Industry Case Study: Expanded Access at Ultradynex

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Introduction to Ultragenyx

A clinical-stage biopharmaceutical company based in Novato, California focused on rare and ultra-rare diseases founded in 2010 with six clinical stage programs.
Rare Diseases and Expanded Access

• *For families*: receiving a diagnosis with a rare disease can be devastating especially for diseases without effective therapies

• *For drug development companies*: unmet medical need has been driving a proliferation of investigational drug programs

Combined these factors create demand for access to investigational medicines that exceed the boundaries of typical clinical trial programs
Managing early access: considerations

• What is the nature of the disease?
  – Life threatening, irreversible outcomes, rapidity of progression?

• What is known about the patient?
  – Medical status, evidence for the disease in question, other treatment options?

• What is known about the investigational therapy?
  – Scientific rationale, evidence of potential benefit and risk?

• Potential impact on the drug development program?
  – Will effective development be harmed? Clinical trial option? Drug supply?

• What is the right thing to do?
Brief Case Studies from Ultragenyx

• Mucopolysaccharidosis VII (MPS VII)
• Long-Chain Fatty Acid Oxidation Defects (LC-FAOD)
Example: MPS VII
MPS VII Disease Background

- Ultra-rare: Perhaps 200 patients diagnosed worldwide \(^1\)
- Caused by a deficiency of \(\beta\)-glucuronidase
- Varied symptoms including cardiac, pulmonary, liver, and skeletal abnormalities
- Spectrum of disease including severe infantile form and attenuated forms

\(^1\)JAMA 281:249-254, 1999
Development of UX003* for MPS VII

- Enzyme replacement therapy (ERT) successful for four other MPS disorders with approved drugs
- Preclinical models supported ERT for MPS VII
- MPS VII considered too rare to fund development
- Ultragenyx licensed investigational ERT (UX003) and planned a phase 1 – 2 study in the UK

*UX003 is an investigational drug. It is not approved in any country.
Matthew

- 12 year old boy from New York with MPS VII
- Became critically ill with acute respiratory failure
- Maximally available supportive care failing
- ERT considered likely to help
- Clinician requested emergency access
Analysis of situation

• Immediately life-threatening situation
• Standard of care treatment options exhausted
• No clinical trial options
• Potential for benefit from investigational therapy
  – In this case, no clinical data to support benefit / risk assessment of UX003
  – Assumption of benefit and understanding of risks extrapolated from other ERTs: respiratory benefit/liver and spleen reduction
• Supply of UX003 available; no harm to development
Final question

What was the right thing to do for Matthew?
Very unusual situation

- First clinical exposure via expanded access
- FDA supportive and collaborative
- Matthew received treatment
Outcome following eIND treatment

• Matthew still on investigational treatment more than 2 years later
• His case became an important part of the UX003 regulatory documents supporting Ph3 program
• The case history was presented at conferences and manuscript published
• Clinical development proceeded as planned
Example: Long-Chain Fatty Acid Oxidation Defects
Long-Chain Fatty Acid Oxidation Disorders (FAOD)

• Collection of genetic diseases* that impair ability of the mitochondria to process fats leading to cellular energy deficits
• Diagnosis: Newborn screening panel
• Wide spectrum of severity
• Symptoms include cardiomyopathy, hypoglycemia, rhabdomyolysis, fatigue, and sudden death
• Current treatment: special diet, avoidance of fasting and MCT oil


Wilken B. J Inherit Metab Dis 2010
Development of UX007*

- Designed to restore mitochondrial metabolism
- Used first under a physician-sponsored IND
  - Compassionate use treatment and no formal endpoint data
  - Publications on impact on heart failure and other symptoms
- Licensed by Ultragenyx to complete formal development through conduct of clinical studies
  - Full drug development program underway
  - Improvements to manufacturing process to ensure pharmaceutical grade supply

*UX007 is an investigational drug. It is not approved in any country.
Expanded Access Requests for UX007

- Emergency requests for infants with cardiac failure after standard of care options exhausted
- No clinical trial options
- Potential for benefit from investigational therapy
  - Supportive data from retrospective review of cardiac failure cases
  - No apparent safety concerns
- Supply of UX007 available
- No impact on development program

- Right thing to do for these critically ill patients
Outcome of Expanded Access Program for UX007 in FAOD

• Clinical outcomes and safety information incorporated into regulatory documents
• FAOD development proceeding as planned
  – Consideration of specific infant cardiomyopathy study
• Ultragenyx continues to receive and support requests for emergency treatment
Summary

• Frequent requests for expanded access in rare disease drug development
• Risks to patients and to drug development program have to be carefully considered
• Expanded access can augment traditional drug development while helping patients in need
• Expanded access programs can raise awareness and support further development process
• Potential for patient benefit must be respected in expanded access decisions