Free Communications 11: Fat, Metabolism and Obesity 2

Long-term Efficacy Results of Diazoxide Choline Extended-Release (DCCR) Tablets in Participants with Prader-Willi Syndrome from the Completed C601 (DESTINY PWS) and C602 Open Label Extension (OLE) Studies

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DISCLOSURE STATEMENT

Dr. Evelien Gevers

☑ I have the following potential conflicts of interest to report:

- ☑ Research Contracts
- ☐ Consulting
- ☐ Employment in the Industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☐ Other(s) – *please include details*

No commercial logos or product names to be included please.

☐ I declare that I have no potential conflict of interest.

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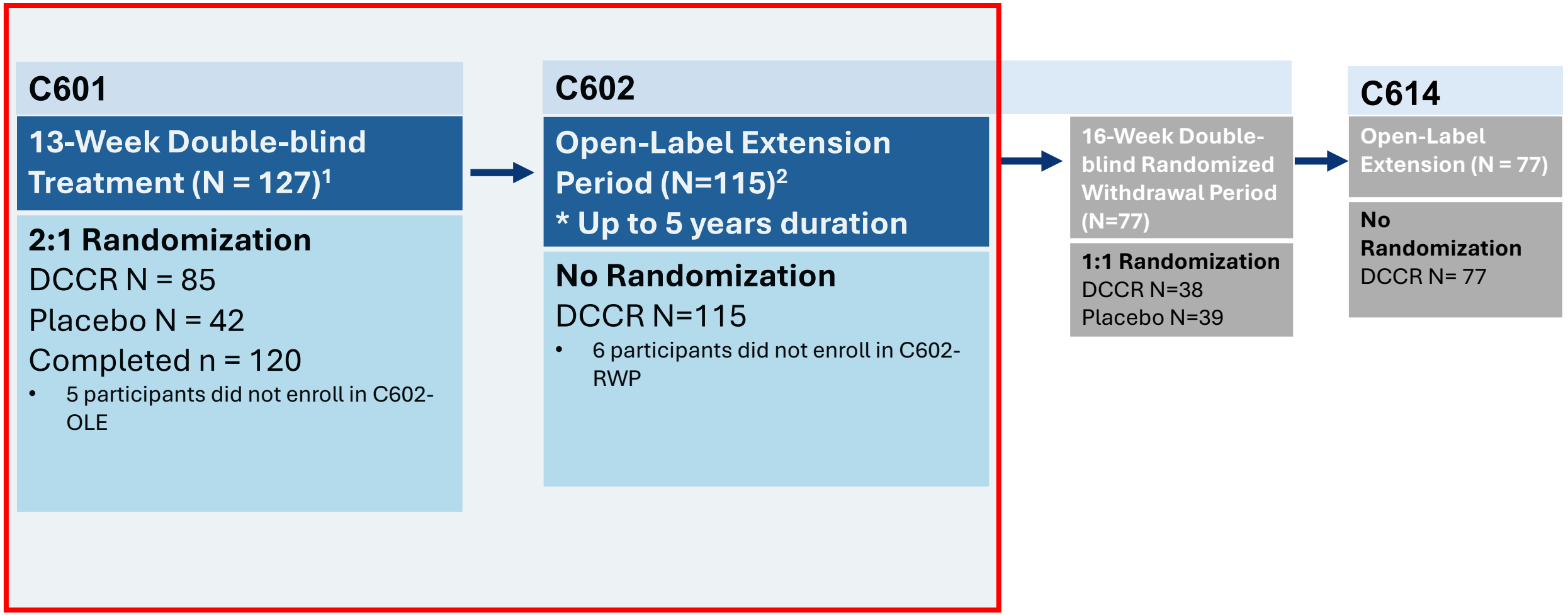
INTRODUCTION

- Prader-Willi syndrome (PWS) is a rare genetic neurobehavioral-metabolic disorder, characterized by hyperphagia, accumulation of excess fat, hypotonia, and behavioral/psychological complications.[1,2]
- There are currently no approved treatments for hyperphagia, a life-threatening hallmark of PWS.
- Diazoxide choline extended-release (DCCR) tablets are an investigational, once-daily oral formulation, which provides for continuous release and absorption throughout the gastrointestinal tract, and stable plasma concentrations.
- DCCR is currently under development as a potential treatment for children and adults with PWS who have hyperphagia.

