KOL Webinar on DCCR for the Treatment of Prader-Willi Syndrome

February 4th 2021

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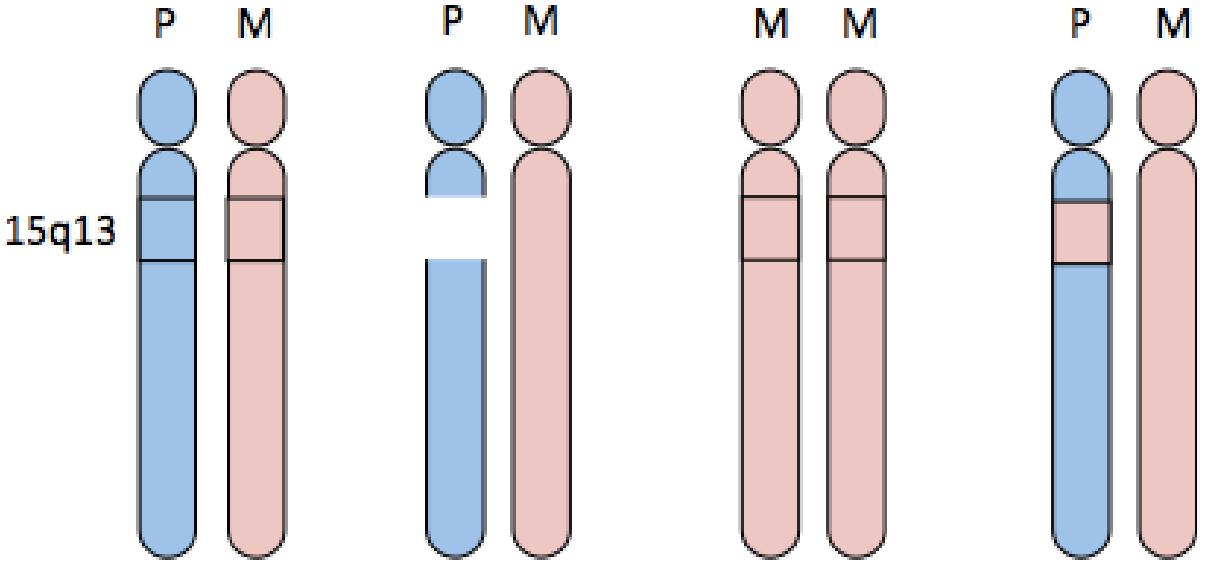
Prader-Willi Syndrome

Jennifer L Miller, MD
University of Florida
Pediatric Endocrinology

Prader-Willi syndrome

- Caused by lack of paternal contribution of Chromosome 15 q11.2-q13 region
- Prevalence= 1:15,000-1:30,000
- Decreased fetal movements, typically about 15% smaller for weight and length at birth than unaffected siblings
- Average age of diagnosis is 1.2 months

Prader-Willi syndrome : Genetic mechanisms



Prader-Willi syndrome

Phenotypic features include:

- FTT in infancy
- Early-onset weight gain
- Weight gain precedes hyperphagia
- Hypotonia
- Speech delay/language impairment
- Multiple endocrinopathies due to hypothalamic/pituitary dysfunction
- Variability in cognitive impairment
- Characteristic behaviors/OCD/anxiety

Progression to hyperphagia in PWS

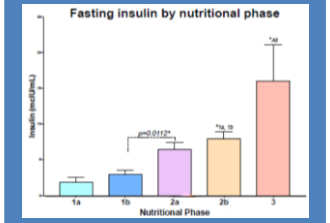
PWS Phase 1a/1b
Dysfunctional Hypothalamus
Hypotonia

Decreased central insulin & central IgF-1 receptors

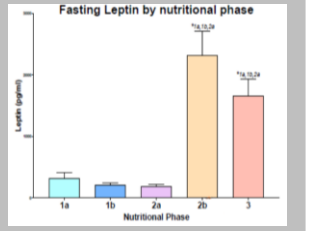
Abnormal Central Insulin Signaling

- Increased hepatic glucose output
- Increased insulin secretion

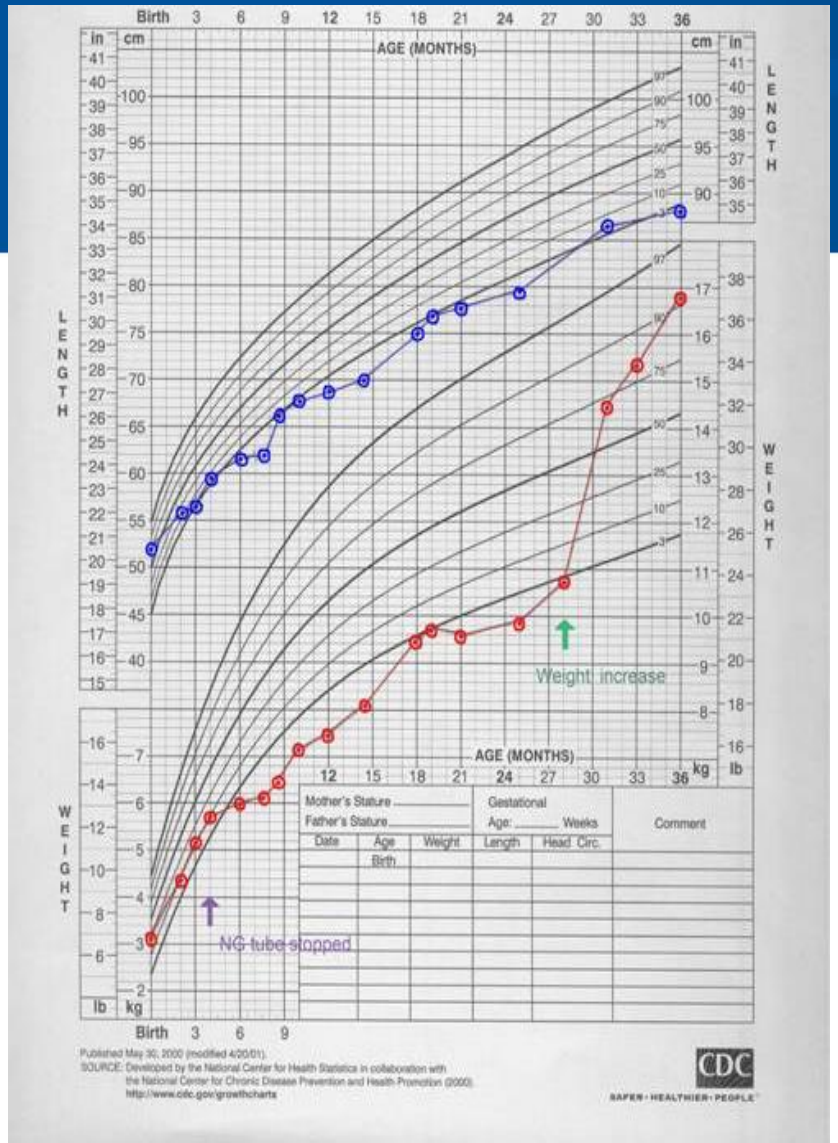
PWS Phase 2a
- Post prandial hyperinsulinema
- Increase in glucose uptake
- Increase in lipogenesis
- Weight gain



PWS Phase 2b
- Decreased insulin sensitivity
- Increased appetite
- Weight gain / obesity



PWS Phase 3
- Obesity, especially if food not controlled
- Low lean body mass to fat mass ratio
- Leptin resistance
- Decreased insulin sensitivity
- Hyperphagia


AGE (MONTHS)
LENGTH
WEIGHT
Weight increase
NG tube stopped
Mother's Stature
Father's Stature
Gestational Age: Weeks
Date
Age
Weight
Length
Head Circ.
Comment
Birth
Published May 30, 2000 (modified 4/20/01).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
CDC
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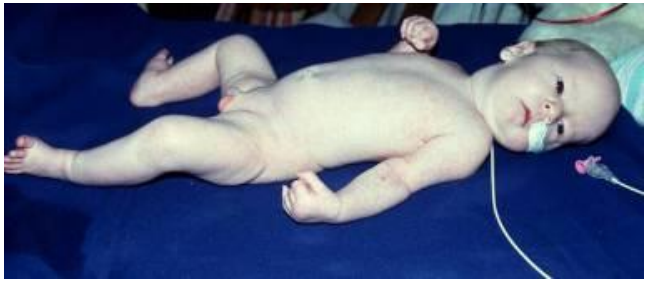

