6th International Prader-Willi Syndrome Caregivers' Conference – ***#PWSCARE24***

May 2024 | Soleno Therapeutics

IPWSO
International
Prader-Willi Syndrome
Organisation

Certain Notices and Disclaimers

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

Prader-Willi Syndrome (PWS)

- Complex genetic neurobehavioral/metabolic disorder due to the loss or lack of expression of a set of genes on chromosome 15
- Birth incidence ~1:15,000 live births
- Elevated mortality rates; average life expectancy ~30 years
- High unmet need for:
  - Hyperphagia
  - Low lean body mass/increased fat mass
  - PWS-related behaviors
- Quality of life for families with a child with PWS is greatly affected
  - Non-PWS siblings show high rates of post traumatic stress syndrome

PWS – Unmet Medical Need

- Based on a 2014 global survey of PWS caregivers by FPWR the greatest needs to address in a new therapeutic are:
  - Reduces hunger and improves behavior around food
  - Reduces fat/increases muscle mass; improves stamina/activity
  - Reduces temper outburst frequency/severity
  - Reduces obsessive compulsive behavior
  - Improved intellect/development
- Psychiatric disease burden is high in PWS, as is psychiatric medication use
  - 51.1% use at least one, 34.9% at least 2, and 20.1% at least 3

DCCR Once Daily Tablets

Daily Dosing Critical to Facilitate Independence and Compliance

Tablet formulation of choline salt of diazoxide (diazoxide choline is an NCE)

DCCR allows for gradual absorption of diazoxide over 24 hours

Protected by multiple issued patents, including composition of matter

More than 330 subjects investigated, including more than 130 with PWS

Ongoing Phase 3 program in PWS

CLINICAL PROGRAM

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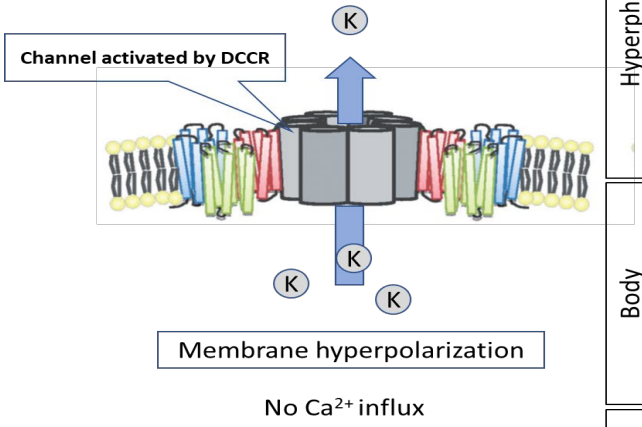
Mechanism of Action in PWS



Hyperphagia	NPY/AgRP/GABA Neurons	Reduced NPY and AgRP secretion - resulting in reduced hyperphagia
	DMV Neurons	Neuronal inhibition - resulting in reduced hyperinsulinemia, improved glycemic control, improved satiety and reduced hyperphagia
	Insulin sensitivity	Increased insulin binding, central, and improved post-receptor response – reduced hyperphagia
	Sweet taste receptors	Reduced detection of sweet taste - resulting in reduced intake of sweet tasting foods and reduced hyperphagia
Body Composition	Adipocytes	Reduced de-novo fatty acid biosynthesis and increased β-oxidation of fat - resulting in reduced fat mass
	Skeletal muscle	Reduced atrophy and improved benefit of exercise - resulting in increased muscle mass
	Pancreatic β-cells	Reduced potential for hyperinsulinemia – reduced fat accumulation and improved insulin resistance
Behavioral Complications	GABAnergic neurons	Reduced neuronal firing rate - resulting in reduced aggressive and maladaptive behaviors, rigidity, depression

