Innovative Approaches for Rare Disease: Cystic Fibrosis Case Study

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A Little Bit About Vertex…

KALYDECO  
Cystic Fibrosis

AGENERASE  
HIV

INCIVEK  
Hepatitis C

VX-787  
Influenza

ORKAMBI  
Cystic Fibrosis

LEXI VA  
HIV

SYMDEKO  
Cystic Fibrosis

VX-150  
Pain

VX-152  
VX-440  
VX-659  
VX-445  
Cystic Fibrosis

VX-970  
VX-803  
VX-984  
Oncology

APPROVED MEDICINES

DEVELOPMENT-STAGE MEDICINES

OUTLICENSED DEVELOPMENT-STAGE
MEDICINES

RESEARCH ENGINE

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A Little Bit about Cystic Fibrosis…

• CF is a rare, lethal disease affecting ~75,000 people worldwide. ~30,000 in US

• CF is an autosomal recessive genetic disease

• Mutations, or errors, in the cystic fibrosis transmembrane conductance regulator (CFTR) gene lead to absence/reduced amounts of or inadequate function of CFTR chloride channel at the surface of epithelial cells

• If the CFTR protein does not function properly, the balance of chloride and fluids is disrupted, causing mucus in various organs to become thick and sticky leading to lung infections, respiratory failure, poor digestion, and problems in the reproductive system.

• High burden of therapy, mostly focused on treatment of symptoms

• Median age of death is 30
The Genetics of Cystic Fibrosis

- ~2,000 mutations have been identified, with ~300 known to result in CF
  - >1,200 CFTR mutations carried by 5 or fewer people in the world

**Approved for use in patients with cystic fibrosis and specific CFTR gene mutations.**

**Compounds under investigation in combination with other therapies.**

- Defective CFTR Function
  - Approved
    - KALYDECO® (ivacaftor)*
  - Approved
    - ORKAMBI® (lumacaftor/ivacaftor)*
  - Investigational
    - SYMDEKO™ (tezacaftor/ivacaftor and ivacaftor)*
  - Research
    - Gene Editing (CRISPR)
    - mRNA (Moderna)

* Approved for use in patients with cystic fibrosis and specific CFTR gene mutations.
** Compounds under investigation in combination with other therapies.
Developing Medicines for All People With CF

**CF Patients**

- United States: 30,000
- Worldwide: 75,000

**34,000 Patients Currently Eligible**

**Triple Combination Regimens**

- F508del/Minimal CFTR Function

**44,000 → 68,000**

**68,000 → 75,000**

**Gene Editing mRNA**

*Potential to treat all people with CF*

**34,000 → 44,000**

**Label Expansions Based on Age**

**34,000 Patients Currently Eligible**

**US - Approved February 2018**

**EU - Expect Approval 2H 2018**

**Residual Function Mutations**

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Original US Approval of Kalydeco and Initial Expansions Based on Clinical Trial Data

- **January 30, 2012** - Approved for patients 6 and older carrying at least one copy of G551D mutation
  - Approximately 1,200 people in the US
  - *First medicine to treat the underlying cause of cystic fibrosis*

- **February 21, 2014** – Approved for patients 6 and older carrying one of eight additional mutations (G128R, S529N, S549R, G551S, G1244E, S1251N, S1255P, G1349D)
  - Expands to approximately 150 people age 6 and older in the US who carry one of the eight additional mutations

- **December 29, 2014** – Approved for patients 6 and older carrying R117H mutation
  - Approximately 500 patients in the US 6 and older
Challenges of further expansion

• Initial approval/Expansions were based on clinical trials
  – Adequate numbers of patients available for study

• Additional mutations where ivacaftor might be effective, but difficult/infeasible to assess
  – >1,500 mutations carried by 5 or fewer patients worldwide

• Innovative approach required to license KLD for patients where direct clinical study may not be feasible
Innovative Regulatory Approach – use of in vitro data

“Many rare cystic fibrosis mutations have such small patient populations that clinical trial studies are not feasible. This challenge led us to using an alternative approach based on precision medicine, which made it possible to identify certain gene mutations that are likely to respond to Kalydeco.” – Janet Woodcock
Innovative Regulatory Approach – use of in vitro data

4 pillars for evaluating use of in vitro data to expand indication in absence of clinical data

- Robust validated assay system
- Comprehensive understanding of CFTR mutations/channels
- Verification of data integrity and findings
- Assay findings consistent with existing clinical data
In Vitro Data Supports Expansion of Kalydeco Indication to Include 23 Addl. Responsive Mutations

Threshold based on data showing patients with at least 10% of normal CFTR activity lack many clinical manifestations of CF compared to patients with less CFTR activity

FDA Targeted Therapies Draft Guidance (Dec 2017)

• Provides recommendations on grouping patients with different genetic mutations of eligibility in clinical trials

• Agency will accept patient groupings if reasonable to expect grouped patients will have similar pharmacological responses based on a strong scientific rationale

• Agency will generally approve drug for all subsets included in the grouping irrespective of whether subsets were represented in the clinical trial(s)
  – Sponsor should include mutation-by-mutation data in the label
Recent Approvals Reinforce Viability of In Vitro Data-Based Approach

- **Fabry Disease** - rare X-linked lysosomal disorder caused by mutated GLA gene; leads to functional impairment of multiple organs and premature death
  - More than 3,000 patients in the US

- Aug 2018 - **Galafold (migalastat)** granted Accelerated Approval for adults with Fabry disease with one of 348 “amenable” mutations based on in vitro data
  - Review package not yet available

- Limited clinical data
  - Efficacy demonstrated in 45-patient PBO-controlled study
    - Specific mutations studied clinically not included in FDA-approved labeling

- In vitro assay used to identify responsive mutations on the basis of relative and absolute increases in alpha-Gal A activity
Questions