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Overview

• Development of new drugs for rare diseases can be very challenging for a company small or large to undertake and therefore present significant risk despite scientific understanding of disease, its pathogenesis, and probable solution.

• Clinical endpoints for trials may require large populations not possible if not associated with very large treatment effects or very long durations if not associated with quick reversal of present symptoms or be very difficult to measure with accuracy or precision.

• Accelerated approval can be an extremely valuable way to get treatment to patients in a timely fashion who desperately need it and allow ROI for those companies willing to pursue it.

• Examples at Genzyme: Ceredase, Cerezyme, Fabrazyme
Orphan and Ultra-Orphans

- Defined by small size of the population: <200,000, <5,000
- This small number raises specific challenges
- Despite small number of affected patients must still obtain regulatory approvals, and return on investment
- Orphan drug laws do not provide for a lesser degree of evidence for safety or efficacy
Major Challenges in Orphan Drug Development

- Economic
- Disease Understanding
- Clinical Trial Development
- Regulatory
- Public Education
- Distribution and Reimbursement
Challenges for the Clinical Drug Development for Ophan Diseases

• Poor understanding or documentation of natural history
  ▪ No prior pathways to follow
  ▪ Clinical endpoints often unclear in effect
  ▪ Sample size limited
  ▪ Patient enrollment challenging
  ▪ Must educate investigators and regulators
The Problem with Using Clinical Endpoints in Many Rare Diseases

• Often unknown which will respond best and how much or how to measure with precision and accuracy

• Not always sure how long it will take to see the difference
  • May not be able to sustain long placebo comparisons

• Variability in baselines, responses require large populations

• Treatment effect must be large,
  • smaller, more usual, but very meaningful effect size may not be detectable in small populations available to study
Illustration of Study Size vs Treatment Effect for an 80% Powered Study

Number of Patients

10% 20% 30% 40% 50% 60% 70% 80%

Treatment Effect

- Cardiac
- Osteoporosis
- MS
- Antibiotic
- Ultra Orphan

\[ \frac{\text{Number of Patients}}{\text{Treatment Effect}} = \text{Study Size} \]

\[ \text{Study Size} = \frac{\text{Number of Patients}}{\text{Treatment Effect}} \]
Illustrative Power Calculation for an $N = 80$ Patient Study

Power

Treatment Effect Where Study has 80% Power

Clinically Meaningful Treatment Effect
Surrogate Marker:
A Laboratory or Clinical Measurement Believed, by Current Knowledge, to Share a Causal Mechanism with the Clinical Outcome.

Surrogate Endpoint:
A Pre-Defined Change in a Surrogate Marker that Is Expected to Predict Clinical Benefit.
Drug Development Process

Drugs for Orphan Diseases

Pre-Clinical Studies → IND → Phase 1 / 2 Clinical Trial → Phase 3 Clinical Trial → AC

Animal Studies: Toxicology Proof of Concept

Surrogate Marker

ACCELERATED APPROVAL

Verification Studies

AC = Advisory Committee
IND = Investigational New Drug Application
Ceredase and Cerezyme for Gaucher Disease

• First successful Enzyme Replacement Therapies

• Gaucher disease
  • Single gene mutation in glucocerebrosidase leading to accumulation of glucoceramide in macrophages and other cells
  • Clinical severity varies but major manifestations are anemia, thrombocytopenia, organomegaly, bone disease in type 1 patients,
  • neurologic disease in type 2 and 3 patients also present

• Ceredase approved 1991
  • Glucocerebrosidase isolated from human placenta with enhanced macrophage uptake due to carbohydrate remodeling
  • Pivotal trial: 12 patients, no control
    • All 12 improved with increased Hgb, platelet counts, spleen and liver size

• Cerezyme approved 1994
  • Recombinant human glucocerebrosidase with same carbohydrate remodeling
  • Comparative trial with Ceredase of 30 patients randomized 1:1
  • Similar improvements in Hgb, platelets, organ size, biomarkers
We have come a long way in Gaucher Disease

Used with patient’s permission for NGF 2010
Eight-Year Clinical Outcomes of Long-Term Enzyme Replacement Therapy for 884 Children With Gaucher Disease Type 1

Hans Andersson, MD\textsuperscript{a}, Paige Kaplan, MBBCh\textsuperscript{b}, Katherine Kacena, PhD\textsuperscript{c}, John Yee, MD, MPH\textsuperscript{c}
Fabry Disease

• Rare, lethal, X-linked inborn error of metabolism
• U.S. prevalence estimated at 3500 classic patients
• Deficient $\alpha$-Galactosidase A ($\alpha$-GAL A) activity
• Deficient $\alpha$-GAL A activity leads to progressive globotriaosylceramide (GL-3) accumulation in multiple cell types and tissues culminating in end organ impairment

