Rare diseases forum:

Case Study: Brineura for the treatment of the CLN2 form of Batten's disease

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Issues in the Development of Brineura

- CLN2 Battens disease is very rare
- Rapidly progressive degenerative disease, leading to vegetative state and death
- Diagnostic latency is significant, frequently > 18 months from symptom onset
- Limited clinical expertise, no published care guidelines
- Significant allelic heterogeneity
- Route of administration: intracerebroventricular infusion every 2 weeks requiring neurosurgical placement and chronic indwelling cranial hardware
- Natural history collected, but descriptions not extensive nor standardized
- No biomarker data, no clear relation of allele to residual activity and phenotype

Design of study was open label treatment arm compared to historical controls

Summary of Review Issues for Brineura

- Comparability of treated population to historical controls
- Comparability of rating scale used to assess efficacy
- Bias minimization
- Analytical methodology
- Small n, requirement for full, verifiable dataset and demonstration of durability of treatment

190-201/202: Design and Objectives

Administered 300 mg by intraventricular infusion every 2 weeks

- Primary Objectives
  - Effectiveness: comparison of rate of 2-point loss in study to natural history
- Secondary Objectives
  - Measurement of brain atrophy using MRI volumetry
  - PK in CSF and plasma
  - Drug specific antibodies in CSF and plasma
- Exploratory Objectives
  - Identify and assess potential disease-related CSF and plasma biomarkers
  - Measure quality of life (QOL) family related outcomes
  - Measure developmental assessments

Endpoints for Efficacy Analysis

- ML (6/normal to 0/complete loss) primary measure
  - Core, impactful and early manifested disease domains
  - Broad neuroanatomical control of ambulation and language
  - Each component has predictable decline with age
  - Each single point decrement is a milestone in loss of function for these critical functions

- Primary analysis is 2-pt decline
  - Each 1 point designation is a category
  - 2-pt change overcomes entry variability, rater and episodic variability
  - 2-pt declines are significant progression in disability

