

24-Month Analysis of BUTTERFLY: A Prospective, Observational Study to Investigate Cognition and Other Non-seizure Comorbidities in Children and Adolescents with Dravet Syndrome (DS)

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Limited prospective long-term data exist on the natural history of DS

- DS is a severe and progressive genetic epilepsy characterized by frequent, prolonged, and refractory seizures, typically beginning within the first year (y) of life
- Available therapies do not adequately control seizures in 90% of DS patients, and they do not address other comorbidities of the disease, including intellectual disability, ataxia/motor abnormalities, behavioral problems, speech impairment, sleep disturbances, and a high risk for sudden unexpected death
- Complications of the disease often contribute to a poor quality of life for patients and their caregivers

BUTTERFLY was designed to evaluate seizure and non-seizure manifestations in patients with DS over 24 months

- Multicenter, prospective, observational, US study with clinical assessments performed at baseline (BL) and 3, 6, 12, 18, 24 months

Primary Objective:

- Neurodevelopmental status from BL to 24m

Secondary Objectives:

- # countable convulsive seizures per 4-week period before visits
- Change from BL in overall clinical status, quality of life, and executive function

Key Inclusion Criteria

- Aged 2-18y (inclusive)
- DS diagnosis with documented mutation in *SCN1A* gene

Key Exclusion Criteria

- Gain-of-function *SCN1A* gene mutation
- Current treatment with sodium channel blocker

BUTTERFLY enrolled 36 patients aged 2 to 18 years with DS

- N=36 with 12 patients in each of 3 age groups: 2-7, 8-12, and 13-18 years
- 61.1% female, 94.4% white, and 13.9% Latino
- Mean age of seizure onset: 5.14 months (range 2.04 to 12.0 months)

Patients were treated with the best available anti-seizure medicines

Median baseline convulsive seizure frequency per 28 days (95% CI), n=26

10.0 (5.50, 15.5)

Most common ongoing anti-seizure medicines, n (%)

Clobazam	25 (69.4%)
Fenfluramine	16 (44.4%)
Stiripentol	14 (38.9%)
Valproic Acid	14 (38.9%)
Cannabidiol	12 (33.3%)
Levetiracetam	8 (22.2%)

