



Small Clinical Trials

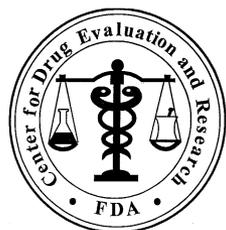
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Outline

- Background
- Flexibility
 - Case examples
- General IND considerations
- Expanded Access
- Key points

Rare Diseases

- Most pediatric disorders are rare diseases
- Rare disease aka Orphan disease defined as:
 - “A disease or condition affecting less than 200,000 persons in the United States”¹
 - In reality though, most rare diseases are far less prevalent than this
- Orphan Drug Act
 - Mainly provides incentives intended to make the development of drugs to treat small populations financially viable
 - Does not provide for separate regulatory standards for Orphan drugs
 - Intention: Patients with rare diseases are as entitled to safe and effective medications as those with common diseases

¹Orphan Drug Act Pub L 97-414, as amended 1984

Rare Diseases: What is different

- Small populations, limited opportunity for study and replication in clinical trials
 - Few treating physicians, few treatment centers
- Highly heterogeneous collection of diseases
 - Within and between diseases
 - E.g., genetic disorders often characterized by wide range of severity, clinical presentation and rate of progression
- Diseases are poorly understood
 - Natural histories incompletely described
 - Diagnosis difficult
 - Often years between presentation and diagnosis
- Most are serious or life-threatening, most have unmet medical needs
 - Lack regulatory/drug development precedent
- Endpoints, outcome assessment tools often lacking
- Many affect pediatric patients
 - Additional ethical considerations and constraints

Rare Diseases: What is the same

- Best access for patients to an efficacious treatment is an approved drug
- Statutory standards for approval apply to all drugs – rare and common
 - Requires establishing a drug’s effectiveness by “substantial evidence”²
- Substantial evidence defined as 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
 - Generally, 2 A&WC trials (affirm and confirm)

²PHS Act 505(d)

Adequate and Well-controlled Trials

- 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
 - RCTs are the gold standard
 - Control can be concurrent or historical
 - Purpose of any control is to measure what *might* have happened without the intervention

³Code of Federal Regulations, title 21, section 314.126, Adequate and well-controlled studies

Flexibility

- Statute allows for flexibility and exercise of scientific judgment in kinds and quantity of data required for a particular drug for an indication⁴

⁴21CFR §314.105 Approval of an application and an abbreviated application

Flexibility: Rare vs. Common Diseases

Table 1. CDER NME/NBE Approvals 2009-2013, Level of Evidence

	All	Rare	Common
Approvals	159	52	107
≥2 A&WC Trials	92 (58)	17 (33)	75 (70)
1 A&WC Trial + Supporting Evidence	61 (38)	31 (60)	30 (28)
Other	6 (4)	4 (8)	2 (2)

NME = new molecular entity; NBE = original biologic (new biologic)

A&WC = adequate and well-controlled

159 approvals = 143 drugs for 159 drugs + indication (at time of initial approval, 3 drugs approved for 3 indications each, 10 drugs from 2 indications each)

⁵Additional reference: Sasinowski F. Quantum of effectiveness evidence in FDA's approval of orphan drugs. Drug Inf J. 2012;46:238-263.

Example #1: Elosulfase (Vimizim)

- Elosulfase (Vimizim)
 - Enzyme replacement therapy (ERT) for the treatment of Morquio Syndrome Type A (Mucopolysaccharidosis (MPS) IVA)
- MPS IVA
 - Rare autosomal recessive enzyme deficiency disorder (lysosomal storage disease (LSD)) results in accumulation of glycosaminoglycans (GAGs) throughout the body
 - Most commonly manifests in early childhood (~18 months of age) with growth deficiency, skeletal and joint development abnormalities, heart problems
 - Wide disease spectrum, attenuated forms may present as late as early adulthood
 - High morbidity, life-limiting, life expectancy 20s-30s years (attenuated forms may be to ~60s)
 - ~500-800 patients in the US (1 in 1-2 million live births)
 - Related disorders: MPS 1-VII

