Twelve-month Analysis of BUTTERFLY: An Observational Study to Investigate Cognition and Other Non-seizure Comorbidities in Children and Adolescents with Dravet Syndrome (DS)

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BUTTERFLY: An observational study of Dravet Syndrome patients

Background

- 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
- Limited prospective long-term data exist on DS

Study Overview

- Multicenter, prospective, observational, US study
- Fully enrolled: 36 patients/age (2-7, 8-12, and 13-18y)
- Assessed at baseline (BL) and 3, 6, 12, 18, 24 months (m)

PRIMARY OBJECTIVE:
- Neurodevelopmental status change 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

This interim analysis includes data available following completion of visit 4, 12m (07MAR2022) by all enrolled patients

Baseline Demographics

- n=12/group: 2-7, 8-12, and 13-18y
- 61.1% female, 94.4% white, and 13.9% Latino
- Mean age of seizure onset was 5.14m (range 2.04-12.0m)
- All patients with ≥1 current convulsive seizure type and 86.1% (n=31) with current generalized tonic-clonic seizures
- Patients took a mean=3.5 (SD 1.56) ongoing anti-seizure therapies at BL; clobazam was most common (63.9%, n=23)
- Across 4-week BL, median convulsive seizure frequency= 10.0/28 days (95% CI, 5.00-16.0, n=26), including 24 patients who had generalized tonic-clonic seizures with median= 7.23/28 days (95% CI, 4.00-12.0)

VABS-III and BSID-III: Change in Raw Scores Baseline to Month 12

VABS-III Subdomain	Estimated LSM (n = 25)	95% CI	P-value	Significant covariates
Receptive communication	2.540	0.477 – 4.603	**0.0162**	None identified
Expressive communication	0.243	-2.086 – 2.572	0.8366	None identified
Interpersonal	1.542	-1.761 – 4.844	0.3573	Baseline social raw score
Gross motor	-2.273	-7.790 – 3.244	0.4138	None identified
Fine motor	1.549	-1.915 – 5.013	0.3770	None identified

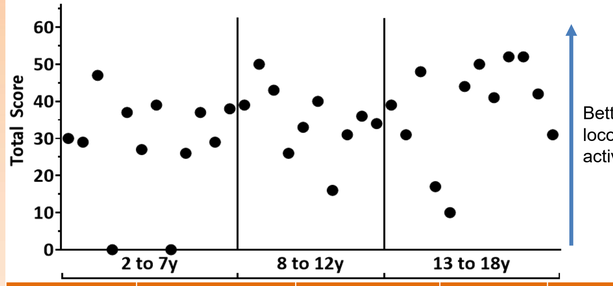
BSID-III Subtest	Estimated LSM (n = 10)	95% CI	P-value	Significant covariates
Cognitive	-3.398	-7.416 – 0.620	0.0954	Age squared; baseline cognitive score
Receptive communication	2.539	0.131 – 4.948	**0.0393**	Age; age squared
Expressive communication	3.567	-1.145 – 8.279	0.1305	Baseline seizure
Gross motor	0.829	-0.764 – 2.421	0.2937	None identified
Fine motor	0.303	-2.673 – 3.279	0.8361	Age squared

Data indicated significant improvement in receptive communication raw scores on both the VABS-III and BSID-III at Month 12 in the all-patient group enrolled in BUTTERFLY. Otherwise, no significant changes in key subdomains or subtests were identified in the all-patient group at Month 12.

Statistical Methods

Outcomes across assessments were analyzed using mixed model repeated measures with AR(1) covariance structure. Patients' age, weight, onset age of first convulsive seizure, visit time from screening, baseline assessment score, baseline seizure frequency, and seizure frequency at each visit were included as covariates in the mixed-effects model.

