Rationale for and Results from a Randomized Withdrawal Period Following Long-Term Administration of Diazoxide Choline Extended-Release Tablets to People with Prader-Willi Syndrome

FPWR Research Conference 2023
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Analyses in this presentation are preliminary and may be subject to change

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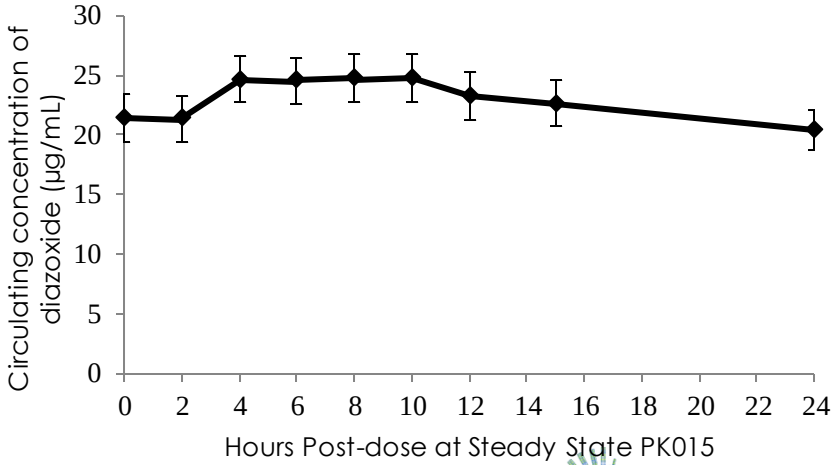
DCCR Was Developed to Facilitate Once Daily Dosing and Improve Response

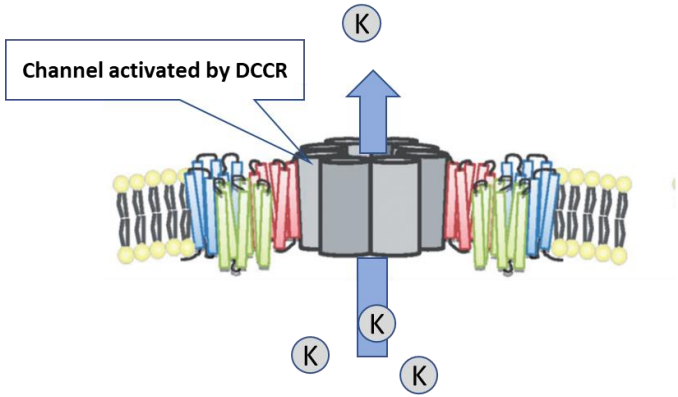
- Choline salt chosen to improve solubility
- Formulation developed to extend absorption throughout the GI tract

- Titration and dosing optimized to safely reach target dose and maintain therapeutic response

- DCCR dosed once daily to achieve stable intraday circulating drug levels
- Strong relationship between circulating drug levels with DCCR and therapeutic responses in PWS



Mechanism of Action in PWS



Membrane hyperpolarization

No Ca^{2+} influx

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

Genes, 11(4), 450. https://doi.org/10.3390/genes11040450.

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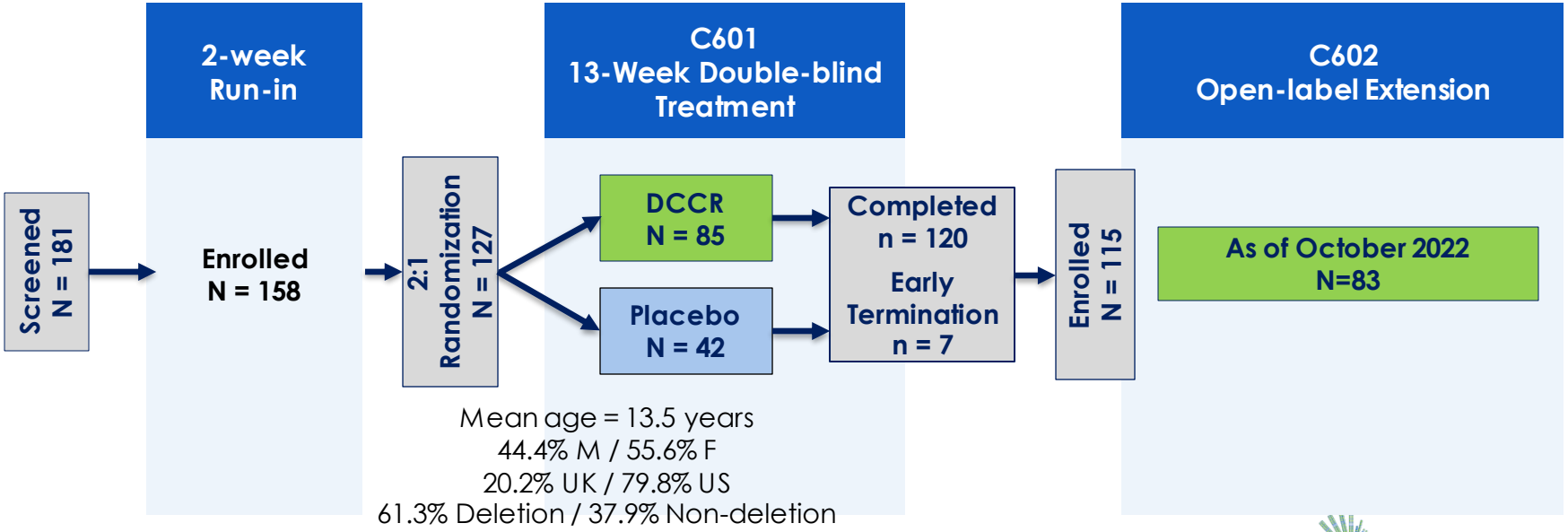
DCCR Phase 3 Clinical Program Design