Elosulfase Clinical Development

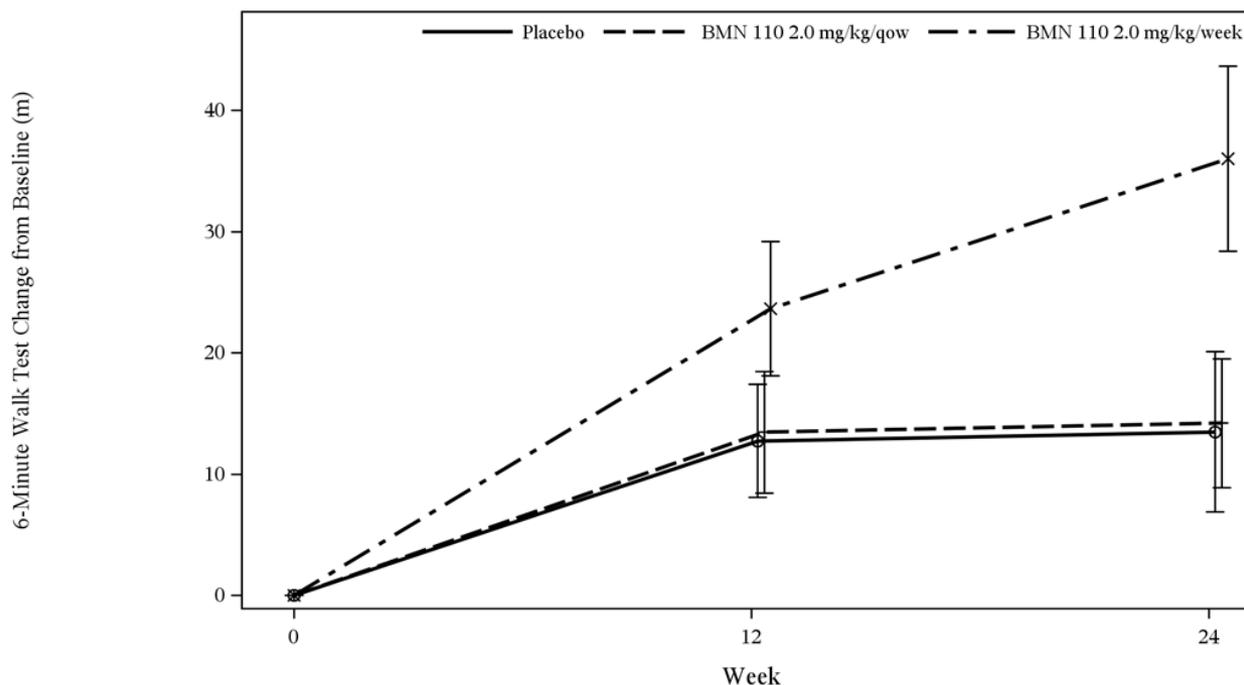
- Elosulfase first AP'd treatment for Morquio
 - 4th ERT approved for an MPS
 - MPS I (Hurler, Hurler-Scheie, Scheie syndromes) laronidase (Aldurazyme) AP'd 2003)
 - MPS VI (Maroteaux-Lamy syndrome) galsufase (Naglazyme) AP'd 2005
 - MPS II (Hunter syndrome) idursulfase (Elaprase) AP'd 2006
- Clinical Program
 - Pivotal trial: 1 A&WC trial: R DB PC trial X 24 weeks, n=176 patients with MPS IVA, ages 5-57 years, randomized 1:1:1 elosulfase qWeek, qoW or PBO
 - Followed by open-label extension where all patients received elosulfase, n=173
 - Primary endpoint: 6MWT
 - Other endpoints: 3- minute stair climb, urinary GAG levels
 - Entire program= 6 clinical trials
 - 1 Phase 3, 1 Phase 1/2 (n=20)
 - 2 on-going extension trial
 - 2 ancillary Phase 2 trials (n~35)

Elosulfase Results

Treatment difference btw Elo qWeek and PBO at Week 24

--22.5 m ($p = 0.0174$)⁶

Largest effect in patients who walked ≤ 200 m at baseline



⁶Source: Johnson T, Clinical Review. BLA 125460, elosulfase alfa, available at “Drugs@FDA”