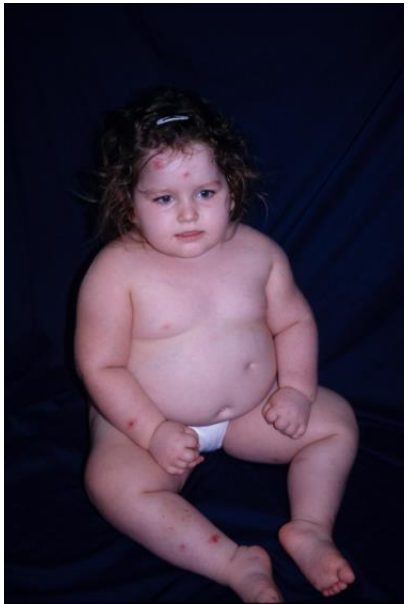

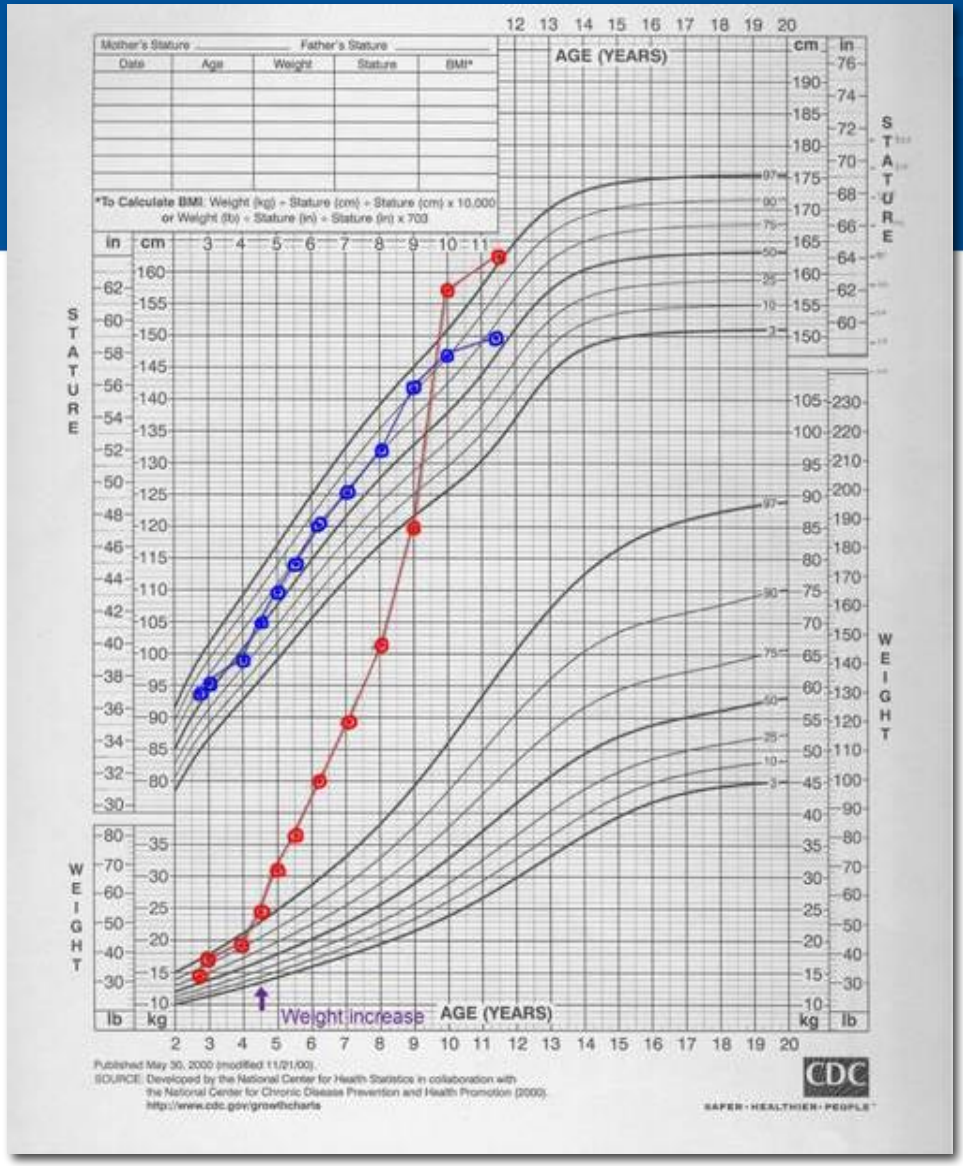
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
Weight increase
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
CDC
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PWS - Body Composition

- Ectopic accumulation of excess body fat
  - Higher total body fat
  - Higher subcutaneous fat and lower visceral fat than similarly obese controls
- Low lean body mass
  - Reduced muscle mass relative to controls with similar BMI
- Contributes to sedentary lifestyle

PWS - Behavioral Problems

- Hyperphagia
  - Constant food seeking, tantrums, meltdowns
- Obsessive compulsive behaviors
  - Self injurious behaviors
- Anxiety
  - Both food-related and non-food-related
- Autistic-spectrum like behaviors
- Aggressive behaviors are common, especially regarding food

PWS - Intellectual Disability

- Mild to moderate cognitive impairment
- Intellectual delay and learning problems apparent by school age
- Cognitive rigidity leading to behavior complications
- May be exacerbated by hypersomnia and food-related behaviors

PWS - Impact on Families

- Burden of care increases from childhood to adolescence and early adulthood, especially when they become hyperphagic
- Strain on family relationships
  - PTSD and behavioral complications among siblings
- Caregivers experience
  - Reduced sleep quality, frequent anxiety, depression and low mood
- Adversely impacts work, and economic opportunities for the family

The Burden

- Appetite typically increases gradually, and then becomes insatiable
- Even if kept thin with environmental controls, the appetite is all consuming
- Will seek and steal food, hide and hoard food, sneak out of home to try to get food, eat frozen food, raw food, food from garbage, non-food

Treatments

- Growth hormone is the only approved treatment
  - FDA-approved for growth failure
- Several other medications may be tried for symptomatic improvements:
  - Hormone replacement (sex steroids, thyroid hormone, etc)
  - Behavioral medications (SSRI's, stimulants)
- No medications approved for hyperphagia

Treatments

- Currently, most families treat the hunger/appetite in PWS by making the home a prison – and the rest of the family the wardens

The Impact of Covid

- The already complex clinical picture of PWS has been further complicated by the pandemic
- The transition to isolation and lack of typical activities is very evident
- FPWR's survey has captured the magnitude of the disruption

Impact of the COVID Pandemic on PWS Families: Results of a Survey

Theresa V. Strong, PhD

Director of Research Programs

FOUNDATION FOR PRADER-WILLI RESEARCH

www.fpwr.org

It takes a (very predictable) village…

- PWS families typically have built a network of support to navigate the challenges of PWS - may include 1:1 educational support; multiple therapies; structured social activities; respite care

- Individuals with PWS thrive on routine and structure, and have tremendous difficulty coping with transitions, unexpected change, and uncertainty.

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GLOBAL PRADER-WILLI SYNDROME REGISTRY

"Impact of COVID" Survey

The COVID pandemic has severely impacted the developmentally disabled population, disrupting education, social activities, and access to medical and supportive care.