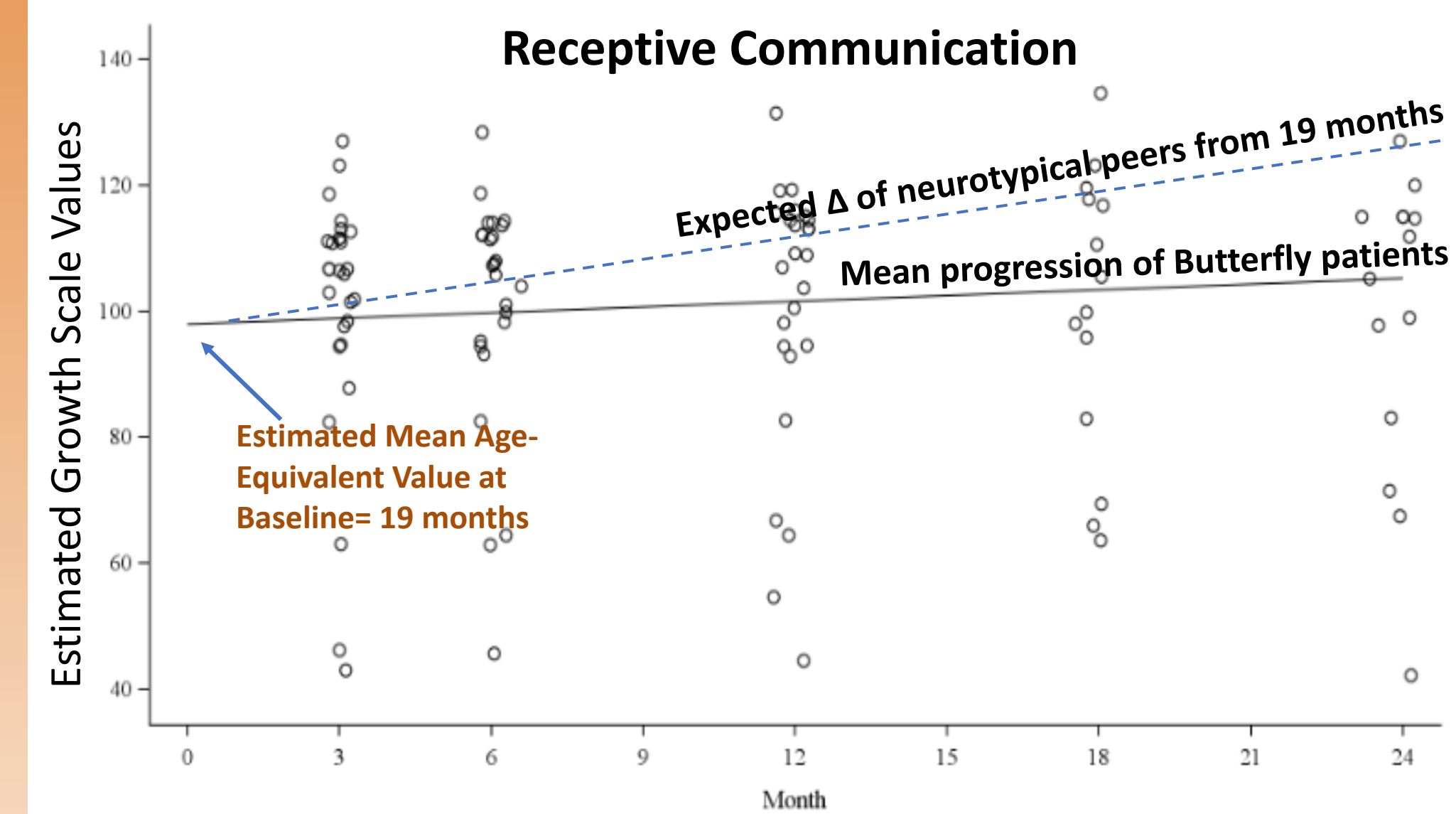
Baseline Clinical Global Impression of Severity of Illness (CGI-S) rating, median (95% CI), n=20

4.0 (4.00 – moderately ill, 6.00 – severely ill)

