

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

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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

Methods

- 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/4 weeks before visits
- Change from BL:

- Overall clinical status
- Quality of life
- Executive function

Inclusion Criteria

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

Exclusion Criteria

- Gain-of-function *SCN1A* gene mutations
- Treatment with sodium channel blocker

- Scan QR code for other Inclusion and Exclusion Criteria

This interim analysis includes data available following completion of visit 2 (3m; 01APR2021) by all enrolled patients.

Baseline Demographics

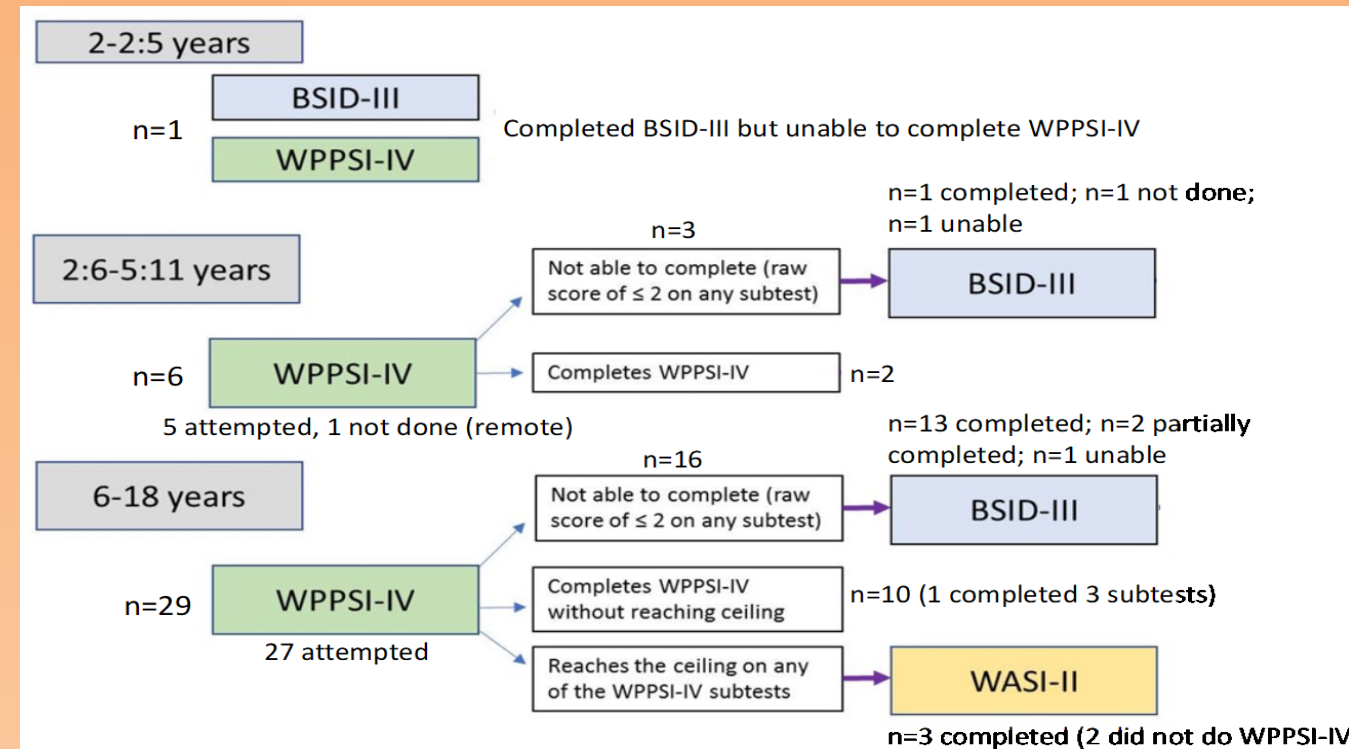
- n=12/group: 2-7, 8-12, and 13-18y
- 61% female, 94% white, and 14% Latinx
- Mean age of seizure onset was 4.8m (range 2.4-12m)
- 100% reported current convulsive seizure type and 75% (n=27) reported current non-convulsive seizure type
- Patients took a mean=3.5 (SD 1.63) ongoing anti-seizure therapies at BL; most common was clobazam (67%, n=36)
- Across 4-week BL, mean convulsive seizure frequency=14.4/28 days (95% CI 8.1—20.7, n=26), including 24 patients who had generalized tonic-clonic seizures with mean=9.1/28 days (95% CI 5.5-12.7)