We developed a survey in the Global PWS Registry to asses the pandemic's impact on the individual with PWS and their caregivers:

- Parent/caregiver reported data – report on peak of impact

This analysis includes responses:

- May – August 2020
- Age 4+
- US and UK

(n=322 families)

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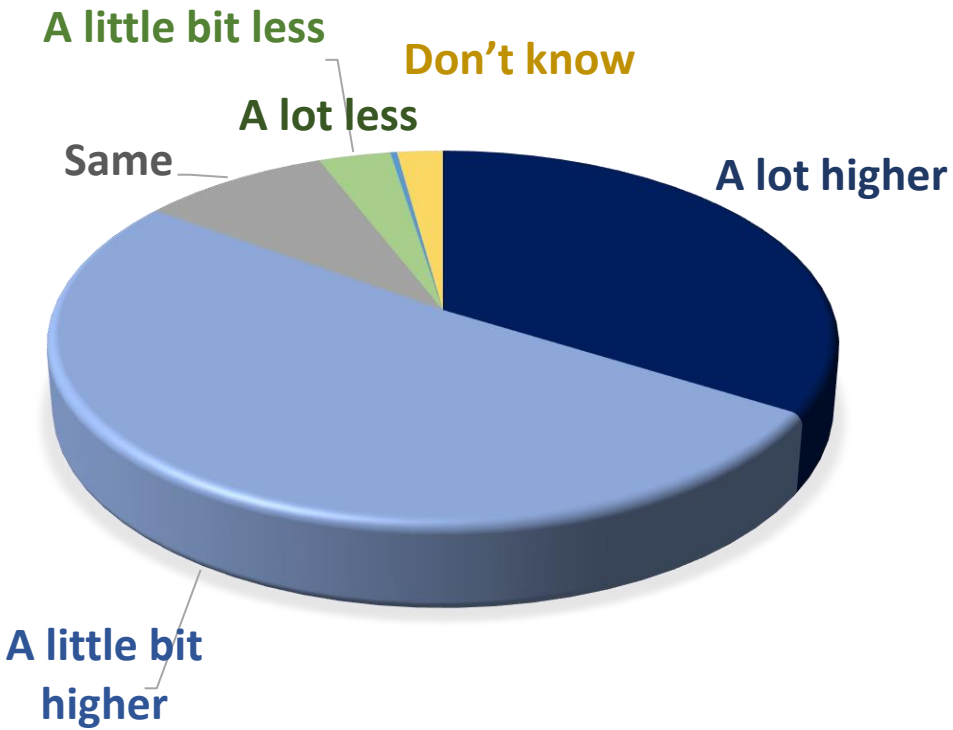
Caregiver stress is up; sleep is down

85% of caregivers report more stress

Biggest concerns

- My loved one with PWS will get sick with COVID-19
- I will get sick with COVID-19 and not be able to care for my loved one with PWS
- That the person with PWS is not receiving adequate educational support and will fall behind



35% report less sleep, while ~50% report the same amount of sleep

GLOBAL PRADER-WILLI SYNDROME REGISTRY

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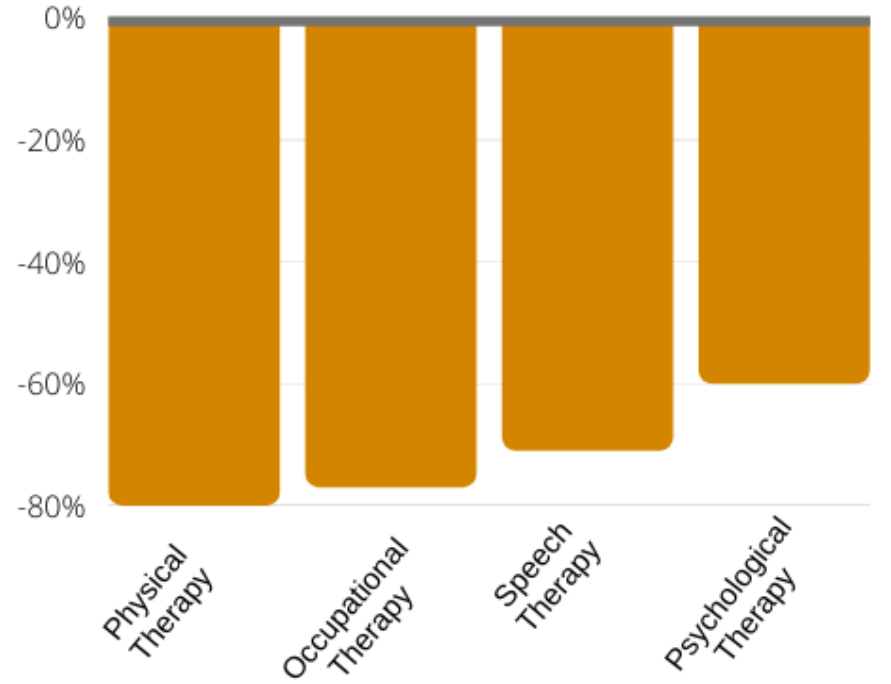
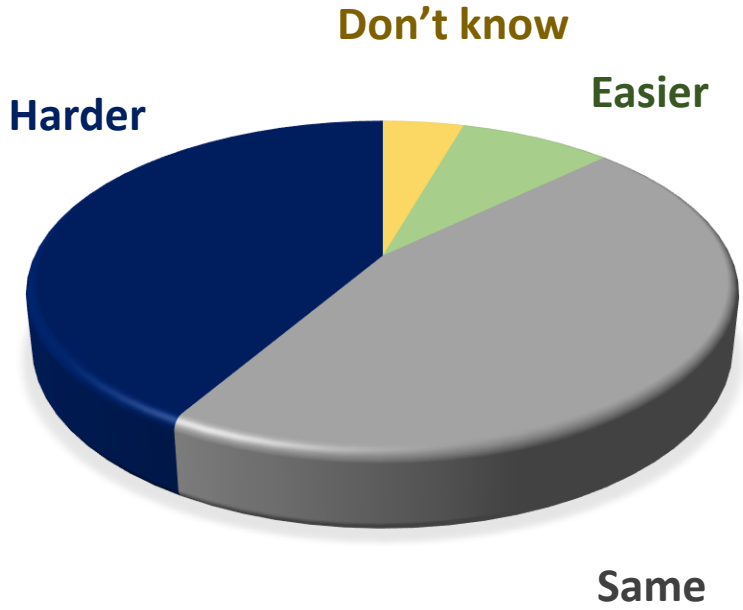
For the majority of families receiving therapies, access was temporarily reduced or eliminated.



Overall, behavior has been more difficult to manage



GLOBAL PRADER-WILLI SYNDROME REGISTRY

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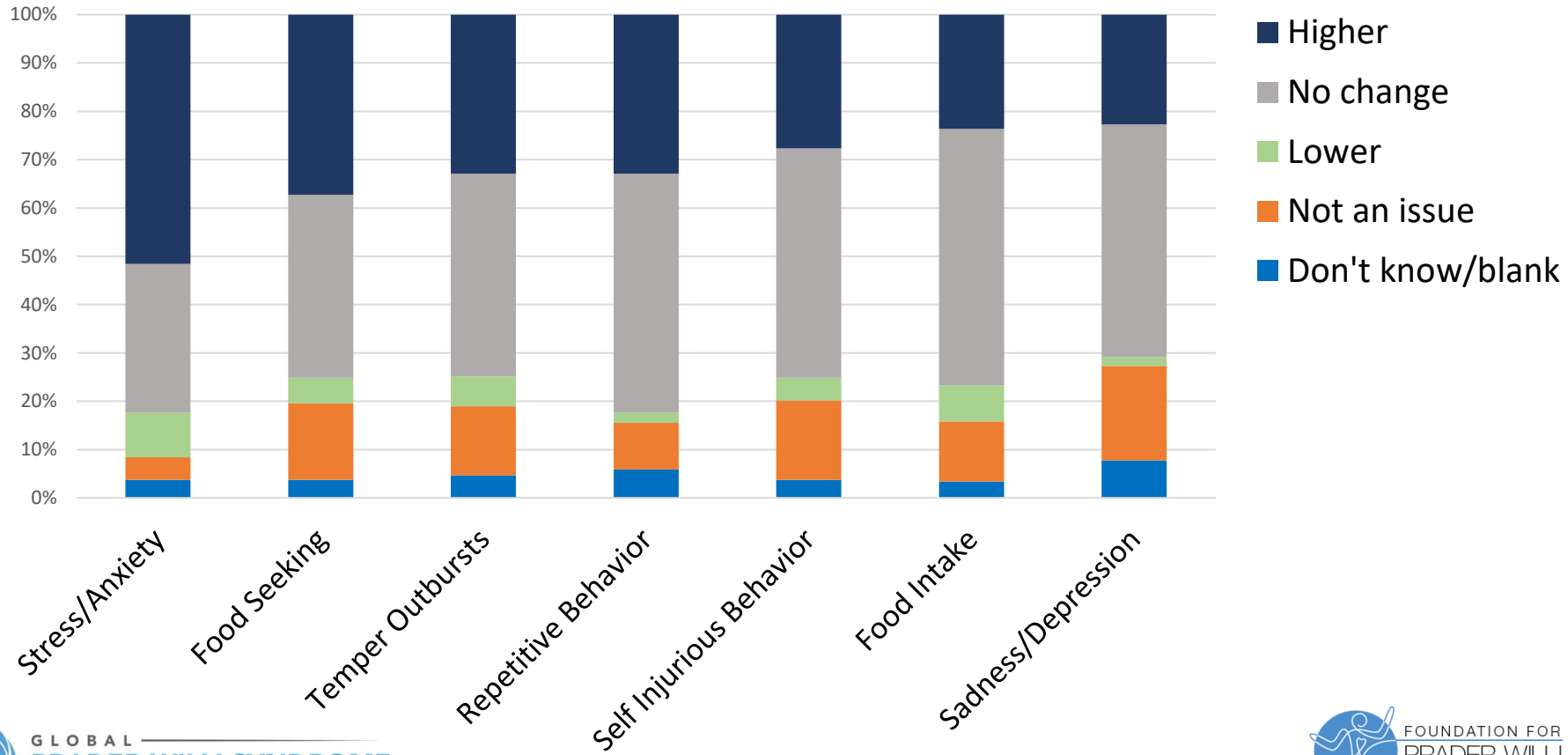
Change in behaviors for the person with PWS