Natural History of CLN2 Disease: Independent Description

Nickel M et al., Lancet Child Adol 2018

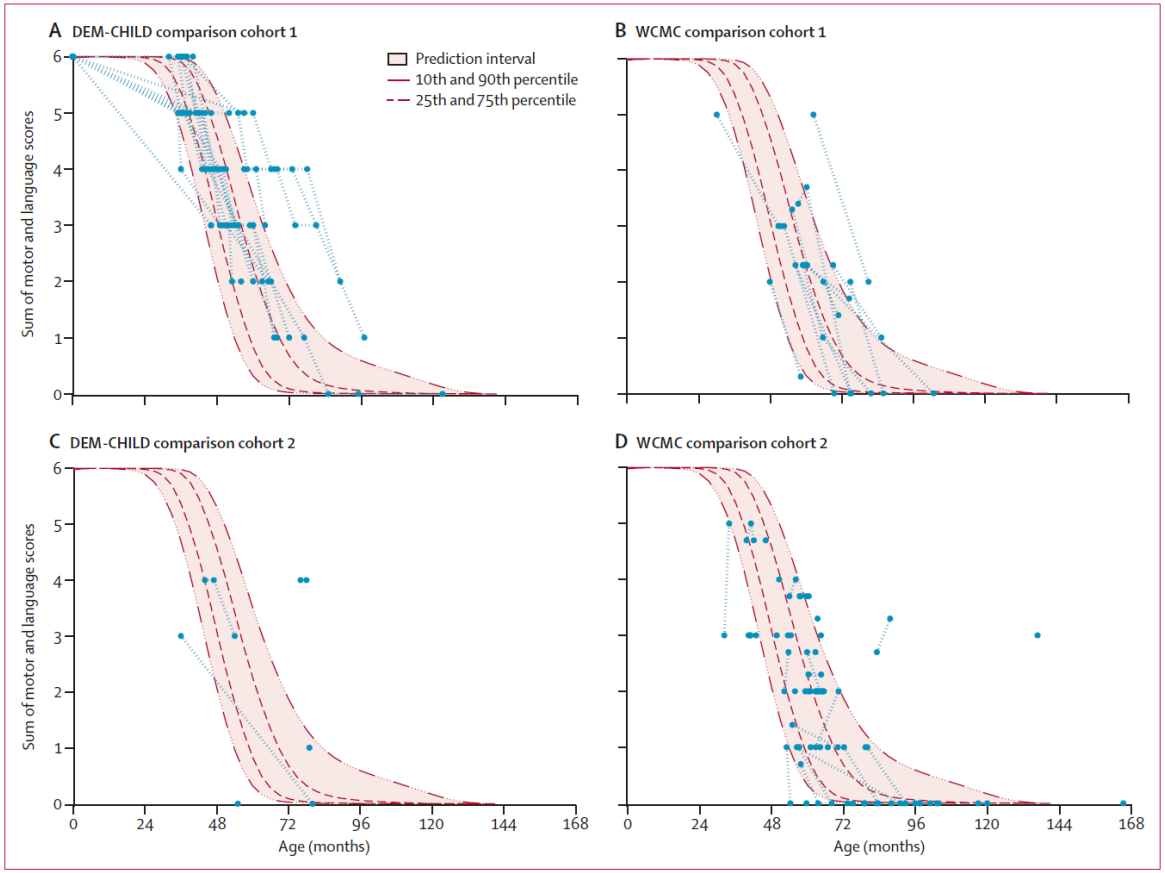


Figure 5: **Motor–language scores of comparison cohorts superimposed on DEM-CHILD core data**
Motor-language score data for DEM-CHILD comparison cohort 1 (A), WCMC comparison cohort 1 (B), DEM-CHILD comparison cohort 2 (C), and WCMC comparison cohort 2 (D). Each assessment is shown as single blue point. Longitudinal assessments for each patient are linked by dashed red lines. Mean scores and 95% CIs, and 10th, 25th, 75th, and 90th percentiles for the DEM-CHILD core data are shown for comparison.

	Hamburg scale		Weill Cornell scale	
	Motor	Language	Gait	Language
Score 3	Walks normally	Normal	Normal	Normal
Score 2	Frequent falls, obvious clumsiness	Recognisably abnormal	Abnormal but independent	Abnormal
Score 1	No unaided walking or crawling only	Hardly understandable	Abnormal, requires assistance	Barely understandable
Score 0	Immobile, mostly bedridden	Unintelligible or no language	Non-ambulatory	Unintelligible or no speech

Adapted from Steinfeld et al[17] and Worgall et al.[18]

Table 1: **Hamburg and Weill Cornell scales for assessing functional ability in patients with neuronal ceroid lipofuscinosis type 2 disease**

	DEM-CHILD dataset (n=67)	WCMC dataset (n=66)
Core data cohort, n	41	0
Comparison cohort 1, n	21	12
Comparison cohort 2, n	5	54

Of the 74 patients in the DEM-CHILD dataset, 67 patients had clinical scoring data available and formed the DEM-CHILD core data and comparison cohorts.