References: Dravet C, et al. *Epilepsia*. 2011;52(suppl 2):3-9; Lagae L, et al. *Dev Med Child Neurol*. 2018;60:63-72; Ragona F, et al. *Epilepsia*. 2011;52:386-392; Genton P, et al. *Epilepsia*. 2011;52(suppl 2):44-49; Brown A, et al. *Epilepsy Behav*. 2020;112:107-319.

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Neurodevelopmental Assessments Progression

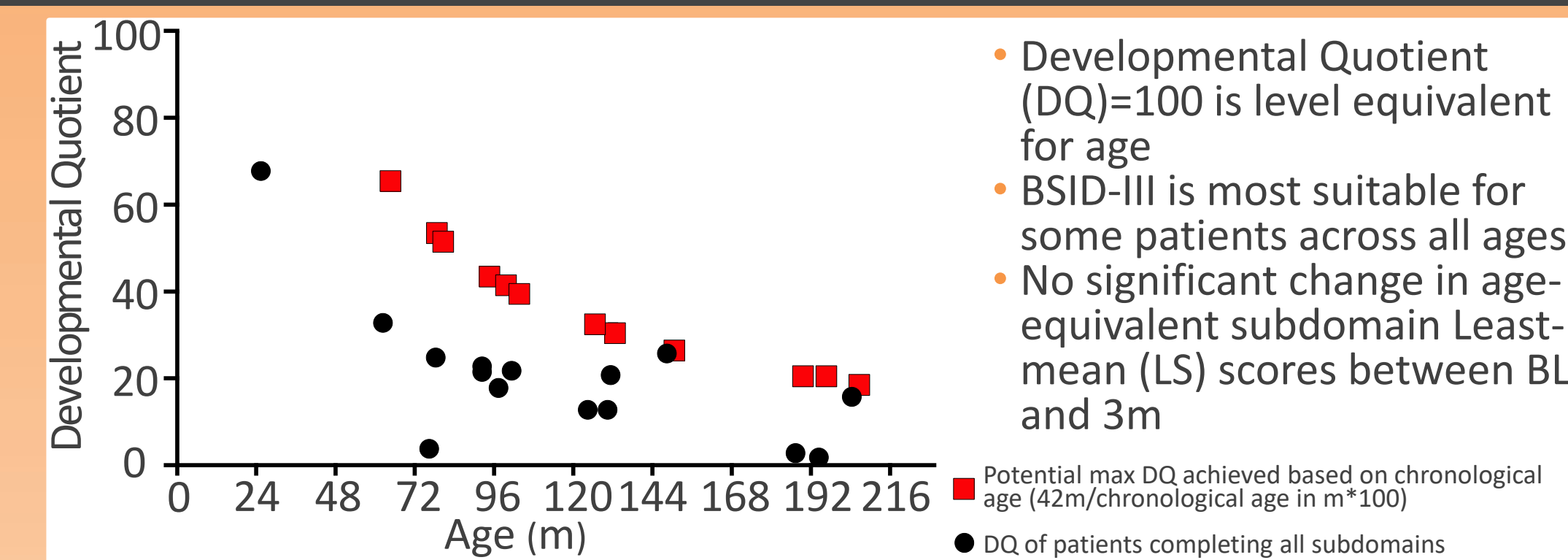
BSID-III: Bayley Scales of Infant Development
WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence
WASI-II: Wechsler Abbreviated Scale of Intelligence
VABS-III: Vineland Adaptive Behavior Scales
 Details are in QR code



Age-Equivalent Scores

	LS Mean Change BL -3m	95% CI	P-value
Cognitive	-1.89	-4.59, 0.82	0.1425
Receptive Communication	0.00	-4.78, 4.78	1.0000
Expressive Communication	3.88	-4.20, 11.95	0.2849
Gross Motor	0.33	-1.12, 1.78	0.5579
Fine Motor	1.13	-2.78, 5.03	0.5075