GLOBAL PRADER-WILLI SYNDROME REGISTRY

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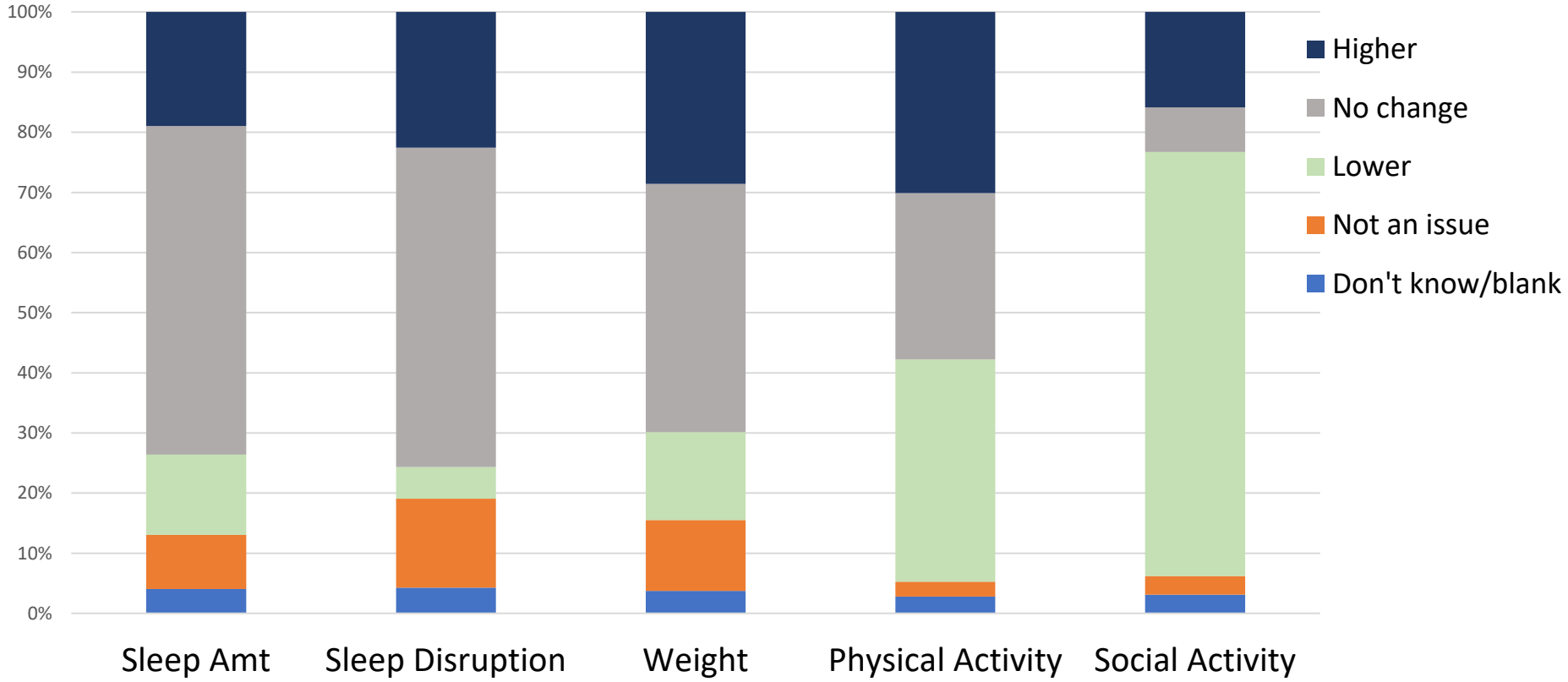
Change in sleep, weight, physical activity and social interaction



GLOBAL PRADER-WILLI SYNDROME REGISTRY

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Summary

- Individuals with PWS and their parents/caregivers experienced significant disruptions during to the COVID-19 pandemic
- Caregivers experienced increased stress as they took on additional responsibilities in schooling, therapies, exercise and as ‘activity coordinator’
- Decreased social opportunities, changes to routine, loss of structure and associated stress have manifested as increased behavioral challenges
- Parents cite stress associated with transition and uncertainty as particularly difficult for their loved ones with PWS

Impact of COVID-19 Pandemic on DESTINY PWS

February 4th 2021

Impact of COVID-19 Pandemic on DESTINY PWS

- Comprehensive analyses undertaken based on
  - Published statistical guidance from the FDA and from industry publications[1,2]
  - Published literature on impact of COVID-19 (COVID) pandemic on childhood psychiatric conditions[3]
  - FPWR Global Registry COVID Pandemic Impact survey[4]
- Expected that subjective endpoints more likely to be impacted
  - HQ-CT
  - Caregiver GI-C
  - PWS Profile (PWSP)
  - Others

[1] U.S. FDA. Guidance for Industry: Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency. June 2020.
[2] Meyer et al. Statistical Issues and Recommendations for Clinical Trials Conducted During the COVID-19 Pandemic. *Statistics in Biopharmaceutical Research*. 2020;12, 2020(4):399-411.
[3] Aman MG, Pearson DA. Challenges for Child and Adolescent Psychiatric Research in the Era of COVID-19. *J Child Adolesc Psychopharmacol*. 2020;30(5):280-284.
[4] Foundation for Prader-Willi Research. PWS Registry Data: Impact of COVID-19 on PWS Families. https://www.fpwr.org/blog/pws-registry-data-impact-of-covid-19-on-pws-families-infographic and unpublished data, January 2021.

Choice of March 1, 2020 as Cutoff

- C601
  - Last patient randomized in late January 2020
  - Last patient last visit late April 2020
  - Topline data received early June 2020
- COVID
  - Declared public health emergency January 31, 2020
  - National emergency declared March 1, 2020
- March 1, 2020 considered to be appropriate "pre-COVID" cutoff (including by other sponsors in PWS space)
  - 86 subjects (69%) completed C601 by March 1, 2020

C601 Primary and Key Secondary Endpoints

Primary Endpoint
Change from Baseline in Hyperphagia at Visit 7
Key Secondary Endpoints
Clinical Global Impression of Improvement at Visit 7 (CGI-I)
Change From Baseline in Body Fat Mass (DXA)
Caregiver Global Impression of Change at Visit 7 (Caregiver GI-C)

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C601 Primary and Key Secondary Endpoints

	All Data		Data through March 1, 2020	
Primary Endpoint	**DCCR (N = 82)**	**Placebo (N = 42)**	**DCCR (N = 80)**	**Placebo (N = 41)**
Change from Baseline in Hyperphagia at Visit 7	-5.94 (0.88)	-4.27 (1.15)	-6.64 (1.00)	-3.51 (1.28)
LS Mean Difference [DCCR-Placebo] (SE)	-1.67(1.29)		-3.13 (1.48)	
p-value	0.198		**0.037**	
Key Secondary Endpoints				
Clinical Global Impression of Improvement at Visit 7 (CGI-I)	**0.03**		**0.015**	
Change From Baseline in Body Fat Mass (DXA) at Visit 7	**0.03**		**0.004**	
Caregiver Global Impression of Change at Visit 7 (Caregiver GI-C)	0.41		**0.031**	

Analyses in this presentation are preliminary and may be subject to change.