Elosulfase: Key Points

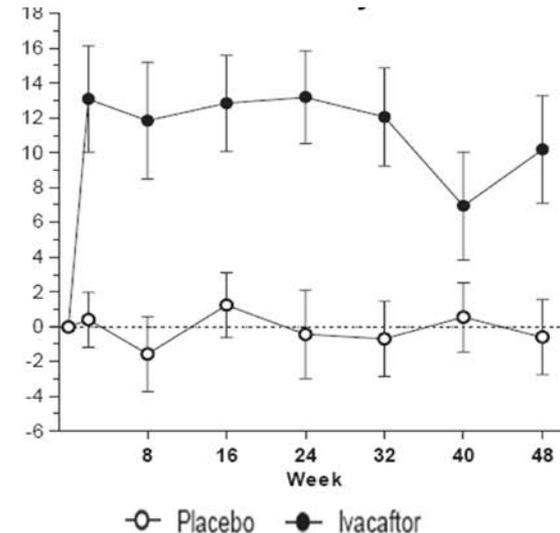
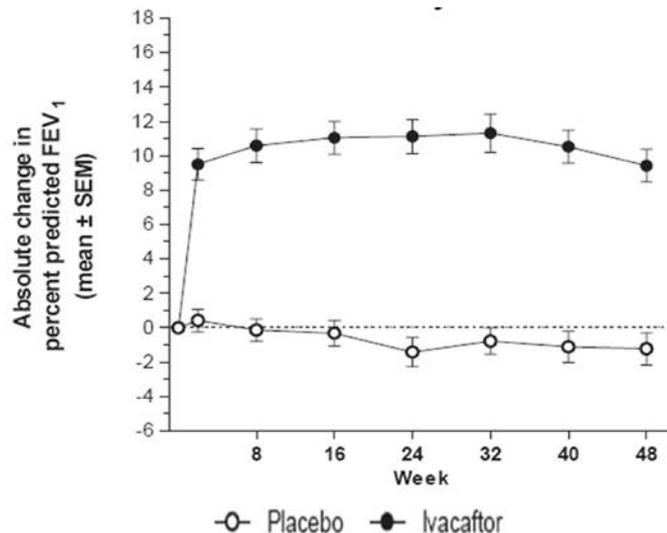
- Disease reasonably well understood and characterized
 - Natural history data
 - Biochemical, pathophysiology described
 - Serious, life-threatening disorder with unmet medical needs
- Close and frequent communication with FDA review division during drug development
- Existing regulatory history from other MPS ERTs (and other LSDs)
 - Relied upon functional endpoints of six- or twelve minute walk tests (6MWT, 12MWT), stair climbs or pulmonary testing PFTs
 - Each relied upon 1 A&WC trial with supporting evidence, small pre-market populations
- Continued evaluation post-approval in a long-term registry
- Use of incentive and expedited programs
 - Orphan drug designation and exclusivity
 - Pediatric Rare Disease Priority Review Voucher
 - Fast Track, Priority Review

Example #2- Ivacaftor (Kalydeco)

- Ivacaftor (Kalydeco)
 - Drug, potentiator of the CFTR protein for the treatment of Cystic Fibrosis (CF) in patients age 6 years and older who have a *G551D* mutation in the *CFTR* gene (initial)
 - Supplemental indication for additional functionally similar mutations
 - Not indicated for most common mutation homozygous *F508del*
- CF
 - Rare autosomal genetic disorder, affects ~30,000 patients in US
 - Patients with *G551D* mutation ~5% of CF patients (~1500 in US)
 - Serious, life-threatening, life-limiting disease with substantial morbidity (pulmonary, GI and other organ systems)
 - Wide variability in disease progression, manifestations
 - Numerous treatments available
 - Well-characterized, well-understood disease
 - E.g., long-standing CF registry (~50+ years) with well-documented disease natural history

Ivacaftor Clinical Development

- Approval supported predominantly by data from 2 A&WC trials⁷
 - Study 1: R DB PC trial in patients ≥ 12 years X 48 weeks, n=
 - Study 2: R DB PC trial in children ages 6-11 years X 48 weeks, n=
 - Primary endpoint: Δ FEV₁ at Week 48
 - Other endpoints: patient reported outcome, weight, pulmonary exacerbations



⁷Source: Durmowicz AG, Cross Discipline Team Leader Review. NDA 2013 188, ivacaftor, available at “Drugs@FDA”

Ivacaftor Key Points

- First approved drug to target underlying genetic defect (2012)
- Disease and disease natural history well-understood
 - Use of multiple endpoints in clinical trials supportive of the primary endpoint based and relevant to the disease
- Close collaboration between drug developer, FDA and patient/advocacy community
- Incentives and expedited programs
 - Orphan drug designation and exclusivity
 - Fast track, priority review
- Continued research and evaluation of additional patient subgroups post-approval