1. Butler MG, Miller JL, Forster JL. Prader-Willi syndrome – Clinical genetics, diagnosis and treatment approaches: An update. Curr Pediatr 2019; 15(4):207-244. 2. Miller Rev JL, Lynn CH, Driscoll DC, et al. Nutritional phases in Prader-Willi syndrome. Am J Med Genet Part A 2011; 155:1040–1049. Photos provided with consent of the caregiver through University of Florida, USA. Abbreviations: PWS, Prader-Willi syndrome; DCCR, diazoxide choline extended-release.

PHASE 3 DCCR PROGRAM



1. Miller et al., J Clin Endocrinol Metab 2023 Jun 16;108(7):1676-1685. 2. Miller et al., Obesity 2024 Feb;32(2):252-261.

Abbreviations: DCCR, diazoxide choline extended-release; DXA, dual-energy X-ray absorptiometry; OLE, open label extension

ENDPOINTS TO BE DISCUSSED

Efficacy endpoints analyzed through 3 years of DCCR exposure.
Metabolic markers analyzed through 1.5 years of DCCR exposure.

Primary Efficacy Endpoint

- Change in hyperphagia per Hyperphagia Questionnaire for Clinical Trials (HQ-CT) Total Score (Range: 0-36)
  - Validated disease-specific scale completed by caregivers
  - 9 questions focused on frequency and intensity of hyperphagia & food related-behaviors within previous 2 weeks

Additional Efficacy Endpoints

- PWS Profile (PWSP)
  - Domains: aggression, anxiety, compulsivity, depression, disordered thinking, rigidity/irritability
- Clinical Global Impression of Severity (CGI-S)
- Caregiver Global Impression of Severity (Caregiver GI-S)
- Body composition per DXA
- Metabolic markers
  - Insulin, HOMA-IR, leptin, & adiponectin

Abbreviations: DCCR, diazoxide choline extended-release; DXA, dual-energy X-ray absorptiometry; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance;OLE, open label extension

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

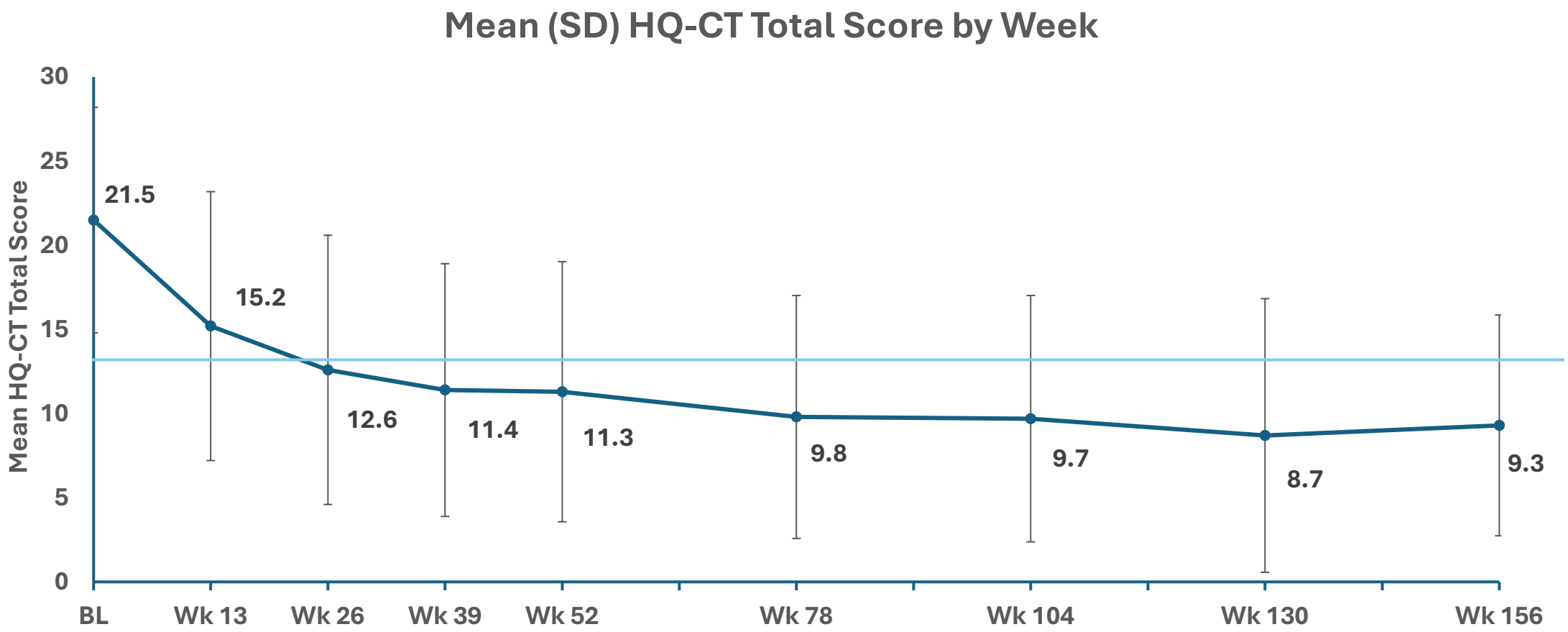
Median duration of DCCR administration: ~3.0 years (maximum: 4.5 years)

