Vtesse Webinar
April 16, 2015
Presenter is Ben Machielse, CEO of Vtesse

Opening Slide shows Vtesse Welcomes the NPC Community

-Parent Advocacy Groups NNPDF NP-UK INPDA
-Parent Led Foundations APMRF, DART, Hide & Seek, SOAR-NPC, Addi & Cassi Fund, Hadley Hope
-Adacemic Scientists
-Janssen R & D
-NICHD NINDS
-Consultants
-Parent Scientists US, EU, Brazil, Rest of World
-NIH TRND

VTESSE

—Manufacture the Highest Quality Product
---Pursue Rapid Path to Approval for VTS-270
---Drive innovation and next generation products

Not patient recruitment center. Just getting thoughts about trial. Interested in listening and learning from a parents perspective
Learn about Vtesse
Clinical perspective on the drug development process
Parent perspective of having a child treated with VTS-270

Put NPC patients and families first----NPC community is committed to help patients and families as is Vtesse
Think beyond limits—operate with a sense of urgency
Hold ourselves responsible---solution-oriented mindset, listen and communicate openly where they can, aspire to deliver on their promise

Active discussions with regulators and cannot share all info until it is finalized. They will always be honest and open as much as they can.

Vtesse Team:

- Developed and sought approval for 20 compounds
- 2 major R&D functions clinical research and technical operations
- Clinical research: launch a global pivotal clinical study for VTS-270
- Technical operations: improve the drug and method of administration

Our panel today:
Ben Machielse, Vtesse
Marc Patterson, Mayo Clinic
Liz Berry-Kravis, Rush University
Phil Marella, Parent
Denny Porter, NIH

Participating: Ravi Venkataramani, Sarah Frech, Jehan Rowlands, Carol Tressler, Siren Interactive

Where We Stand Today:
We have the right ingredients to drive the program forward and seek approval for VTS-270 to treat NPC

- Licensed rights from NIH
- Transferred Investigational New Drug (IND) application and the Orphan Drug Designations for US & EU
- Raised money from investors to conduct the pivotal clinical trial
- Completed initial interactions US and EU regulators

Our immediate goal : initiate a pivotal clinical study to seek approval for VTS-270

Longer term vision: evaluate potential second-generation drug
Method of administration that decreases burden to patient

<u>VTS-270</u>

About VTS-270

- A formulation of 2 hydoxylpropyl-B-cyclodextrin (HPBCD)
- Extensive safety profile in multiple applications
- Deep preclinical knowledge
- HPBCDs are complex mixtures
- Currently in Phase I testing in US

Efficacy

- Strong efficacy results in mice and cat models of NPC disease
    - Prevents cerebellar dysfunction such as ataxia
    - Preserves Purkinje cells
    - Prolongs lifespan

- Route of administration is important in treating the neurological disease
    - In cats, administration directly into the brain improves neurological disease more than injecting into the body

- Intrathecal/intracranial is better than intravenous/subcutaneous for neurological disease

A Clinicians' Perspective
Marc Patterson-Professor of Neurology, Pediatrics and Medical Genetics
Mayo Clinic Children's Center

Unmet needs and challenges of NPC April 2015

-No approved disease modifying therapy in the US
-Delayed diagnosis-significant disease burden before interventions can be pursued
-Unclear which measures will be accepted globally by regulators as evidence of efficacy of treatment
-Animal studies provide strong data supporting benefit from 2 hydroxypropyl-cyclodextrin in NPC but - there is no controlled data yet on efficacy of cyclodextrin in humans.

Natural History Study is huge and helpful!!!

Why pursue a controlled clinical trial?

- To determine if perceived benefits in animal studies (preclinical studies) also occur in humans under controlled conditions
- To determine if the agent is safe in humans
- Both control and intervention groups studies using appropriate statistical methods are essential to ensure that variations in outcomes are related to the agent being teste, and not just chance
- To provide data for regulatory approval (by the FDA in the US, different agencies in other countries)

Controls (2 groups that are pretty much the same..one gets the drug and one does not)
The power of the study was discussed. Very critical number. Selection of patients is very critical. These selections are done very carefully. The trial is the only way to get approval by the FDA!

