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

Joseph Sullivan[1], Elaine Wirrell[2], Kelly G Knupp[3], Muhammad Zafar[4], Robert Flamini[5], Dillon Chen[6], Pam Ventola[7], Javier Avendaño[8], Charlene Brathwaite[8], Carrie Condon[8], James Stutely[8], Nancy Wyant[8], Kimberly A Parkerson[8], Barry Ticho[8]

[1]UCSF; [2]Mayo Clinic; [3]Children's Hospital Colorado; [4]Duke University Hospital; [5]Panda Neurology; [6]UCSD; [7]CogState; [8]Stoke Therapeutics

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

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 in *SCN1A* gene

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

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

Scan QR code for additional study information

BASELINE DEMOGRAPHICS

- n=12/group: 2-7, 8-12, and 13-18y
- 61% female, 94% white, and 14% Latino
- Mean age of seizure onset was 5.1m (range 2-12m)
- All patients with ≥1 current convulsive seizure type and 86% (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 (64%, n=23)
- Across 4-week BL, median convulsive seizure frequency=10.0/28 days (95% CI 5.0-16.0, n=26), including 24 patients who had generalized tonic-clonic seizures with median=7.2/28 days (95% CI 4.0-12.0)

VABS-III and BSID-III

VABS-III Age-equivalent Scores (All Age Groups)

Key Subdomains	LS Mean Change from BL to 12m (in m)*	95% CI	p-value
Receptive Communication	5.49	0.56, 10.41	0.030*
Expressive Communication	2.37	-0.10, 4.85	0.060
Interpersonal Relationships	2.99	-1.22, 7.20	0.16
Gross Motor	1.90	-3.24, 7.05	0.45
Fine Motor	3.59	-1.93, 9.11	0.19

n=24-36 across key subdomains and visits except motor n=9-20

BSID-III Age-equivalent Scores (All Age Groups)

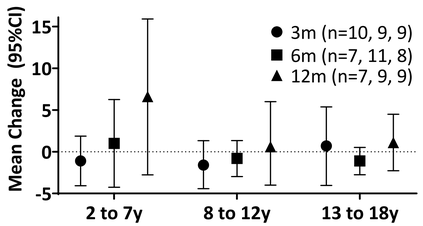
Subtests	LS Mean Change from BL to 12m (in m)*	95% CI	p-value
Cognitive	-1.08	-3.53, 1.37	0.37
Receptive Communication	3.68	0.48, 6.89	0.027*
Expressive Communication	3.23	-1.66, 8.11	0.18
Gross Motor	0.61	-1.12, 2.35	0.46
Fine Motor	0.45	-3.33, 4.23	0.80

n=6-17 across all subtests and visits

- Small improvements in receptive communication were observed from BL to 12m and appear driven by younger patients
- There was strong correlation (0.83-0.92) between BSID-III and VABS-III receptive communication scores at BL and 12m

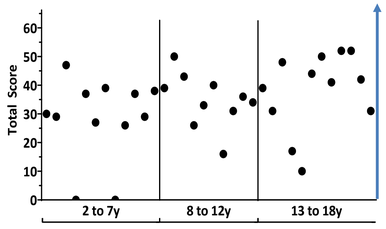
*Mixed model of repeated measures with visit as fixed effect and BL value as covariate

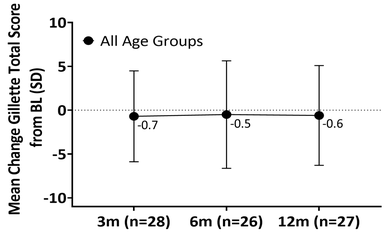
VABS-III Receptive Communication Raw Scores



BSID-III: Bayley Scales of Infant Development-III; VABS-III: Vineland Adaptive Behavior Scales-III; LS: Least squares

GILLETTE FAQ

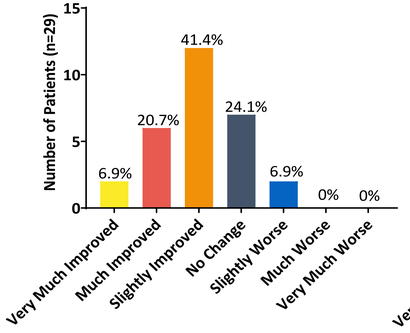




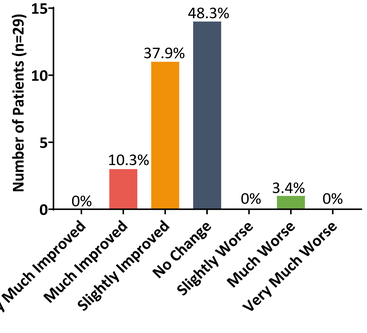
- Gillette Functional Assessment Questionnaire (FAQ) Total Scores range from 0 to 66; most patients performed in the dynamic range
- Minimal change was observed over 12m

