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January 22, 2019

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

1 to 3 years	2 to 4 years	3 to 4 years	4 to 5 years	5 to 6 years	7 to 8 years	8 to 12 years
Language delay	New onset, unprovoked seizures Febrile seizures may also occur	Ataxia, Progressive dementia, Motor decline	Drug resistant seizures, Myoclonus, Spasticity, Dystonia, Visual deterioration	Wheelchair dependent/ bedridden	Blindness	Premature death

All photos used with family permission.

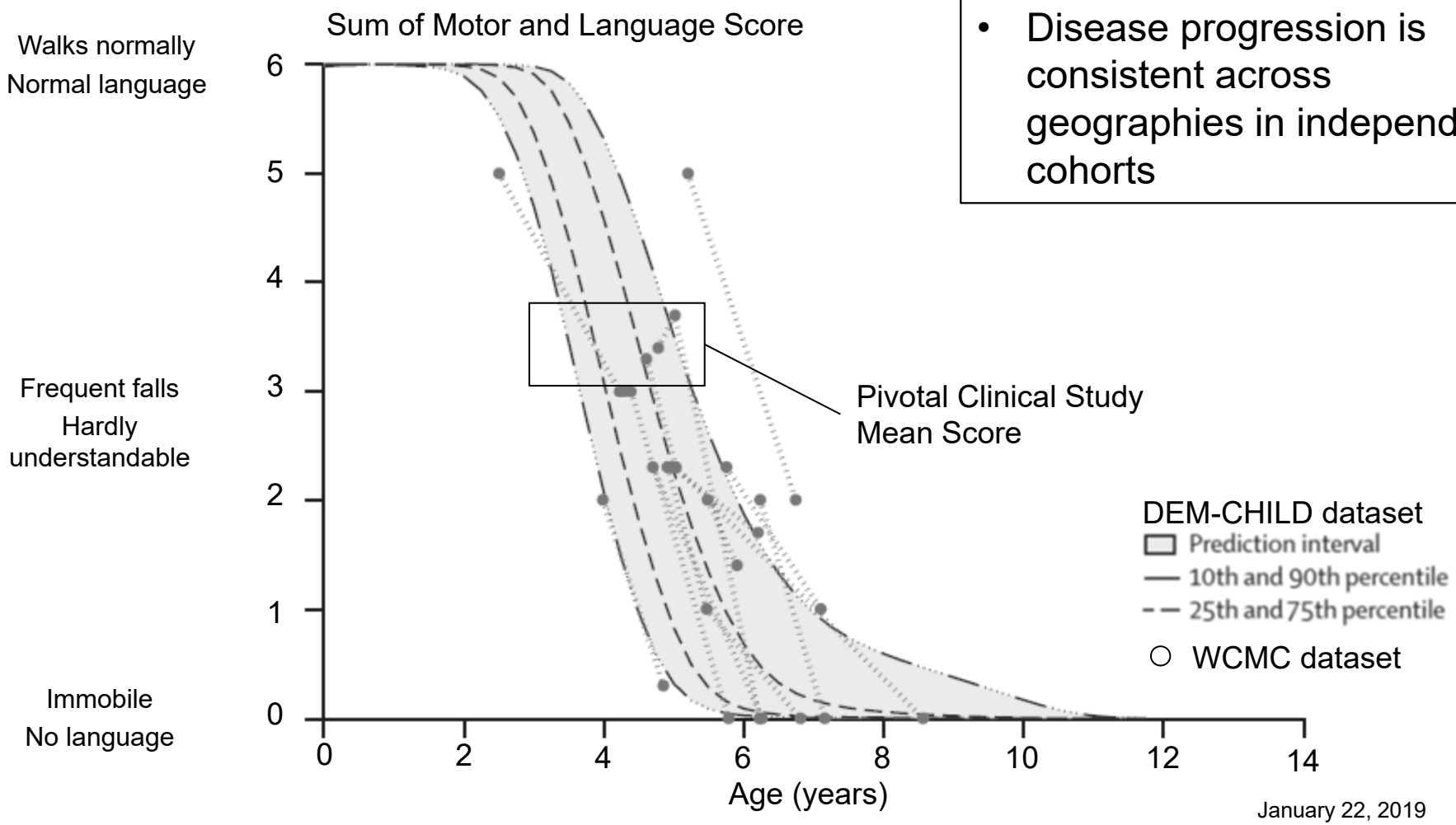
- CLN2 Battens disease is very rare (approximately 2,000 patients worldwide)
- Rapidly progressive degenerative disease, leading to vegetative state and death
- Diagnostic latency is significant, frequently > 18 months from symptom onset
- Care is palliative