- 105 (84%) participants >1 year
- 90 (72%) participants >2 years
- 71 (57%) participants >3 years

Baseline Characteristics	DCCR-Treated Participants N = 125
Age, years	
Mean (±SD)	13.4 (6.98)
Median (range)	12 (4-44)
Race (% White / % Black / % Multiple)	84.8 / 4.8 / 6.4
Weight (mean [±SD]), kg	62.06 (30.15)
Body mass index (mean [±SD]), kg/m^2	27.56 (9.62)
Body mass index z-score (mean [±SD])	1.29 (1.12)
Growth hormone use (n [%])	103 (82%)
Geography: USA / UK (%)	80.0 / 20.0
HQ-CT total score (0-36) (mean [±SD])	21.5 (6.70)
PWS subtype	
Deletion (n [%])	77 (61.6)
Non-deletion (n [%])	47 (37.6)
Missing (n [%])	1 (0.8)

Abbreviations: BMI, body mass index; DCCR, diazoxide choline extended-release; HQ-CT, Hyperphagia Questionnaire for Clinical Trials; SD, standard deviation

REDUCTIONS IN HYPERPHAGIA OBSERVED AT ALL POST-BASELINE TIMEPOINTS



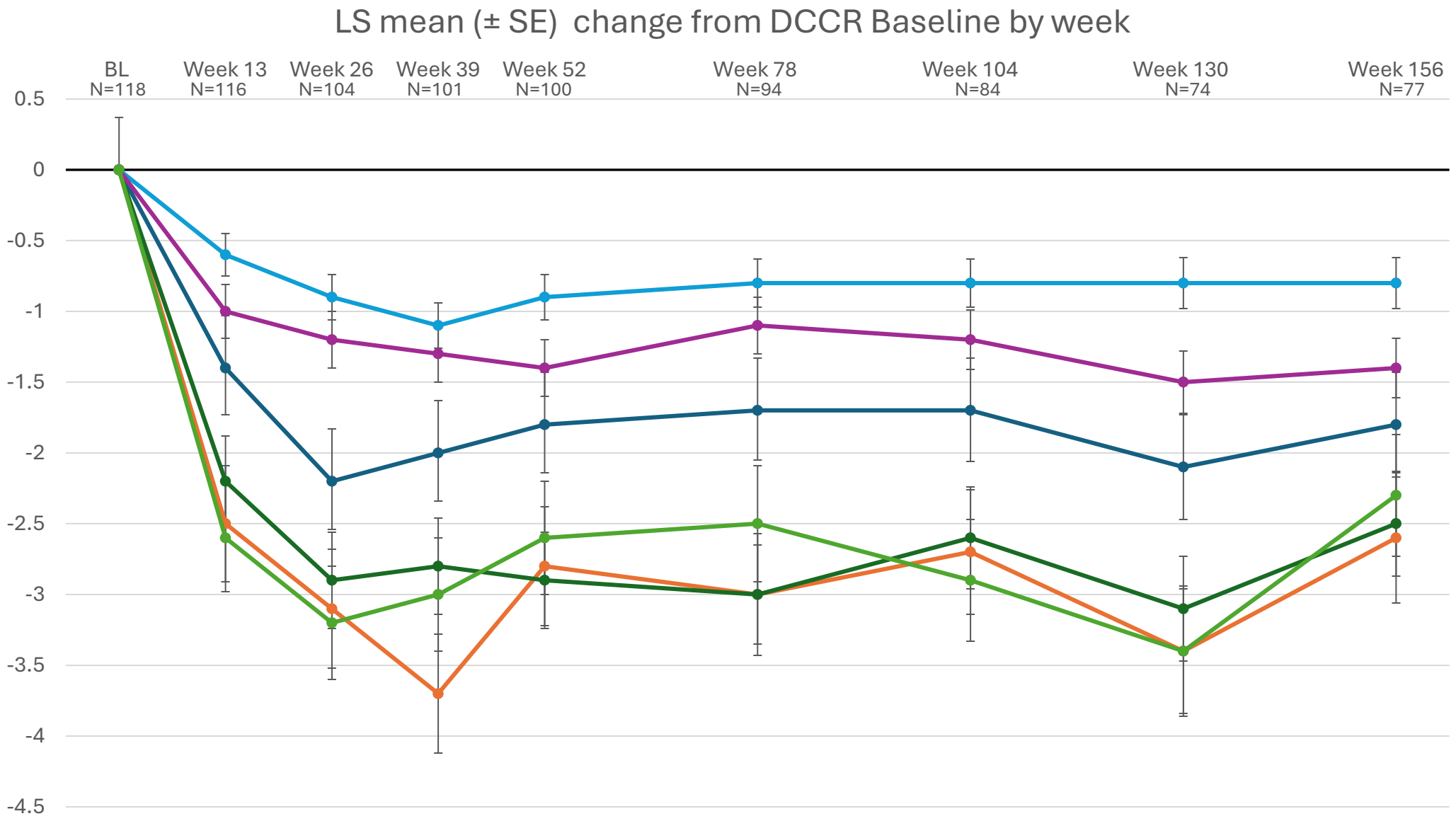
N	125	121	107	105	97	97	86	73	81

Abbreviations: BL, baseline; HQ-CT, Hyperphagia Questionnaire for Clinical Trials; SD, standard deviation

PRADER-WILLI SYNDROME PROFILE (PWSP)

Significant improvements in each of the 6 PWSP domains at all time points through 3 years ($p<0.001$)

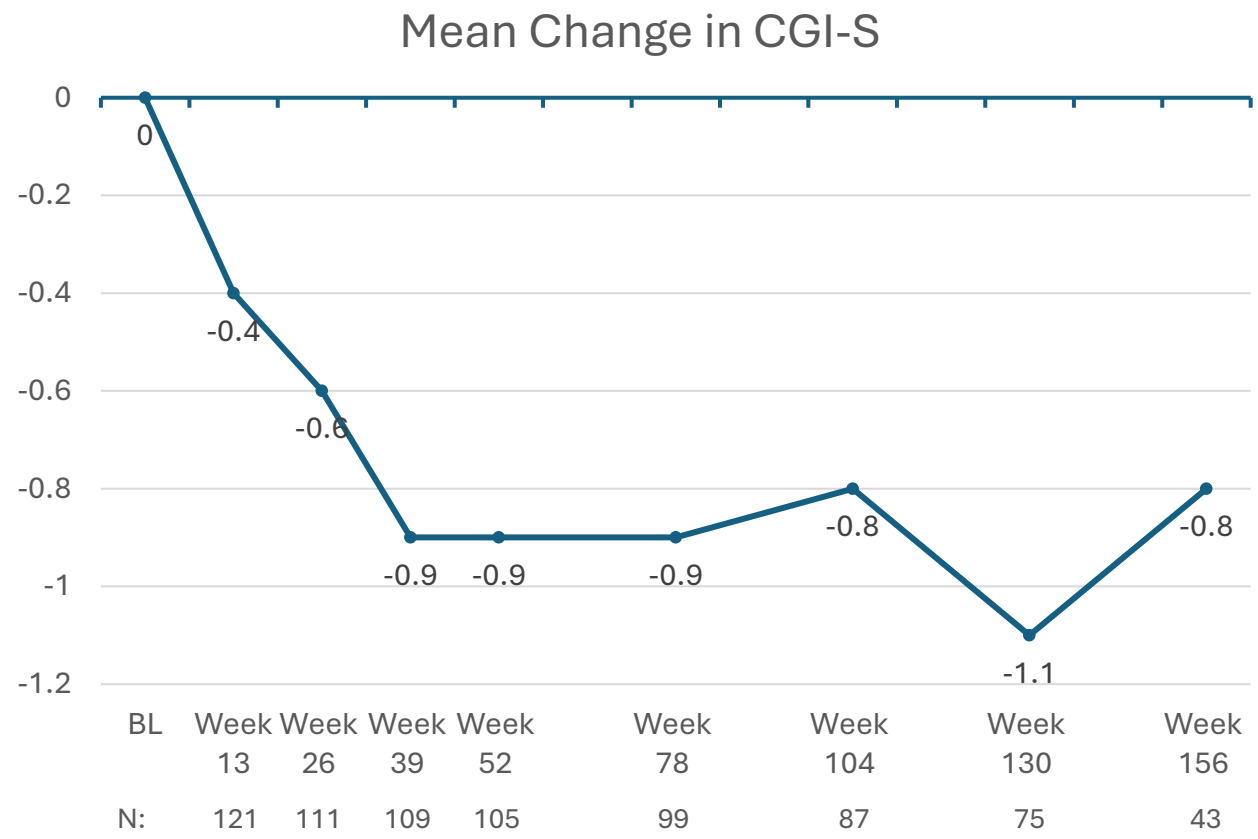
Domain Scale Ranges
Depression: 0-10
Disordered Thinking: 0-12
Aggressive Behaviors: 0-18
Rigidity/Irritability: 0-20
Compulsivity: 0-20
Anxiety: 0-22