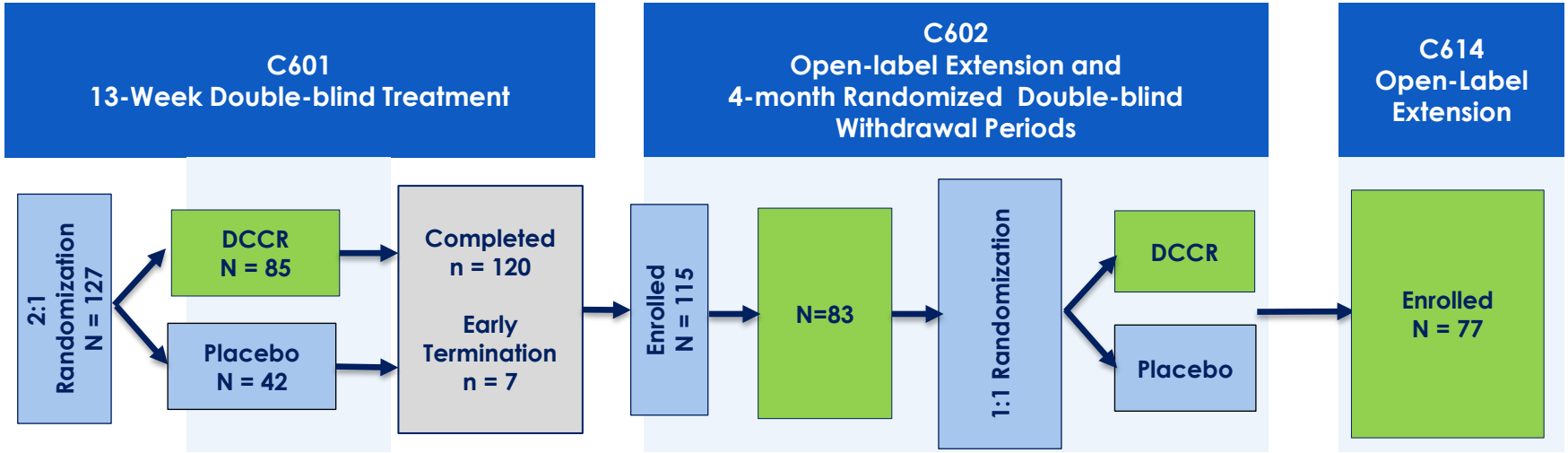
Adapted from Genes, 11(4), 450. https://doi.org/10.3390/genes11040450.

Phase 2 Study in PWS

- Single site (UC Irvine) – 13 obese or overweight people with PWS – no hyperphagia inclusion criteria
- 10 weeks open label and 4 weeks RW
- What we learned
  - Significant reductions in hyperphagia
  - Significant loss of body fat
  - Significant increase in lean body mass
  - Significant reduction in aggressive, threatening and destructive behaviors
  - Target dose is ~4.2 mg/kg

DCCR Phase 3 Clinical Program Design

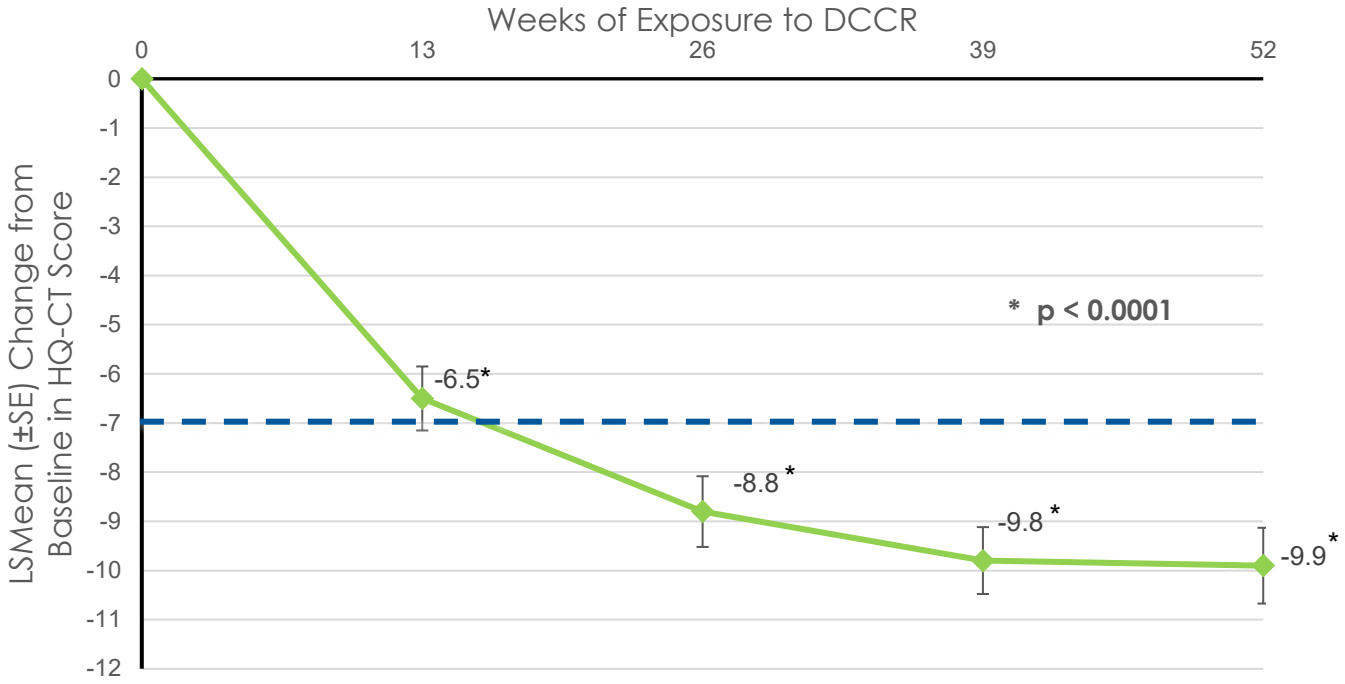
- C601 (DESTINY PWS): Multi-center, randomized, double-blind, placebo-controlled, parallel arm study in patients with PWS (Phase 3)
- C602: Study with open-label extension (OLE) and randomized double-blind withdrawal (RW) periods
- C614: Open-label safety extension study