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C601 HQ-CT Change from Baseline

- Visits on or before March 1, 2020

HQ-CT: Change from Baseline to Week 13	DCCR N=80	Placebo N=41
LS Mean Change from Baseline (SE)	-6.64 (1.00)	-3.51 (1.28)
LS Mean Difference	-3.13	
p-value	**p = 0.037***	

* Analysis performed using a linear mixed model for repeated measures with change from Baseline as the dependent variable

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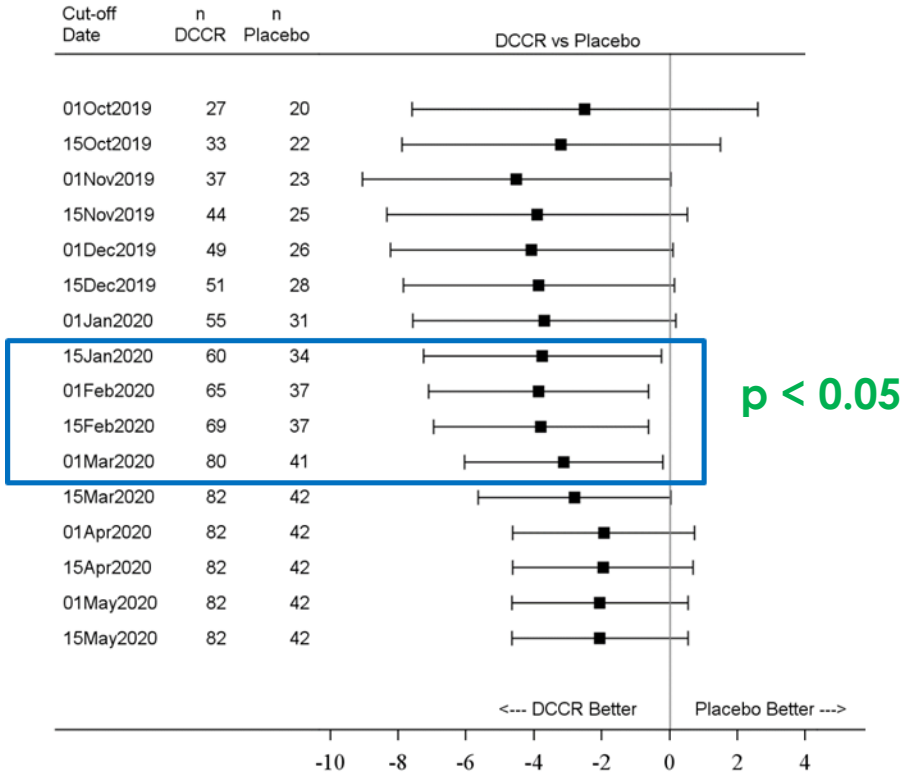
C601 HQ-CT Changes in HQ-CT by Cut-off Date



p < 0.05

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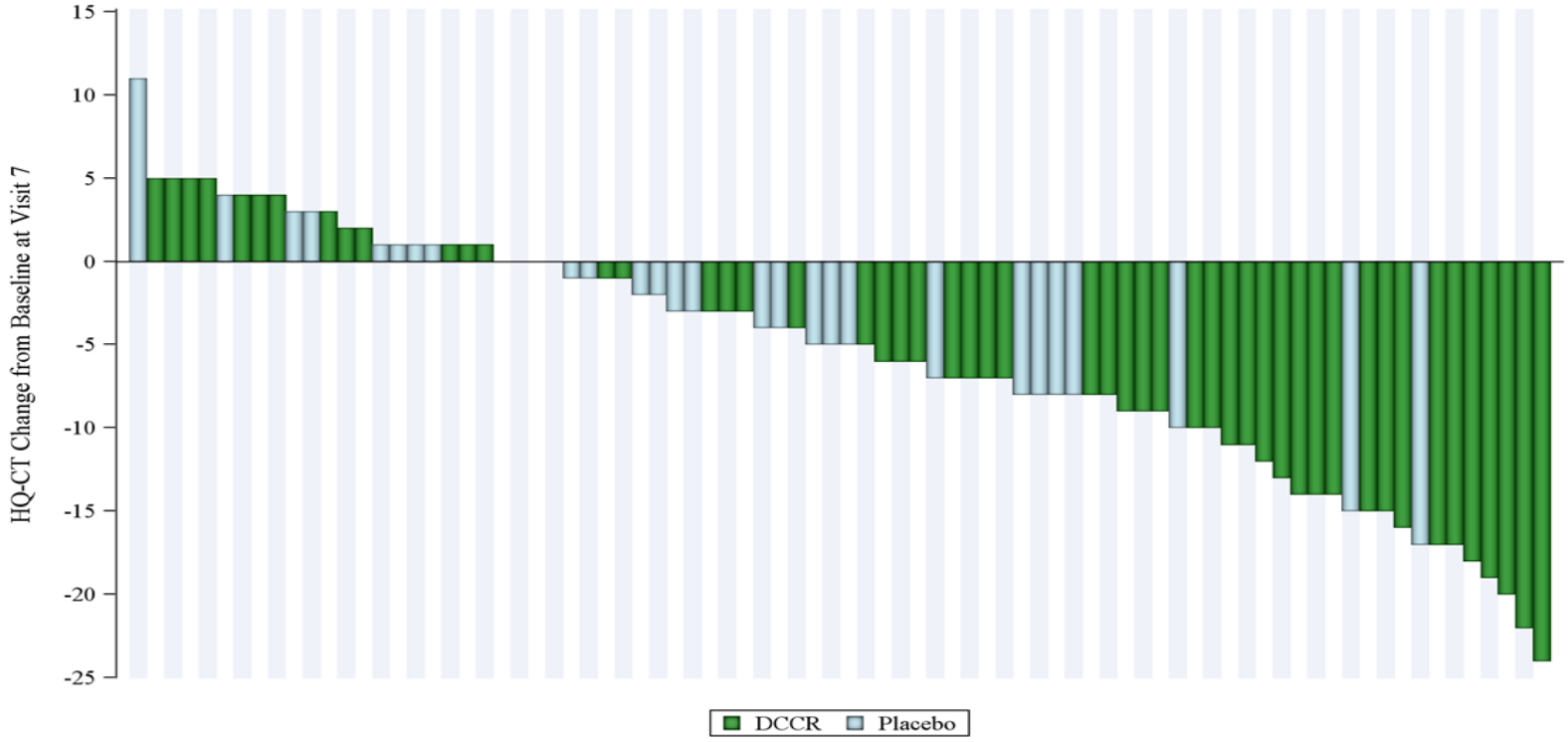
HQ-CT Changes from Baseline Waterfall Plot through March 1, 2020