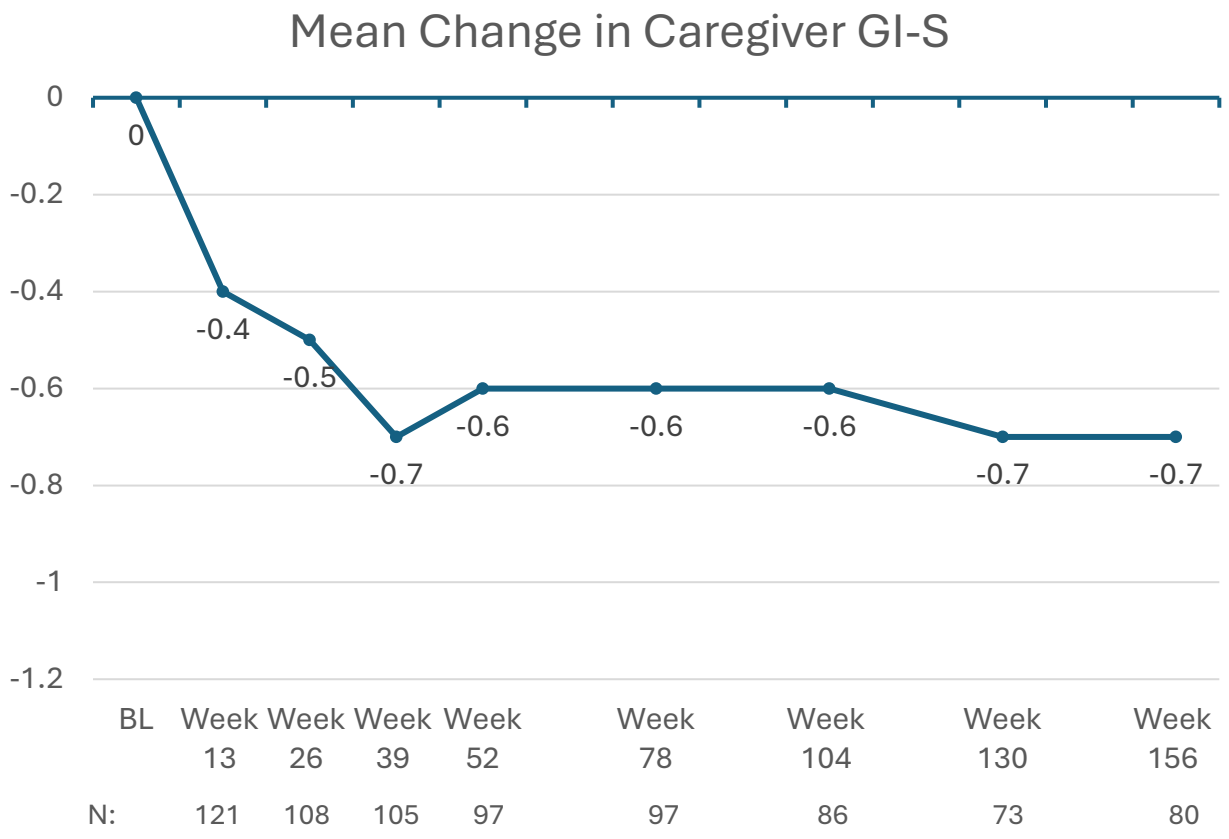


Abbreviations: BL, baseline; DCCR, diazoxide choline extended-release; LS, least squares; PWSP, Prader-Willi syndrome profile questionnaire; SE, standard error

CGI-S and CAREGIVER GI-S

Significant reductions compared to baseline in CGI-S ($p<0.0005$) and Caregiver GI-S ($p<0.0001$) at all timepoints through 3 years.