- C601 (DESTINY PWS): Multi-center, randomized, double-blind, placebo-controlled, parallel arm study in patients with PWS (Phase 3)
- C602: Open-label safety extension study



C601 Primary and Key Secondary Endpoints

Primary Endpoint	All Data		Observed Data through March 1, 2020	
	DCCR (N = 82)	Placebo (N = 42)	DCCR (N = 82)	Placebo (N = 42)
Mean (SE) 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	**p-value**		**p-value**	
Clinical Global Impression of Improvement at Visit 7 (CGI-I)	**0.03**		**0.015**	
Mean Change From Baseline in Body Fat Mass (DXA) at Visit 7	**0.023**		**0.003**	
Caregiver Global Impression of Change at Visit 7 (Caregiver GI-C)	0.41		**0.031**	

Data previously reported.

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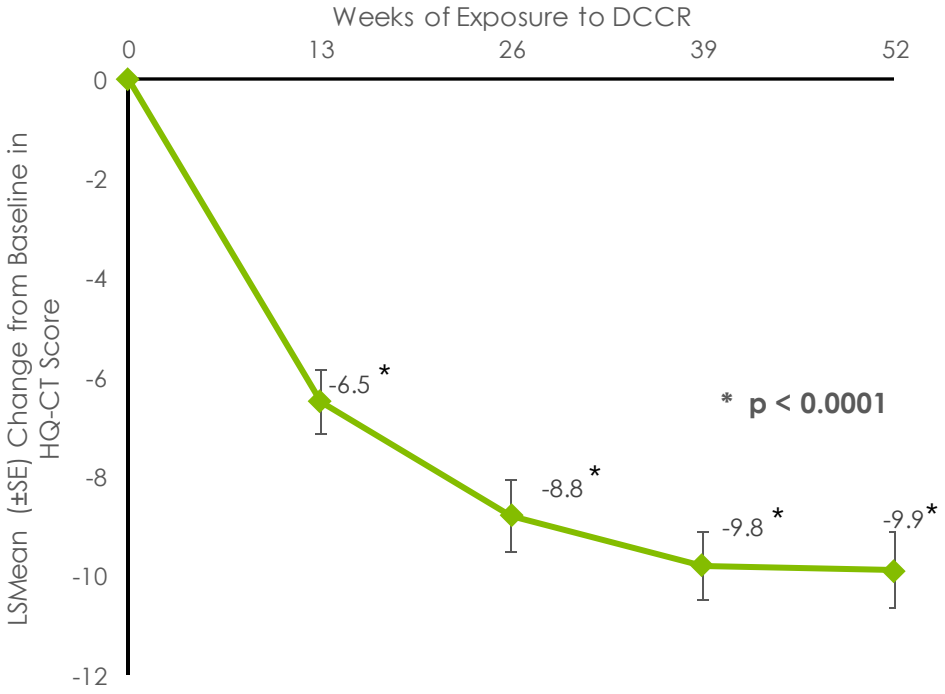
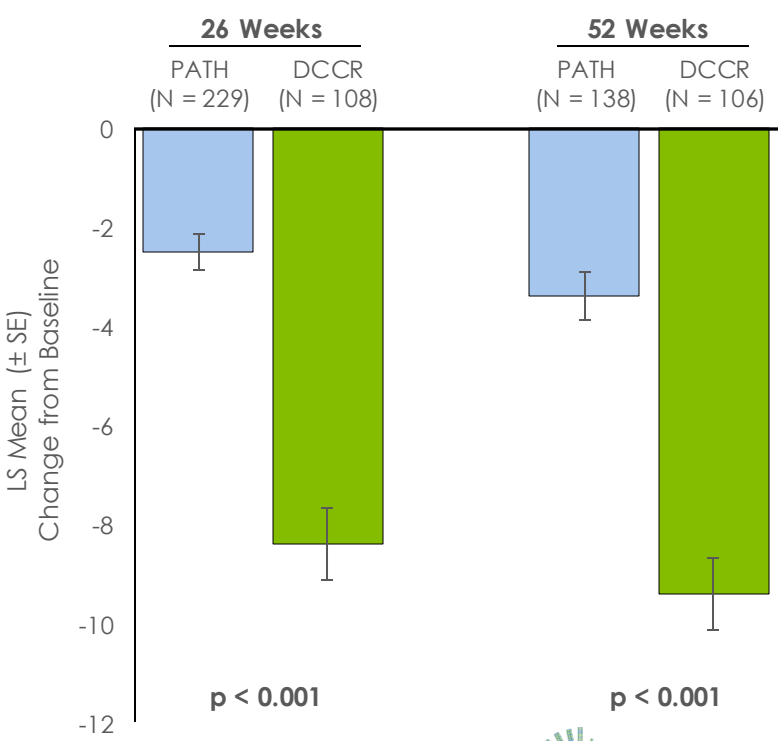
C601/C602 Hyperphagia Change from Baseline and Comparison to PATH for PWS





Data previously reported.
PATH for PWS (PATH) is an ongoing natural history study, which involves the completion of several questionnaires online every 6 months, including HQ-CT, by caregivers of people with PWS.