1. Schulz A, Kohlschütter A, Mink J, Simonati A, Williams R. NCL diseases– clinical perspectives. *Biochim Biophys Acta*. 2013;1832:1801-1806.
2. Mole SE, Williams RE. Neuronal ceroid-lipofuscinoses. 2001 Oct 10 [Updated 2013 Aug 1]. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. GeneReviews.
3. Claussen M, Heim P, Knispel J, Goebel H, Kohlschütter A. Incidence of NCL in West Germany. Am J Med Genet. 1992;.= 42L536-538.

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

Nickel M et al., Lancet Child Adol 2018

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



TPP1-null Dachshunds recapitulate human CLN2 disease and demonstrate treatment effect

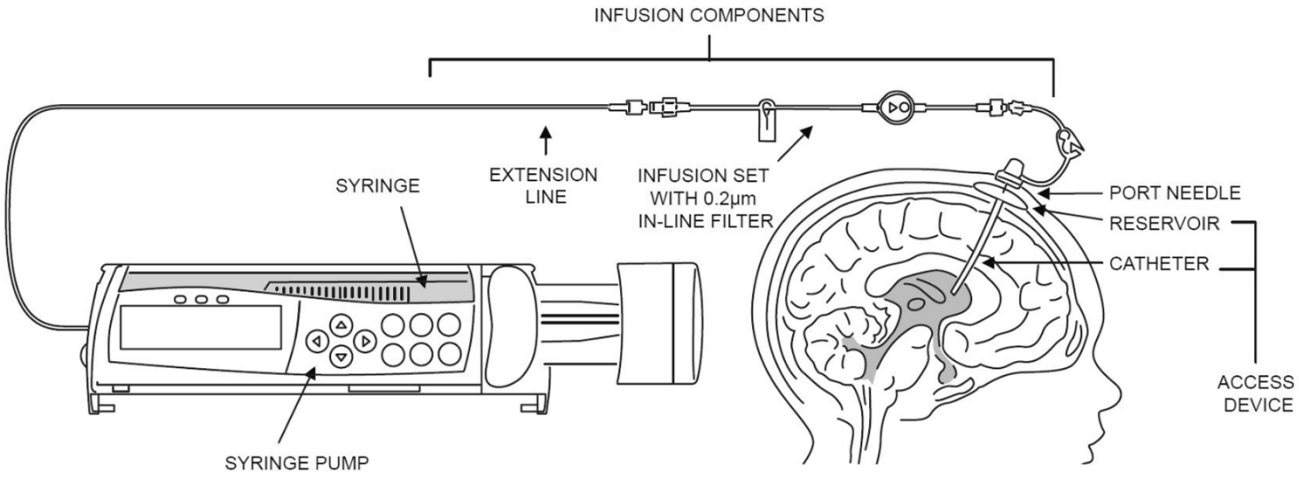
- Brineura® (cerliponase alfa) is a recombinant human form of tripeptidyl peptidase 1 enzyme (rhTPP1)
- Administration of rhTPP1 via infusion into the CSF every other week resulted in:
  - Significant delays in disease progression
  - Improved performance on a cognitive function test
  - Reduced brain atrophy by brain MRI
  - Increased life span

