Observational Study to Investigate Cognition and Quality of Life in Children and Adolescents with Dravet Syndrome: Baseline Analysis of the BUTTERFLY Study

Joseph Sullivan[1], Muhammad Zafar[2], Robert Flamini[3], Kelly Knupp[4], Julie Ziobro[5], M. Scott Perry[6], Javier Avendaño[7], James Stutely[7], Pam Ventola[8], Elizabeth Merica[7], Charlene Brathwaite[7], Nancy Wyant[7], Kimberly Parkerson[7], Barry Ticho[7]

[1]University of California, San Francisco, CA, USA; [2]Duke University, Durham, NC, USA; [3]CIRCA, Atlanta, GA, USA; [4]Children's Hospital Colorado, Aurora, CO, USA; [5]University of Michigan, Ann Arbor, MI, USA; [6]Cook Children's Medical Center, Fort Worth, TX, USA; [7]Stoke Therapeutics, Bedford, MA, USA; [8]Cogstate Ltd. New Haven, CT, USA

BUTTERFLY
An observational study of Dravet Syndrome patients

BACKGROUND

- Dravet syndrome (DS) is a severe and progressive genetic epilepsy, beginning within the first year of life
- DS is characterized by high seizure frequency and severity, and >90% of patients suffer from comorbidities, including:
  - Intellectual and developmental disabilities
  - Motor and speech impairment
  - Behavioral problems
  - Sleep abnormalities
- Normal neurologic and cognitive function are typically reported in patients with DS up to age 2 years, but the proportion with intellectual disabilities increases, with almost all having intellectual impairment after 4 years of age
- Limited prospective long-term data exist on the clinical course of DS patients
- The BUTTERFLY observational study aims to evaluate change in non-seizure and seizure manifestations over 24 months in patients 2 to 18 years of age with DS

STUDY DESIGN

- Multicenter, longitudinal, prospective, observational study conducted in the United States
- Patients will be assessed at baseline and at 3, 6, 12, 18, and 24 months
- Approximately 36 patients will be enrolled, equally divided among age groups (2-7 years, 8-12 years, and 13-18 years of age)

PRIMARY OBJECTIVE:

- Evaluate neurodevelopmental status and change from baseline to 24 months

SECONDARY OBJECTIVES:

- Evaluate number of countable convulsive seizures per 4-week period before each study visit
- Evaluate change from baseline in overall clinical status
- Evaluate change from baseline in patients' quality of life
- Evaluate change from baseline in executive function

STUDY POPULATION

Inclusion Criteria

- Aged 2-18 years (inclusive)
- 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
- Documented pathogenic, likely pathogenic, or variant of uncertain significance in *SCN1A* gene
- ≥2 convulsive seizures in the 4 weeks prior to screening
- ≥2 prior treatments for epilepsy that were discontinued due to lack of seizure control or adverse event
- Receiving ≥1 anti-epileptic drug at a stable dose for ≥2 weeks

Exclusion Criteria

- Specific mutations of *SCN1A* gene demonstrated to cause gain-of-function
- Currently being treated with an anti-epileptic drug acting predominantly as a sodium channel blocker
- Clinically significant unstable medical condition(s) other than epilepsy

This poster presents the preliminary baseline patient characteristics and baseline neurodevelopmental data reported to date (14 August 2020)

REFERENCES AND ACKNOWLEDGMENT

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;112:107319.