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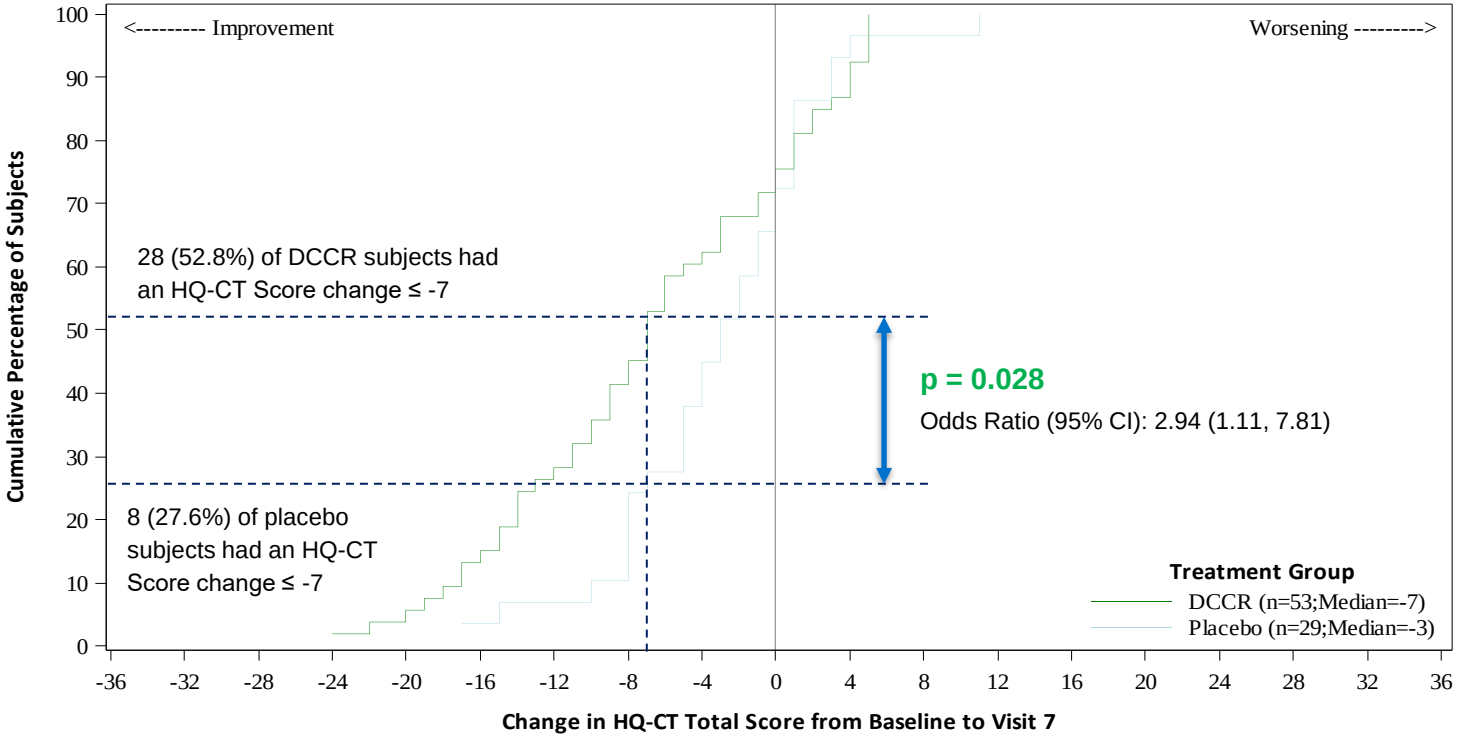
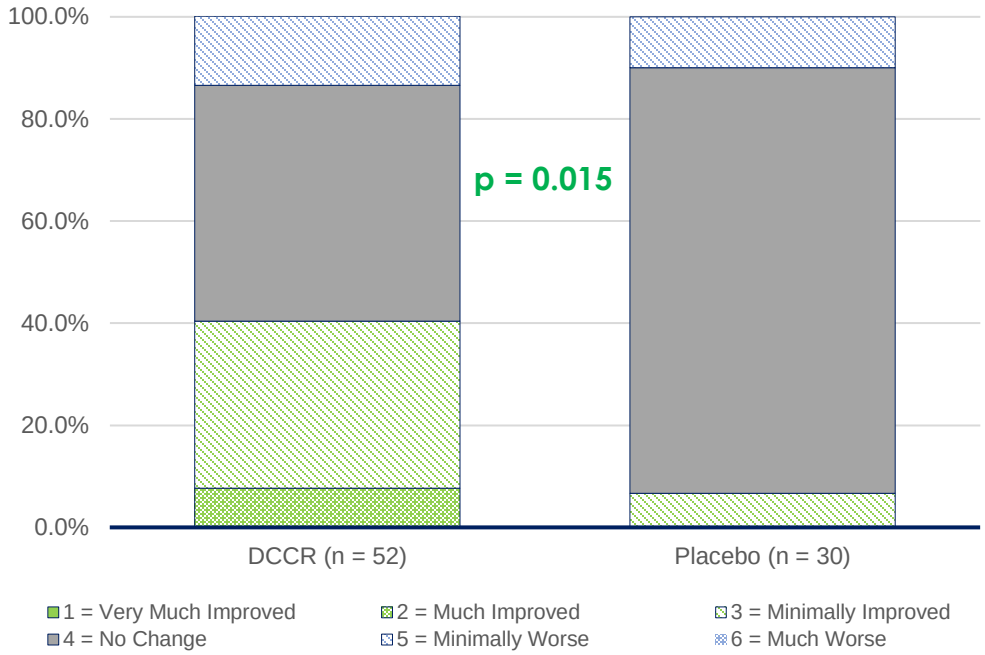
C601 HQ-CT Responder Analysis through March 1, 2020



- p-value and odds ratio for DCCR vs placebo obtained using a CMH chi-square test and observed data at Visit 7.

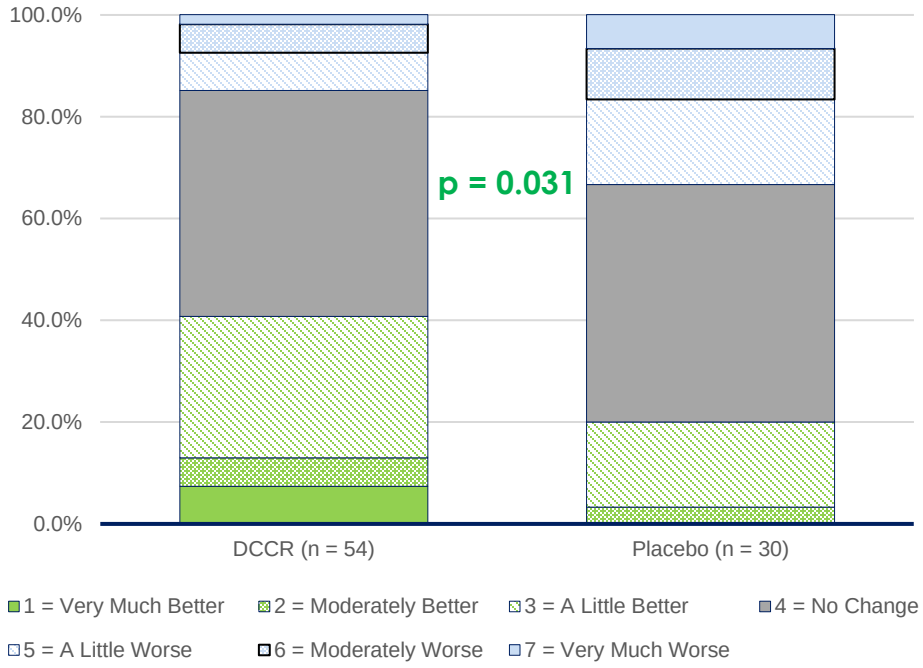
C601 Key Secondary Endpoint: CGI-I



CGI-I Rating	DCCR (n = 52)	Placebo (n = 30)
Improved	40.4%	6.7%
No Change	46.2%	83.3%
Worse	13.5%	10.0%

p-value using CMH; all observed values through March 1, 2020
Using imputation for missing data p = 0.037

C601 Key Secondary Endpoint: Caregiver GI-C



Caregiver GI-C Rating	DCCR (n = 54)	Placebo (n = 30)
Better	40.8%	20.0%
No Change	44.4%	46.7%
Worse	14.9%	33.4%

p-value using CMH; all observed values through March 1, 2020
Using imputation for missing data p = 0.086

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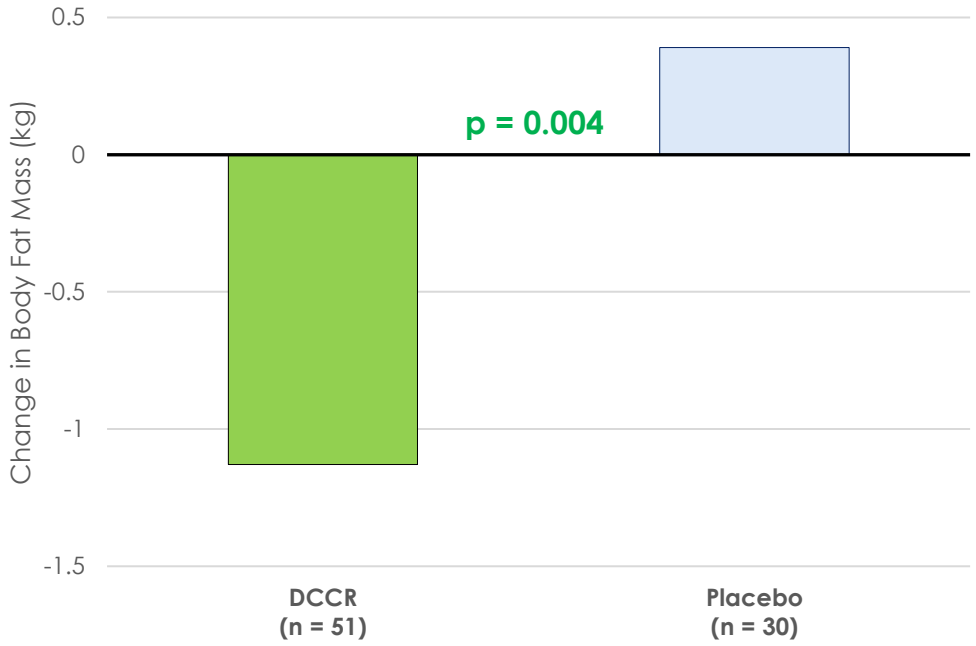
C601 Key Secondary Endpoint: Body Fat Mass