Table 2: **Overview of included cohorts**

Genotype: Phenotypic Similarity in a Grouped Analysis

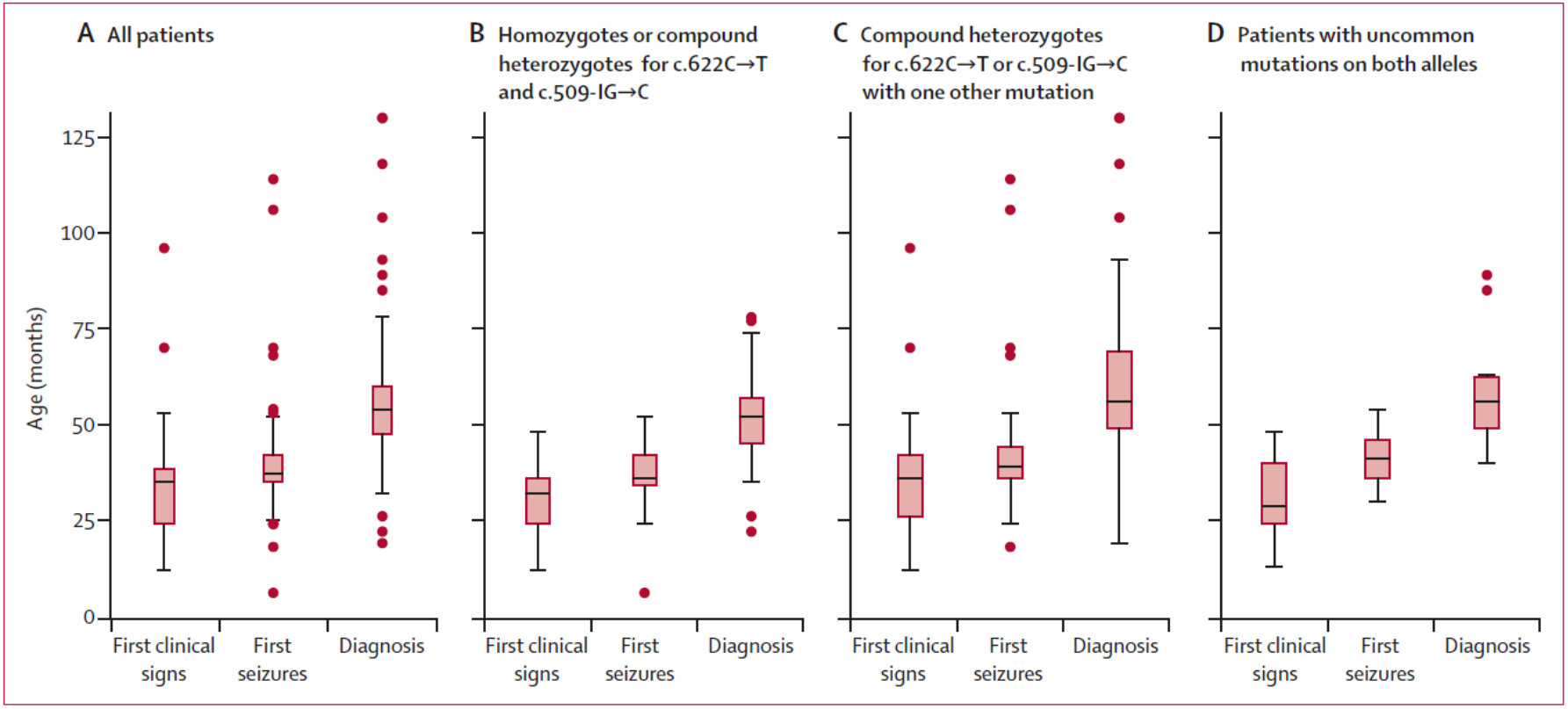


Figure 2: **Age at first clinical sign, first seizure, and diagnosis**

55

Data are combined from both DEM-CHILD and WCMC cohorts (n=140). Boxes show median values (middle lines) with 25th and 75th percentiles; whiskers show values within two-thirds of the IQR. Circles represent data points that fall outside this range. CLN2= Late-infantile neuronal ceroid lipofuscinosis type 2.

Natural History Contributions to Review

- Covariates age and baseline score related to decline; genotype and sex did not have major contributions to variability
- Matching analyses to treatment population provided valuable sensitivity information for the efficacy analysis
  - 1:1 using age (3m), batched genotype, score and sex as covariates
  - 1: all regardless of covariates
  - Population comparison adjusted for covariates
- Performance of scale similar with differences in definitions, acquisition methodology and raters
- North American cohort very similar to European cohort
- Analysis of progression not dependent on date of diagnosis