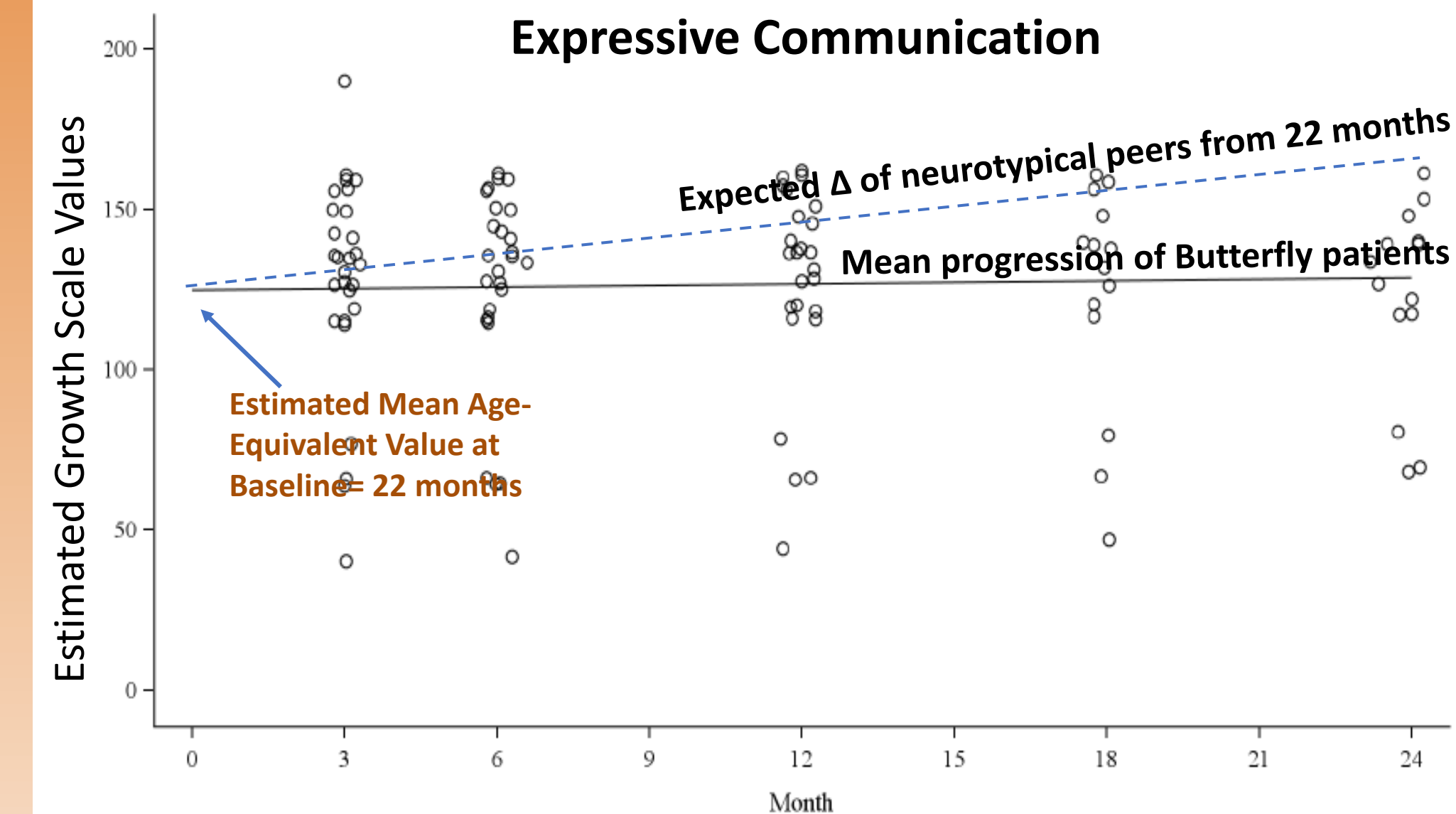
Disease progression models were developed to assess average change over time across multiple clinical measures

