IMPORTANCE OF RESEARCH PARTICIPATION



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The following personal financial relationships with commercial interests relevant to this presentation existed during the past 12 months:

> Principal Investigator, SIGNAL Principal Investigator, WAVE Principal Investigator, Enroll-HD



So why should you consider participating in a clinical trial?

- Clinical trials play a critical role in medical research; without them, innovative discoveries and breakthroughs wouldn't make it to the patients that need them
- Unfortunately, clinical trials are often under-enrolled
 - 37% of clinical trials don't enroll enough patients to move forward
 - 11% fail to enroll even one patient





Clinical trials are necessary!



- Clinical trials are a required step in bringing new
 breakthroughs to the patient
- These studies evaluate the effects of an experimental test or treatment, and allow the U.S. Food and Drug Administration to determine if it's safe and effective, and should be made available to the public
- And these trials won't happen without the participation of volunteers.



The smartest minds in medicine designed this for you

- Clinical trials are not designed by one doctor on the fly, but a large collection of physicians, pharmaceutical pioneers, and large collaborative international work groups, with experienced regulatory oversight
- Trials compare head-to-head two (or more) therapy options—usually the current standard vs. a potentially better experimental option. If the experimental arm didn't have a chance of improving outcomes, the trial would never happen.





- Clinical trials staff monitor you closely
 - Clinical research staff adhere to protocols -- look at every lab, medicine, symptom, and carefully interrogate the impact on you, your care, and your outcome
- Institutional Review Boards protect your rights
 - An IRB is an independent body designated to evaluate and monitor all clinical research at your health system to protect the rights and welfare of research subjects. The process is unique to trials and doesn't exist in standard practice
 - There is no independent group of people reviewing your care and watching out for your best interest unless you are In a clinical trial.



Clinical trials help others!

- Participation is critical in helping prevent, diagnose, and cure diseases and illnesses
- Trial participation is altruistic. There may or may not be benefits to you but When you participate in a clinical trial, you are contributing to research that could bring new treatments one step closer to reaching patients
- The trial may not only help advance the science for your disease or illness, but could also make progress for related areas of science.

"I feel anyone who volunteers for research is a pioneer and I appreciate all who have gone before me."



Clinical trials can save your loved ones!

- If you have a disease or illness like HD that's genetic, your participation could end up helping your loved ones by making new treatments available and advancing scientists' understanding of the disease or illness
- The study could even be the one that leads to a cure.





Clinical trials give you access to new treatments!

- Participating in a clinical trial may give you access to experimental, cutting-edge treatment options
- Plus, you will have access to a medical team that carefully monitors your disease and your overall health.





Clinical trials need participants from all backgrounds to participate!

- You are important for clinical trials!
- Participants of all backgrounds are needed as Trials are often widely criticized for not having enough gender, age, race, geographic, or socioeconomic diversity
- Whatever your age, race, gender or background clinical trials need YOU!





Clinical research and clinical trials facts

- Clinical trials are medical research that follows a defined protocol developed to answer specific patient care questions
- Clinical trials may investigate the effectiveness of new drug treatments, new combinations of drugs, procedures, or behavioral and lifestyle modifications
- A clinical trial is led by a PI and research team
- Clinical trial sponsors may be institutions, companies, government agencies, or other organizations that are responsible for initiating, managing or financing the clinical trial, but do not conduct the research.



Clinical research and clinical trials facts

- Informed consent is the process of providing you with key information about a research study before you decide whether to participate
- The informed consent document includes details about the study--its purpose, how long it's expected to last, tests or procedures that will be done as part of the research;who to contact for further information. The informed consent document also explains risks and potential benefits
- You can then decide whether to sign the document. Taking part in a clinical trial is voluntary; you can leave at any time.



Phases of clinical trials

- **Phase I:** Tx tested in a small group of people (20–80) for the first time. The purpose is to learn about safety and identify SEs
- **Phase II:** Tx given to a larger group of people (100–300) to determine its effectiveness and to further study its safety
- **Phase III:** Tx given to large groups of people (1,000–3,000) to confirm its effectiveness, monitor SEs, compare it with standard tx, collect information to allow it to be used safely
- Phase IV: After a drug is approved by the FDA and made available to the public, researchers track its safety in the general population, seeking more information about a tx's benefits, and optimal use.



What does "placebo", "randomization", and "blinded" mean in clinical trials?

- **Placebo** is an inactive product that resembles the test product, but without its tx value--fastest and most reliable way to show effectiveness
- **Randomization** is the process by which txs are assigned by chance rather than choice—avoids any bias in assigning tx
- Blinded studies are designed to prevent members of the research team and study participants from influencing the results—to reduce bias. In single-blind studies, only the research team knows. In a double-blind study, neither the patient nor the research team know.





POTENTIAL BENEFITS

- Help others by contributing to knowledge about new treatments or procedures
- Gain access to new research treatments before they are widely available
- Receive regular and careful medical attention from a highly skilled research team of health professionals.

RISKS

- Possible unpleasant, serious, or even life-threatening effects of experimental treatment
- May require more time than standard tx, including study site visits, blood tests, procedures, or complex dosing





Vaccinex Receives FDA Fast Track Designation for VX15 Antibody for the Treatment of Huntington's Disease

August 2016



Fast track often leads to priority review, expedited review, and faster approval



September 2016

"A pre-specified interim analysis of data from six months of double-blind treatment with VX15/2503 or placebo (Cohort A) was completed. No safety signals were identified that warranted stopping or modifying the study."