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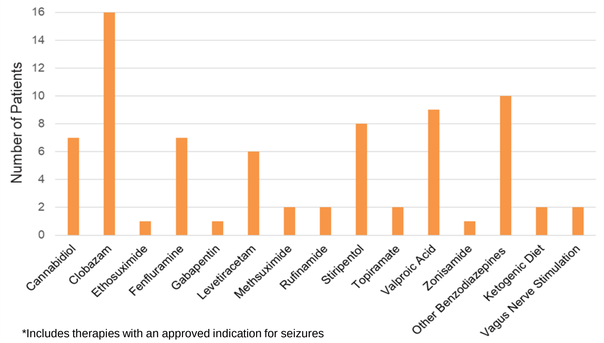
BASELINE RESULTS

Patient demographics and baseline anti-epileptic therapy

- As of 14 August 2020, 22 patients enrolled: 11 in youngest age group (2-7 years), 4 in 8-12 years group, and 7 adolescents (13-18 years)
- Females: 64%; White: 91%; Latinx: 14%
- 16 of 22 (73%) patients reported clobazam as baseline therapy (Figure)

Current Anti-epileptic Therapies at Baseline*

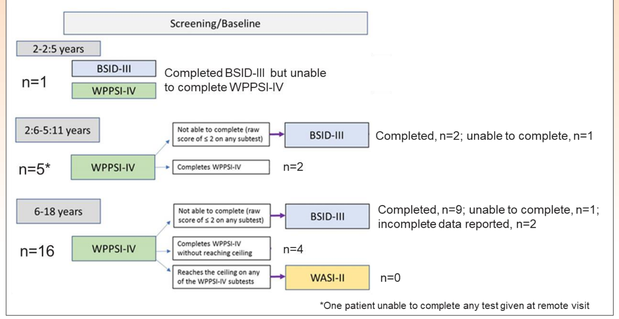


*Includes therapies with an approved indication for seizures

Neurodevelopmental Study Assessments

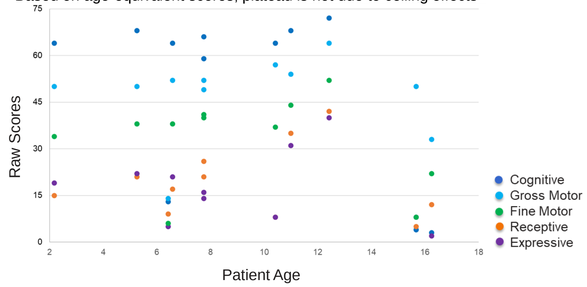
Assessments	Completer	Details
BSID-III: Bayley Scales of Infant Development, 3rd Ed	Patient	• Assesses development across cognitive, language, and motor domains • Designed for use from birth to 3:6 (42 months)
WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence, 4th Ed	Patient	• Assesses verbal and nonverbal intellectual functioning • Designed for use from age 2:6 to 7:7
WASI-II: Wechsler Abbreviated Scale of Intelligence, 2nd Ed	Patient	• Assesses verbal and nonverbal intellectual functioning • Designed for use from age 6:0 to 90:11
VABS-III: Vineland Adaptive Behavior Scales, 3rd Ed	Caregiver	• Measures adaptive behavior across communication, daily living skills, socialization, motor skills, and maladaptive behavior • Designed for use from birth to age 90 years

- At baseline, 11 patients completed BSID-III and 6 patients completed WPPSI-IV without floor or ceiling effects (1 completed WPSSI-IV version 2:6 to 3:11; 5 completed version 4:0 to 7:7 based on chronological age)



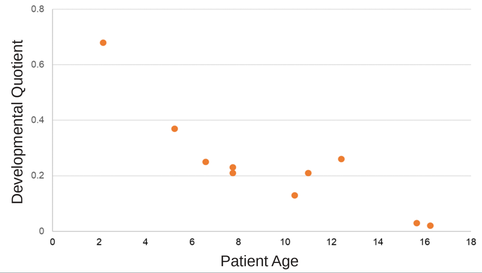
Baseline Bayley (BSID-III) Raw Scores

- 11 patients completed full cognitive, language, and motor assessments
- As a group, DS patients who complete the BSID-III appear to plateau in cognitive and gross and fine motor skills with age; there may be some acquisition of language skills
- Based on age-equivalent scores, plateau is not due to ceiling effects