- Disease progression for each clinical endpoint was modeled using mixed models with random effects for intercept and slope (coefficient of time in months), allowing for heterogeneity among patients in their individual disease progression, while providing an estimate of average disease progression
- Patients' age at enrollment, age at seizure onset, sex, body mass index, *SCN1A* genotype, baseline score of the assessment, and baseline convulsive seizures were tested as covariates in mixed-effects models
- Covariates were considered significant if $p < 0.1$. Covariates denoted with an * have p-value between 0.1 and 0.3

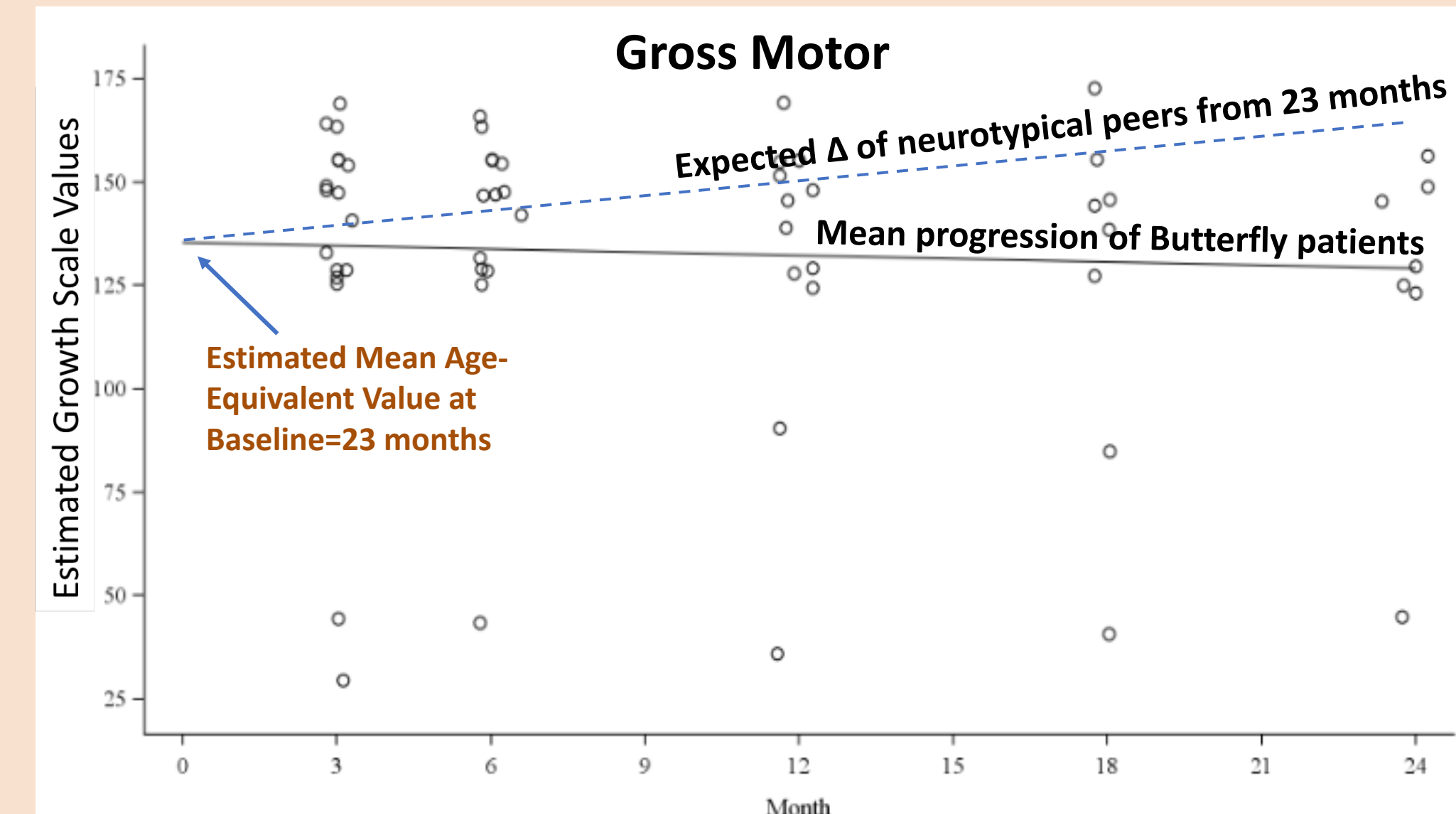
BUTTERFLY patients exhibited substantially less improvement over 24 months compared to neurotypical peers across key Vineland-III subdomains