Challenges:
- Acquisition of data
- Type of data
- Verification of data

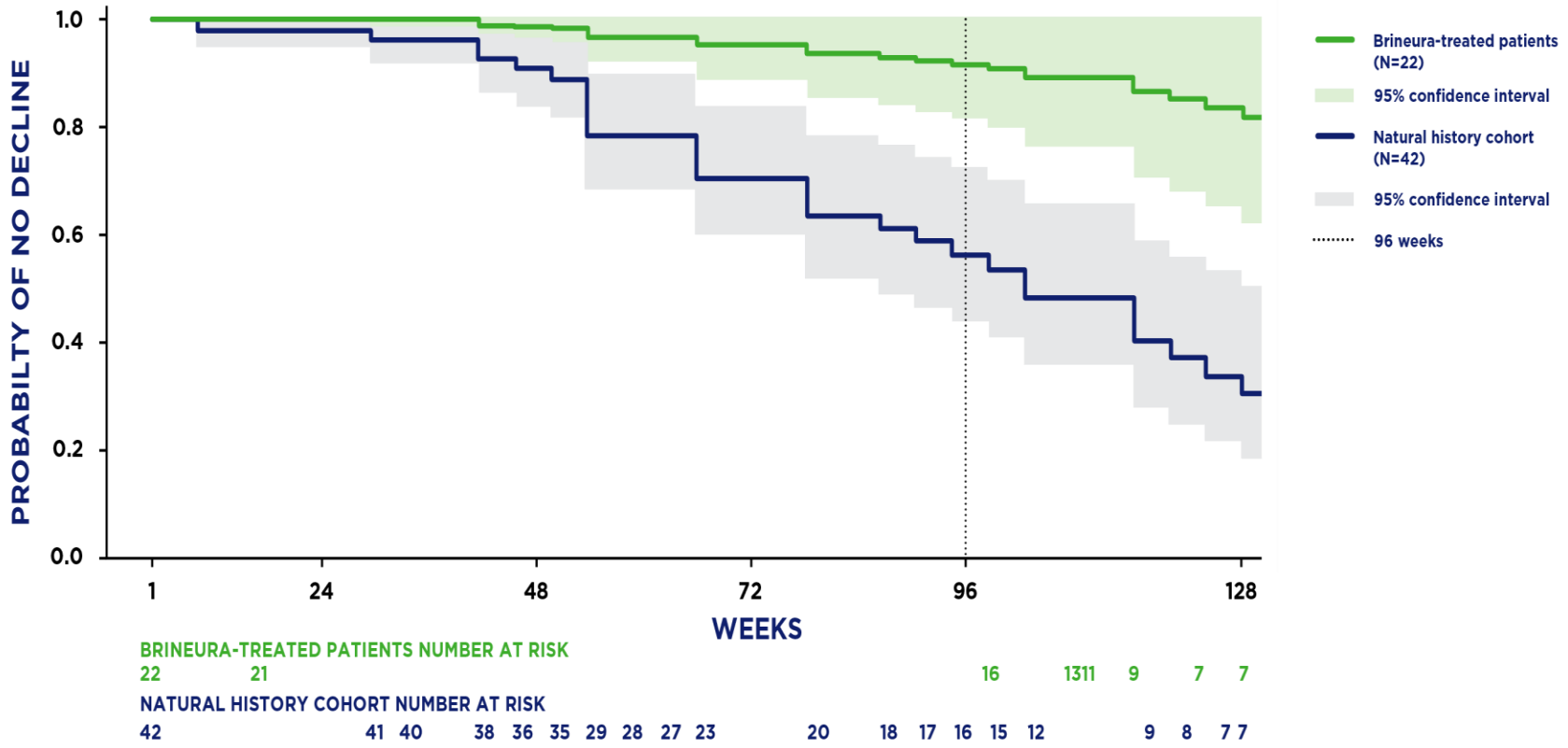
Effect due to bias minimized by:
- Comparability of populations
- Effect of standards of care, site, rater

FDA Review Resulted in Solutions for Brineura

- Comparability of treated population to historical controls
  - Addition of second natural history cohort
  - Tighter definition of covariates of untreated progress
  - Data integrity
- Comparability of rating scale used to assess efficacy
  - Performance testing of scale using historical rater and study video
- Bias minimization
- Analytical methodology
  - Treatment of data as categorical, not continuous
  - Open to multiple sensitivity methodologies
- Small n, requirement for full, verifiable dataset and demonstration of durability of treatment
  - Submission of updated study outcomes during review

