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 was confidential and proprietary

- Discussed his family and their family perspective

Ben Machielse, Vtesse

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
Open label extension until the time of approval (both the treatment and control arms will get the drug)

If a decline in patients they are evaluating if they can remove them from trial and give them the drug

Presentation is over!

Questions:

Lumbar puncture---repeat administration of lumbar punctures…

Liz---has been very well tolerated…process is not difficult. They have to be still during the process. Lidocaine cream for back. Inject some additional lidocaine because the back has been numbed. Some headaches and some vomiting but seems that if they use a different needle it is not as bad.

Denny---focus on this with parents as they are concerned about it. He agrees with Liz. It is simple procedure. Scarier in concept in actuality. The risks are the post LP headache and the plus or minus of nausea. 1 episode nausea in 25 LP's. Short in duration for the headache usually gone in 24 hours. Very minor problem. Kids tolerate it very well. At least ½ the kids do it at the bedside. Younger kids do have to be sedated.

Marc---general public has a misunderstanding of this procedure. Very different from a clinical trial where you have people that do this all the time. Don't see major problems in this. Easier than drawing blood.

Controlled trial—why is a controlled trial important

it shows it is effective

need a reference point
shortens the duration of the trial
effects of the drug are found
what will the drug do and not do is so important

Administer drug every 2 weeks!!!

Specific questions about the trial cannot be answered as they have not been approved as of yet.

Travel:

Burden of travel ….sites will be located as to where patients are….the qualities of facilities they can find in that area. They will do the best to get everyone that wants to participate to be able to participate.

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