A Phase III Study of DCCR in Prader-Willi Syndrome: Effects on Body Composition and Adipokines

Authors: Parisa Salehi, MD, Jennifer Miller, MD and Jack Yanovski, PhD, MD on behalf of the DESTINY PWS Investigators

Presented by: Parisa Salehi, MD

Obesity Week
November 3, 2020

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

UW Medicine
UW SCHOOL OF MEDICINE

Prader-Willi Syndrome (PWS)

- Due to the lack of expression of genes within the imprinted region of chromosome 15q11.2-q13
- Unique characteristics include: hyperphagia, behavioral difficulties, endocrinopathies, disordered sleep
- Hyperphagia in PWS leads to significant morbidity/mortality
- No approved treatments for PWS hyperphagia

Note on Lean Body Mass

- Individuals with PWS have excess body fat and low lean body mass than weight matched individuals without PWS

- This is a near universal characteristic with an unknown etiology

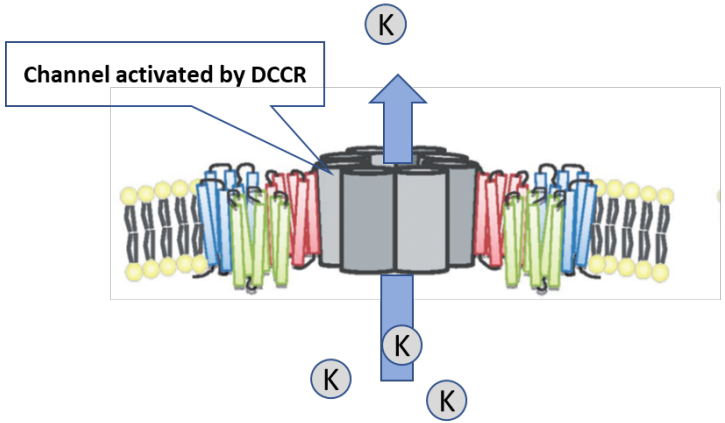
Introduction to DCCR

- DCCR is a once daily tablet formulation of the choline salt of diazoxide
  - K_{ATP} channel agonist

- Prior to the first study in PWS, it had been evaluated in 5 Phase I studies and 2 Phase II studies

- PC025 pilot study: 13 PWS subjects ages 10-22 years
  - DCCR treatment resulted in significant reductions in hyperphagia, loss of body fat, increases in lean body mass and reductions in aggressive behaviors

Mechanism of Action in PWS



Membrane hyperpolarization

No Ca^{2+} influx

Mechanism of action of DCCR on lean body mass is, yet, unknown

NPY/AgRP/GABA Neurons → Reduced NPY and AgRP secretion resulting in reduced hyperphagia

Subsets of DMV Neurons → Neuronal inhibition resulting in reduced hyperinsulinemia, improved insulin sensitivity, improved satiety and reduced appetite

Adipocytes → Reduced de-novo fatty acid biosynthesis and increased β-oxidation of fat resulting in reduced fat mass

Pancreatic β-cells → Reduced insulin secretion resulting in reduced hyperinsulinemia

Seattle Children's HOSPITAL • RESEARCH • FOUNDATION

UW Medicine UW SCHOOL OF MEDICINE

Genes 2020; 11:450

DESTINY PWS

- C601 (DESTINY PWS): International, multi-center, randomized, double-blind, placebo-controlled, parallel arm study in patients with PWS (Phase III)

- C602: Open-label safety extension study

Sites

US Sites
Children's Minnesota
Rady Children's Hospital of San Diego
Kansas University Medical Center
Children's Hospital Colorado
U of Florida Gainesville
Seattle Children's Hospital
University Hospitals Cleveland Medical Center
Vanderbilt University
Boston Children's Hospital
Stanford University
NYU Winthrop
University of Utah
National Institutes of Health
The Research Institute at Nationwide Children's Hospital
UC Irvine
Emory Children's Center
Indiana University School of Medicine
Sparrow Clinical Research Institute
St. Joseph's University Medical Center
Research Institute of Dallas

