Clinical Studies in Enzyme Deficiency Disorders

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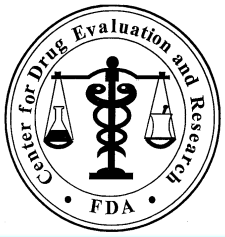


Outline

- Enzyme deficiency diseases historical perspective
- Drug development considerations
- Examples
  - Taliglucerase
  - Carglumic acid
  - Icatibant
- Key points

Regulatory Experience & Enzyme Deficiency Disorders

- Active area of drug development –- and approvals[1]
- Selected moments in orphan enzyme deficiency history

1983 Passage of Orphan Drug Act

1983
Hemin

1986
Na+benzoate
Na+phenylacetate

1987
α-1-antitrypsin

1990
Factor IX

1990
pegadamase

1991
alglucerase

1990s-2000s+
numerous LSD ERTs

1996
betaine

2002
nitisinone

2003
miglustat

2007
sapropterin

[1]Talele SS et al. Therapies for inborn errors of metabolism: What has the orphan drug act delivered? Pediatrics 201;126:101-106

Enzyme Deficiency Disorders

- Highly diverse:
  - Collection of disorders, e.g.
    - Amino acid metabolism, lysosomal storage disorders, coagulation factors, and others
  - Disease manifestations, e.g.
    - Multi-system vs. limited disease or target major morbidity
  - Strategies, targets, e.g.

Replace enzyme -enzyme replacement therapy -gene therapy -stem cell transplantation -organ transplantation -delivery to "inaccessible" compartments	**Enhance residual enzyme activity** -chaperones -co-factors	**Alter gene transcription** -e.g., anti-sense RNAs
Target substrate/ substrate production -substrate reduction therapy -target upstream pathway -exploit alternate pathways -enzyme substitution	**Target products** -exploit alternate pathways - downstream pathways -non-specific reduction of toxic catabolites	**Target clinical outcome** -enhance function -ameliorate disease manifestations

Drug Development Considerations

- Diverse diseases, outcomes, and products necessitate different approaches to drug development
- For marketing approval:
  - Demonstrate "*substantial evidence*"[2] of efficacy, safety and quality
    - Efficacy → clinically meaningful benefit/outcome
      - Impact upon how a patient feels, functions or survives
    - Favorable benefit-risk
  - Or Accelerated Approval based on:
    - Surrogate endpoint reasonably likely to predict clinical benefit, or
    - Clinical endpoint other than survival or irreversible morbidity
    - Subject to requirement for further study to verify clinical benefit in the post-marketing period

[2]PHS Act 505(d)

Substantial Evidence

- For both pathways, efficacy evidence from adequate and well-controlled (A&WC) trials:

  "on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use"[2]

- A&WC = Trial has been designed well enough so as to be able "to distinguish the effect of a drug from other influences, such as spontaneous change…, placebo effect, or biased observation"[3]
- Regulations allow for "flexibility" and "scientific judgment" in how this is achieved[4]
  - E.g., ~2/3 of rare disease marketing approvals rely upon one A&WC trial + supporting evidence (usual standard is 2)[5,6]
  - Considerable diversity in study designs, endpoints, etc.

[2]PHS Act 505(d) [3]21CFR §314.126, Adequate and well-controlled studies.
[4]21CFR §314.105 Approval of an application and an abbreviated application
[5]Sasinowski FJ. Quantum of effectiveness evidence in FDA's approval of orphan drugs. Drug Inf J 2012;46:238-263
[6]Guidance for Industry, Providing clinical evidence of effectiveness for human drug and biological products. 1998

Examples

- Recent enzyme deficiency disorder product approvals in CDER
  - Taliglucerase (Elelyso)[7] for treatment of Gaucher disease type 1, an LSD (2012)
  - Icatabant (Firazyr)[8] for treatment of hereditary angioedema (HAE) (2011)
  - Carglumic acid (Carbaglu)[9] for treatment of N-acetylglutamate synthase (NAGS) deficiency, an urea cycle disorder (UCD) (2010)

Drugs@FDA, Label and Approval History. Elelyso (taliglucerase alfa),[7] Firazyr (icatibant acetate),[8] Carbaglu (carglumic acid).[9] Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name

Taliglucerase

- Gaucher disease type 1
  - Glucocerebrosidase deficiency leading to glucocerebroside accumulation in cells t/o body, especially spleen, liver, bone marrow
  - Prevalence ~1/50,000-100,000 in US
  - Hepatosplenomegaly, anemia, ↓platelets, bone disease
- 4th enzyme and 5th approved product to treatment Gaucher disease type 1. Prior approvals based-on:

