EVERYLIFE FOUNDATION FOR RARE DISEASES

A Strategy for Managing Early Access for Orphan Drugs

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No Disease Is Too Rare to Deserve Treatment

Disclosures

- Founder, executive employee and stock owner Ultragenyx
- 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

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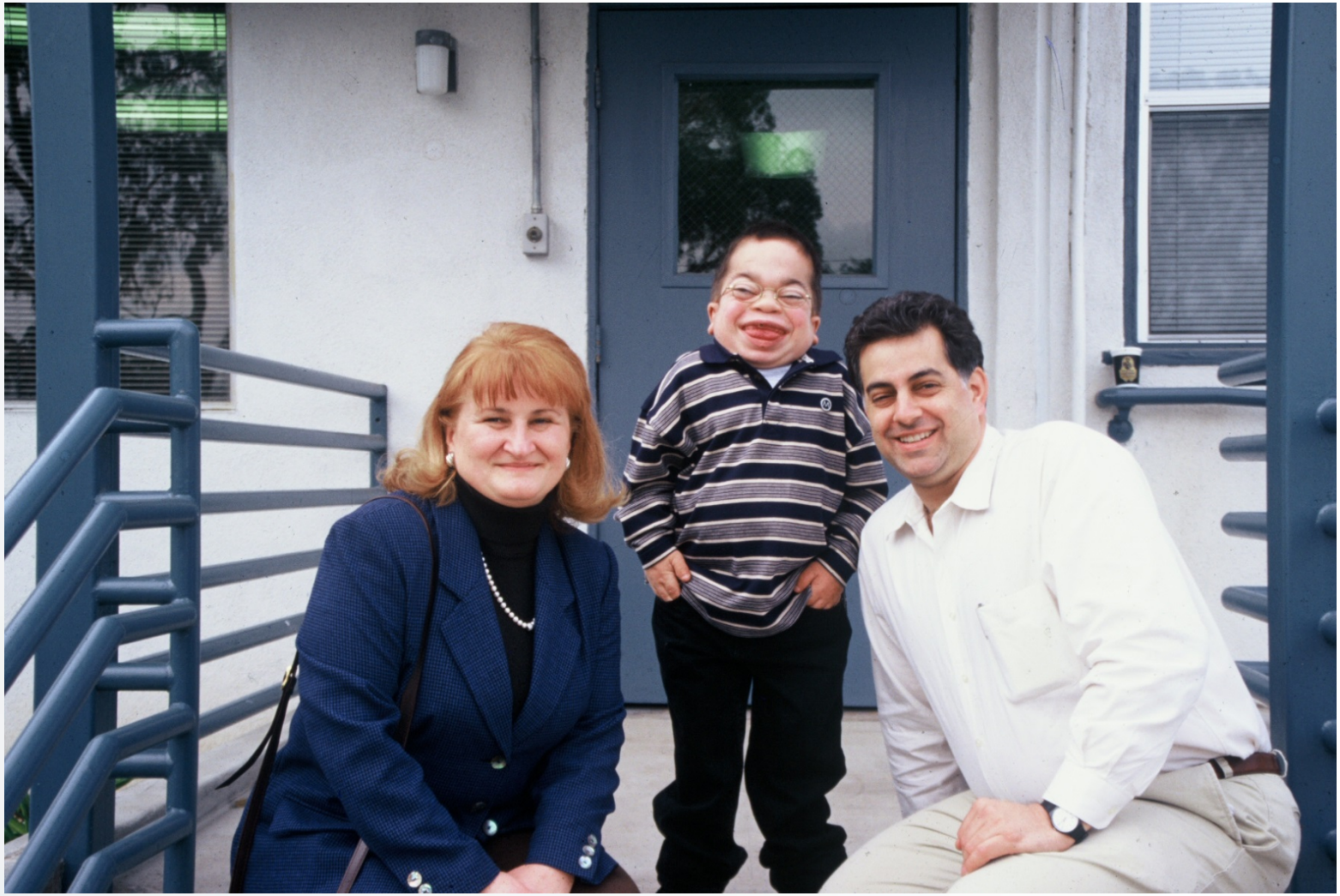

Early Access for laronidase:

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

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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……

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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

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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