• **Key pathology:** vascular endothelial deposition
Clinical - Pathologic Correlations

- Hypercholesterolemia
- Fabry Disease
- Phenylketonuria (PKU)
- Adrenoleukodystrophy (ALD)

![Graph showing clinical progression and pathologic substrate accumulation over age (years)]
Fabry Disease: Clinical Manifestations

Classical Phenotype (< 1% activity)
+++ endothelial accumulation

Age

- Acroparesthesia
- Renal Failure
- CNS Disease
- Cardiac Disease
Phase III Clinical Trial

- Double-blind, placebo-controlled, randomized, multicenter, multinational
  - 8 sites in 4 countries

- 58 Fabry patients
  - 56 males, 2 females
  - >16 years old; Cr ≤ 2.2 mg/dL

Phase III Clinical Trial

• Primary endpoint (unvalidated surrogate)
  • GL-3 clearance in vascular endothelium of kidney

• Secondary endpoints
  • Composite score of GL-3 clearance in vasculature of heart, kidney, skin
  • GL-3 reduction in urinary sediment and kidney tissue
  • Pain reduction (McGill Pain - short form)
Phase III Primary Efficacy Endpoint

- Morphologic assessment of GL-3 inclusions in renal capillary endothelium
  - Three independent pathologists
    - Blinded to treatment assignment and pre/post biopsy sampling
    - Light microscopy (LM) assessment
    - 0 (none) to 3 (severe) severity scale

- Percentage of patients with 0 scores at week 20
Phase III
Primary Endpoint Rationale

- Renal failure is the most common devastating feature of Fabry disease

- Vascular endothelial deposition is the pathologic basis of morbidity and mortality

- 0 score clinically important
  - Restoration to near normal state
  - Reasonably predictive of normal function and clinical benefit
Primary Endpoint Result
Kidney Histology: Capillary Endothelium Clearance

Assessments were independent of:
• site
• pathologist
• age

p < 0.001 (2x2 Chi Square)

Placebo  Fabrazyme

0/29  0%
20/29  69%

Week 20*
Renal Capillary Endothelium

Baseline: Score = 3

Week 20: Score = 0
Secondary Efficacy Endpoints
Mean Capillary Endothelium Scores
(Scale 0-3)

P value = < 0.001

Fabrazyme

Placebo

Skin
Kidney
Heart

Baseline
Week 20

P value =  < 0.001
FDA Approves First Treatment for Fabry Disease

• Said FDA Commissioner Mark B. McClellan, M.D., Ph.D.:

• "This priority approval of an orphan drug (Fabrazyme) illustrates FDA's commitment to approving innovative new therapies for patients with serious and life-threatening diseases quickly, based on response to treatment of biological markers likely to predict long-term clinical benefit."

• “By approving this new biotechnology therapy under the 'accelerated approval' process, we are making this product available more quickly to patients who need it.”
Risk Reduction 43%

Placebo = 13 Events (42%) (n=31)

Fabrazyme = 14 Events (27%) (n=51)
Proteinuria Ratio Adjusted Predicted Probability of an Event
ITT Population (N=82)

Risk Reduction 53%*

Placebo (N=13 Events)

Fabrazyme (N=14 Events)

*p=0.058
Risk Ratio 0.47
Proteinuria Ratio Adjusted Predicted Probability of an Event
PP Population (N=74)

Risk Reduction 61%*

Placebo (12 Events)
Fabrazyme (13 Events)

*p=0.034
Risk Ratio 0.39
Why was this unvalidated surrogate agreed upon and successful?

- Pathogenesis of the disease well understood
  - Single gene mutation
  - Direct pathway from gene mutation to abnormal enzyme to accumulation of substrate in cells to disrupt function

- Mechanism of action for drug well understood
  - Replacement of mutated enzyme with normal human enzyme
  - Deliverable to cells of consequence

- Able to directly measure consequence of treatment on cause of pathology in the direct path of the problem
  - Complete removal of pathogenic substrate in site of major pathology
  - Non quantitative, complete removal signals likelihood of clinical benefit

- Surrogate shared by all patients and measurable in a small number in a reasonable time frame
Summary

• Challenges are large for development of products to treat small populations
• The economics are daunting
  • Costs high and inhibitory to new products.
  • Orphan exclusivity, tax credits, premium prices helpful
  • Clinical Endpoints for traditional approval often difficult and prohibitive
  • Surrogate markers, accelerated approvals educated regulators and investigators helpful
• The problem remains the need for treatments for patients with thousands of orphan diseases who have none