Observed values through March 1, 2020
Using imputation for missing data p = 0.005

C601 Behavioral Endpoints, data through March 1, 2020

PWSP Domain	p-value DCCR vs Placebo
Aggressive Behaviors	**0.048**
Anxiety	**0.018**
Rigidity, Irritability	**0.003**
Compulsivity	**0.008**
Depression	**0.185**
Disordered Thinking	**0.011**
DBC-2	
Total Score	**0.009**
Communication Disturbance	**0.003**
Social Relating	**0.008**

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Analyses of Data

- No significant differences in the demographics compared with topline ITT population
- In general, DCCR showed statistically significant improvements in several other subjective endpoints that were not significant in the topline analyses
- Objective endpoints, mostly significant in the topline analyses, generally remained so
- The safety profile was similar to that observed in the topline ITT population

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Conclusions

- Clear impact of COVID pandemic on the caregivers and subjects in DESTINY PWS
- Primary, subjective key secondary, and several other efficacy variables that were not significant in the topline analyses, are significant with pre-March 1, 2020 analyses
- No differences observed in the safety of DCCR compared to the profile seen in the topline analyses

DCCR in C601/C602 Patients

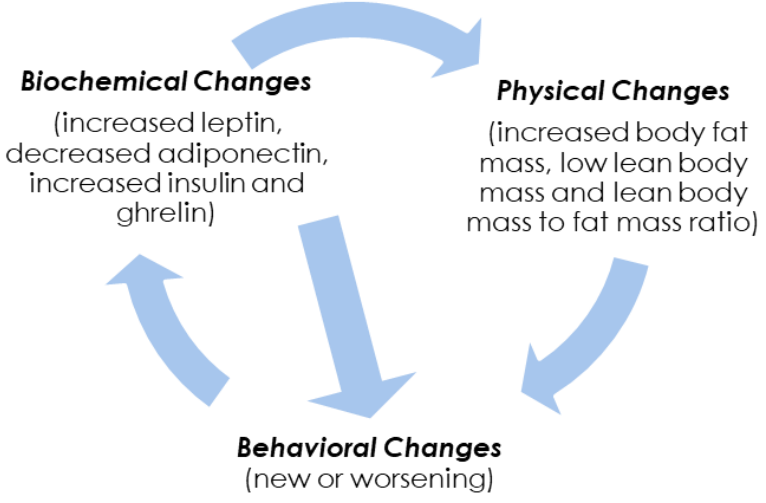
Jennifer L Miller, MD
University of Florida
Pediatric Endocrinology

DCCR in PWS

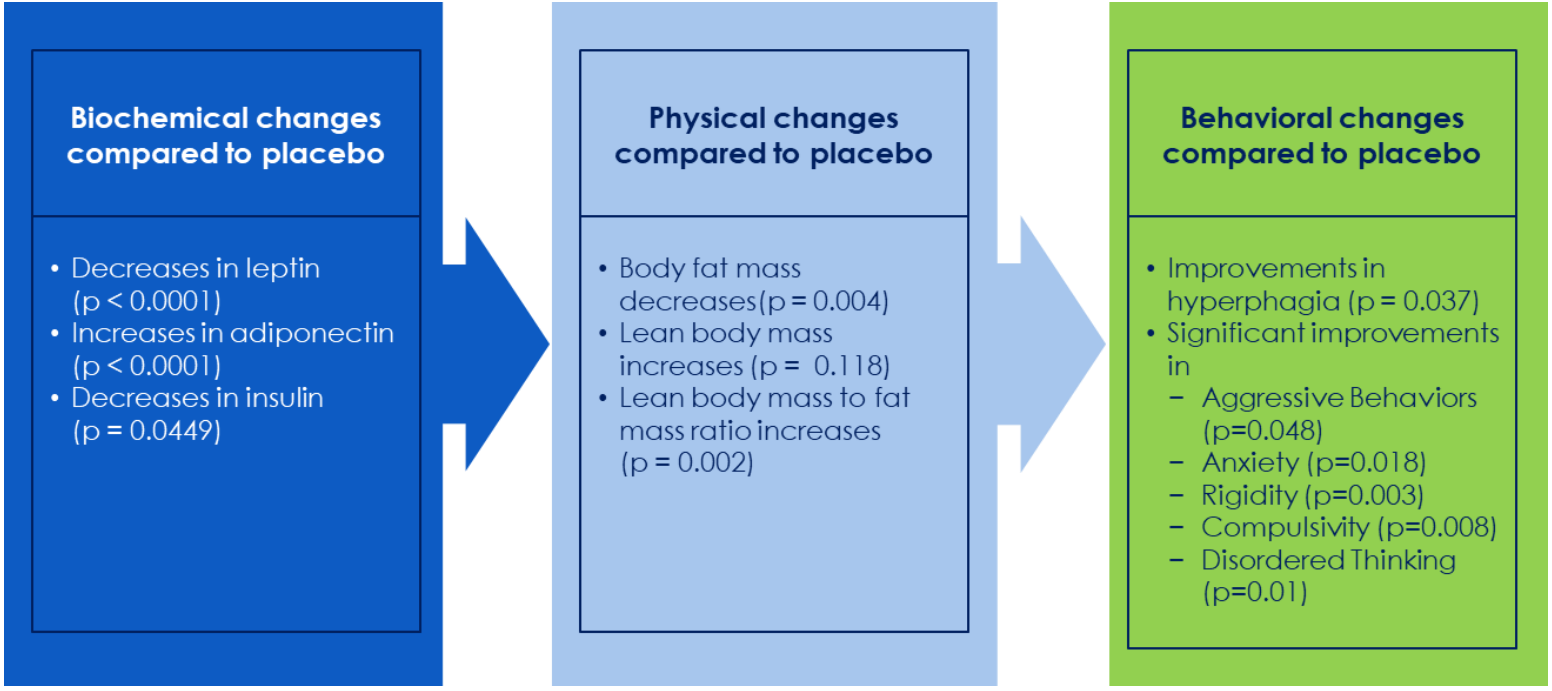
- Observations of my patients in the C601 and C602 studies
  - Earliest enrolled patients have been on DCCR in C602 for more than 2 years
  - Anecdotes include my clinic patients participating at other study centers
- Observations do not apply to every patient

The Cycle of PWS

- In PWS, the loss of Snord116 leads to excess NPY and AgRP synthesis and secretion by NPY/AgRP neurons
  - Exacerbated by leptin resistance and insulin resistance leading to both physical changes and behavioral changes, including hyperphagia
  - Unmanaged hyperphagia continues to fuel the cycle



DCCR Effects on PWS



Source: Soleno Therapeutics Preliminary Analysis

Improvements in Hyperphagia

- Food is no longer top-of-mind, allowing them the ability to focus on and think about other things
- Can be distracted from talking about food
- Meal schedule can be relaxed, mealtimes less stressful
- May be able to unlock the refrigerator, kitchen, and pantry
- May be able to take the PWS patient to the grocery store, restaurants, the movies or family gatherings
- Improvement of behavior around food

Improvements in Behaviors Other than Hyperphagia

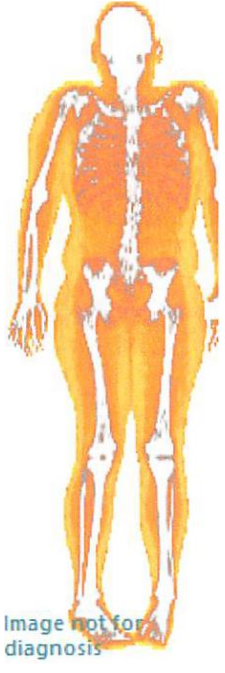
- Improved family dynamics
- Improved social interactions
- Less anxiety
- Decreased compulsive behaviors
- Decreased skin picking
- Decreased repetitive questioning

Improvements in Body Composition

- Increased strength, stamina and exercise capacity
- Ability to perform tasks otherwise unusual (biking, rollerblading, etc.)
- Increased voluntary energy expenditure
  - Treated patients can increase their food intake without gaining weight
- Overall sense of well-being

