CMC Strategy During the Accelerated Development of Brineura (cerliponase alfa)

SUCCESSES AND CHALLENGES OF DRUG DEVELOPMENT WHEN SPEED IS CRITICAL FOR THE PATIENT

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WCBP
29 January 2019
Outline

- Disease Background
- Clinical Trial Design and Results
- CMC Keys to Success
- Regulatory Pathways
- Key Take-aways
CLN2 is associated with a predictable and rapid decline in motor and language function

CLN2 Disease Natural History – Symptom Onset

- CLN2 Battens disease is very rare (approximately 2,000 patients worldwide)
- Rapidly progressive degenerative disease, leading to vegetative state and death
- Diagnostic latency is significant, frequently > 18 months from symptom onset
- Care is palliative

Rapid development is necessary and possible based on well-characterized natural history

Nickel M et al., Lancet Child Adolesc 2018

- Relevant clinical scale
- Disease progression is consistent across geographies in independent cohorts

![Graph showing sum of motor and language score over age with relevant clinical scale and disease progression data.](image)
TPP1-null Dachshunds recapitulate human CLN2 disease and demonstrate treatment effect

- Brineura® (cerliponase alfa) is a recombinant human form of tripeptidyl peptidase 1 enzyme (rhTPP1)

- Administration of rhTPP1 via infusion into the CSF every other week resulted in:
  - Significant delays in disease progression
  - Improved performance on a cognitive function test
  - Reduced brain atrophy by brain MRI
  - Increased life span

Katz et al. / Journal of Neuroscience Research 92 (2014) 1591-8
Vuillemenot et al. / Molecular Genetics and Metabolism 114 (2015) 281–293
Brineura® Administration

- Brineura® (cerliponase alfa) does not cross the blood-brain barrier (66 kDa)
- Administration targeted to the lateral cerebral ventricles
  - Intraventricular / Intracerebroventricular (ICV)
- 300 mg dose every 14 days via infusion over ~ 4 hours

Novel delivery:
- Surgical implantation of access device required (Rickham or Ommaya type)
- Chronic administration
- Implant usage for up to 4 years
Brineura® (cerliponase alfa)  
Single Pivotal Clinical Trial  
Open Label Design  
Comparison to Historical Controls
Brineura® Case Study: A Success Story with Numerous ‘Firsts’ for BioMarin

U.S. Breakthrough Therapy Approval
April 27, 2017

E.U. Accelerated Assessment Approval
May 30, 2017
# Development Timeline Comparison

<table>
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<tr>
<th>Year 1</th>
<th>Year 2</th>
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**Brineura® Single Pivotal Trial**

**Brineura® Timeline:** 3 yrs 7m from First patient to MA approval

**Typical Timeline ~ 6.8 yrs\(^1\) from Phase 1 to first MA approval**

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\(^1\) Profiles of New Approaches to Improving the Efficiency and Performance of Pharmaceutical Drug Development, A Tufts Center for the Study of Drug Development White Paper, MAY 2015. Mary Jo Lamberti, PhD, Senior Research Fellow; Kenneth Getz, MBA, Director of Sponsored Research Programs and Research Associate Professor
Key Factors Enabling Clinical and CMC Success

• Strong clinical efficacy data drove internal commitment to aggressive timeline
• Patient-centric development influenced risk-based strategies and speed
• Able to leverage prior manufacturing process and product knowledge
• Concurrent development of clinical and commercial manufacturing strategy enabled us to file initial applications from GMP facilities at clinical scale
• Health authority interactions were essential to gain alignment on strategy
• Available regulatory pathways enabled rapid review and approvals
On the path of rapid development we encountered some hurdles…

The novel route of administration to the brain for a biologic presented two major challenges

**Formulation Development**

- Formulation designed to mimic CSF because of limited data available on brain-delivered excipients
- Complex frozen labeling and supply chain distribution resulted from the need to protect the product during manufacturing, storage, and shipping
- Established product-specific analytical acceptance criteria to address challenges with particle formation

**Drug Delivery**

- The intraventricular/intracerebroventricular route not commonly used for chronic administration
- Limited number of devices available for ICV administration (syringes, infusion tubes/filters, etc.)
- Compatibility data for long term implantation and use
Brineura® is a Combination Product (U.S. 21 CFR Part 4)

- Device strategy developed late in clinical development
- Reached agreement with FDA on CP requirements ~7 months prior to BLA
  - Administration Kit contained product-contacting devices not specifically cleared for intraventricular/intracerebroventricular use → combination product!
  - Device development activities were extremely accelerated!