Example #3 – raltegravir (Isentress)

- Raltegravir (Isentress)⁸
 - Integrase inhibitor for treatment of HIV-1 in combination with other antiretroviral agents
 - First-in-class drug
 - First approved 2007 based on clinical trials in patients with HIV ≥ 16 years of age
 - Reduced viral load (<400 copies/mL) at Week 16 in >75% of raltegravir-treated patients (stats sig vs. PBO)
- Pediatric clinical development
 - Required under Pediatric Research Equity Act (PREA), deferred to post-approval period (partial extrapolation)
 - Post-marketing Requirement (PMR) to support efficacy, safety and dosing in pediatric patients 2-18 years of age, and 4 week to 4 years of age
 - For patients 2-18 years, open-label non-comparative trial X 24 weeks, pediatric formulation (chewable tablets)

⁸Source: Belew, Y. Cross Discipline Team Leader Review. NDA 203045, raltegravir, available at “Drugs@FDA”

A Few Words on IND Studies

- FDA will review with these principles in mind
 - Study designs expected to vary widely depending on many factors
 - E.g., novelty of drug, previous experience, developmental phase, etc.
 - Generally will contain, at minimum⁹
 - Animal pharmacology and toxicology studies
 - Manufacturing information
 - Clinical protocols and investigator information adequate for phase of investigation
 - Please note, same ethical and safety standards apply to rare and common disease drug IND applications

⁹21CFR 312.23 IND Content and Format

IND Studies: Common Concerns

- Early/Pre-IND Phase
 - Usually safety related
 - Hold criteria – two most common¹⁰
 - Subjects would be exposed to an unreasonable and significant risk of illness or injury
 - Insufficient information to assess risks to subjects
- Later phase - hold criteria
 - Safety concerns (as above), and
 - Plan/protocol for the investigation is clearly deficient in design to meet its stated objectives

¹⁰§312.42 Clinical holds and requests for modification

A Few Words on Expanded Access (EA)¹¹

- Aka “compassionate use”
 - Purpose:
 - Provide access to investigational drugs outside of a clinical trial
 - Patients with serious or life-threatening conditions
 - No comparable or satisfactory alternative treatment options
 - Enables these patients to access products that are still in development for treatment purposes
 - Includes
 - Emergency INDs (E-IND)
 - Single-patient investigational new drug applications (IND)
 - Small or medium-sized group INDs
 - Treatment INDs

Expanded Access (2)¹²

- Intended to provide access to investigational drugs to patients with serious or life-threatening conditions with no satisfactory alternatives
 - EA INDs **NOT** likely to describe effectiveness
 - EA INDs **NOT** likely to provide evidence for marketing applications
- EA use **cannot “interfere with** the initiation, conduct or completion of clinical investigations that could support marketing approval... or otherwise compromise the potential development” of the product

¹²Physician request for an individual patients IND under Expanded Access for Non-emergency or emergency use, available at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm107434.htm>

Key Point #1

- Best access for patients to effective, safe, quality products is through approved drugs
 - Investigational agents do not yet have safety and effectiveness described
 - Demonstrate evidence through well-designed appropriate clinical trials
 - Ideally, clinical investigations proceed in a stepwise manner toward defining benefit-risk

Key Point #2

- For rare diseases (and many serious or life-threatening conditions)
 - Opportunity for study and replication will be limited
 - “Getting it right” from the start is critical
 - Careful planning, frequent and quality communication (especially early communication) between FDA and drug developer is strongly recommended

Key Point #3

- IND-enabling and foundational science (e.g., translational research, disease natural history)
 - Critical to designing, initiating and conducting successful clinical trials
 - Proposed clinical plan needs to be supported by information in the IND submission

Key Point #4 – Incentives

- Orphan drug designation
 - Separate process and considerations from IND/NDA submissions
 - Need to specifically apply for Orphan Designation prior to NDA filing
 - Please contact: Office of Orphan Products Development
<http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>
- Pediatric Rare Disease Priority Review Voucher
 - New in 2012
 - Additional information:
<http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/RarePediatricDiseasePriorityVoucherProgram/default.htm>
- Best Pharmaceutical for Children Act (BPCA)
 - Pediatrics resource page:
<http://www.fda.gov/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/default.htm>