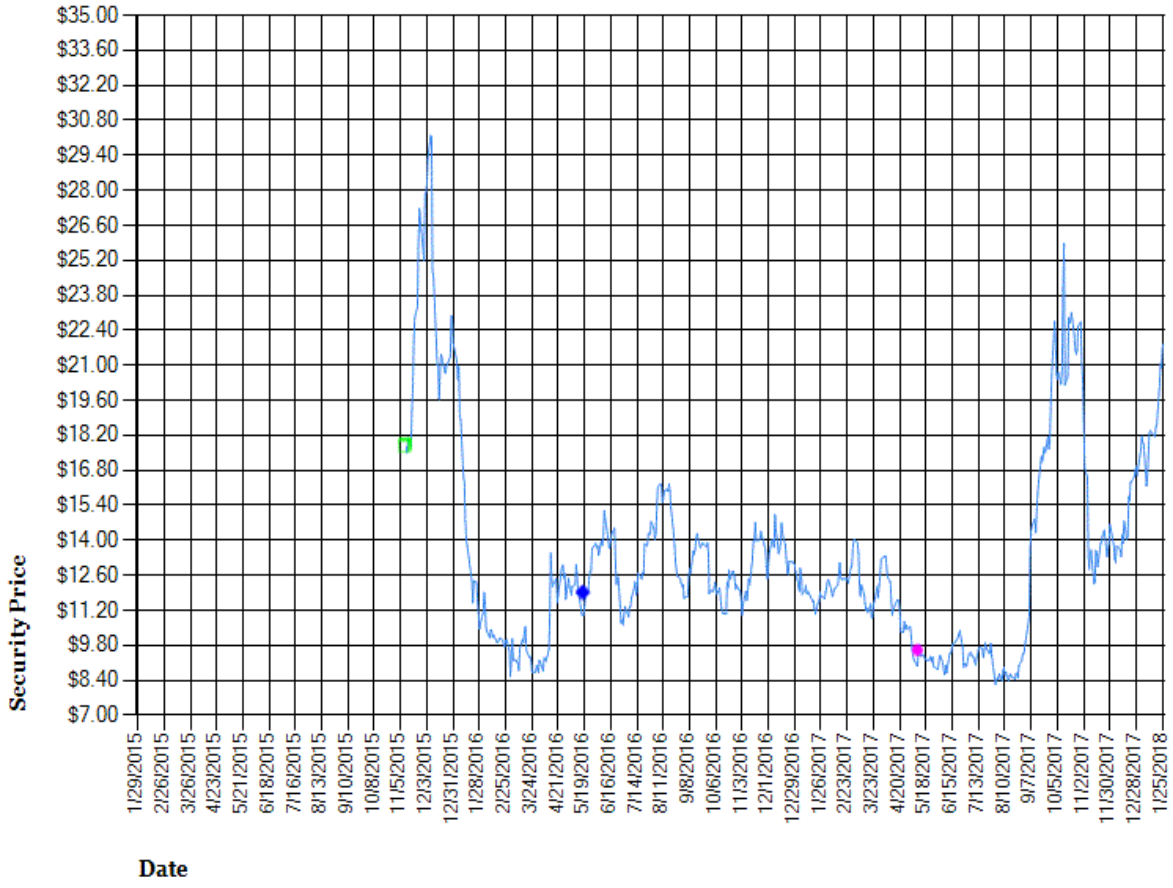
- ▲ Rating Upgrade
- ● Price Target/Val Range Change
- ◆ Initiation, Resumption, Drop or Suspend
- ■ Analyst Change
- ▯ Split Adjustment

Rating Code Key

1	Outperform/Buy	SR	Suspended
2	Market Perform/Hold	NR	Not Rated
3	Underperform/Sell	NE	No Estimate

Voyager Therapeutics, Inc. (VYGR) 3-yr. Price Performance



Date	Published Price ($)	Rating Code	Price Target	Val. Rng. Low	Val. Rng. High	Close Price ($)
11/11/2015		IPO at $14.00				
5/20/2016		Birchenough, MD				
5/20/2016	11.33	1	NE	35.00	43.00	11.83
5/10/2017	8.97	1	43	NE	NE	9.56

Source: Wells Fargo Securities, LLC estimates and Reuters data

Symbol Key

- Rating Downgrade
- Rating Upgrade
- Price Target/Val Range Change
- Initiation, Resumption, Drop or Suspend
- Analyst Change
- Split Adjustment

Rating Code Key

1	Outperform/Buy	SR	Suspended
2	Market Perform/Hold	NR	Not Rated
3	Underperform/Sell	NE	No Estimate

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IONS: Risks to our price target include clinical trial failures, unexpected toxicity, and failure to gain approval or to achieve commercial success.
SGMO: Risks include further delay to clinical trial initiations, sub-optimal efficacy in early experience in Hurler's and hemophilia A, or failure to approach meaningful clinical benefit in lead programs, competitive with existing therapies or emerging gene editing/therapy platforms.
VYGR: Risks to our outlook include an inability to achieve reproducible putamen coverage, individual patient variability in terms of response to putamen coverage, overall inability to demonstrate benefits beyond historical placebo effects, unanticipated safety issues and inability to successfully commercialize VY-AADC01.

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