Product	Major Endpoints in Efficacy Trials
Alglucerase[10]	Δ liver and spleen volume, Δ hgb and plt counts
Imiglucerase[11]	Δ liver and spleen volume, Δ hgb and plt counts
Miglustat[12]	Δ liver and spleen volume, Δ hgb and plt counts
Velaglucerase[13]	Δ liver and spleen volume, Δ hgb and plt counts

[10]Barton NW et al. Replacement therapy for inherited enzyme deficiency—macrophage-targeted glucocerebrosidase for Gaucher's Disease. N Engl J Med 1991;324:1460-1470

[11]Grabowski GA et al. Enzyme therapy in type 1 Gaucher disease: Comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources. Ann Int Med 1995;122:33-39

[12]Zavesca (miglustat) Package Insert 2010 [13]Elelyso (taliglucerase alfa) Full Prescribing Information 2012

Taliglucerase Development Program

- Efficacy and safety assessed in one trial
  - Study 1: DB, R (to dose), 2-dose cohort study in 31 adult tx-naïve patients X 9 months
  - Results[14]

	Mean Δ from Baseline	
Parameter	**Tali 30 U/kg, n=15**	**Tali 60 U/kg, n=16**
Spleen volume (% BW) MN	-0.9 -4.5	-1.3 -6.6
Hgb (g/dL)	1.6	2.2
Liver volume (% BW)	-0.6	-0.6
Plt (mm^3)	11,427	41,063
MN = multiples of normal adjusted for body weight		

  - Supportive Study 2: OL, single-arm S&E in 25 patients on stable treatment with imiglucerase, switched over to taliglucerase
    - Spleen and liver volume, Hgb and plt were stable on average through 9 mos of treatment

[14]Yao LP. Cross-Discipline Team Leader Review. NDA 22-458, Elelyso. May 1, 2012. Drugs@FDA, Label and Approval History. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name