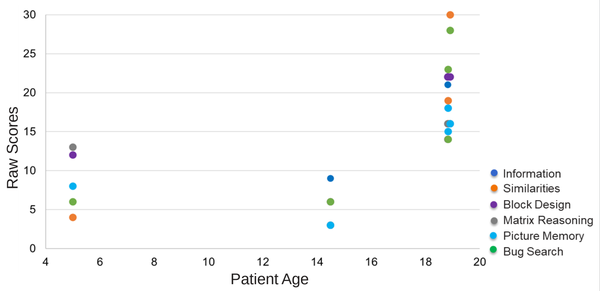
Baseline Bayley (BSID-III) Developmental Quotient

- 10 of 11 patients who completed BSID-III reported Developmental Quotients (DQ)
  - DQ is calculated as the ratio of mean age-equivalent score for all subtests divided by chronological age of patient x 100
- Consistent with an apparent plateau in raw scores, the gap in overall development (cognition, expressive and receptive communication, fine and gross motor skills) appears to widen with increasing age



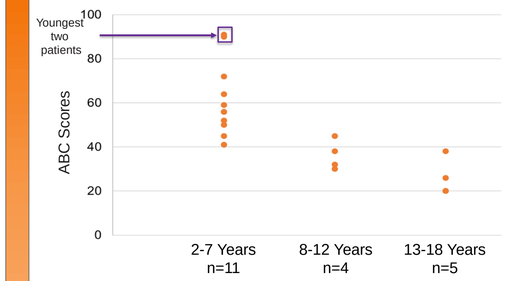
Baseline Wechsler (WPPSI-IV 4:0-7:7) Raw Scores

- 5 patients completed the WPPSI-IV 4:0-7:7
- Patient numbers are currently limited, but early data suggest that as a group, DS patients who complete WPPSI-IV 4:0-7:7 may acquire some new skills across intellectual domains with age



Baseline VABS-III Adaptive Behavior Composite (ABC)*

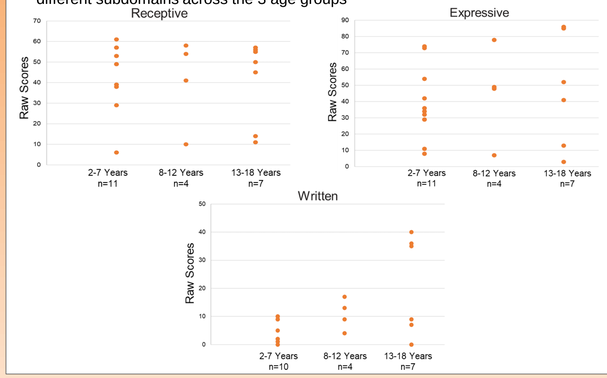
- 20 of 22 (100%) patients with baseline VABS-III assessments had ABC scores available (2 scores from 13-18 years age group were not reported)
- Relative gap in overall level of adaptive functioning appears to widen across the 3 age groups



*ABC score based on Communication, Daily Living, and Socialization domains and expressed relative to normative mean of 100

Baseline VABS-III Data

- 22 of 22 (100%) caregivers across all age groups completed baseline VABS-III
- Lowest scores were achieved in written communication and domestic and community daily living skills
- Large variability exists among patients in all 3 communication domains
- DS patients appear to plateau or show some acquisition of communication skills in different subdomains across the 3 age groups



BUTTERFLY Study: Baseline Data Conclusions

- Patients enrolled to date appear representative of patients with DS
- Majority of patients were able to complete either BSID-III or WPPSI-IV
  - These cognitive measures are appropriate for use in assessing neurocognition in patients with DS
- Patients with DS show substantially decreased neurocognitive abilities compared to children of same chronological age level despite use of multiple anti-epileptic therapies
- Collectively, gap in adaptive functioning and overall intellectual development appears to widen with age
- These data provide initial insights into the adaptive behavior and neurodevelopmental status of children and adolescents (2 to 18 years) with DS and may inform studies of future novel treatments for DS