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Other Significant Endpoints at 1 Year

- Other significant endpoints at 1 year of DCCR administration
  - Behavioral:
    - Improvements in all domains of the PWSP and DBC2 total score and all subscales (all $p<0.0001$)
  - Body composition
    - Lean body mass and lean body mass/fat mass ratio increased (both $p<0.001$)
  - Hormonal and endocrine
    - Leptin, insulin and HOMA-IR decreased (all $p<0.004$) and adiponectin increased ($p<0.0001$)
  - Disease severity
    - Clinical Global Impression of Severity and Caregiver Global Impression of Severity improved (both $p<0.0001$)

Data previously reported.

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DCCR Safety Profile

- ~100 patients treated for more than one year
- Safety profile generally consistent with prior experience with DCCR and the known profile of diazoxide
- The most common adverse events reported were hypertrichosis, peripheral edema and hyperglycemia
- Most events were Grade 1 or 2 in severity, no Grade 4 or higher events
- Typically self-limiting, some needing dose adjustment or treatment (e.g., with oral antidiabetics or short course diuretics)
- No DCCR-related serious unexpected adverse events (SUSARs)

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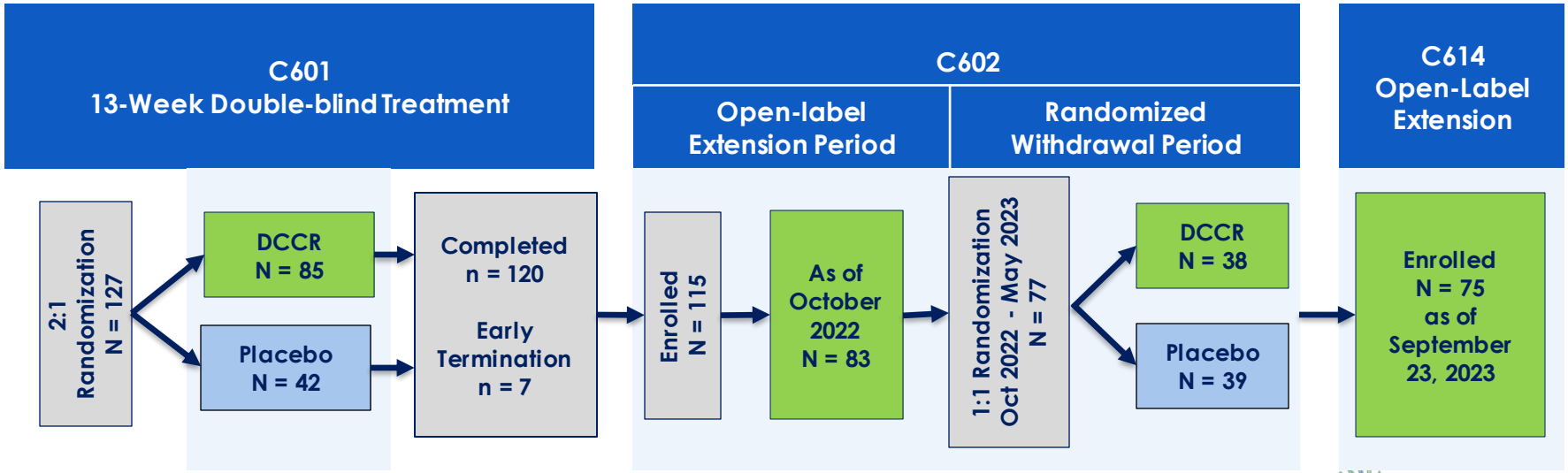
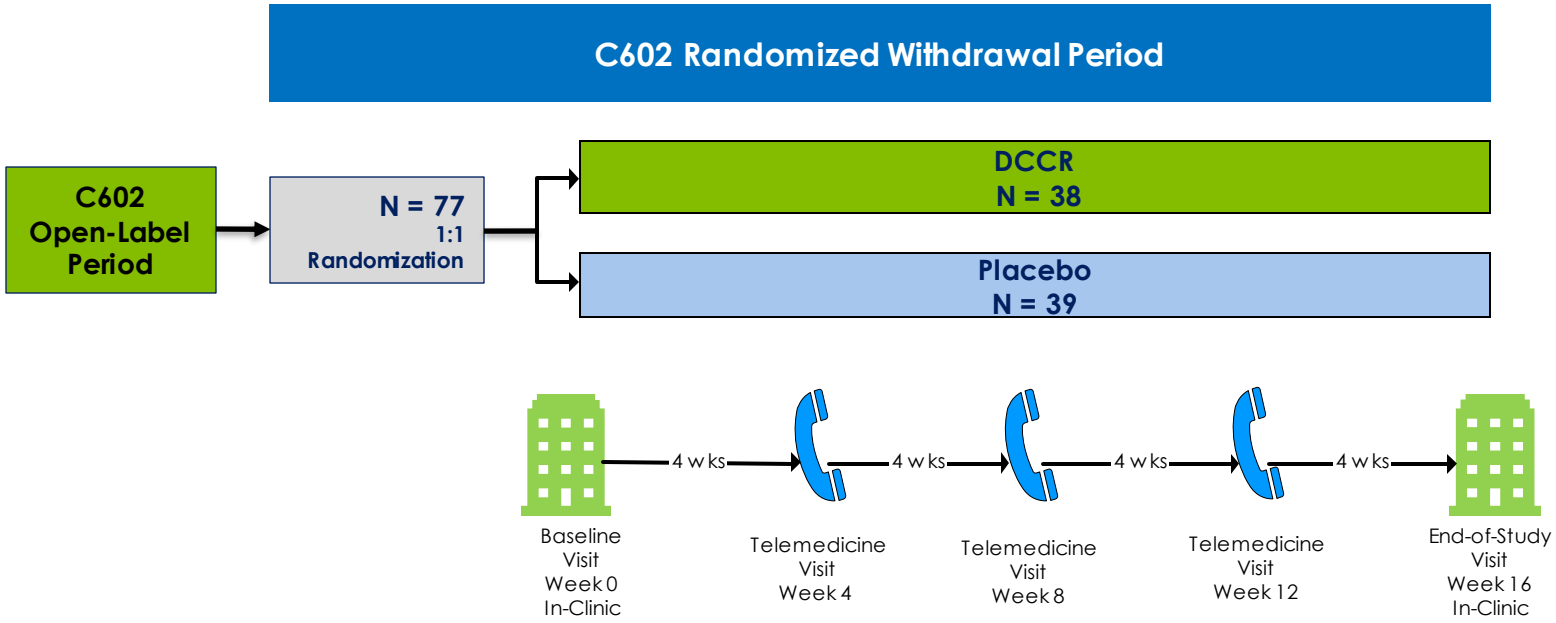
DCCR Phase 3 Updated Clinical Program