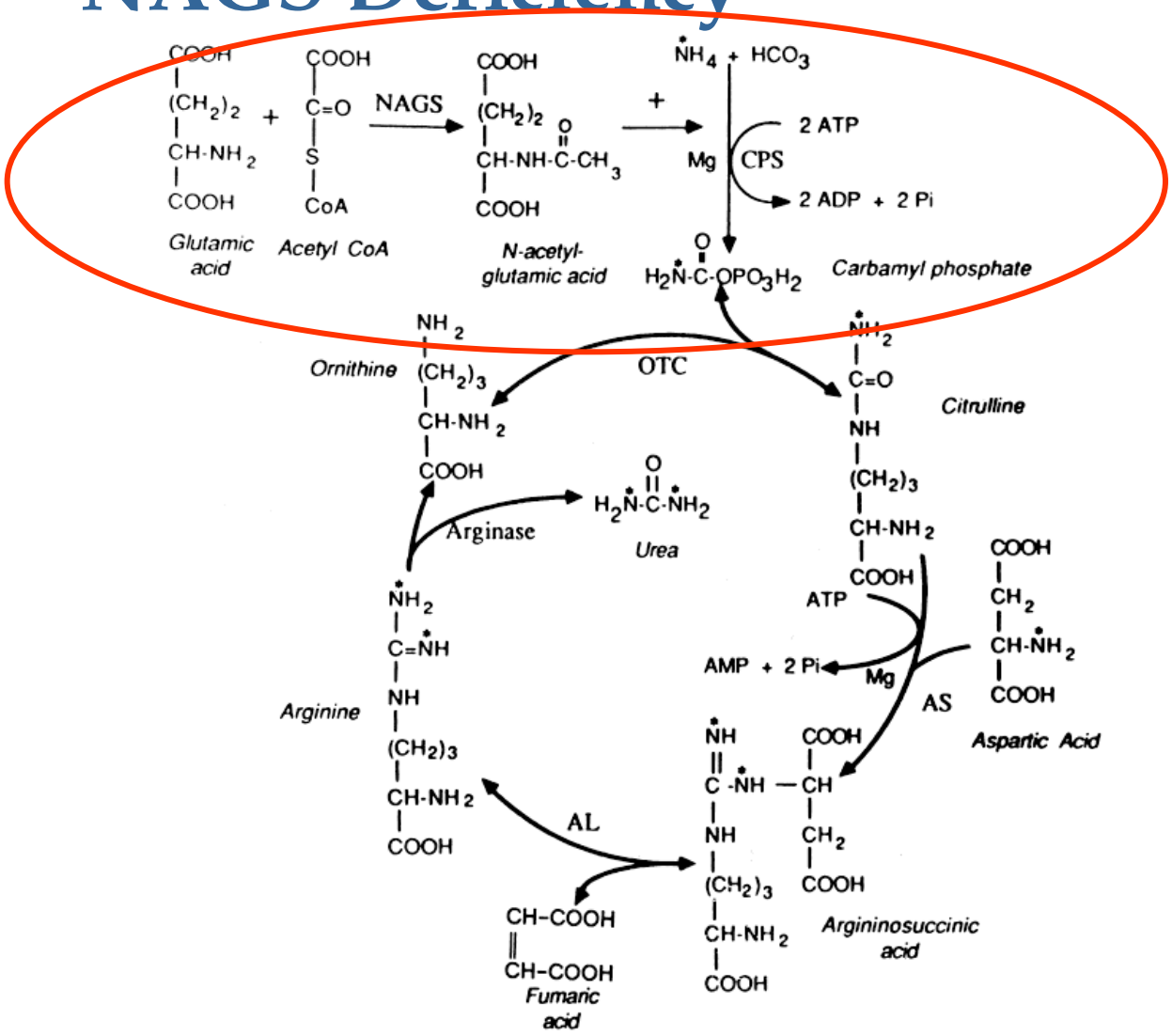
Taliglucerase Key Points

- Clinical development program well-planned and based on existing body of knowledge
  - Natural history well understood
  - Prior, long-term history with similar products
    - Informed regulatory path and trial design
    - Existing long-term Gaucher patient registries
  - Objective, pharmacodynamic endpoints relevant to the disease and important clinical manifestations
  - Robust, statistically significant findings, large magnitude
    - Small efficacy trial
  - Relevant populations (tx-naïve, maintenance) included in development program to support labeling

Carglumic Acid

- NAGS deficiency, rarest of UCDs
  - Deficiency results in inability to metabolize amino acids
  - Prevalence ~50 patients worldwide, <10 in US
  - Hyperammonemia, recurrent neurologic crises resulting in progressive severe CNS impairment and premature death
- Prior to AP, 3 approved non-specific treatments for UCDs
  - Na+phenylbutyrate (Buphenyl)
  - Na+benzoate + Na+phenylacetate (Ammonul, Ucephan)
- Carglumic acid approved in EU~10 years earlier

NAGS Deficiency[15]



Carglumic acid = synthetic structural analogue of NAG, an essential allosteric activator of carbamoyl phosphate synthetase 1 (CPS 1)

[15]Brusilow SW. Horwich AL. The biochemistry of the urea cycle. In: *The Online Metabolic & Molecular Bases of Inherited Disease.* Chapter 85: Urea Cycle Enzymes. 2013

Carglumic Acid Development Program

- Retrospective case series in 23 patients with NAGS deficiency treated over 16 years[16]
  - 13 evaluable patients with "complete" documentation of ammonia levels and clinical course
  - 6 evaluable patients without concomitant ammonia lowering therapies or protein restriction
- Efficacy outcomes
  - Plasma ammonia, glutamine and citrulline levels in short and long term
  - Growth, neurological and psychomotor developmental outcomes
- No formal statistical analysis, historically controlled
  - Historical controls are one of the valid accepted controls
  - To be meaningful, require well-defined and well-understood disease histories

