A Strategy for Managing Early Access for Orphan Drugs

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No Disease Is Too Rare to Deserve Treatment
Disclosures

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• Prior employee and stockowner BioMarin
• President EveryLife Foundation for Rare Diseases
Queen Mary Celebration of First Laronidase Study Completion, Oct. 1998

Patients from the first MPS I enzyme study
Request for Early Access
Early Access for laronidase:
A prospective plan was not in place

- Requests received from seriously affected patients who could not qualify for Phase 3
- Concerns that any death might have on the regulatory review and approval process
- Costs and distraction from development
- Concerns about drug supply though there was sufficient supply
- FDA not convinced of benefit after Ph2

Two MPS 1 patients died without drug
Considerations in the Crisis in Early Access to laronidase for MPS I

• **Regulatory Issues:** Drug still in development
  – Not “proven” benefit/risk despite Ph2 data

• **Developer Issues:** Need to complete studies
  – Harm to drug profile/regulatory process of an adverse event, costs, distractions, supply

• **Patient Issues:** They will die before Ph3 is done and they don’t qualify
Is this a question of science/logic or about being compassionate?
The rare disease patient, in a lake, slowly drowning in the dark

- Do you throw them a rope, whatever you have?
- Or just discuss the arcane rules of rope usage, rope length and strength or responsibility if rope fails, ethics of rope usage......
If you cannot treat everyone, treat no-one?
Managing early access: considerations

• Nature of the drug and the data for it
  – Positive efficacy indication/safety?

• Nature of the disease: Life threatening, irreversible outcomes, rapidity?

• Probability of benefit or risk?

• Impact on the drug development program
  – Will effective development be harmed?
Preparing for Early Access Requests

- Learning from the past
- Realize that we are in a Life and Death Business
- Be proactive to mitigate crisis requests
  - Set of Programs are needed in your clinical development program
  - You can’t treat all—create criteria for eligibility
The industry needs to engage in the crisis that exists in the lives of patients that we mean to eventually help:

- There is more than one solution needed
- The solutions should be prospectively defined

Combination of Three Strategies to Consider

- Expanded access (compassionate use)
- Companion studies for non-qualifying patients
- Investigator-sponsored trials (IST’s)
Managing Early Access: Expanded Access Program

Setting: After Phase 2 data suggest efficacy/safety and in the same indication in development

- Considerations for Expanded Access
  - Life-threatening/disabling, rapid progression disease, with serious/irreversible repercussions
  - Phase 2 positive efficacy/safety signal positive
  - Treated patients not subjects for trials
    - Non-qualifying or regional location
  - Reasonable medical belief of Rx benefit/safety
  - Supplies are adequate and can be supported
  - Costs/logistics can be managed and be compliant
  - Must operate at the speed of the crisis
Alternate Access Approaches

Companion Study for Ph3 Non-Qualifiers

After Phase 2 data suggest efficacy/safety for a less urgent or non-life threatening situation

- Considerations for a Companion study to a Phase 3 for the non-qualifier subjects
  - Not urgent life-threatening; slower disease
  - Study specifically designed for these patients
  - Can be smaller, easier to conduct & less costly
  - Timing can start just after Ph3
  - Cannot treat all but at least some patients
  - Collects some useful data for filings
Alternatives to Expanded Access

Developing a non-ambulatory study for Ace-ER in GNE Myopathy

- Decided against early access program
  - Not possible to supply large numbers yet
  - Progression rate relatively slower
  - No potential acute life-saving/changing benefit

- Phase 3 study enrolls walkers >200m
  - More advanced non-ambulatory patients cannot qualify

- Developed non-ambulatory Ph2 study
  - Access for those that don’t qualify for Ph3
  - Study to start after Ph3 enrollment completed
Early Access in other indications:

**Investigator Sponsored Studies**

For indications not in the development program:
The use of investigator-sponsored studies

- Receive requests commonly for one product in many other indications
- Research and science to support plan
- Compound has good safety profile
- Request opportunity to test drug in new indication
No easy answers for early access

• Sponsors should consider variety of strategies to support patient access
  – Must still maintain and drive development
• Acute EAP for acute cases with possible positive benefit/risk considered
• Managing access to Phase 3 studies with supportive studies non qualifying patients
• IST’s for very select other indications
• Standards and process in prospective plan
Proposed Framework for Managing Early Access

- **Patient-Focused Transparency**
  - Point of Contact (on Website)

- **Prospective process for managing cases**
  - Qualifying rules, process for deciding cases
  - Team to manage requests

- **Set of Programs in the clinical development portfolio, based on urgency of disease**
  - Expanded access for critical urgent cases
  - Non-qualifier companion study for less urgent but important access need
  - Investigator sponsored protocols to consider for other indications outside of core area
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