Untreated

Treated

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

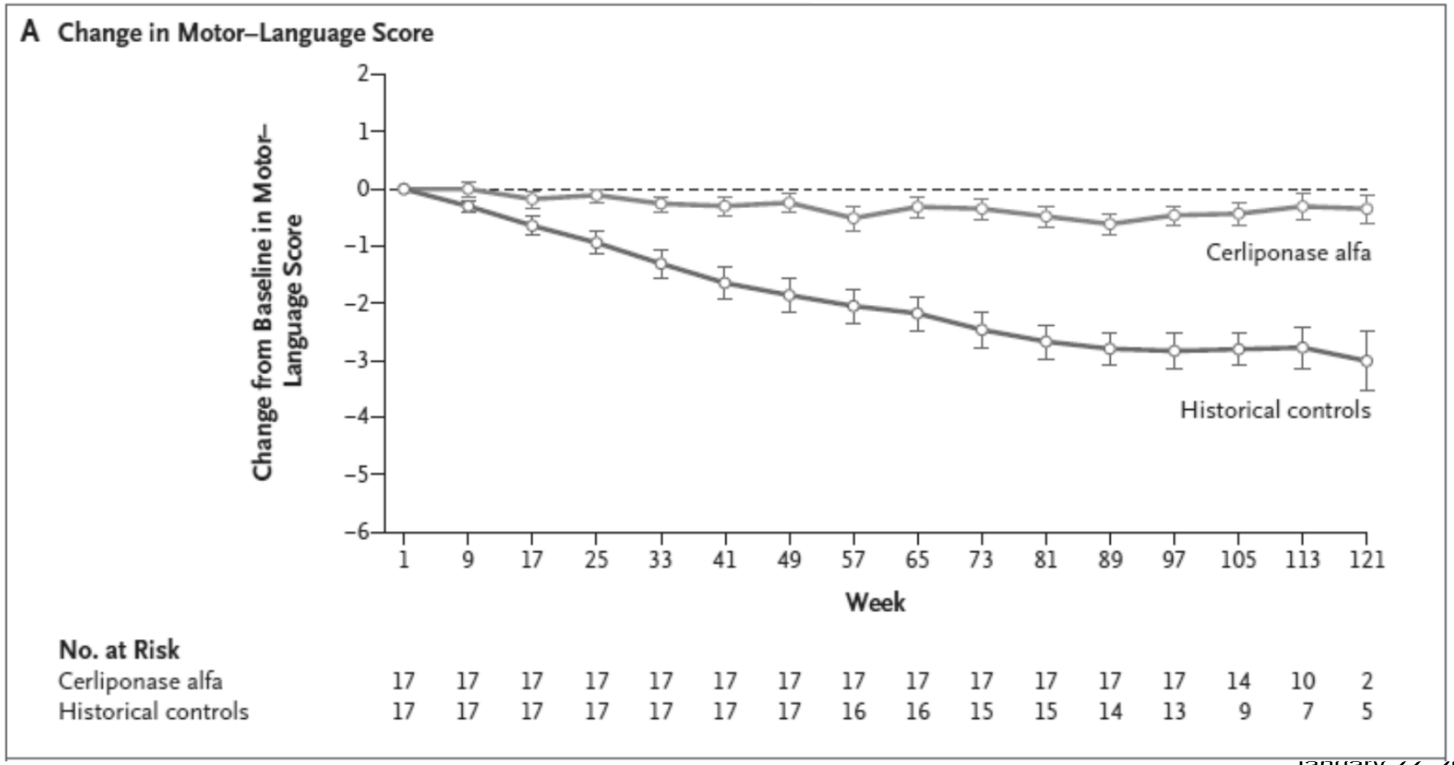
Comparison to Historical Controls

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Study of Intraventricular Cerliponase Alfa for CLN2 Disease

Angela Schulz, M.D., Temitayo Ajayi, M.D., Nicola Specchio, M.D., Ph.D., Emily de Los Reyes, M.D., Paul Gissen, M.B., Ch.B., Ph.D., Douglas Ballon, Ph.D., Jonathan P. Dyke, Ph.D., Heather Cahan, M.D., Peter Slasor, Sc.D., David Jacoby, M.D., Ph.D., and Alfried Kohlschütter, M.D., for the CLN2 Study Group*