- FDA stated that additional controlled data are necessary to support an NDA submission
- In June 2022, the FDA acknowledged that data from a proposed randomized withdrawal period of C602 would potentially suffice
  - Subjects currently enrolled in C602, no new subjects



C602 Randomized Withdrawal Study Design



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C602 RWP Participant Demographics and Baseline Characteristics Comparable Across Treatment Groups

At RWP Randomization	DCCR N=38	Placebo N=39	All Subjects N=77
Age (Range) (yrs)	15.6 (7 – 29)	14.2 (9 – 23)	14.9 (7 – 29)
Female / Male (%)	47 / 53	64 / 36	56 / 44
Race (% White / % Black / % Multiple)	84 / 5 / 11	87 / 8 / 5	86 / 7/ 8
Weight (Range) (kg)	73.7 (29.7 – 143.2)	61.7 (33.3 – 92.4)	67.6 (29.7 – 143.2)
BMI (Range) (kg/m^2)	28.5 (15.6 – 49.0)	25.3 (16.1– 37.6)	26.9 (15.6 – 49.0)
Growth Hormone Use (n)	33	36	69
USA / UK (%)	84 / 16	77 / 23	81 / 20
HQ-CT Total Score	9.0 (0 – 26)	8.1 (0 – 19)	8.5 (0 – 26)
HQ-CT Category (<13 / 13-36 [%])	74 / 26	77 / 23	75 / 25

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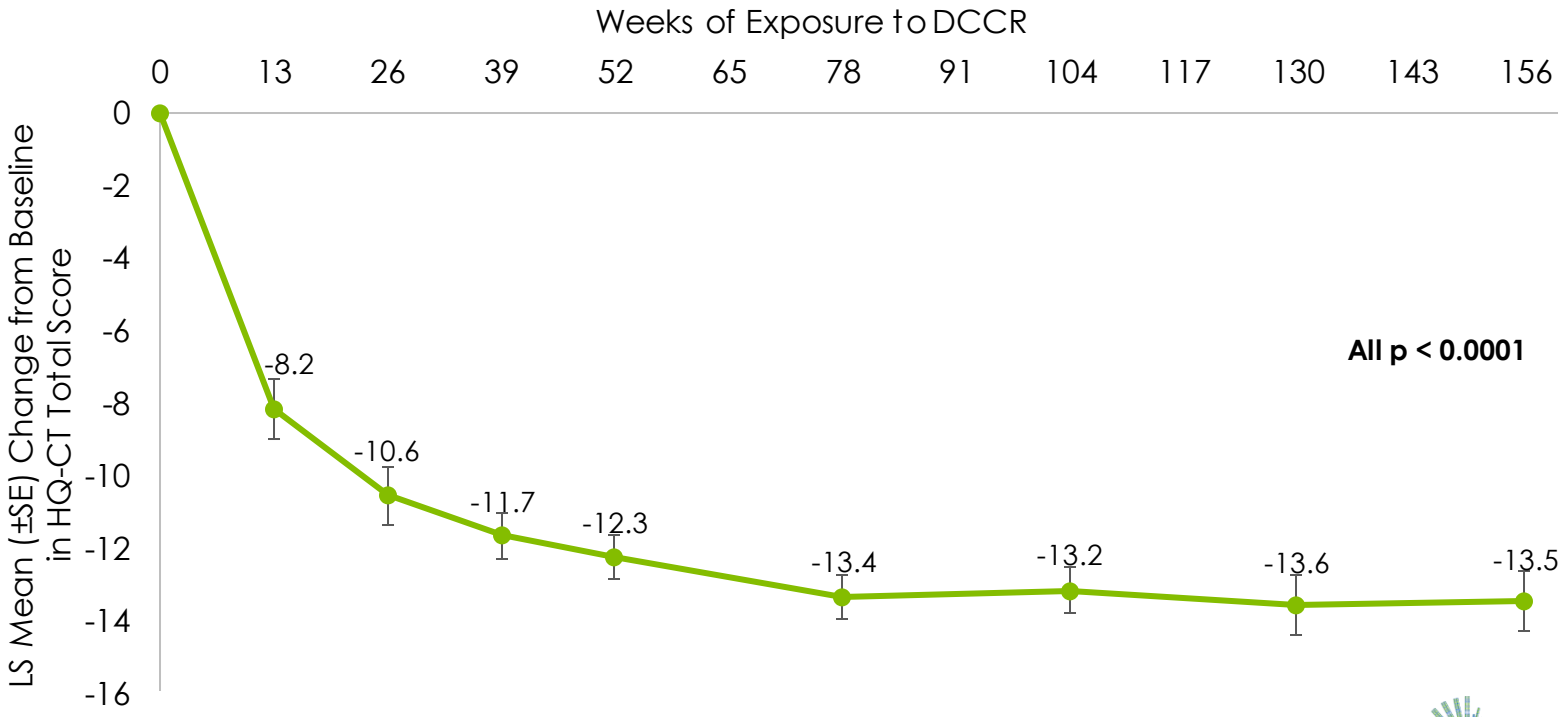
C602 Long-term HQ-CT Changes from Baseline