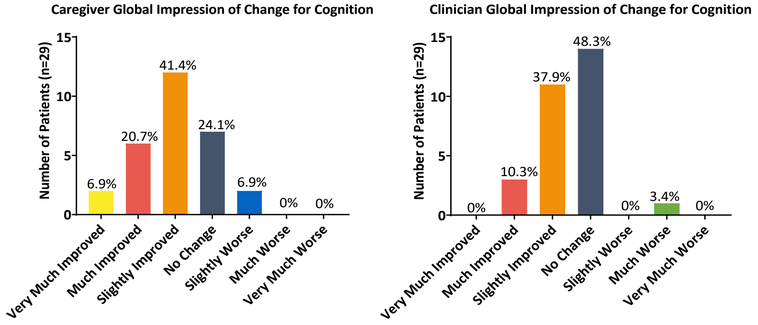
GILLETTE FAQ: Baseline Total Score and Change in Total Score at Month 12



Gillette Functional Assessment Questionnaire (FAQ) Total Scores range from 0 to 66; most patients performed in the dynamic range of the scale
No significant change in Gillette FAQ total scores were identified in the all-patient group at Month 12.

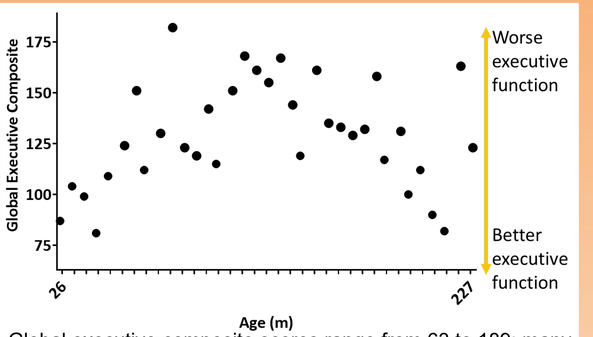
Test	Estimated LSM	95% CI	P-value	Significant covariates
Gillette FAQ	-0.021	-2.451 – 2.493	0.9863	Weight; log(age); log(baseline)

Caregiver and Clinical Global Impression of Change at Month 12



Most caregivers and clinicians reported no change to slightly improvement of patients in overall clinical status focused on cognition at Month 12. Seizure frequency and age were significant covariates.

BRIEF-P: Baseline Composite Scores



Global executive composite scores range from 63 to 189; many patients scored on the higher end which suggests difficulty with executive function.

BRIEF-P: Change in Scores Baseline to Month 12

BRIEF-P Index/ Composite	Estimated LSM (n = 26)	95% CI	P-value	Significant covariates
Inhibitory Self-Control Index	-0.146	-3.287-2.995	0.9268	Baseline ISCI score
Flexibility Index	0.530	-1.589- 2.649	0.6215	Baseline flexibility score
Emergent Metacognition Index	-1.556	-4.794-1.683	0.3436	Baseline EMI score; age*
Global Executive Composite	0.603	-4.890-6.096	0.8283	Baseline GEC score

No significant changes in summary index or composite scores were identified in the all-patient group at Month 12.
*Marginal significance (P>0.05).

Summary

- BUTTERFLY includes patients with DS aged 2-18y with documented mutation in the *SCN1A* gene
- Previous interim analysis showed a gap in adaptive and intellectual functioning between patients with DS and neurotypical children as assessed by the VABS-III and BSID-III (not shown; Sullivan et al 2022)
- Data indicated significant improvement in receptive communication raw scores on both the VABS-III and BSID-III at Month 12 in the all-patient group with no significant change in other key subdomains or subtests
- Most patients performed in the dynamic range of Gillette FAQ at BL with no significant change in total scores for the all-patient group at Month 12
- Many patients performed on the higher end of the BRIEF-P global executive composite scale suggesting difficulties with executive function with no significant change in summary index or composite scores for the all-patient group at Month 12
- Most caregivers and clinicians rated patients as not changed to slightly improved at Month 12 on the global impression scale adapted for cognition
- Data, including lack of significant change at Month 12, will inform these outcomes in future DS studies

BSID-III: Bayley Scales of Infant Development-III; BRIEF-P: Behavior Rating Inventory of Executive Function-Preschool Version; VABS-III: Vineland Adaptive Behavior Scales-III; LSM: Least-squares mean; CI: Confidence Interval

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