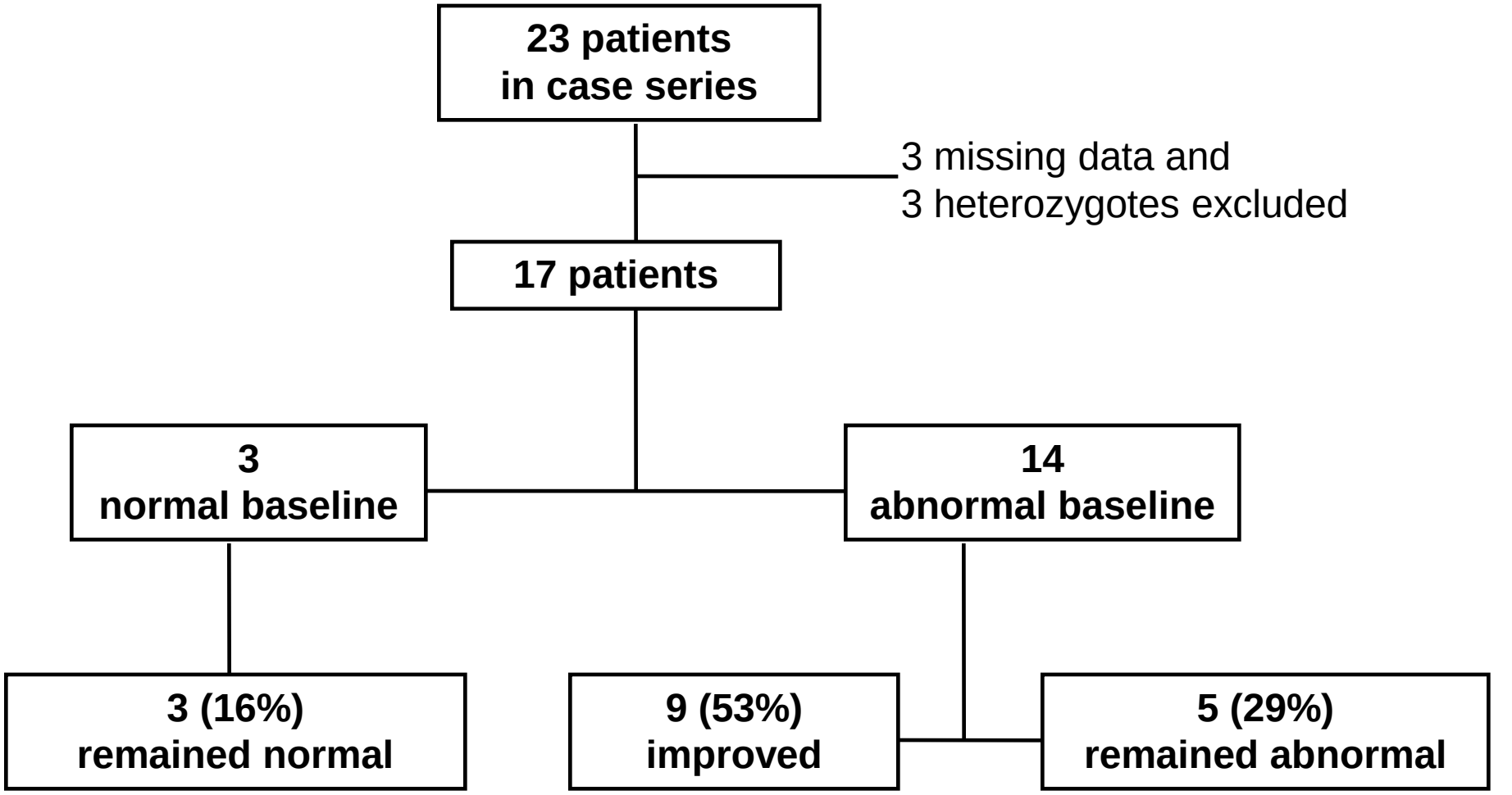
[16]Carbaglu (carglumic acid) Drugs@FDA, Label and Approval History. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name

Efficacy Evaluation: Plasma Ammonia

	Baseline	Short-term (Day 1)	Short-term (Day 2)	Long-term
N	13	10	8	13
Mean (SD)	270.8 (358.8)	180.7 (357.7)	68.5 (78.0)	23.0 (6.89)
Median	**157.0**	**64.5**	**44.0**	**24.0**
Range	72.0-1428.0	25.0-1190.0	11.0-255.0	9.0-34.0

- Long-term treatment: Median 5.8 years; range 1.3-16 years
- All patients demonstrated consistent and sustained lowering of plasma ammonia levels
- All were treated exclusively with carglumic acid in the long-term
- Some of these patients were treated initially with other ammonia lowering therapies

Efficacy Evaluation: Neurologic Outcome



Icatibant

- HAE
  - Deficiency of the C1 esterase inhibitor,
    - Protein of the complement system
    - Affects 1 in 10,000-50,000 individuals worldwide
  - Unpredictable recurrent attacks of angioedema (swelling of face, extremities, GI tract and upper airways), abdominal pain, vomiting, laryngeal edema
  - 3rd product approved for treatment of acute attacks of HAE
    - Plasma-derived C1 inhibitor (Bertinert)
    - Ecallantide (Kalbitor), a kallikrein inhibitor