C601 Primary and Key Secondary Endpoints

Primary Endpoint	**DCCR (N = 82)**	**Placebo (N = 42)**
Mean Change from Baseline in Hyperphagia at Visit 7	-5.94 (0.879)	-4.27 (1.145)
LS Mean Difference [DCCR-Placebo] (SE)	-1.67 (1.294)	
p-value	0.1983	
Key Secondary Endpoints		
Clinical Global Impression of Improvement at Visit 7 (CGI-I)	**0.029**	
Mean Change From Baseline in Body Fat Mass (DXA)	**0.023**	
Caregiver Global Impression of Change at Visit 7 (Caregiver GI-C)	0.409	

C601/C602 Hyperphagia Change from Baseline



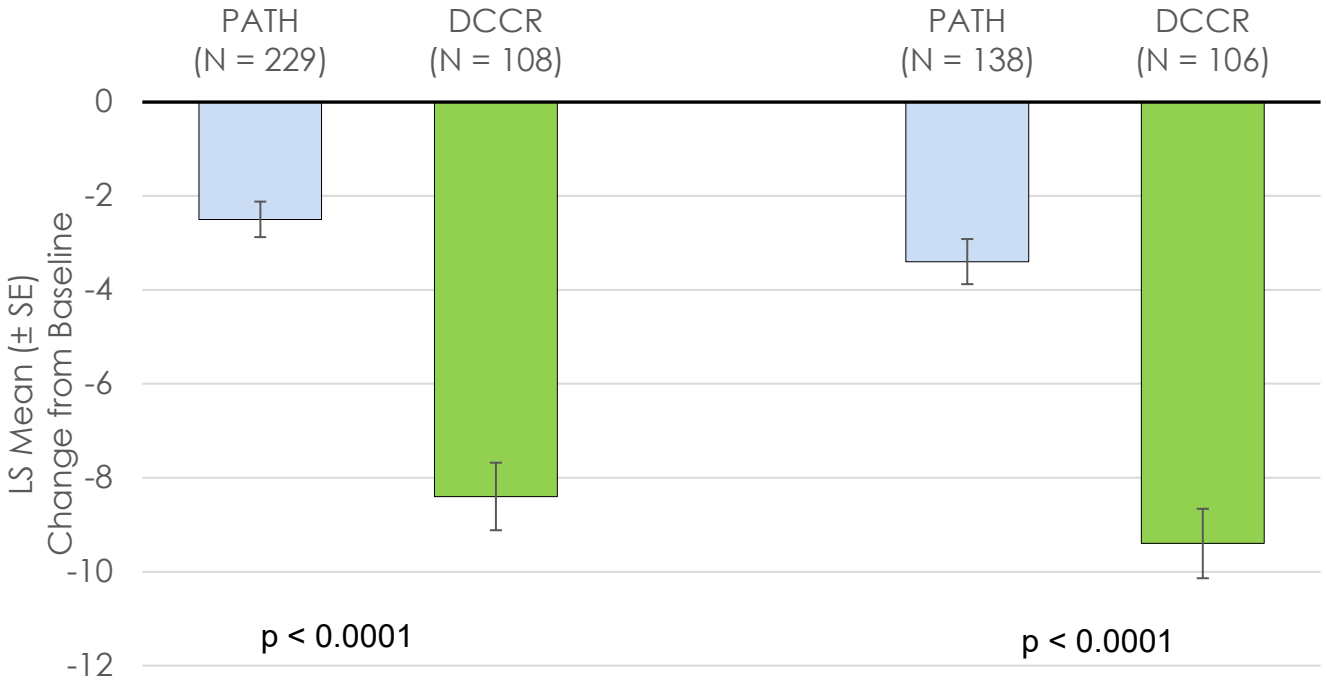
C601/C602 PWS Profile Behavioral Change Results after One Year of DCCR