UK Sites
Hammersmith Hospital
Chelsea and Westminster Hospital
Royal London Hospital
Fulbourn Hospital
Aintree Hospital
Birmingham Women's and Children's Hospital
The Queen Elizabeth University
Alder Hey Children's Hospital NHS Foundation Trust
Hull and East Yorkshire Hospitals NHS Trust

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

UW Medicine
UW SCHOOL OF MEDICINE

Methods

- Subjects with genetically confirmed PWS > 4 years old between 20-134 kg with moderate to severe hyperphagia

- Subjects were divided into 5 weight bands
  - Similar mg/kg target dose (3.3-5.8 mg/kg)
  - Titrated to target dose over a period up to 6 weeks
  - Fixed titration to target dose within weight band

- There was no BMI or body fat inclusion criteria

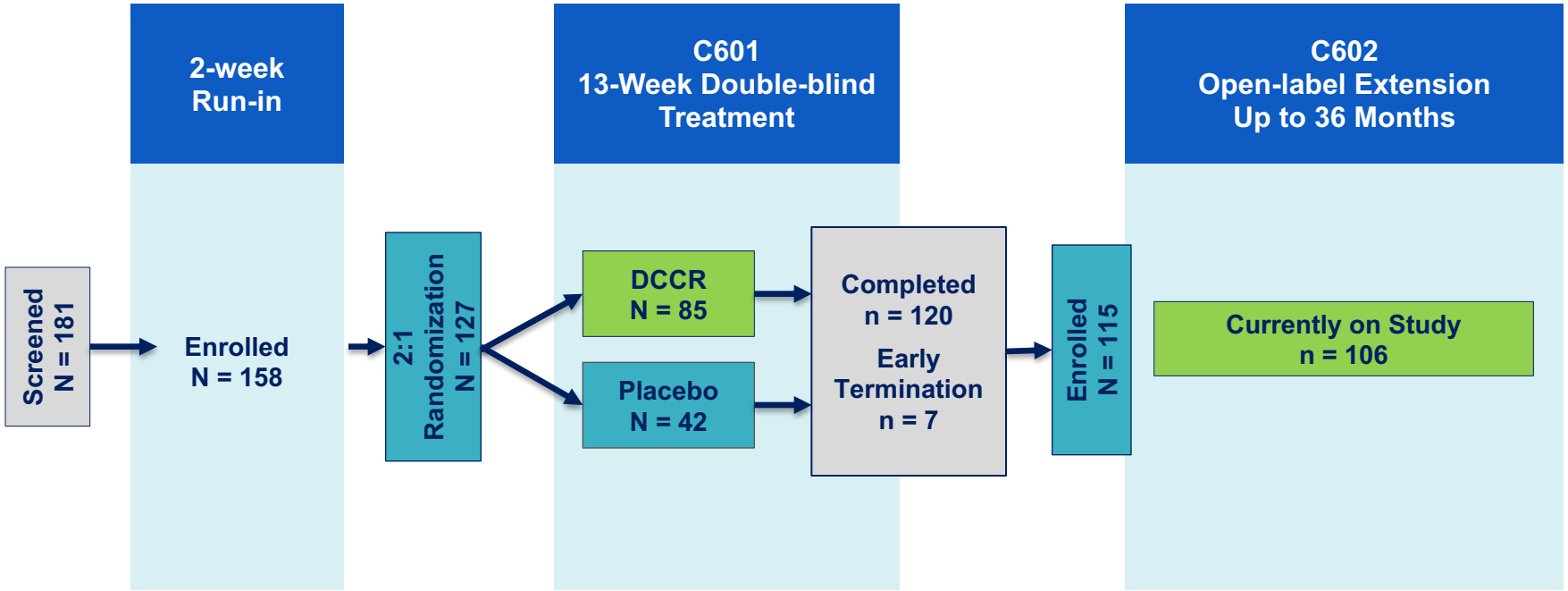
- There was no recommended reduction in energy intake

Methods

- Body composition measured by DEXA Scan at baseline and 13 weeks

- Leptin, Adiponectin measured at baseline and 13 weeks

Phase III Program Design



Randomization stratified by baseline HQ-CT score and growth hormone status

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

UW Medicine
UW SCHOOL OF MEDICINE

Covid-19 Impacts on the Study

- Week 13 Visits taking place after about March 15 were conducted by telemedicine and did not include DXA or weight data
  - DCCR: 14 affected visits (17.1%)
  - Placebo: 3 affected visits (7.1%)

