AUDENTES

Developing Medicines for Rare, Genetic diseases of Childhood

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Courageous Patients.
Bold Effort.™

Overview

- Audentes Therapeutics
- Developing medicines for rare and severe conditions
- How is a gene therapy different to a drug?
- What do we need to consider, when performing clinical trials in children as opposed to adults
- What is it like to take part in a clinical trial?

DEVELOPING MEDICINES FOR RARE AND SEVERE CONDITIONS

Developing medicines for rare and severe conditions

The Vision

Ongoing technological advances in Bio-Pharmaceutical drug development, drug delivery, and translational science offer increasing prospects of treating rare and ultra-rare conditions. This would allow otherwise chronically ill individuals to lead full and healthy lives.

The Task Ahead

High development costs, scientific challenges, pressing medical needs, and limited patient numbers raise clinical and regulatory, challenges.

Characteristics of rare conditions

- Often severe, chronic, degenerative and life-threatening
- Often have onset in childhood
- Disabling, and represent a considerable loss of autonomy
- Carry a large psychosocial burden, with suffering aggravated by despair, lack of therapeutic hope and absence of practical support
- Incurable, often without effective treatments
- Difficult to diagnose and complex to manage
- Difficulties for manufacturers in developing therapies for rare conditions

➤ *Evidence suggests society is willing to support patients with severe, rare conditions*

European Organization for Rare Conditions, 4th Eurordis Survey on Orphan Drugs

Developing medicines for rare and severe conditions: practical challenges

Perspective	Challenges
Patient	Timely referral to appropriate specialists Lack of information about the condition Feeling of despair relating to inability ‘to find an answer’
Physician	Low awareness and understanding of the condition Limited experience of diagnosing and managing the condition Diagnostic tools unavailable Heterogeneity of symptoms complicates diagnosis
Industry	Endpoints difficult to study over the short-term Lack of validated biomarkers Few patients available for clinical trials Animal models may not be available Use of placebo may be unethical
Regulators	Ill-defined regulatory pathways due to lack of predecessors Design considerations based on condition, drug effect and population Judge effectiveness and safety on less than substantial evidence

Adapted from Prasad S, James E, Challenges associated with developing therapies for rare Condition, 2009, Brit J Hosp Proc

HOW DOES GENE THERAPY DIFFER TO A TRADITIONAL MEDICINE?

How does a gene therapy approach work?

- Enzymes are protein molecules that 'do things' in the body ie each protein has a specific function
- The absence or lack of an enzyme can cause a deficit in the capacity of an organ or tissue or cell to function appropriately in the body ie the individual loses some functional capability
- This absence or lack of an enzyme is usually due to a genetic defect ie the piece of DNA that is responsible for coding for that protein is missing

How does a gene therapy approach work?

How do we treat this lack of function due to an enzyme deficit?

- The way to treat this 'lack of function' could be to:
  - Give a drug that somehow increases the level of the missing enzyme
    - Eg by stimulating production of the enzyme
  - Synthesize the enzyme outside of the body, and then put the enzyme into the body
  - Take a gene therapy approach – ie administer the gene that is missing or defective which then gets incorporated into the patients own DNA, and then starts to produce the missing protein

WHAT DO WE NEED TO CONSIDER WHEN RUNNING A CLINICAL TRIAL IN CHILDREN AS OPPOSED TO ADULTS?

HOW ARE CHILDREN DIFFERENT TO ADULTS?

How are children different to adults?

- Children have a different physiology to adults
- Children are developing
- Children have a different psychology to adults
- Children have a different level of communication and social interaction

Children in clinical studies – important perspectives

- Children are a vulnerable population
- The balance or risks and benefits for children is different
- Children lack full autonomy
- Laws and rights around children are evolving as society continues to evolve
- Children do represent our future

CLINICAL TRIALS

What needs to happen before a clinical trial in patients can occur?

We need to ensure appropriate manufacturing rigour

- ie we need to demonstrate that
  - we can make enough of the product
  - the production system is reliable and consistent
  - The production suite is a fully sterile and controlled environment
  - The experts making the product are appropriately qualified
  - Ultimately that the production system meets international standards (something called 'GMP')

What needs to happen before a clinical trial in patients can occur?

We need to learn what we can from the pre-clinical (animal) work

- We are in a fortunate position with MTM in that we have 2 disease models (a dog and a mouse)
- The models have some differences between each other, but the gene therapy product appears to work quite nicely in both models
  - BUT there are still differences between animals and humans
- There are still several more animal studies that are planned which will inform us further

What needs to happen before a clinical trial in patients can occur?

We actually need to design the clinical trial

- We need to give the science behind the study some careful consideration and make some key decisions
- We need to make sure that we can practically run the trial (this is known as clinical trial operations)

What operational decisions need to be made in order to run a clinical trial?

- Where will the trial take place?
  - How many and which countries?
  - Which centers?
  - Which specialists?
- What is the set up at each clinical trial site?
  - Can the centers run gene therapy studies?
  - What are the teams there like?
  - Are they used to processing samples of tissue?
  - Are they used to running clinical studies?

What scientific decisions need to be made?

- How many patients will take part in the study?
- Will there be a placebo control?
- What will the inclusion criteria for the study be?
- What will the exclusion criteria for the study be?
- What safety monitoring will be performed?
- What endpoints will be selected and what tests will be done?

What do we mean by a clinical trial endpoint?

- An endpoint is defined as an overall outcome that a clinical trial aims to measure
- This outcome can be a disease characteristic, health state, symptom, sign or test (eg lab or radiology)
- Whether an intervention (drug, device, procedure) achieves an endpoint determines if it is a success or a failure
- An endpoint MUST be clinically relevant
- Responsive – ie demonstrates deficit at baseline and improves with treatment

THE XLMTM CLINICAL DEVELOPMENT PROGRAM – WHERE ARE WE NOW?

Where are we now?

- Currently speaking with experts internationally to complete the design of the clinical trial
- Animal work, manufacturing work, laboratory research is continuing

Summary

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Any questions?