Brineura® Case Study: A Success Story with Numerous 'Firsts' for BioMarin

Brineura® (cerliponase alfa)

U.S. Breakthrough Therapy Approval
April 27, 2017

E.U. Accelerated Assessment Approval
May 30, 2017

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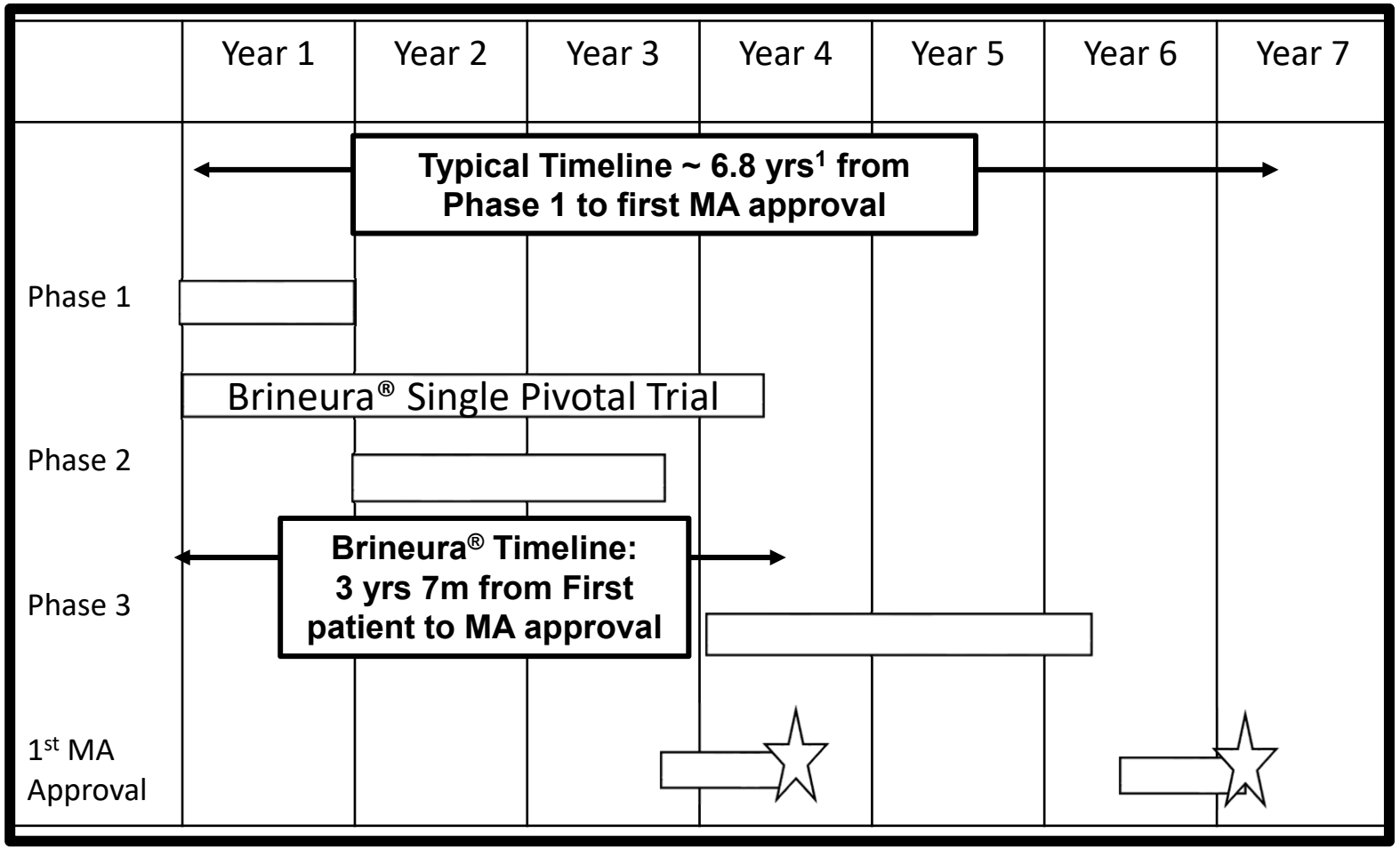
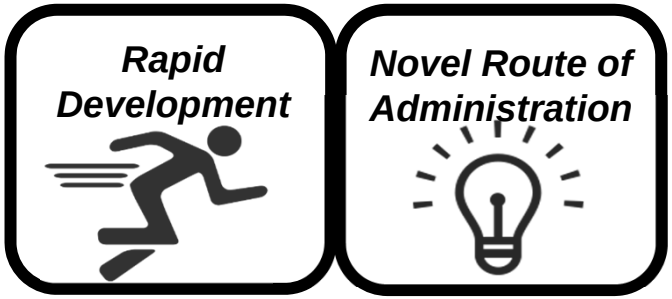
Development Timeline Comparison