Demographics and Baseline Characteristics

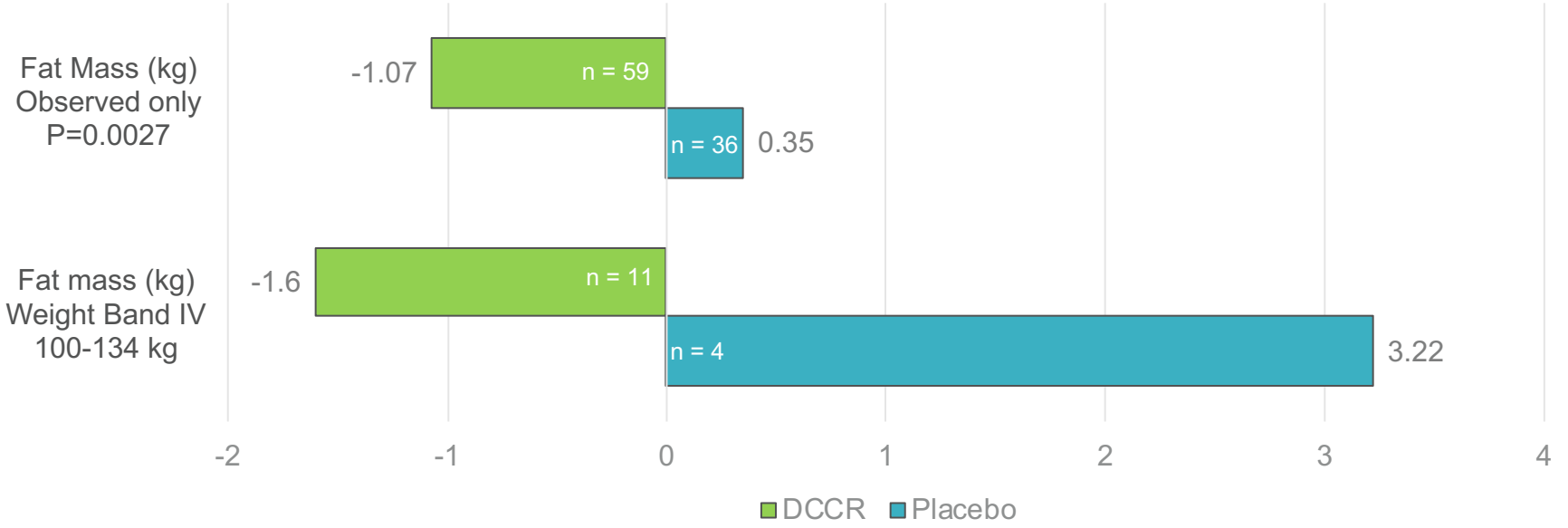
	DCCR (N=82)	Placebo (N=42)	Overall (N=124)
Age (years)	13.4 (6.82)	13.6 (7.37)	13.5 (6.98)
Gender F/M	46/36	23/19	69/55
Height (cm)	146.3 (18.50)	147.5 (20.09)	146.7 (18.98)
Weight (kg)	62.2 (30.40)	60.4 (29.56)	61.6 (30.01)
Body Mass Index (kg/m^2)	27.7 (9.47)	26.7 (9.88)	27.3 (9.58)
DXA Fat Mass* (kg)	27.67 (16.62)	26.46 (17.58)	27.25 (16.90)
DXA Lean Body Mass* (kg)	29.25 (14.16)	28.31 (12.52)	28.92 (13.56)
US/UK	63/19	36/6	99/25
Growth Hormone Treated	69 (84.1)	35 (83.3)	104 (83.9)