Domain	p-value
Aggressive Behaviors	<0.0001
Anxiety	<0.0001
Compulsivity	<0.0001
Depression	<0.0001
Disordered Thinking	<0.0001
Rigidity Irritability	<0.0001

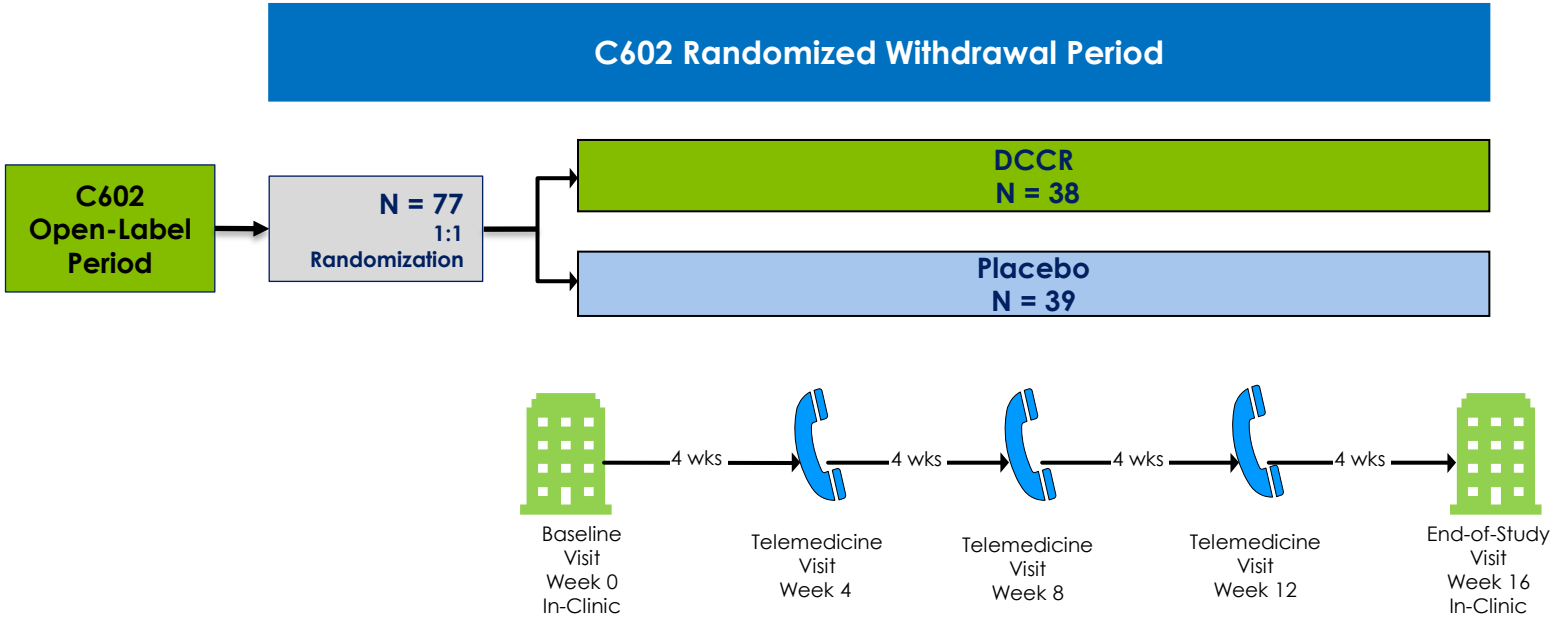
C601/C602 and PATH for PWS (PATH)

- C602 was an open-label extension study of DCCR in subjects who completed DESTINY PWS successfully
- PATH was an ongoing study evaluating the natural history of subjects with PWS
  - Sponsored by FPWR
  - ~ 650 active participants
  - Completion of several questionnaires online every 6 months, including HQ-CT and PWSP by caregivers of people with PWS
  - PATH for PWS analysis set included subjects who met C601/602 inclusion criteria of age, baseline hyperphagia, weight and caregiver
- The statistical comparison of DCCR data to PATH was conducted by an independent CRO