Brineura® Treatment Maintains Motor Function in CLN2 Battens Children

Cox proportional hazard model: estimate of hazard ratio 0.08

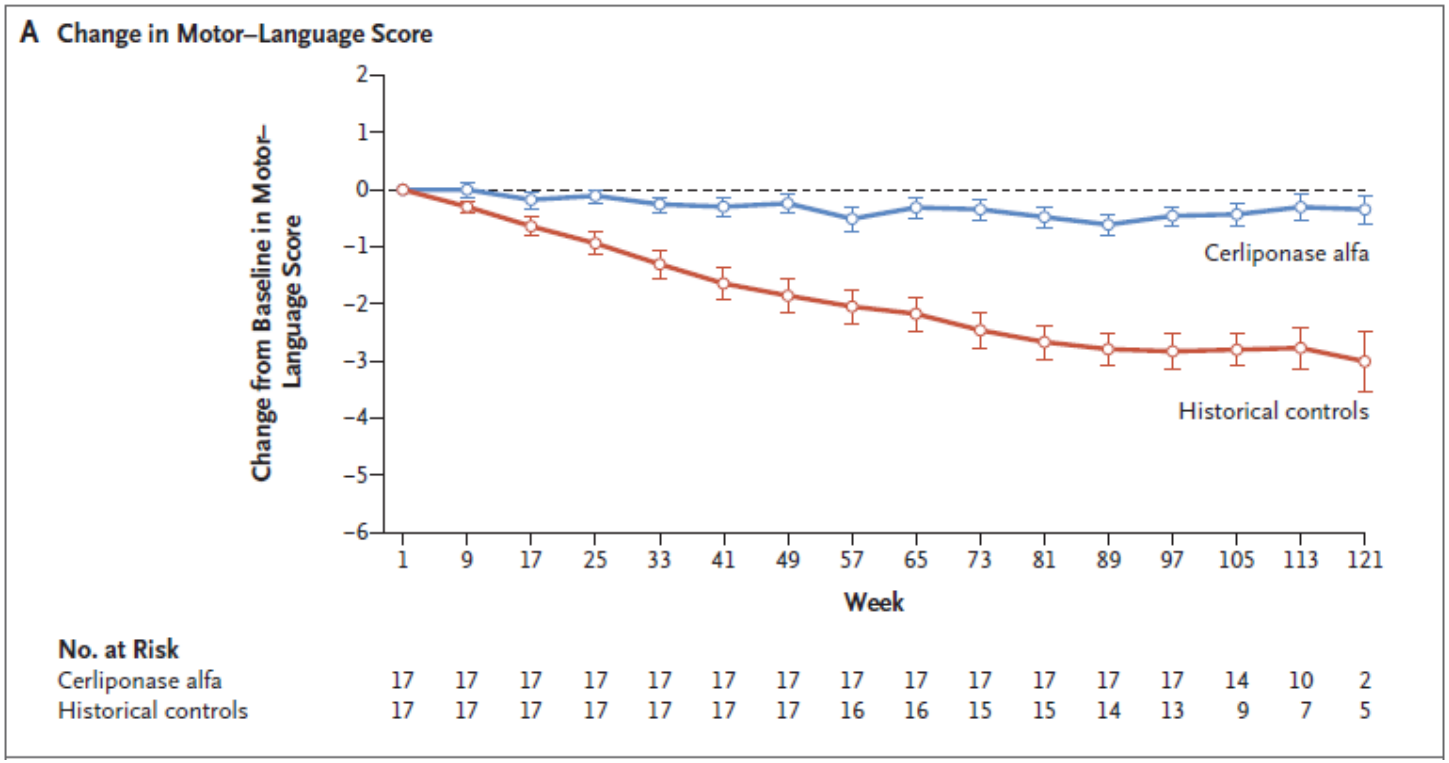


The NEW ENGLAND JOURNAL of MEDICINE

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*



THANK YOU

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