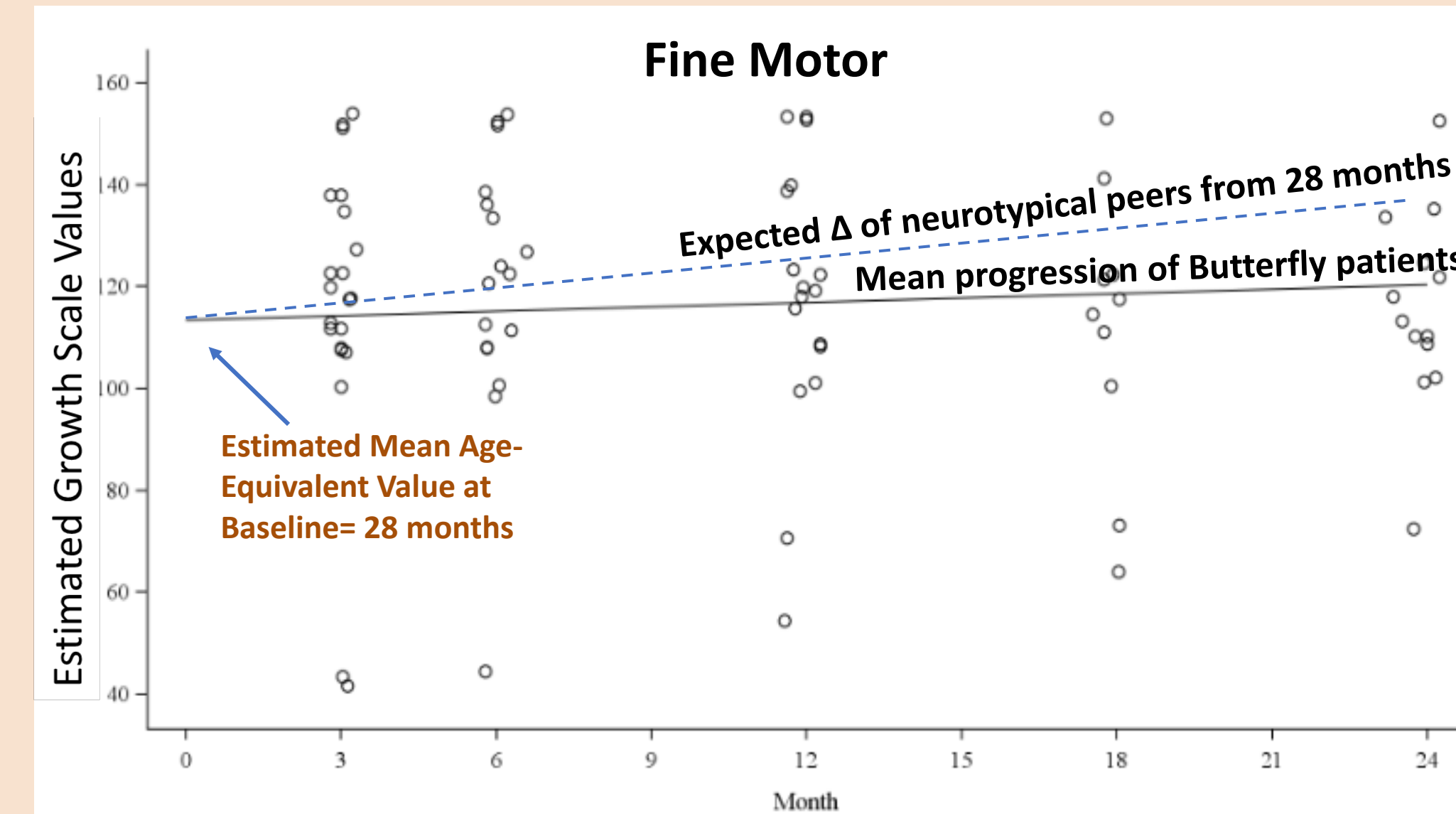
N	Parameter	Estimated Result	95% CI	p-value	Significant covariates	Estimated Value at BL
32	Slope	0.30	0.054, 0.549	0.0189	Ln BL score	97.90
	Δ Baseline to Month 24	7.25	1.30, 13.19	-		



N	Parameter	Estimated Result	95% CI	p-value	Significant covariates	Estimated Value at BL
32	Slope	0.16	-0.005, 0.323	0.0565	BL score, Age at seizure onset*	124.78
	Δ Baseline to Month 24	3.81	-0.12, 7.75	-		