Durable Response Over >2 years



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C602 RWP Primary Endpoint: HQ-CT Total Score at Week 16

Change from Baseline – Highly Statistically Significant

Week 16	DCCR N=38	Placebo N=39	DCCR vs Placebo
LSMean Change from Baseline in HQ-CT Total Score	2.6 (0.3, 4.8)	7.6 (5.4, 9.7)	-5.0 (-8.1, -1.8)
			p=0.0022

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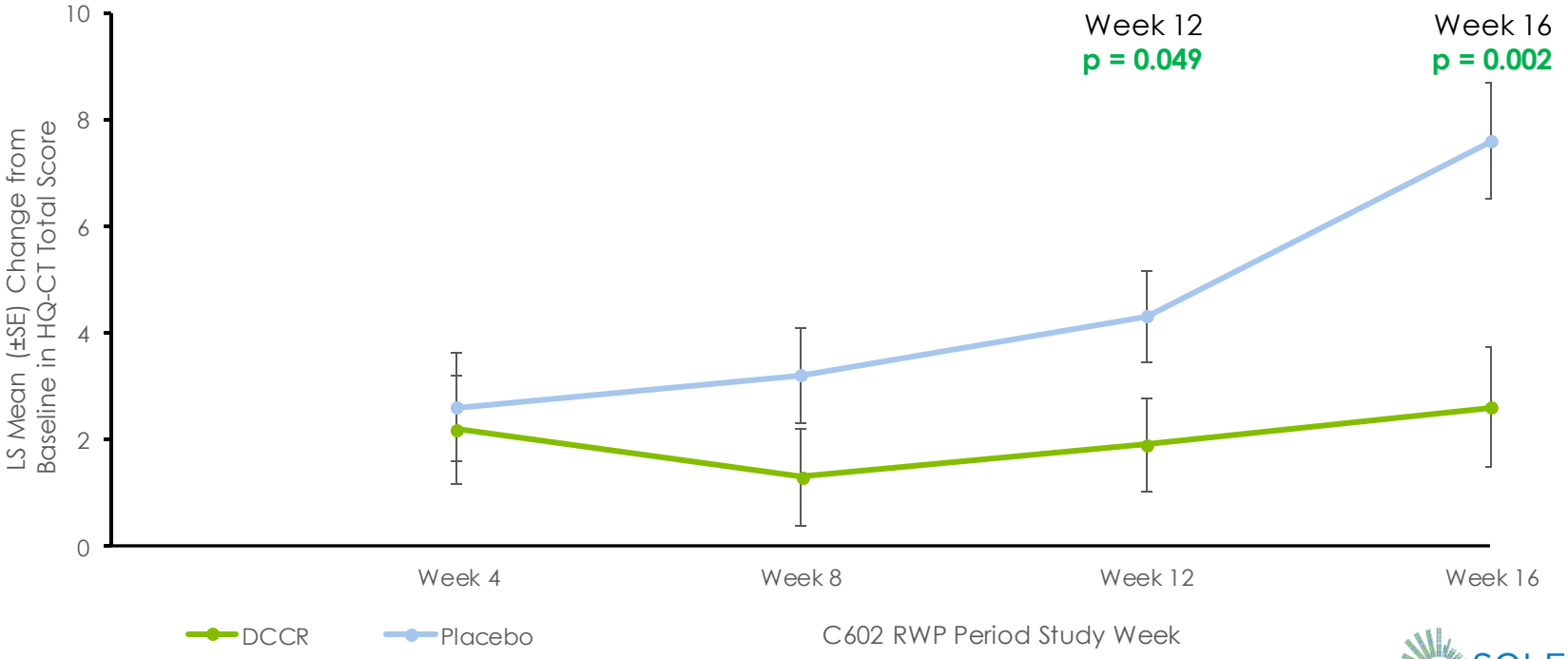
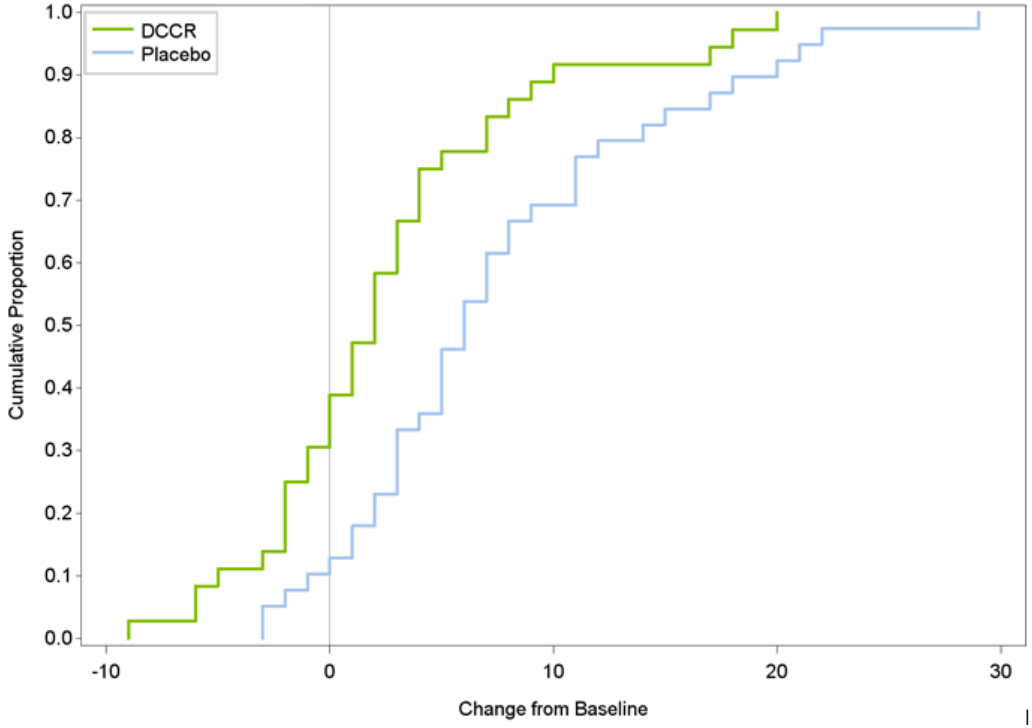
C602 RWP HQ-CT Total Score at Week 16
Change from Baseline for DCCR Compared to Placebo