GLOBAL IMPRESSION OF CHANGE – CAREGIVER AND CLINICIAN

Caregiver Global Impression of Change for Cognition

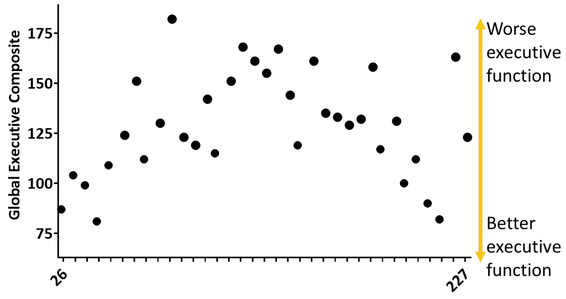


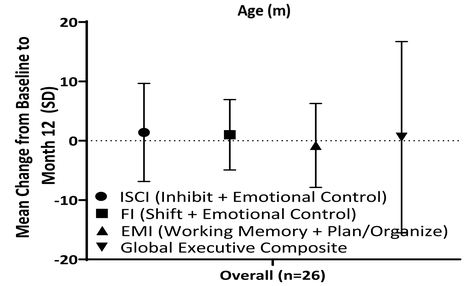
Clinician Global Impression of Change for Cognition



- Most caregivers and clinicians rated patients as no change to slightly improved over 12m

BRIEF-P





- Global executive composite scores range from 63 to 189; many patients scored on the higher end which suggests difficulty with executive function
- Little change was observed in mean BRIEF-P scores across all scales over 12m

BRIEF-P: Behavior Rating Inventory of Executive Function-Preschool Version

OVERALL SUMMARY

- BUTTERFLY includes patients with DS aged 2-18
- Small improvements in receptive communication over 12m were observed in patients and appear to be driven by younger patients
- Most patients performed in the dynamic range of Gillette FAQ at BL with little change observed in mean total scores over 12m
- Many patients performed on the higher end of the BRIEF-P global executive composite scale suggesting difficulties with executive function; little change was observed in mean BRIEF-P scores across all scales over 12m
- Most caregivers and clinicians rated patients as not changed to slightly improved at 12m on the global impression scale adapted for cognition
- Seizure frequency showed variability but no clear trends from BL to 12m (data not shown)
- Data, including lack of significant change over 12m, will inform measurements of these outcomes in future studies in DS

ACKNOWLEDGEMENTS

Study is supported by Stoke Therapeutics. We thank investigators, health care providers, research staff, patients, and caregivers who participated in this study.

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BUTTERFLY
An observational study of Dravet Syndrome patients

BUTTERFLY KEY STUDY CRITERIA

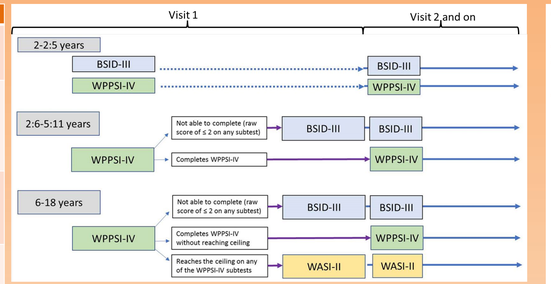
Key Inclusion Criteria
- Aged 2-18y (inclusive)
- DS diagnosis with documented mutation of *SCN1A* gene
- Diagnosis of DS as defined by: Onset <12 months of age with recurrent seizures (focal motor, hemiconvulsive, or generalized tonic-clonic); No history of causal MRI lesion; No other known etiology; Normal development at seizure onset

Key Exclusion Criteria
- Gain-of-function *SCN1A* gene mutations
- Treatment with sodium channel blocker as maintenance treatment
- Clinically significant medical condition(s) other than epilepsy

NEURODEVELOPMENTAL ASSESSMENTS

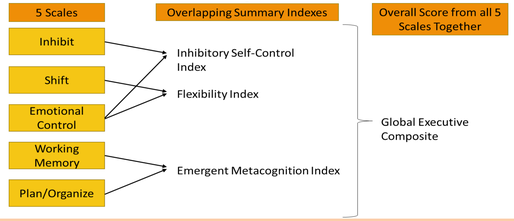
Assessments	Rater	Details
BSID-III: Bayley Scales of Infant Development, 3rd Edition	Neuropsychologist directly examining patient	• Assesses development across cognitive, language, and motor domains • Summary score is Developmental Quotient (DQ) • Designed for use from **birth to 3:6y (42 month)**
WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence, 4th Edition	Neuropsychologist directly examining patient	• Assesses general intellectual functioning • Designed for use from **age 2:6 to 7:7y**, through two test versions • **2:6 to 3:11y**: evaluates verbal comprehension, visual spatial, and working memory • **4:0 to 7:7y**: evaluates verbal comprehension, visual spatial, fluid reasoning, working memory, and processing speed
WASI-II: Wechsler Abbreviated Scale of Intelligence, 2nd Edition	Neuropsychologist directly examining patient	• Assesses general intellectual functioning through screening battery • Designed for use from age **6:0 to 90:11y** • Evaluates verbal comprehension and perceptual reasoning • Data not shown
VABS-III: Vineland Adaptive Behavior Scales, 3rd Edition	Interview of Caregiver by qualified rater	• Measures adaptive behavior (what patients do to function in daily life) across communication, daily living skills, socialization, motor skills, and maladaptive behavior • Summary score as Adaptive Behavior Composite (ABC) • Designed for use from **birth to age 90y**