*Calculated as the sum of right and left arms, right and left legs and trunk

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

UW Medicine
UW SCHOOL OF MEDICINE

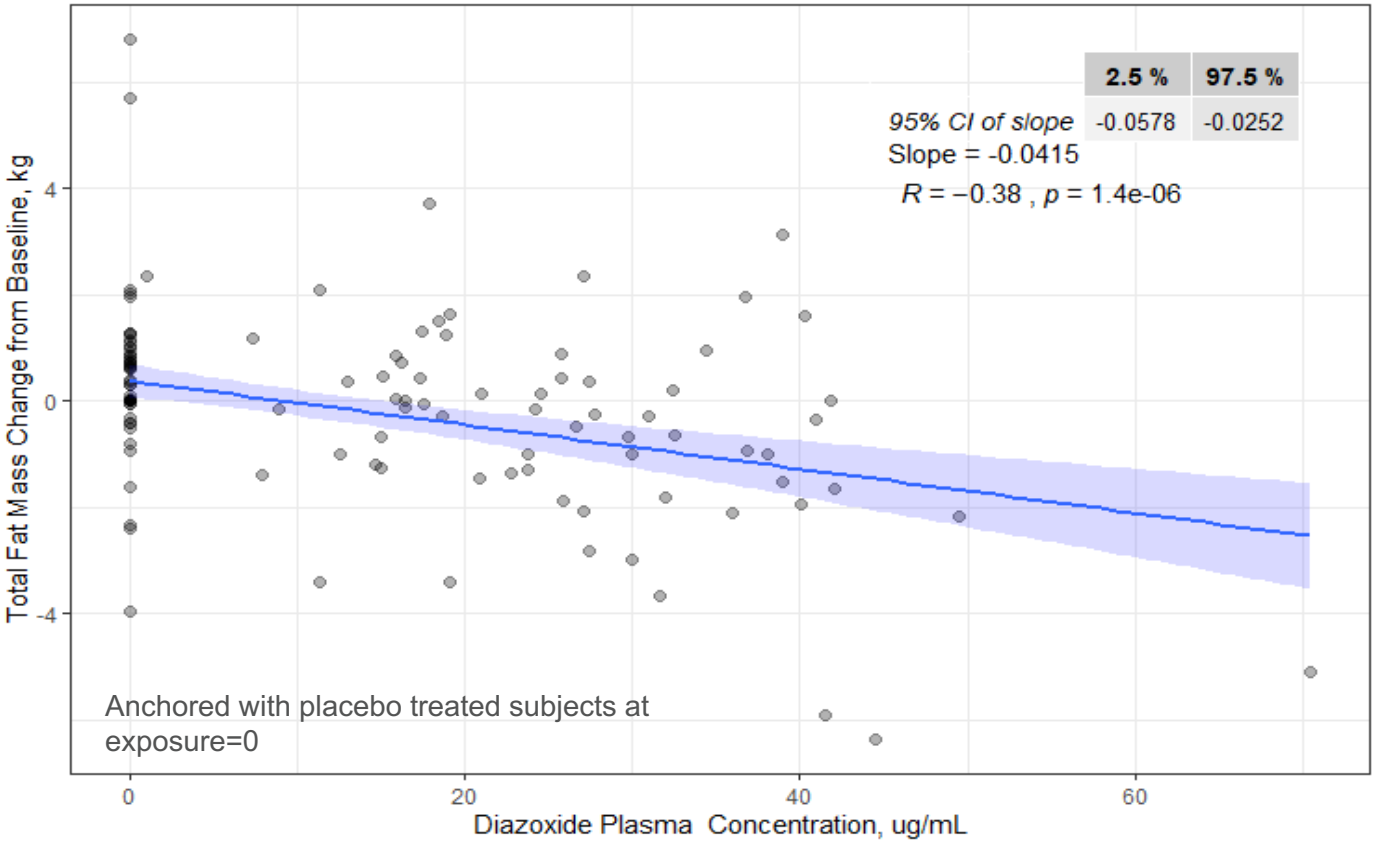
C601 Changes in Body Composition



Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

UW Medicine
UW SCHOOL OF MEDICINE

C601 Linear Relationship Between Change in Fat Mass at Week 13 and Exposure



UW Medicine
UW SCHOOL OF MEDICINE

C601 Lean Body Mass

	DCCR (N = 59)	Placebo (N = 36)
Baseline Mean (SE)	31.29 (1.90)	28.09 (2.04)
LS Mean Change from Baseline (SE)	1.4 (0.36)	0.5 (0.42)
Change as a Percent of Baseline	4.5%	1.8%
LS Mean Difference [DCCR-Placebo] (SE)	0.9 (0.46)	
p-value	0.0576	