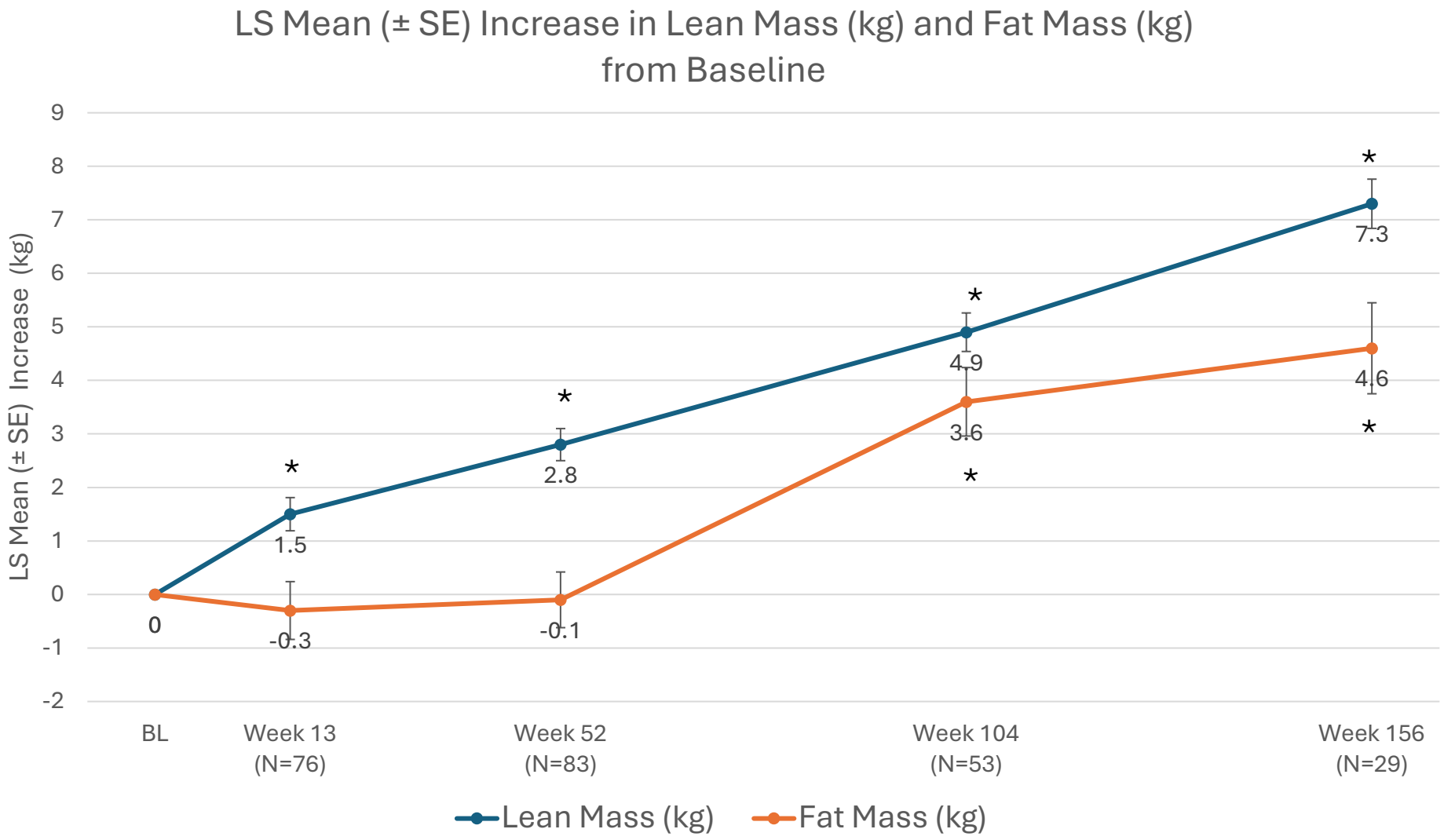


CGI-S scale ranges 1-7 (7 most severe), and Caregiver GI-S scale ranges from 1-4 (4 most severe)

Abbreviations: BL, baseline; CGI-S, Clinical Global Impression of Severity; GI-S, Global Impression of Severity

LEAN BODY MASS and FAT MASS

- Progressively increasing improvements in lean body mass at all time points
- LS mean change [SE] in lean mass significant at all timepoints (*p<0.0001)