[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

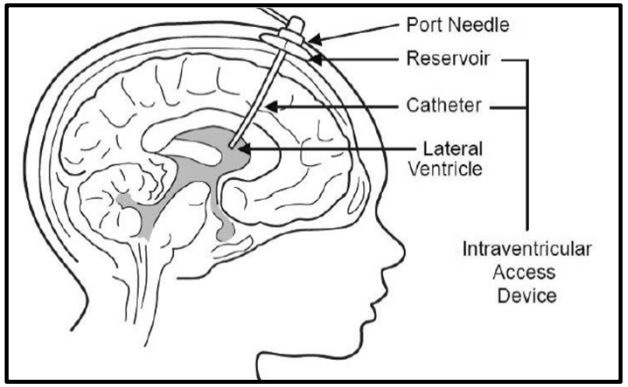
- Strong clinical efficacy data drove internal commitment to aggressive timeline
- Patient-centric development influenced risk-based strategies and speed
- Able to leverage prior manufacturing process and product knowledge
- Concurrent development of clinical and commercial manufacturing strategy enabled 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

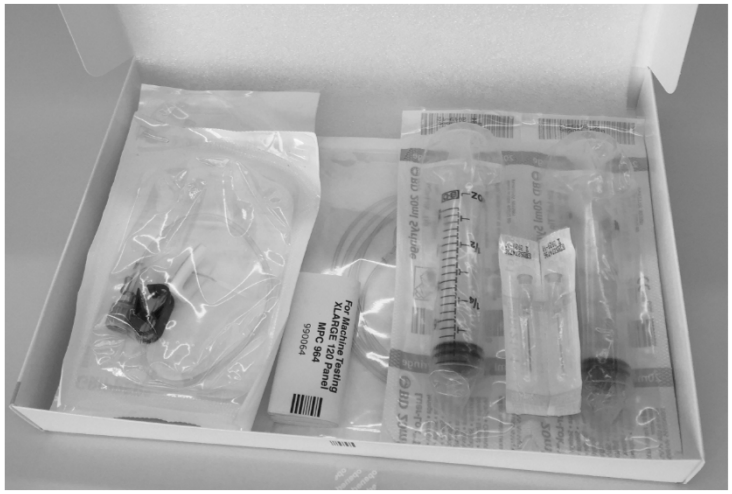


Drug Delivery

- 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

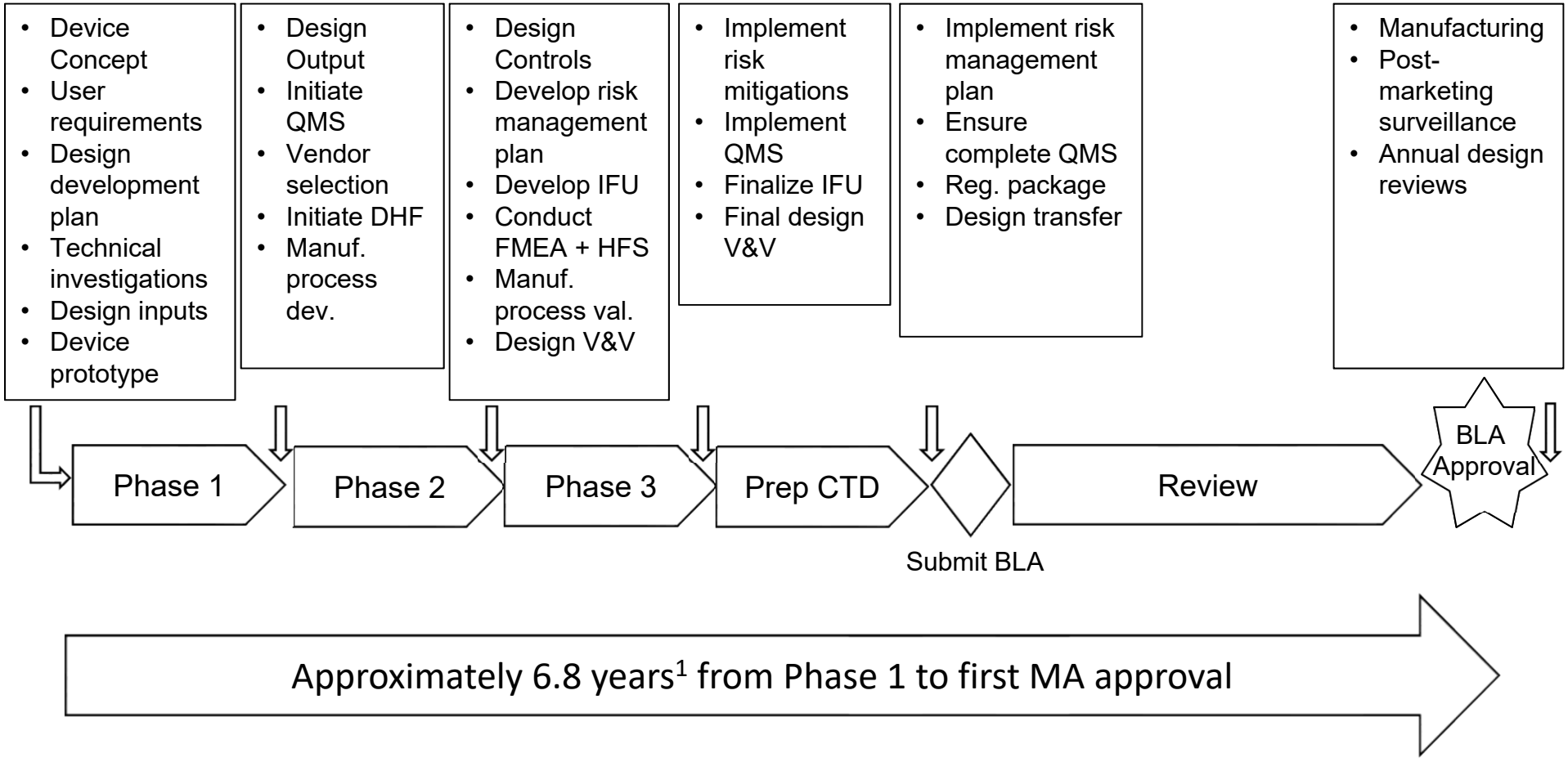
Brineura® is a Combination Product (U.S. 21 CFR Part 4)