A New Investigational Approach to Early Treatment of HD





- Phase 2 trial for people who are at risk for HD and have early signs of HD
- Study will assess the safety, tolerability, and effectiveness of VX15 (novel mAb):
 - Monoclonal antibody that blocks the activity of semaphorin 4D (SEMA4D)

What is different about this research trial?



- First time use of a monoclonal antibody for potential treatment of HD
- Once-a-month study drug delivery through 60-minute intravenous infusion
- Use of advanced brain scan techniques and analyses (MRI and PET)
- Enrollment extended



GENE SILENCING IONIS-HTTRX (RG6042)

H

Antisense oligonucleotide (ASO) A single strand of chemically altered DNA

Anti-sense oligonucleotide

designed to reduce the production of all forms of the huntingtin protein, including the mutated one IONIS-HTT_{RX} in the brain: Promising results from preclinical studies

- In monkeys, the drug lasts 3-4 weeks in the brain; lowering of huntingtin protein lasts up to 4 months
- Aim is to reduce protein levels by 50% in the cortex
- Belief is that this will allow reduction of striatum levels by 15%





Objectives of Ionis trial of HTTRx for HD

- Is IONIS-HTT safe and well-tolerated?
- How long does it stay in the human nervous system?
- Does it affect huntingtin protein level, other biomarkers or symptoms?





IONIS-HTT RX TRIAL: Safety, tolerability, pharmacokinetics, and pharmacodynamics of ISIS-HTTRx in patients with early manifest HD

- Safety, tolerability, pharmacokinetics, and pharmacodynamics of ISIS-HTTRx in patients with early manifest HD; Phase 1/2 study
- ISIS-HTTRx (or placebo) is administered intrathecally at 4 week intervals over the course of a 13-week treatment period for dose levels A, B, C, and D
- Subjects must be 25 to 65 years; able to tolerate MRI scans, blood draws and LPs
- Only 6 participating locations in Canada, Germany, UK; estimated enrollment=46





IONIS-HTT RX TRIAL: Safety, tolerability, pharmacokinetics, and pharmacodynamics of ISIS-HTTRx in patients with early manifest HD

- Phase 1/2a trial main focus is safety
- 46 patients with early HD
- 3 sites in UK, 1 in Canada, 2 in Germany
- Placebo-controlled
- ISIS-HTTRx (or placebo) is administered intrathecally at 4 week intervals over the course of a 13-week treatment period for dose levels A, B, C, and D (escalating)



ASO drug is injected into HD patients' cerebrospinal fluid in a process similar to a lumbar puncture or spinal tap.



Cerebrospinal Fluid (CSF) flow



Results confirms Huntington's disease 'gene silencing' trial on track Feb 2018

 Participants who received the two highest doses showed an average reduction of 40% in mHTT levels in their CSF; some as high as 60%.



- Researchers believe these reductions correspond to an estimated 55-85% decline of mHTT levels in the cortex, and 20-50% in the caudate; large enough to yield clinical benefits.
- No serious AEs; most were mild and considered unrelated
- Next step is to conduct larger/longer studies to confirm these results, to investigate whether IONIS-HTTRx slows disease progression, and evaluate long-term safety.
- OLE for the 46 pts who completed the Phase 1/2 trial will transition to Roche, which will manage this and future trials



- clinical trials of two new drugs: novel approaches to lowering mHtt
- targets Single Nucleotide Polymorphisma (SNPs) associated with the disease-causing mutation in the mHTT gene.
- WAVE's approach enables selective silencing of the disease-causing HTT allele, while leaving the healthy HTT allele to produce normally functioning protein (allelespecific)
- WVE-120101 is the first of our two lead allele-specific antisense programs for HD



The WAVE ASO acts like a drone that wants to shoot down the bad HD gene, or kite, but can't tell the difference between the good and bad kites. However, it can recognise the different coloured ribbons in the tail. Shooting at the ribbon instead of the kite is good enough to take down the whole thing. Image credit: Mike Flower WAVE Life Sciences launches PRECISION clinical trial to suppress mHtt protein

-ASOs target two SNPs (tiny genetic differences) in the HTT gene

-about 2/3 of patients will have one or the other SNP to allow them to participate in one of the two trials



Early days, long way to go to show that it's safe and effective



PRECISION-HD 1 and 2: Phase 1b/2a

- eligible people will have a genetic test to see if they have either of the two SNPs
- drug will be injected into the CSF by LP which will also allows researchers to measure levels of mHtt
- plan is to recruit 50 people with HD over the age of 18 worldwide onto each of the two trials
- current study will start in Canada, then will enroll patients in Europe and the US
- Impt to realize that even if we are successful in lowering mHTT in pts, may not be effective!

What can I do right now?

- Make sure you're under regular care with a doctor or team with HD experience (like an HDSA Center of Excellence or university HD clinic)
- Follow the news at HDBuzz and on HDSA's website. Check out HD Trialfinder or clinicaltrials.gov for research opportunities
- Participate in Enroll-HD
- Weigh the pros and cons of participating in a clinical trial
 - Vaccinex SIGNAL
 - Wave Precision
 - Ionis HTTRx