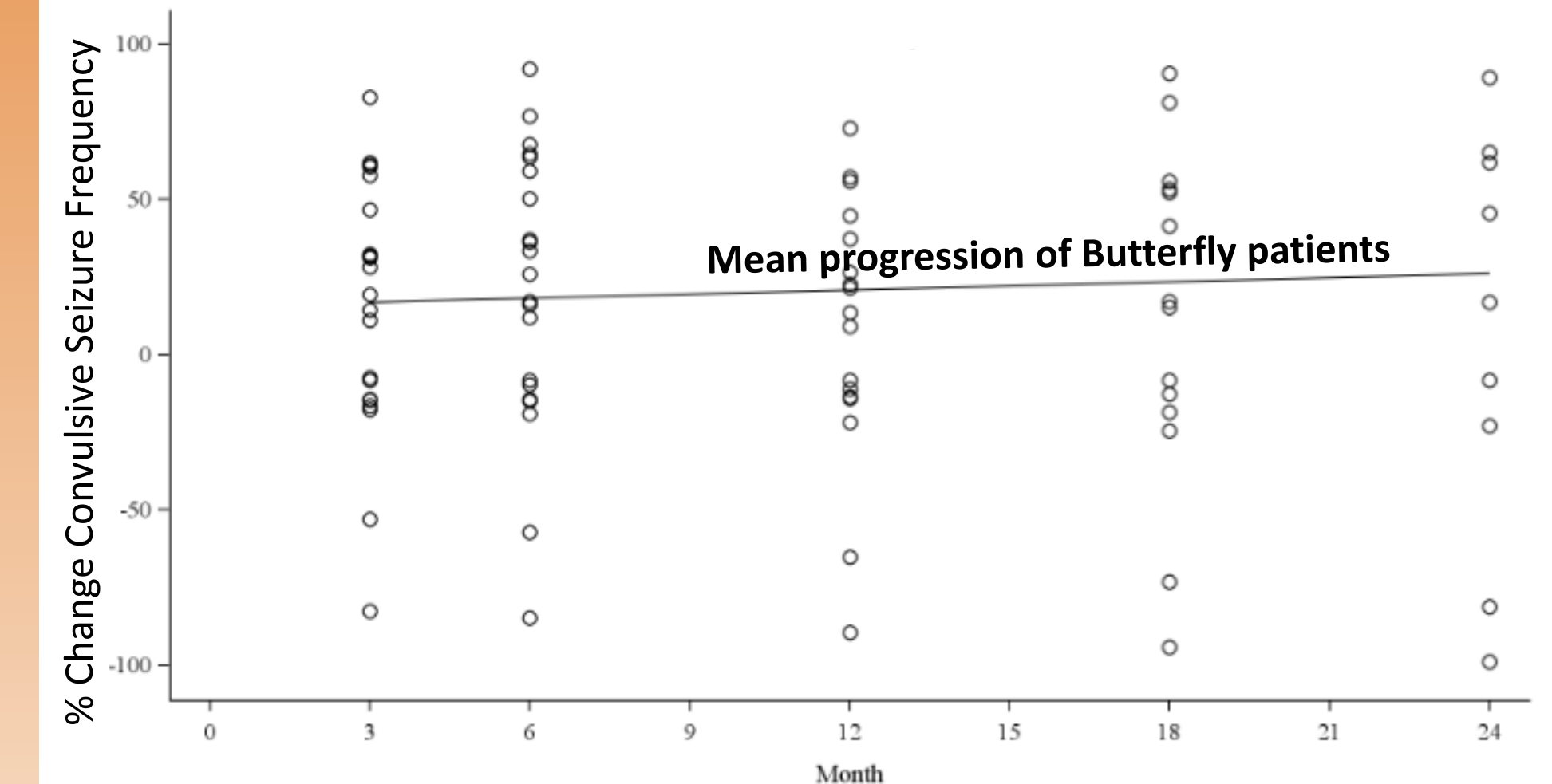
N	Parameter	Estimated Result	95% CI	p-value	Significant covariates	Estimated Value at BL
21	Slope	-0.26	-0.849, 0.329	0.3560	Ln BL score, BL convulsive seizures*	135.33
	Δ Baseline to Month 24	-6.23	-20.37, 7.90	-		



N	Parameter	Estimated Result	95% CI	p-value	Significant covariates	Estimated Value at BL
27	Slope	0.29	-0.026, 0.604	0.0707	BL score	113.39
	Δ Baseline to Month 24	6.93	-0.64, 14.49	-		

CI: Confidence Interval; Ln: Natural Log; Vineland-III: Vineland Adaptive Behavior Scales, Third Version; Data cutoff: after last patient, last visit in BUTTERFLY

BUTTERFLY patients experienced lack of improvement in convulsive seizure frequency over 24 months



N	Parameter	Estimated Result	95% CI	P-value	Significant covariates
23	Slope	0.44	-1.37, 2.26	0.6280	Ln BL convulsive seizures*, Ln age at screening, Age at seizure onset
	Δ Baseline to Month 24	10.61	-32.97, 54.19	-	

BUTTERFLY is the largest, prospective, longitudinal natural history study of patients with genetically-confirmed DS

- There was heterogeneity across patient scores on clinical measures at baseline
- BUTTERFLY patients did not have statistically significant change from baseline in the majority of key Vineland-III measures over 24 months of observation
- Despite treatment of BUTTERFLY patients with the best available anti-seizure medicines, on average:
 - rate of improvement over 24 months on multiple clinical measures, including key domains of the Vineland-III, was substantially below that of neurotypical peers
 - patients continued to experience convulsive seizures over 24 months at similar frequency to that at baseline
- Data from BUTTERFLY will inform outcomes in future DS studies

Acknowledgements

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