C601 Lean Body Mass/Fat Mass

	DCCR (N = 59)	Placebo (N = 36)
Baseline Mean (SE)	1.189 (0.056)	1.278 (0.104)
LS Mean Change from Baseline (SE)	0.1(0.03)	0 (0.03)
Change as a Percent of Baseline	8.4%	0.0%
LS Mean Difference [DCCR-Placebo] (SE)	0.1(0.04)	
p-value	0.0011	

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

UW Medicine
UW SCHOOL OF MEDICINE

C601 Weight

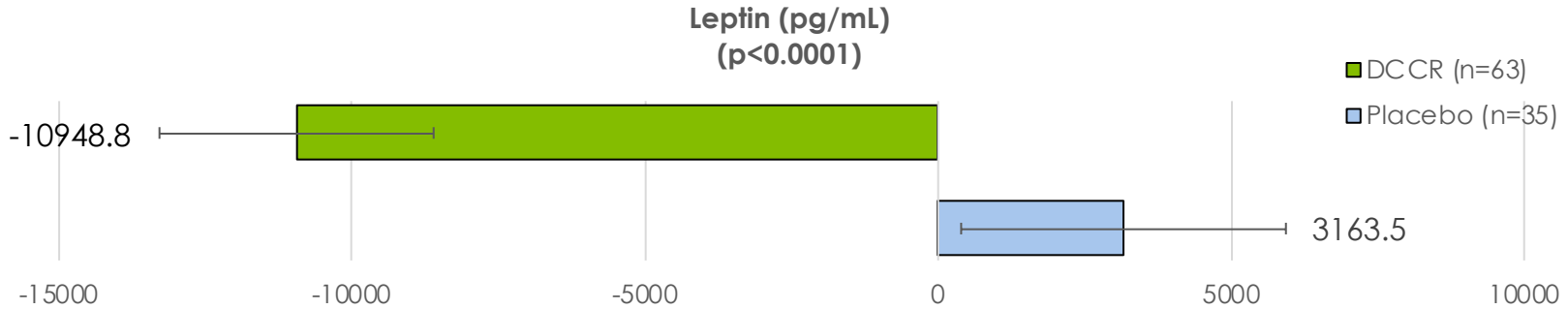
	DCCR (N = 75)	Placebo (N = 42)
Baseline Mean (SE)	63.04 (3.51)	60.44 (4.56)
LS Mean Change from Baseline (SE)	0.9 (0.36)	1.1 (0.42)
Change as a Percent of Baseline	1.4%	1.8%
LS Mean Difference [DCCR-Placebo] (SE)	-0.2 (0.46)	
p-value	0.6161	

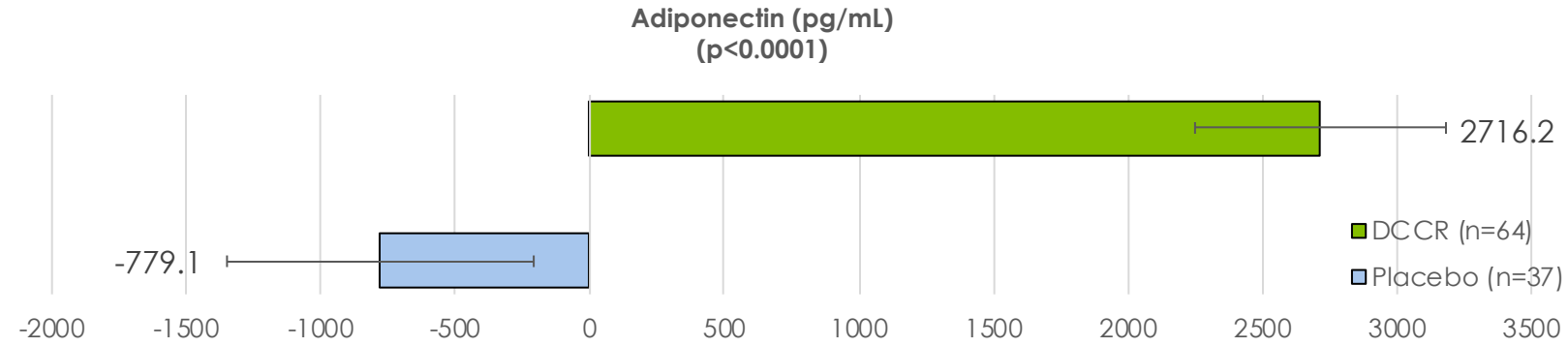
- In the DCCR arm the increase in weight was due to a loss of body fat and a marked increase in lean body mass while in the Placebo arm there was an increase in body fat and smaller increase in lean body mass.

