24-Month Analysis of BUTTERFLY

A Prospective, Observational Study to **Investigate Seizures and Comorbidities** in **Children and Adolescents** with **Dravet Syndrome**

Poster P788

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BACKGROUND

- Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy caused primarily by sodium channel type 1 alpha subunit (*SCN1A*) gene variants[1]
- Patients with DS experience refractory seizures along with significant cognitive and behavioral comorbidities[2,3]
- Despite treatment, 90% of children and adolescents experience uncontrolled seizures[4]
- Intellectual, behavioral, motor, and speech problems are common in patients with DS[2,3]
- **The BUTTERFLY study aims to assess the impact of DS on adaptive functioning and neurodevelopment over two years in patients receiving standard of care treatment with the best available antiseizure medications**

METHODS

- BUTTERFLY was a multicenter, US-based, longitudinal, prospective, observational study (**Figure 1**)
- Patients participating in BUTTERFLY received standard of care treatment with the best available antiseizure medications

Figure 1. Study design

Key inclusion criteria
- Age 2–18 years
- DS diagnosis with documented variant in *SCN1A* gene

Key exclusion criteria
- Gain-of-function *SCN1A* variant
- Current treatment with sodium channel blockers

	Visit 1 Baseline	Visit 2 Month 3	Visit 3 Month 6	Visit 4 Month 12	Visit 5 Month 18	Visit 6 Month 24
Vineland-3	✓	✓	✓	✓	✓	✓
BSID-III/WPPSI-IV	✓	✓	✓	✓	✓	✓
Gillette FAQ	✓	✓	✓	✓	✓	✓
BRIEF-P	✓	✓	✓	✓	✓	✓
CaGI-C/CGI-C		✓	✓	✓	✓	✓

Primary objective: Neurodevelopmental status (Vineland-3, BSID-III, WPPSI-IV) from baseline to Month 24

Secondary objective: Number of countable convulsive seizures per 4-week period before visits; change from baseline in overall clinical status (CaGI-C/CGI-C), locomotor skills (Gillette FAQ), and executive function (BRIEF-P)

BRIEF-P, Behavior Rating Inventory of Executive Function – Preschool Version; BSID-III, Bayley Scales of Infant Development, Third Edition; CaGI-C, Caregiver Global Impression of Change for Cognition; CGI-C, Clinical Global Impression of Change for Cognition; Gillette FAQ, Gillette Functional Assessment Questionnaire; Vineland-3, Vineland Adaptive Behavior Scales, Third Edition; WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition.

- Average change over time across the clinical measures was assessed using disease progression models
- Patients' age at enrollment, age at seizure onset, sex, body mass index, *SCN1A* genotype, baseline scores, and baseline convulsive seizures were tested as covariates in mixed-effects models

Key Findings

1. **Compared to neurotypical peers, adaptive functioning and neurodevelopment in patients with DS generally plateaued with a widening developmental gap over time**
2. **Seizure rates over 24 months remained high despite treatment with standard of care antiseizure medications**
3. **These findings support the urgent need for disease-modifying therapies addressing the genetic cause of DS to improve long-term outcomes**

RESULTS

Baseline characteristics

- BUTTERFLY patients experienced an average of 14.3 seizures/28 days despite receiving best available antiseizure medications (**Table 1**)
- Overall, patients reported a mean (range) of 3.5 (0–7) ongoing seizure therapies at baseline
- Most common ongoing antiseizure medications included clobazam (69.4%), fenfluramine (44.4%), stiripentol (38.9%), valproic acid (38.9%), cannabidiol (33.3%), and levetiracetam (22.2%)

Table 1. Summary of baseline characteristics and patient demographics

Parameter	2–7 years (n=12)	8–12 years (n=12)	13–18 years (n=12)	All enrolled (N=36)
Gender, n (%)				
Female	5 (41.7)	7 (58.3)	10 (83.3)	22 (61.1)
Male	7 (58.3)	5 (41.7)	2 (16.7)	14 (38.9)
Race, n (%)				
White	11 (91.7)	12 (100.0)	11 (91.7)	34 (94.4)
Asian	1 (8.3)	0 (0.0)	0 (0.0)	1 (2.8)
Other	0 (0.0)	0 (0.0)	1 (8.3)	1 (2.8)
Baseline convulsive seizure frequency per 28 days*				
Mean (SD)	7.9 (6.2)	13.6 (8.4)	21.6 (23.5)	14.3 (15.6)