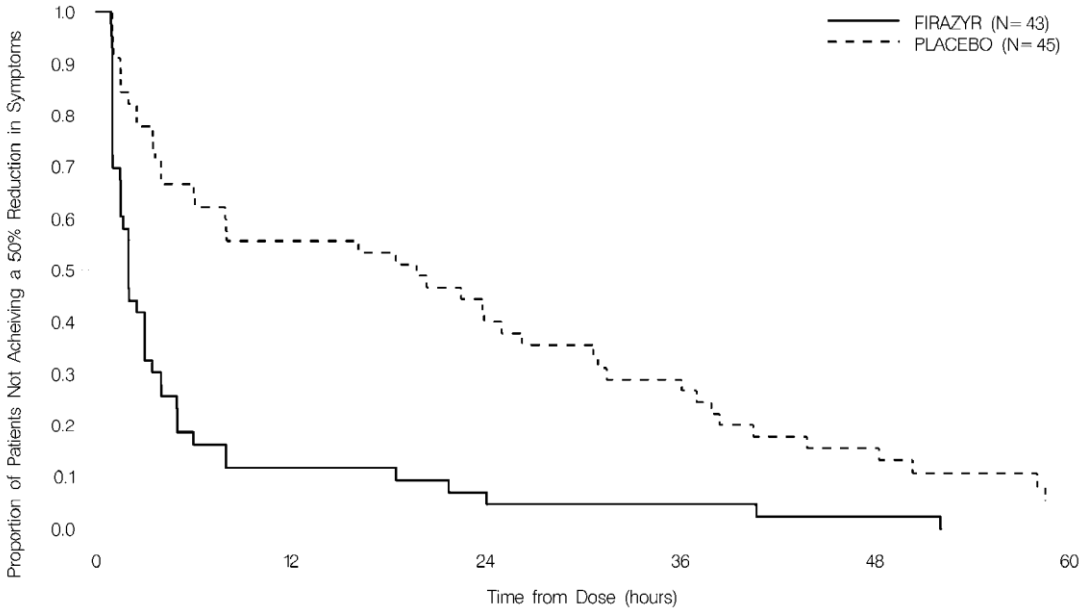
Icatibant Development Program

- Three efficacy trials – largely similar in design
  - Study 1: R, DB, PC trial in 64 patients
  - Study 2: R, DB, active-controlled (vs. tranexamic acid) trial in 77 patients
  - Study 3: R, DB, PC trial in 98 patients
  - OL, long-term extension study to all 3 trials
- For Study 3
  - New Patient Reported Outcome (PRO) development for the efficacy trials
    - 3-symptom Visual Analog Scale for a skin swelling, skin pain, abdominal pain (VAS-3)
      - Responder defined as ≥50% reduction in 3-symptom composite VAS (abd pain, skin pain, skin swelling) sustained over 3 consecutive timepoints
    - PRO supported by conduct of an observational, non-interventional study in 80 adult HAE patients, patient debriefing interviews, literature review, and expert opinion
  - Primary endpoint time to onset of symptom relief in VAS-3

[17]Limb S. Cross-Discipline Team Leader Review. NDA 22-150, Firazyr. August 8, 2011. Drugs@FDA, Label and Approval History. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name

Icatibant Results

- Study 3: Time to onset of symptom relief based on VAS-3



  - Median time to 50% reduction in symptoms was 2 hours in icatabant group vs. 19.8 hours in placebo group

[17]Full Prescribing Information. Firazyr 2011. Drugs@FDA, Label and Approval History. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name

Development Program Highlights

- Enzyme deficiency disorders characterized by substantial diversity (both between and within diseases)
  - E.g., chronic progressive vs. episodic, time course
  - Organ systems affected
  - Symptomatic assessment vs. objective measurements (e.g., biomarkers)
- Interventions are also diverse
  - Biologics vs. drugs
  - ERT vs. co-factor replacement
  - Expected time course of intervention/measureable results
- Study designs considerably different
  - what makes sense for the disease, drug and expected outcomes

Key Point #1: Keep Goals in Mind

- We all want the same thing
  - Effective drugs with favorable benefit-risk
  - Based on substantial evidence of effectiveness, safety and quality
  - Efficient clinical development programs
  - Correct public health decisions

Key Point #2: Getting to Goal

- A&WC trials designed from understanding of disease, drug's expected effects, population under study, how effects will be measured and over what period of time, among other things
  - Study designs will vary
- Scientific foundation, knowledge base are critical to success
  - Disease natural history
  - Pathophysiology
  - Drug's MOA
  - Regulatory experience, prior knowledge with related products or similar diseases, and pilot studies with the investigational agent
  - Endpoint development/outcome assessments
    - May need lead-time for development
- For rare diseases, there is a limited opportunity for study and replication
  - Careful planning is essential
  - Maximize all opportunities for learning