Co-Packaged Administration Kit
Typical Development Timeline for Combination Products

Phase 1
- Device Concept
- User requirements
- Design development plan
- Technical investigations
- Design inputs
- Device prototype

Phase 2
- Design Output
- Initiate QMS
- Vendor selection
- Initiate DHF
- Manuf. process dev.

Phase 3
- Design Controls
- Develop risk management plan
- Develop IFU
- Conduct FMEA + HFS
- Manuf. process val.
- Design V&V

Prep CTD
- Implement risk mitigations
- Implement QMS
- Finalize IFU
- Final design V&V

Review
- Implement risk management plan
- Ensure complete QMS
- Reg. package
- Design transfer

Manufacturing
- Post-marketing surveillance
- Annual design reviews

BLA Approval
Submit BLA

Approximately 6.8 years\(^1\) from Phase 1 to first MA approval

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\(^1\) Profiles of New Approaches to Improving the Efficiency and Performance of Pharmaceutical Drug Development, A Tufts Center for the Study of Drug Development White Paper, MAY 2015. Mary Jo Lamberti, PhD, Senior Research Fellow; Kenneth Getz, MBA, Director of Sponsored Research Programs and Research Associate Professor

January 22, 2019
Brineura® US Administration Kit – Product Timeline

Phase 1/2

- User requirements
- Technical investigations
- Device planning
- Design inputs
- Kit prototype
- Design outputs
- Initiate QMS
- Vendor selection
- Initiate DHF
- Manuf. process dev.
- Design controls
- Develop risk management plan
- Conduct FMEA
- Manuf. process val.
- Implement risk mitigations
- Implement QMS
- Design val. and verif.
- Develop IFU
- Reg. package

Data from device suppliers was essential to meet FDA requirements:
- Legal agreements
- Rate - limiting

• Confirm Brineura will be a combination product in US

Prep MA

Review

Submit BLA

BLA Approval

Approximately 2 years from CP agreement to BLA approval

January 22, 2019
## Concurrent Development of Clinical And Commercial Manufacturing Scales & Facilities

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<td>Commercial Manufacturing Drug Substance</td>
<td>Commercial Manufacturing Drug Product</td>
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- **FPI**: Brineura® Single Pivotal Trial
- **BLA Approval (DRUG SUBSTANCE)**
- **PAS Approval (DRUG SUBSTANCE)**
- **PAS Approval (DRUG PRODUCT)**
- **MAA Approval (DRUG SUBSTANCE)**
- **TYPE II Approval (DRUG SUBSTANCE)**

**Rapid approval in two jurisdictions for multiple major changes**
**Brineura® Global Approval Pathways**

<table>
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<th>Health Authority: Accelerated Pathway</th>
<th>Number of HA Meetings</th>
<th>Months to Approval</th>
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<td>EU: Accelerated Assessment</td>
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<td>Canada: Priority Review</td>
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Mexico: Orphan Drug Designation; Approval in 8 months

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**New accelerated regulatory pathways enabled rapid approvals due to the devastating nature and rarity of the disease**
Key Take-Away Messages

- Multiple, multi-year clinical studies for rare disease patient populations may not be feasible or necessary if natural history of disease is known.
- Strong clinical data used for risk/benefit assessments.
- Prior product and process knowledge is essential under acceleration.
- Risk assessment / risk mitigation helps to focus development and CMC lifecycle management strategy.
- When things are new for you, they may also be new for Health Authorities.
- Health Authorities have identified pathways to address urgent needs of small patient populations.
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PI= Principle Investigator, SI=Sub-Investigator; SC= Study Coordinator

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