How drugs are developed and approved

Mission of regulatory agencies

- FDA: "The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that drugs marketd in this country are **safe and effective."**
- EMA: "to foster **scientific excellence** in the evaluation and supervision of medicines, for the benefit of public and animal health"

    - Basically the FDA and EMA do things differently. They each have their own rules and requirements.

Regulatory agencies typically do not test drugs

- Although they sometimes conduct limited research in the areas of drug quality, safety, and effectiveness to help with enforcement activities.

******Clinical trials are experiments that use human subjects to see whether a drug is effective, and what side effects it may cause!**** (very important)

www.fda.gov/drugs/developmentapproval process/howdrugsaredevelopedand approved

Why pursue drug approval?

- The cost of approved drugs is usually covered by insurance, meaning that most patients should be able to gain access to agents regarded as safe and effective.

- The drug approval process will also prove a better understanding of the objective efficacy of the drug.

- Regulatory agencies continue to monitor drugs for safety after approval.

- Approval of one drug provides a road map for subsequent studies of new drugs to treat the same condition.

A Parent's Perspective
Phil Marella
Father of Dana and Andrew

Information is confidential and proprietary

- March 2015: our son, Andrew, received 1st dose at 900mg
  - Andrew had a significate loss of hearing in the mid-conversational range
- For Andrew's April visit, we're thrilled his hearing has come back nicely
  - Hearing impact was a Grade 1 loss
- Realizing that NPC is already taking Andrew's hearing, we bought hearing aids for Andrew
  - Andrew is hearing things he has not heard in years
  - Hearing aids are usually covered by insurance for children
- We worried non-stop about risking Andrew's hearing
  - Now feel comfortable that the loss can be addressed
  - Excited to see Andrew more talkative and walking better

It's a very personal decision, but it is important to remember that NPC is impacting hearing anyway, and it's the other, devastation, mental and physical deterioration we hope to dramatically slow down.

Lesser Challenges

Things that are not as bad as they seem

- Lumbar punctures
    - Andrew has had almost 25+ LPs since 2006, and only 1 with some post-LP nausea. The last 3 were with just local anesthesia, and he did great.
    - To move quickly with the treatments, which is so crucial for all of these children, LP seems the best way to go. Ommaya reservoir was a clever idea, but it cost us all critical months of delay.
- Frequent travel to the site
    - A necessary sacrifice to have the proper control, but hopefully enough approved locations to make it as convenient as possible. The locations have to be facilities that can meet the standards for potential approval.
- Control arm in the experiment-Promised my family I'd always work to avoid another "Zavesca Situation"
- After that everyone will be enrolled in an open label extension where they will get the treatment.

Our Hope

- Quality-of-life and longevity that we have seen in mice and in cats is the strongest that we have seen with any drug
- This drug has been used safely in several other drugs as a carrier-has a large safety record behind its use.

- Controlled experiment
    - Only a clinical trial will demonstrate if we can see the kind of success in children with quality-of-life and longevity that we have seen in cats
    - We cannot have ANY more treatments which some of the children can get and other children cannot. That takes FDA approval.
    - The Zavesca approval process underscores this – the panel even accepted that there was a "suggestion of benefit", there was plenty of personal evidence but not enough scientific evidence for approval
    - Controlled clinical trial will help get that evidence and accelerate the approval process

<u>Ben Machielse, Vtesse</u>

How do we get VTS-270 approved?

Clinical trials are experiments to answer several key questions;

- Does the drug work
- Which aspects of the disease does the drug treat

- What are the risks and side effects
- What is the does where the drug works bets (best efficacy)and has the lowest risks/side effects (best safety)

Current Phase I will provide initial answers for some of these questions; provides the basis of Phase II/III clinical trials

Vtesse will conduct a combined phase II and phase iii clinical trial that will seek to provide definitive answers to these questions

Regulatory bodies will review our data to see if we have established a safety and effectiveness

Our Current Thinking for a Pivotal Clinical Trial

Global, 50 patients, multi-site study to begin no later than late 2015 (Q3 is the hope)
Looking at travel for patients

Controlled study (treatment and control arms) in 2 stages:

- 1 stage to select best does
- 2nd stage patients get the best dose

Intrathecal, bi-weekly administration of VTS-270 with 1 year duration

Followed by an open label extension until the time of approval

- both the treatment and control arms will get the drug

Presentation is over!

Next webinar will be scheduled as soon as they have more information to share!