- At Year 3: **+7.3 kg** (+40.3%) lean mass change from Baseline



Abbreviations: BL, baseline; LS, least squares; SE, standard error

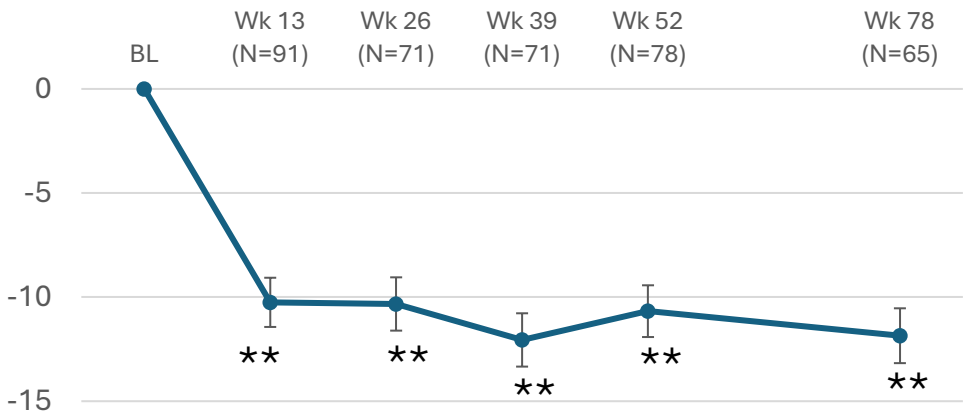
METABOLIC MARKERS

Significant improvements ($p<0.05$) from Baseline in metabolic markers at all but one timepoint through Week 78 (1.5 years)

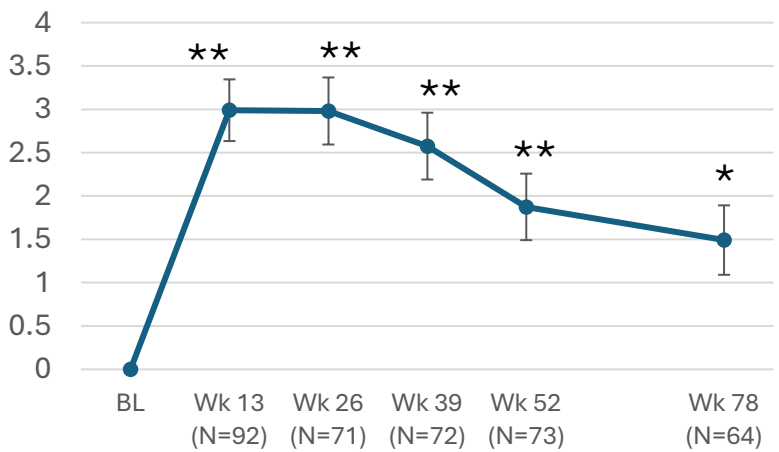
Desired changes would include: decrease in leptin, decrease in insulin, decrease in HOMA-IR (insulin resistance), and increase in adiponectin