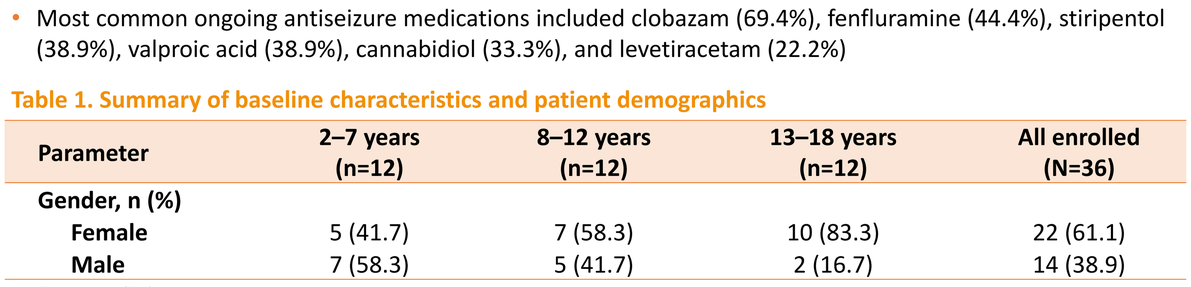
*Number of patients for baseline convulsive seizure frequency were n=9 (2–7 years), n=8 (8–12 years), n=9 (13–18 years), and n=26 (all enrolled).

Neurodevelopmental assessments

Adaptive behavior: Vineland-3

- Disease progression modeling indicated no improvements in Expressive Communication, Personal Skills, Gross Motor, or Fine Motor through Month 24, with statistically significant improvements indicated only in Receptive Communication (*P*=0.0189; n=32) and Coping Skills (*P*=0.0114; n=32) (**Figure 2**)
- Overall, comparisons between BUTTERFLY patients and neurotypical peers revealed a substantial neurodevelopmental gap that widened over time
- Baseline score, but not baseline seizure frequency, was a significant covariate across all analyzed subdomains

Figure 2. Trajectories for Vineland-3 subdomains Receptive Communication and Coping Skills in patients with DS and neurotypical peers



Growth scale values obtained from Vineland-3 were used for modeling disease progression. Modeling accounted for patients with DS who were assessed at baseline and at least one post-baseline visit. Progression for neurotypical peers was plotted using normative tables from the Vineland-3 manual that show correlations between age equivalents and growth scale values. *P*-values are provided for statistically significant changes.

Development across cognitive, language, and motor domains: BSID-III

- Disease progression modeling did not detect statistically significant changes in any BSID-III subtests through Month 24 (all *P*'s>0.21, n=10–13)
- The progression of BUTTERFLY patients in the BSID-III subtests diverged substantially compared to their expected progression in neurotypical peers starting from the same mean developmental age-equivalent level

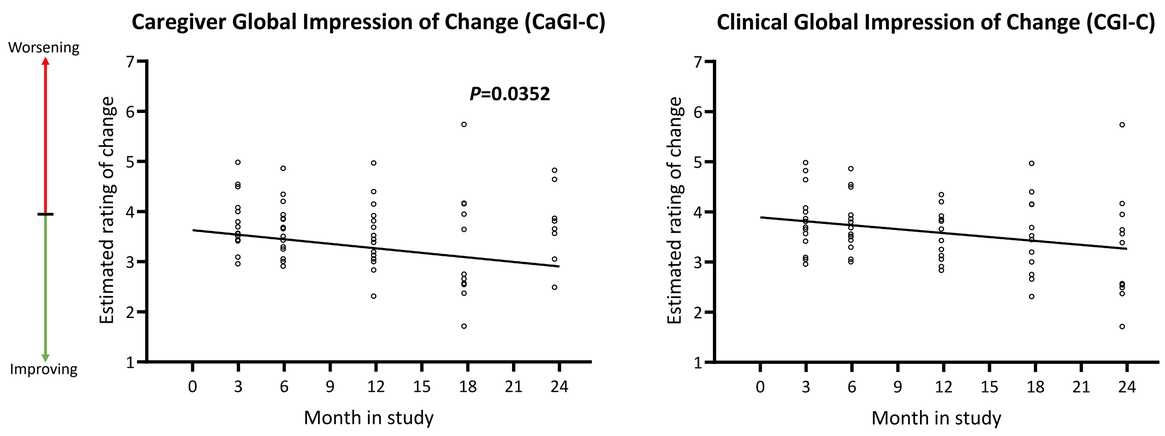
General intellectual functioning: WPPSI-IV