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

UW Medicine
UW SCHOOL OF MEDICINE

C601 Changes in Leptin and Adiponectin

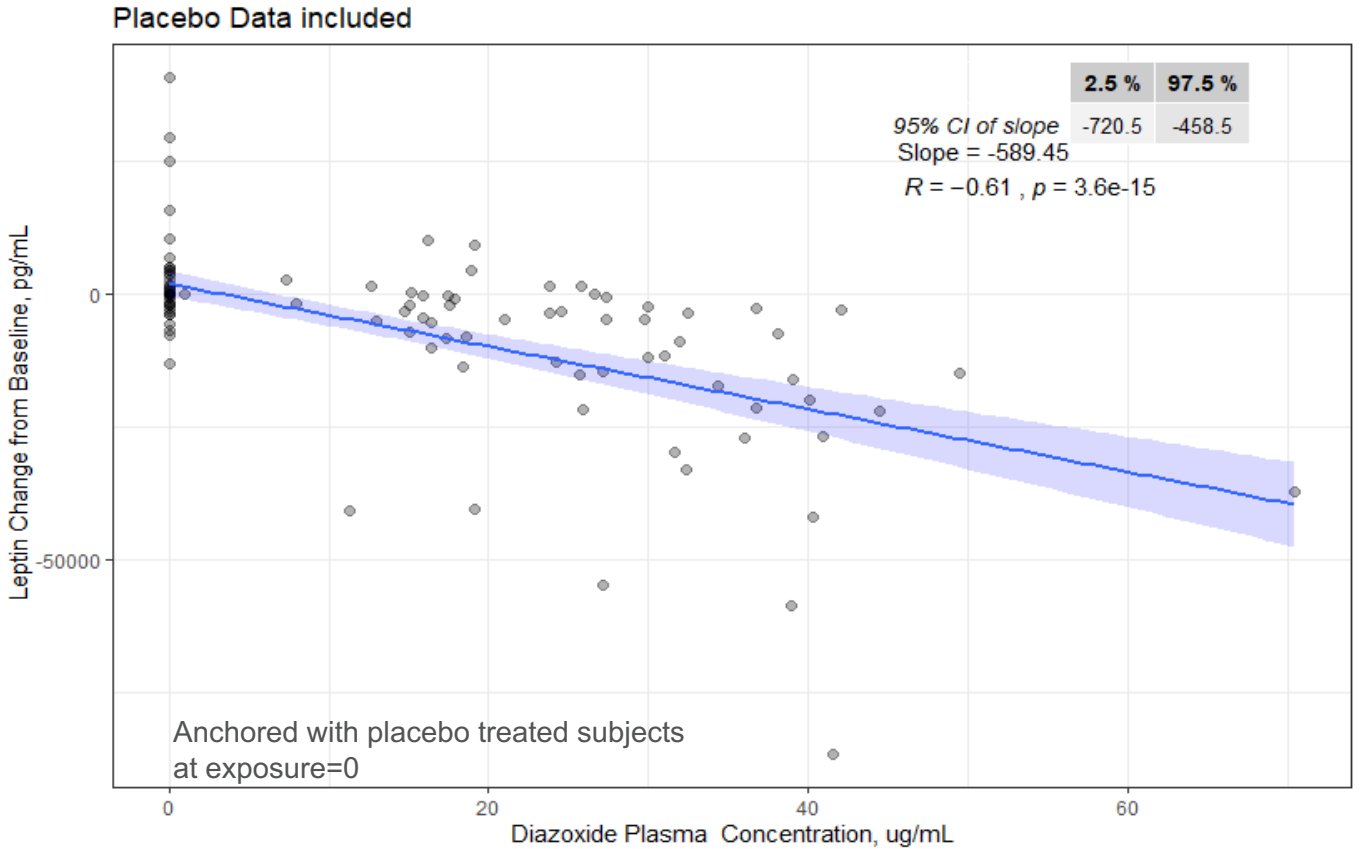




Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

UW Medicine
UW SCHOOL OF MEDICINE

Linear Relationship Between Change in Leptin at Week 13 and Exposure



UW Medicine
UW SCHOOL OF MEDICINE

C601 Safety

Summary of Adverse Events		
Number (%) of subjects with at least one:	**DCCR (N=84) n (%)**	**Placebo (N=42) n (%)**
Any TEAE	70 (83.3)	31 (73.8)
TEAE resulting in premature discontinuation of study drug	4 (4.8)	1 (2.4)
Any SAE	6 (7.1)	0 (0)
SAE related to study drug	1 (1.2)	0 (0)
SAE leading to premature discontinuation of study drug	2 (2.4)	0 (0)

TEAEs in >5% of DCCR Subjects		
Preferred Term	**DCCR (N=84) n (%)**	**Placebo (N=42) n (%)**
Hypertrichosis	30 (35.7)	6 (14.3)
Hirsutism	6 (7.1)	3 (7.1)
Upper Respiratory Tract Infection	9 (10.7)	5 (11.9)
Edema, peripheral	17 (20.2)	4 (9.5)
Pyrexia	5.0 (6)	0 (0)
Headache	5 (6)	6 (14.3)
Blood glucose increased	5.0 (6)	2 (4.8)
Hyperglycemia	10 (11.9)	0 (0)

C601 Safety (continued)

TEAEs Leading to Drug Discontinuation		
Preferred Term	DCCR (N=84) n (%)	Placebo (N=42) n (%)
Abdominal pain upper*, ^	0 (0)	1 (2.4)
Oedema, peripheral*	1 (1.2)	0 (0)
Lower respiratory tract infection^	1 (1.2)	0 (0)
Hyperglycemia*	1 (1.2)	0 (0)
Aggression	1 (1.2)	0 (0)
Pulmonary Oedema*, ^	1 (1.2)	0 (0)
Rash papular*	1 (1.2)	0 (0)

Serious Adverse Events		
Preferred Term	DCCR (N=84) n (%)	Placebo (N=42) n (%)