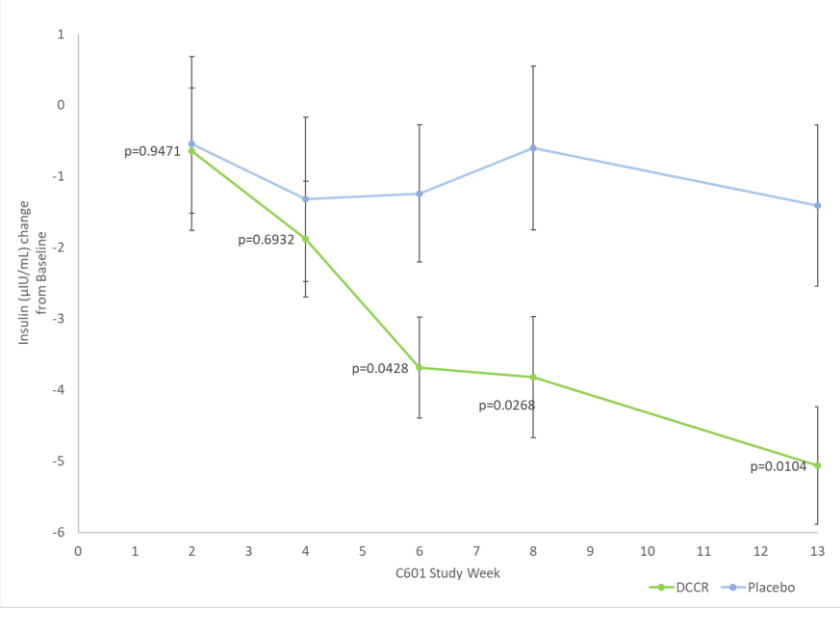
DXA Results for DCCR Treated PWS Patient

C601 Baseline	Body Composition Parameter	After 12 months Open-label DCCR
121.28 kg	Total Mass (kg)	94.72
62.26 kg	Fat Mass (kg)	31.69
55.93 (kg)	Lean Mass (kg)	59.63
52.7% (kg)	% Body Fat	34.7%



Improvements in Biochemical Markers

Insulin
Change from Baseline

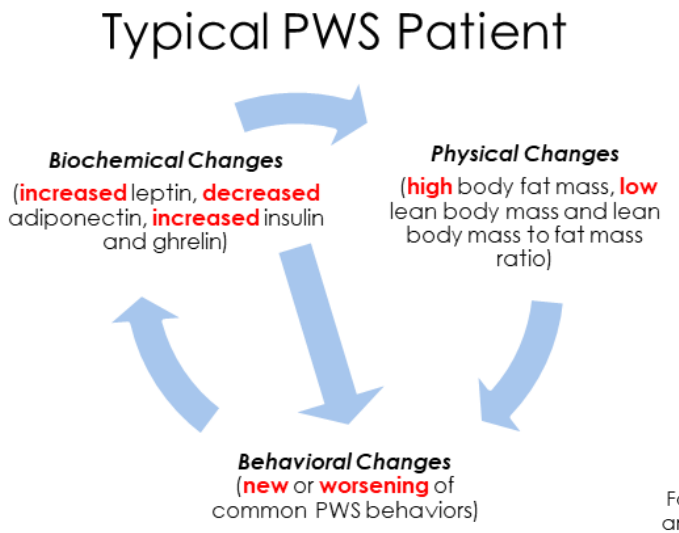


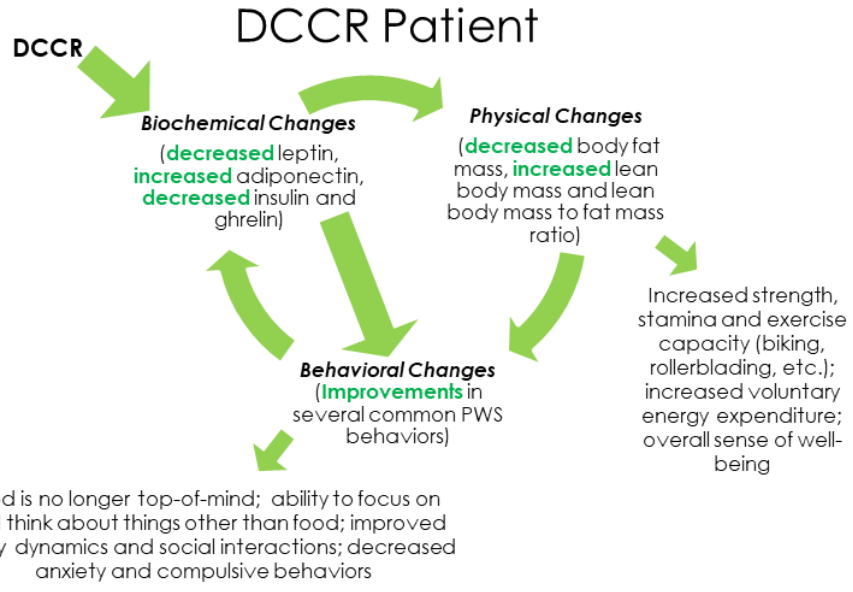
Change from Baseline to Visit 7 (through March 1, 2020)	DCCR vs Placebo p-value
Decreased Acylated Ghrelin (active form)	**0.009**
Decreased Leptin	**<0.0001**
Increased Adiponectin	**<0.0001**

Source: Soleno Therapeutics Preliminary Analysis

Clinical Global Impression of Improvement

- Assessment allows investigators to think about the whole patient, not just each individual endpoint and the impact of those changes





Safety / Risk-Benefit

- The adverse event profile for DCCR has been consistent with that of diazoxide and prior experience with DCCR
- Most common AEs are hypertrichosis, increases in blood glucose levels and edema
- Given the significant unmet need in PWS, DCCR has a desirable risk-benefit profile

Conclusions

- Data from DCCR studies to date suggests statistically significant and clinically meaningful benefits to PWS patients
- The benefits appear to span behavioral as well as metabolic endpoints
- These effects of DCCR, if sustained, may have the potential to change the natural history of PWS

Commercial Opportunity

US Patient Population

Patient Population

- Overall US diagnosed PWS prevalence rate: ~2.7 per 100k persons[1]
- 8,870 estimated patients with diagnosed PWS in 2018[1]
- Elevated mortality rates; mean life expectancy ~30 years
- Estimated current US prevalence of approximately 10,000 – 20,000[2]

US Prevalence per 100k (IQVIA data)[1]

Age	Diagnosed
0 - 2	3.9
3 – 8	5.2
9 – 17	4.5
18 – 26	4.2
27 – 49	2.5
≥ 50	1.1

PWS patients were identified via the presence of ≥ 2 claims with a diagnoses code for PWS

[1] McCandless SE, et al. (2020) - Rare causes and conditions of obesity: PWS, Lipodystrophy
[2] Bohonowych J, et al. The global Prader-Willi syndrome registry: Development, launch and early demographics. Genes (Basel) 2019; 10(9):713

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Small Commercial Footprint to Reach Patient Population

- Primary treating physicians
  - Predominantly Pediatric Endocrinologists
    - ~1,000 Pediatric Endocrinologists in the US
    - <150 Pediatric Endocrinologists treating PWS: 70 listed on PWSA USA website[1]
  - Minority by others, such as medical geneticists, psychiatrists or adult endocrinologists
  - Increasing number of centers where multidisciplinary clinics are available
- Active Patient Advocacy Groups
  - Two major organizations in the US (FPWR and PWSA USA)
    - PWSA USA has state-level chapters in most states

[1] As per PWSA USA website: Healthcare Provider Directory: Endocrinology - Pediatric

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DCCR Commercial Considerations

- No alternative approved treatment
- Once daily tablet
- Patient's environment is highly structured with defined routines suggesting higher than average compliance and adherence
- Distribute to patients via 3PL, Specialty Pharmacy and Hub
- Orphan pricing

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Pipeline – Other Opportunities for DCCR

	Potential Upside Opportunities for DCCR	Estimated US Prevalence
Syndromic Obesity	Fragile X-PWS Phenotype	6,700 - 8,500
	Schaaf-Yang syndrome	200 - 300
	Smith Magenis syndrome	13,000 - 22,000
	MC4R deficiency	32,700 - 163,000
Other	Chronic Hyperinsulinism	820 - 1,100
	Glycogen Storage Disease Type 1	2,800 - 6,800

Key Takeaways for Creating Shareholder Value

- PWS is a rare disease, US estimate of 10,000 – 20,000 people
- DCCR is focused on treating the highest unmet needs of PWS for which no approved treatments exist
- Once a day tablet formulation with orphan pricing
- Focused physician population that can be targeted by a small commercial footprint
- Substantial potential upside with other rare disease indications

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KOL Webinar on DCCR for the Treatment of Prader-Willi Syndrome

Q&A