- Disease progression modeling for WPPSI-IV subtests indicated no statistically significant changes across any of the subtests through Month 24 (all *P*'s>0.12; n=9–11)

Overall clinical status

- Disease progression modeling indicated a statistically significant improvement in CaGI-C (*P*=0.0352; n=14), but not in CGI-C (*P*=0.3006; n=14) (**Figure 3**)
- Mean CaGI-C and CGI-C scores at the end of Month 24 were 3.26 and 2.90, respectively, indicating "slightly improved"
- Baseline convulsive seizure frequency was predictive of clinical status as measured by CaGI-C and CGI-C, with high baseline convulsive seizure frequency correlating with less improvement in overall clinical status

Figure 3. Disease progression modeling of overall clinical status

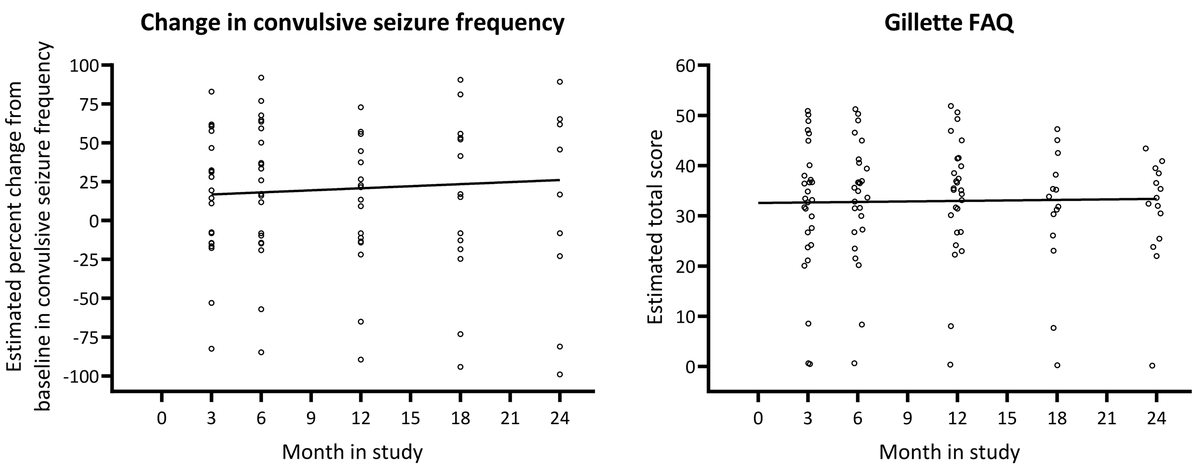


For both assessments, change was scored on a 7-point scale with improvement ranging from "very much improved" (scored as 1) to "very much worse" (scored as 7). *P*-values are provided for statistically significant changes.

Convulsive seizure frequency, locomotor skills, and executive functioning

- Disease progression modeling indicated no significant change in convulsive seizure frequency through Month 24 (*P*=0.6280; n=23) (**Figure 4**)
- Disease progression modeling indicated no significant changes in locomotor skills (Gillette FAQ; *P*=0.5707; n=32) (**Figure 4**) or executive functioning (BRIEF-P; *P*=0.8867 for BRIEF-P global executive composite; n=33) through Month 24

Figure 4. Disease progression modeling of convulsive seizure frequency and Gillette FAQ



Disease progression modeling accounted for patients with DS who were assessed at baseline and at least one post-baseline visit.

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