LS Mean change from baseline highly statistically significant at Week 16; also statistically significant at Week 12

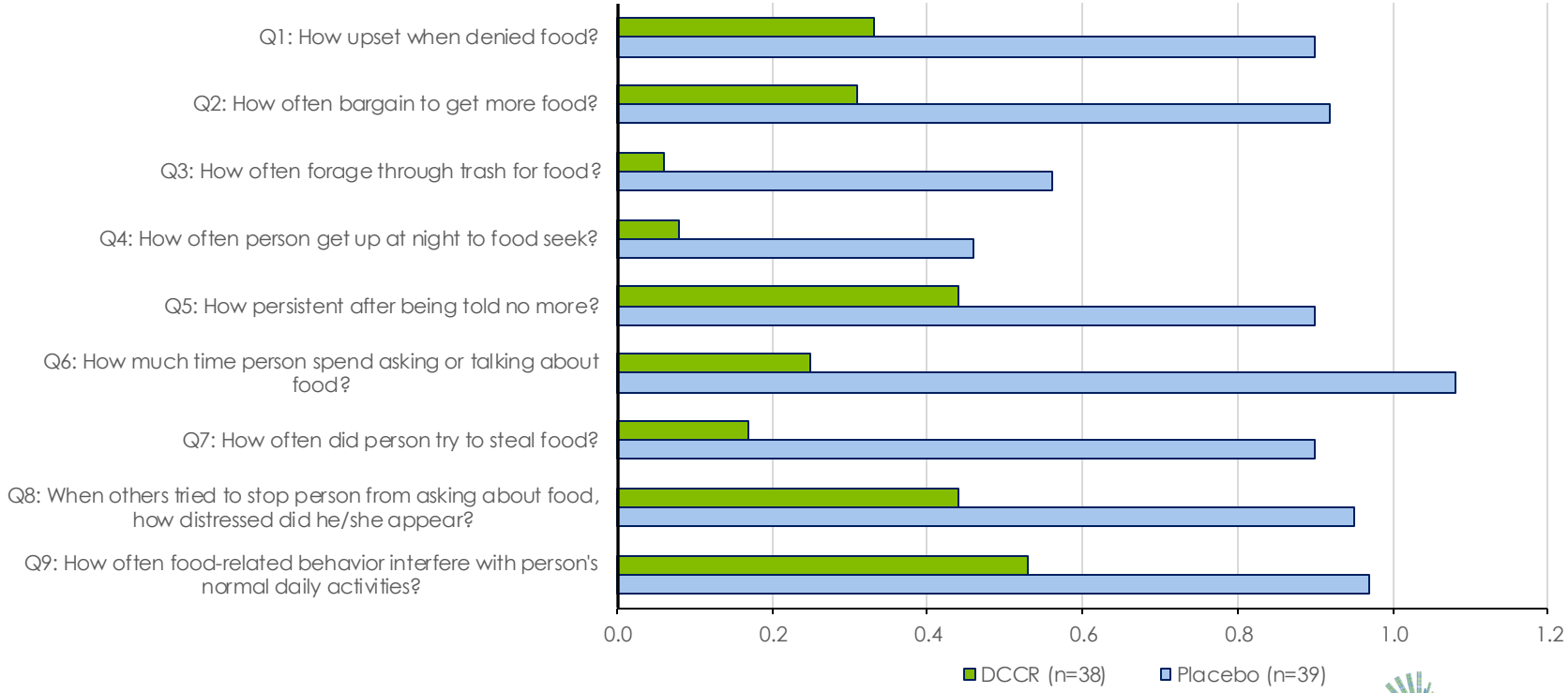


eCDF of Changes from Baseline HQ-CT Total Score to Week 16



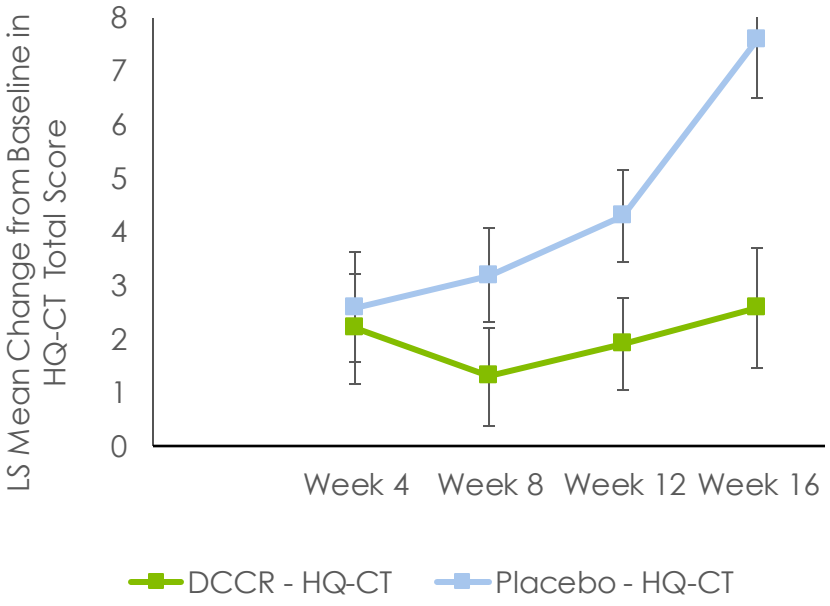
C602 RWP HQ-CT Question by Question at Week 16

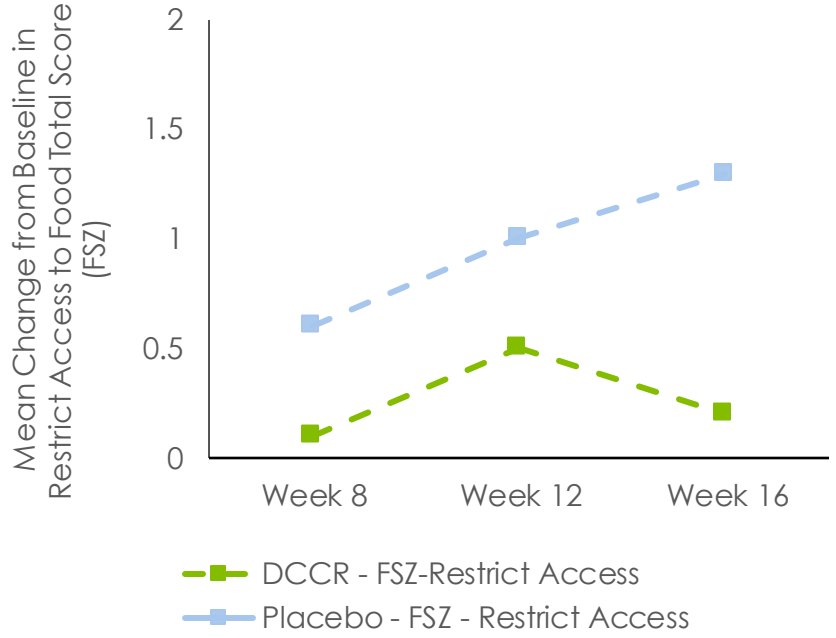
Mean changes from baseline were worse (i.e., increased) for placebo than for DCCR on every question



C602 RWP Changes from Baseline in HQ-CT

Greater restrictions on food access in placebo group compared to DCCR





C602 RWP HQ-CT Total Score at Week 16
Statistically Significant Changes from Baseline in Subgroups

Subgroup	LS Mean Difference (95% CI)	p-value
Overall	-5.0 (-8,1, -1.8)	**0.0022**
Sex		
Male	-6.0 (-11.0, -1.1)	**0.019**
Female	-4.7 (-9.0, -0.5)	**0.031**
RWP Baseline HQ-CT Total Score		
< 13	-4.9 (-8.6, -1.1)	**0.012**
13 - 36	-6.5 (-12.4, -0.6)	**0.033**
Country		
USA	-4.5 (-8.3, -0.7)	**0.020**
UK	-7.9 (-12.3, -3.6)	**0.002**

C602 RWP Secondary Endpoints at Week 16
Strong trends showing worsening with Placebo

Secondary Endpoint	DCCR vs Placebo
Clinical Global Impression of Severity (CGI-S)	p = 0.079
Clinical Global Impression of Improvement (CGI-I)	p = 0.092

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C602 RWP Behavioral Endpoints at Week 16

All PWSP Domains Trending in Favor of DCCR

PWSP Domain	DCCR worse than Placebo	Placebo worse than DCCR
Aggressive Behaviors		✓
Anxiety		✓
Rigidity, Irritability		✓
Compulsivity		✓
Depression		✓
Disordered Thinking		✓

p = not significant

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C602 RWP LSMean (SE) Changes from Baseline at Week 16 in Body Weight and BMI