* p=<0.05
** p=<0.0001

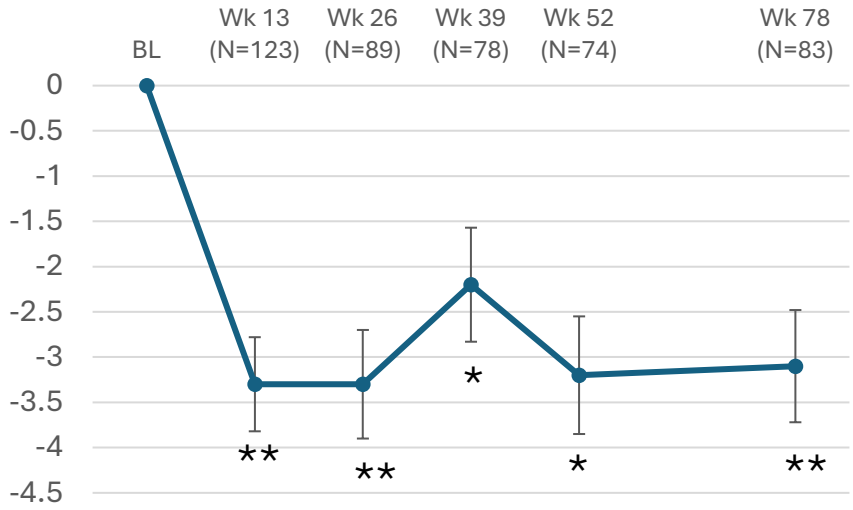
LS Mean (± SE) Change in Leptin (ng/mL)



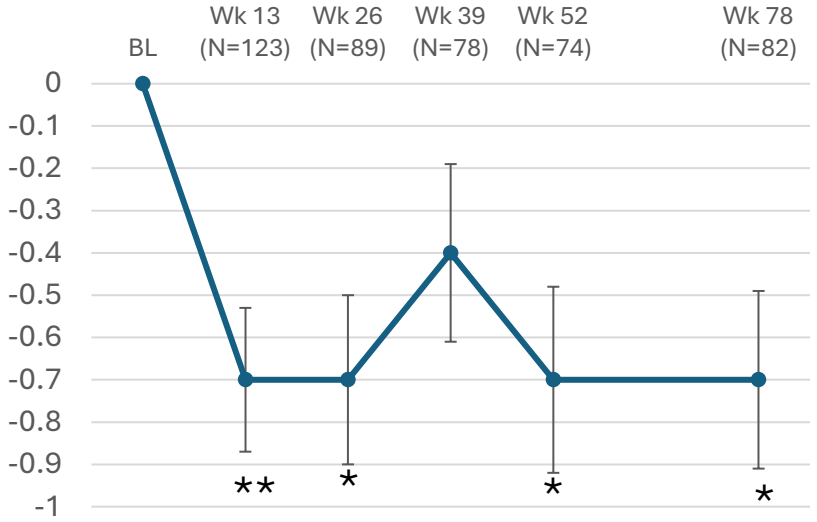
LS Mean (± SE) Change in Adiponectin (µg/mL)



LS Mean (± SE) Change in Fasting Insulin (uIU/mL)



LS Mean (± SE) change in HOMA-IR



Abbreviations: BL, baseline; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; LS, least squares; SE, standard error

CONCLUSIONS

Long-term administration of DCCR (for up to 3 years) was associated with statistically significant, clinically meaningful, durable changes in key outcome measures in people with PWS.

- Improvement in hyperphagia per HQ-CT Total Score from Baseline
- Improvement in PWS behaviors per PWSP domains from Baseline
- Improvement in CGI-S & Caregiver GI-S from Baseline
- Increase in lean body mass from Baseline
- Improvement in key metabolic markers (insulin, HOMA-IR, leptin, & adiponectin) from Baseline (measured up to 1.5 years)

In conclusion, these results support the long-term efficacy of DCCR as a potential treatment of hyperphagia and related problems in children and adults with PWS

Abbreviations: DCCR, diazoxide choline extended-release; OLE, Open-Label Extension; PWS, Prader-Willi syndrome; RWP, Randomized-Withdrawal Period

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Abbreviations: FPWR, Foundation for Prader-Willi Research; PWS, Prader-Willi syndrome; PWSA, Prader-Willi Syndrome Association; UK, United Kingdom; USA, United States of America