NEURODEVELOPMENTAL ASSESSMENT STUDY FLOW

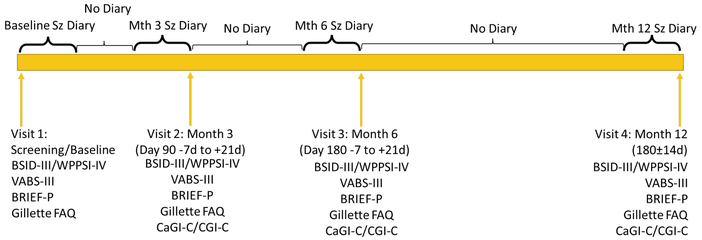


BRIEF-P OVERVIEW

- Standardized rating scale designed to be completed by parents, teachers or other caregivers to assess executive functioning in children aged 2 to 5y
- 63 items in 5 scales
- Lower scores indicate less difficulty with Executive Function; higher scores indicate more difficulty with Executive Function
- Used scale for all patients (i.e., out of range) based on expected developmental level



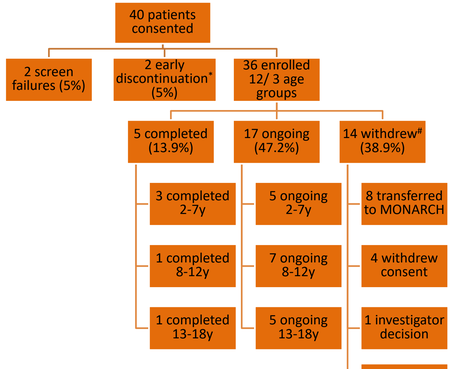
STUDY OVERVIEW THROUGH MONTH 12



Adaptive Behavior = VABS-III
Neurodevelopment = BSID-III/WPPSI-IV
Gait = Gillette FAQ
Executive Function = BRIEF-P
Overall Clinical Status = CGI/CaGI-C

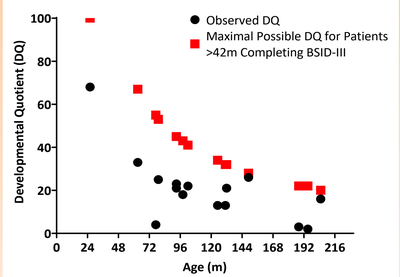
*diary data excluded if outside of specified visit windows; diary considered missing if <50% of period duration recorded (i.e. missing >14 days for 4-week period)

CONSORT FLOW DIAGRAM

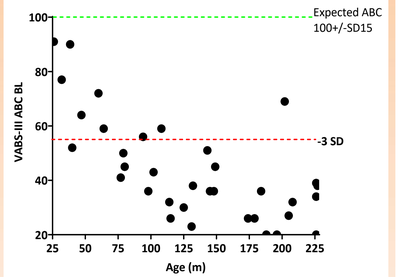


*Did not meet criteria for DS by The Epilepsy Study Consortium;
#5 patients withdrew prior to Visit 4 (Month 12)

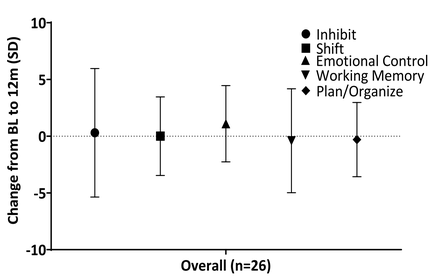
BASELINE BSID-III DQ



BASELINE VABS-III ABC



BRIEF-P



WPPSI-IV

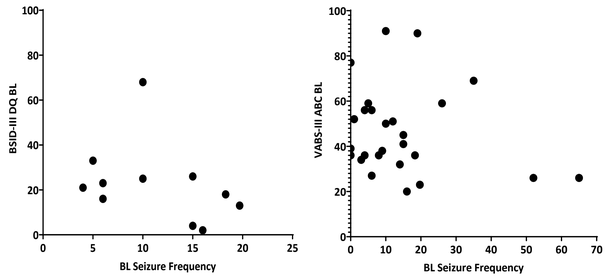
WPPSI-IV 12-month Raw Scores (All Age Groups)

Subtests	LS Mean Change from BL to 12-month (months)*	95% CI	p-value
Information	1.52	-1.20, 4.24	0.25
Similarities	4.21	0.17, 8.25	0.042*
Block Design	2.35	-0.64, 5.33	0.12
Matrix Reasoning	-0.62	-3.23, 1.99	0.62
Picture Memory	-0.48	-3.06 2.09	0.69
Bug Search	-0.71	-5.63, 4.20	0.76

n=7-11 across all components and visits

*Mixed model of repeated measures with visit as fixed effect and BL value as covariate. LS: Least squares.

BASELINE BSID-III DQ and VABS-III ABC VS. SEIZURE FREQUENCY



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