Parameter	DCCR (N = 38)	Placebo (N = 39)	Difference (95% CI)	p-value
Body Weight (kg)	0.8 (0.58)	2.4 (0.56)	-1.6 (-3.1, -0.1)	**0.035**
BMI (kg/m^2)	0.2 (0.22)	0.8 (0.22)	-0.6 (-1.2, -0.1)	**0.034**

C602 RWP Safety Summary

No DCCR-related serious TEAEs and no new safety signals

Adverse Event Overview

No. of subjects who experienced at least one:	DCCR N = 38 n (%)	Placebo N = 39 n (%)	All Subjects N = 77 n (%)
TEAE	28 (73.7)	29 (74.4)	57 (74.0)
TEAE related to study drug	7 (18.4)	11 (28.2)	18 (23.4)
TEAE leading to premature discontinuation of study drug	0	0	0
Serious TEAE (SAE)	0	1 (2.6)	1 (1.3)
SAE related to study drug or leading to death	0	0	0

TEAEs – Most Frequent

Preferred Term	DCCR N = 38 n (%)	Placebo N = 39 n (%)	All Subjects N = 77 n (%)
Dermatillomania	5 (13.2)	6 (15.4)	11 (14.3)
Abnormal behavior	5 (13.2)	5 (12.8)	10 (13.0)
Aggression	3 (7.9)	5 (12.8)	8 (10.4)
Hypertrichosis	2 (5.3)	5 (12.8)	7 (9.1)
Food craving	3 (7.9)	4 (10.3)	7 (9.1)

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Summary

C602 RWP Highly statistically significant change in primary endpoint supported by secondary and key objective endpoints

Primary Endpoint	Secondary Endpoints		Objective Endpoints	
HQ-CT Total Score	CGI-S	CGI-I	Body Weight (kg)	BMI (kg/m^2)
p = 0.0022	p = 0.079	p = 0.092	**p = 0.035**	**p = 0.034**

- Mean differences all PWS behavioral domains of the PWSP (i.e., aggressive behaviors, anxiety, rigidity/irritability, compulsivity, depression, and disordered thinking) favored DCCR over placebo
- No new safety signals, no DCCR-related serious TEAEs

CGI-S = Clinical Global Impression of Severity
CGI-I = Clinical Global Impression of Improvement

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C614 Open Label Extension

- 76 of 77 completed C602 RWP
  - 1 subject discontinued early due to withdrawal of caregiver consent, not due to safety issues
- 74 of 76 have entered C614 and back on DCCR
  - 2 subjects scheduled to start shortly
- 1 subject who had declined to participate in C602 RWP has also started C614

Soleno wishes to extend their heartfelt appreciation and thanks to:

- The study participants, your caregivers and your families for your participation in our development program for > 3 years
- FPWR, PWSA-USA, PWSA-UK, IPWSO, and individual advocates for their continued support
- Our investigators and their study staff for conducting these studies

C602 Investigative Sites – 20 (US), 9 (UK)

Site #	Principal Investigator	Institution	Location
50	Tony Goldstone	Hammersmith Hospital	London
51	**Nicola Bridges**	**Chelsea & Westminster Hospital**	**London**
52	**Evelien Gevers**	**Royal London Hospital**	**London**
53	**Tony Holland**	**Fulbourn Hospital**	**Cambridge**
54	John Wilding	Aintree Hospital	Liverpool
55	Timothy Barrett	Birmingham Children's Hospital	Birmingham
56	**Guftar Shaikh**	**Royal Hospital for Children**	**Glasgow**
57	Poonam Dharmaraj	Alder Hey Children's Hospital	Liverpool
58	**Verghese Mathew**	**Hull Royal Hospital**	**Hull**
70	**Jennifer Abuzzahab**	**Children's Minnesota**	**St. Paul MN**
71	**Lynne Bird**	**Rady Children's Hospital / UCSD**	**San Diego CA**
72	Merlin Butler	Kansas University Medical Center	Kansas City KS
73	Shawn McCandless	Children's Hospital Colorado	Aurora CO
74	**Jennifer Miller**	**University of Florida**	**Gainesville FL**

Site #	Principal Investigator	Institution	Location
75	**Parisa Salehi**	**Seattle Children's Hospital**	**Seattle WA**
76	Laura Konzcal	UH Medical Center	Cleveland OH
77	**Ashley Shoemaker**	**Vanderbilt University**	**Nashville TN**
78	**Amy Fleischman**	**Boston Children's Hospital**	**Boston MA**
79	**David Stevenson**	**Stanford University**	**Palo Alto CA**
80	**Jorge M. Corletto**	**Winthrop University Hospital**	**Mineola NY**
81	**David Viskochil**	**University of Utah**	**Salt Lake City UT**
82	**Jack Yanovski**	**NICHD**	**Baltimore MD**
83	**Kathryn Obrynba**	**Nationwide Children's Hospital**	**Columbus OH**
84	**Virginia Kimonis**	**UC Irvine**	**Irvine CA**
86	**Eric Felner**	**Emory University**	**Atlanta GA**
87	**Melissa Lah**	**Indiana University Hospital**	**Indianapolis IN**
88	**Elizabeth Littlejohn**	**Sparrow Clinical Research Institute**	**Lansing MI**
89	**Katerina Harwood**	**St. Joseph's Medical Center**	**Paterson NJ**
90	**Heidi Shea**	**Research Institute of Dallas**	**Dallas TX**

Blue, bold text = C602 RWP Sites
17 (US), 5 (UK)

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