- 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



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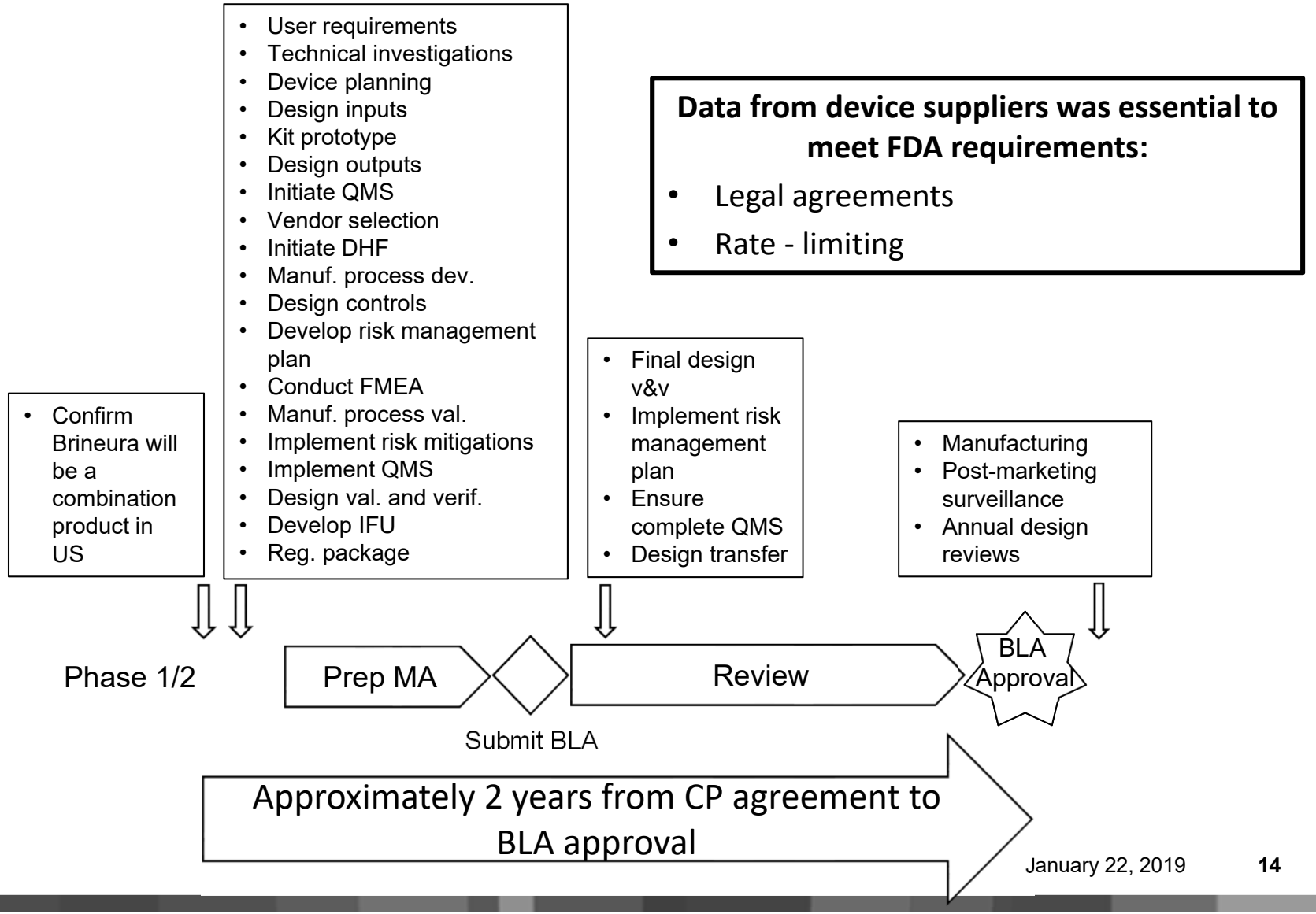
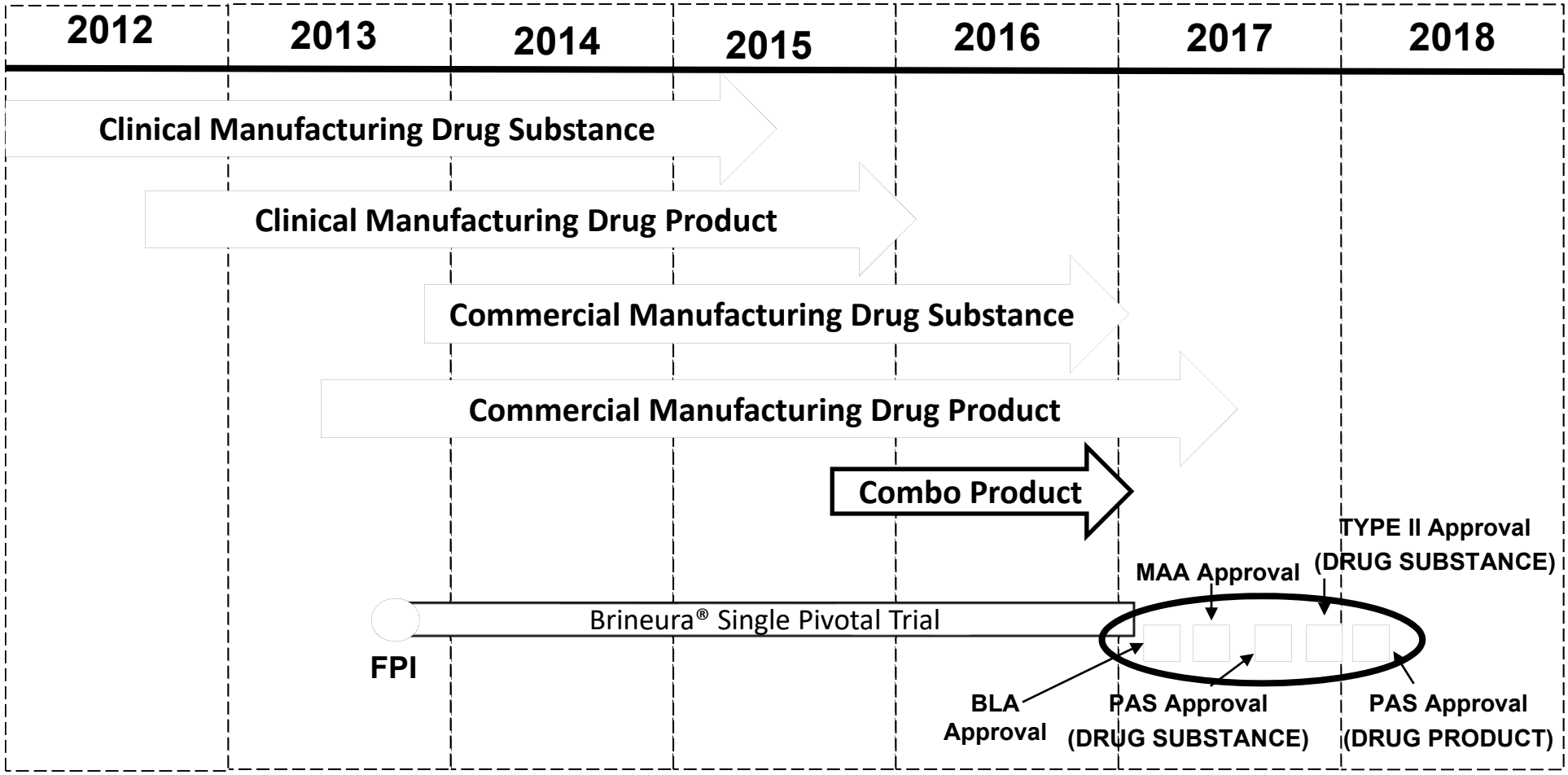
Brineura® US Administration Kit – Product Timeline



Concurrent Development of Clinical And Commercial Manufacturing Scales & Facilities



Rapid approval in two jurisdictions for multiple major changes

Brineura® Global Approval Pathways

Health Authority: Accelerated Pathway	Number of HA Meetings	Months to Approval
USA: Breakthrough Therapy Designation, Priority Review	18	11
EU: Accelerated Assessment	7	12
Ukraine: Fast-track Procedure for Orphan Drug Products	0	8
Brazil: RDC 205 - Special Procedure for treatment of rare diseases	2	5
Australia: Priority Designation	1	8
Canada: Priority Review	1	6

Mexico: Orphan Drug Designation; Approval in 8 months

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

Brineura®

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PI= Principle Investigator, SI=Sub-Investigator; SC= Study Coordinator

THANK YOU

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