BSID-III



VABS-III

Raw Scores	Communication									Daily Living Skills								
	Receptive			Expressive			Written			Personal		Domestic		Community				
	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI			
2-7y	12	44.4	34.70, 54.13	12	39.0	25.88, 52.12	10	5.7	2.76, 8.64	12	37.0	26.46, 47.54	10	4.5	1.39, 7.61	10	6.5	3.26, 9.74
8-12y	12	43.3	31.63, 54.87	12	47.6	31.69, 63.48	12	14.5	7.10, 21.90	12	40.1	32.04, 48.13	12	3.7	1.02, 6.31	12	9.8	4.82, 14.68
13-18y	11	47.7	35.34, 60.11	11	61.2	40.27, 82.10	11	20.1	8.41, 31.77	11	59.2	37.71, 80.65	11	13.2	4.18, 22.18	11	21.4	7.14, 35.58
Max Score		78			98			76		110		60		116				

Raw Scores	Socialization						Motor Skills								
	Interpersonal			Play & Leisure			Coping			Gross			Fine		
	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI
2-7y	12	35.3	28.50, 42.00	12	22.4	16.05, 28.78	12	21.3	16.38, 26.29	12	46.8	32.68, 60.82	12	29.3	19.86, 38.64
8-12y	12	32.0	23.81, 40.19	12	19.3	9.81, 28.85	12	15.0	8.82, 21.18	9	65.6	54.54, 76.58	8	33.8	26.51, 40.99
13-18y	11	48.7	32.52, 64.93	11	31.7	17.05, 46.41	11	26.8	16.10, 37.53	8	64.8	47.75, 81.75	8	42.4	25.38, 59.37
Max Score		86			72			66		86		86			

- Mean subdomain raw scores show stability to slight increase from younger to older ages
- No significant change in age-equivalent subdomain scores between LS mean BL and 3m

WPPSI-IV

Raw Scores	Information			Similarities			Block Design			Matrix Reasoning			Picture Memory			Bug Search		
	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI
2-7y	1	13.0	-	1	4.0	-	1	12.0	-	1	13.0	-	1	8.0	-	1	6.0	-
8-12y	3	11.3	-1.17, 23.84	3	5.3	-4.71, 15.37	3	11.0	-10.66, 32.66	3	7.3	4.46, 10.20	3	8.3	2.08, 14.58	3	9.0	-3.91, 21.91
13-18y	7	14.6	8.58, 20.56	6	16.0	4.28, 27.72	7	15.6	8.33, 22.81	6	11.8	6.34, 17.32	7	10.9	5.45, 16.26	6	14.8	5.02, 24.64
Max Score		29			40			34			26			35			66	

Raw Scores	LS Mean Change from BL - 3m	95% CI	P-value
Information	0.43	-2.51, 3.37	0.7230
Similarities	0.71	-2.28, 3.70	0.5661
Block Design	2.14	-2.05, 6.33	0.2456
Matrix Reasoning	0.29	-3.17, 3.75	0.8403
Picture Memory	-0.71	-6.62, 5.19	0.7685
Bug Search	-0.71	-7.27, 5.84	0.7905

- More patients in older groups reliably completed the WPPSI-IV
- No significant change in raw component scores between BL and 3m (age-equivalent scores not calculated)

Conclusions

- VABS-III, BSID-III, and WPPSI-IV (4:0-7:7) are appropriate for assessing neurodevelopment and adaptive behavior in patients with DS
- Gap in overall intellectual development and adaptive function between patients and neurotypical children appears to widen with age
- Based on mean VABS-III scores across age groups and more patients in older groups completing WPPSI-IV, some patients appear to gain neurodevelopmental and adaptive function skills, though magnitude and rate are low
- VABS-III, BSID-III, and WPPSI-IV show relatively low intra-patient variability and no significant change from BL to 3m
- Current data suggest these scales may be useful for clinical studies in DS