Pneumonia	2 (2.4)	0 (0)
Oedema, peripheral*, ^	1 (1.2)	0 (0)
Lower respiratory tract infection^	1 (1.2)	0 (0)
Staphylococcal infection	1 (1.2)	0 (0)
Abnormal behavior	1 (1.2)	0 (0)
Aggression	1 (1.2)	0 (0)
Pulmonary edema*, ^	1 (1.2)	0 (0)
Respiratory failure	1 (1.2)	0 (0)
Erythema multiforme	1 (1.2)	0 (0)

* Possibly / Probably Related
^ Same Subject

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

UW Medicine
UW SCHOOL OF MEDICINE

DCCR Safety Profile

- The safety profile of DCCR in C601 was generally consistent with the known profile of diazoxide and prior experience with DCCR
  - Most events were Grade 1 in severity
  - No Grade 4 or higher events were reported in this study

- There were no suspected unexpected serious adverse reactions (SUSARs) related to DCCR

Conclusions

DCCR treatment of subjects with PWS resulted in:

- Significant and clinically relevant changes in body composition
  - Occurred in the context of stable GH treatment and without a reduction in energy intake
- Significant improvements in adipokines
- Treatment was well tolerated

C602 Interim Results

- Highly significant reductions in hyperphagia (~-50%)
- Highly significant reductions in PWS related behaviors
  - Aggressive behaviors, anxiety, compulsive behaviors, depression, rigidity/irritability, and disordered thinking

Thank You

- Subjects and their caregivers
- Sites and study personnel in US/UK
- FPWR, PWSA

Seattle Children's
HOSPITAL • RESEARCH • FOUNDATION

UW Medicine
UW SCHOOL OF MEDICINE