Change in Hyperphagia with DCCR Compared to PATH

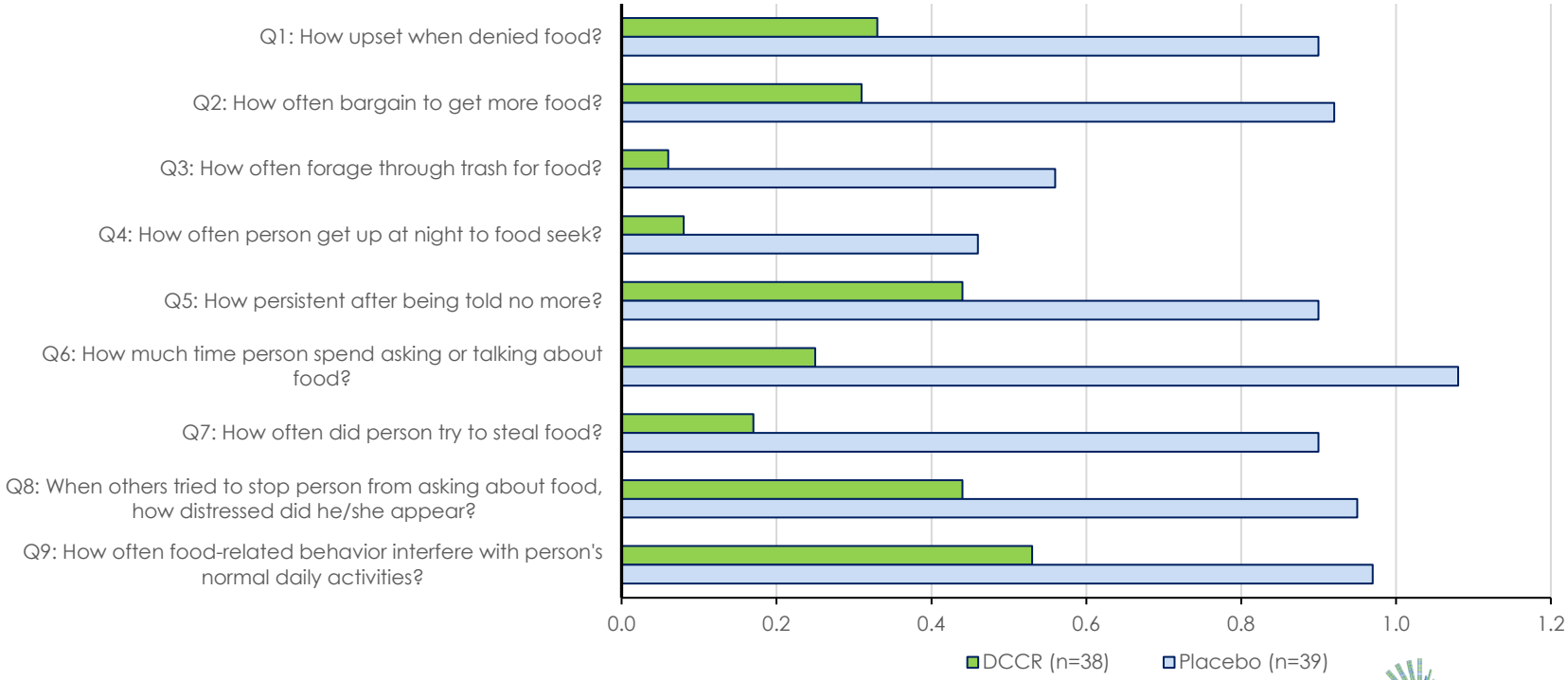


C602 Randomized Withdrawal Study Design



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 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

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

SAFETY PROFILE

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Safety Profile Consistent with Prior Experience

- Substantial long-term safety database for rare disease
  - Mean duration of exposure: 2.5 yrs (max: 4.5 yrs)
  - 105 patients ≥1 yr; 90 patients ≥ 2 yrs
- Most common AEs:
  - Hypertrichosis (68.8%)
  - Peripheral edema (34.3%)
  - Hirsutism (27.2%)
  - Hyperglycemia (27.2%)
- Most AEs grade 1-2 (75.2%), most resolve without treatment
  - Otherwise, dose adjustments/temporary drug holidays, or Rx with diuretic or glucose-lowering agents for edema or hyperglycemia
- Only 8% of patients discontinued due to AEs

Impact of DCCR

- *Photos provided with consent of the DCCR study participant's caregiver through University of Florida, USA*
- *Changes not representative of all participants*
- *Changes occurred over 12 or more months of DCCR once daily*

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SOLENO THERAPEUTICS - EUROPE

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Soleno Therapeutics Europe

- EU HQ based in Dublin, Ireland
- Oversight of Europe (EU & the UK) activities:
  - Regulatory submissions for DCCR
  - Market access & reimbursement submissions for DCCR
- Focus for 2024 – prepare for regulatory submission in the EU & the UK

DCCR – regulatory planning

Initiated activities in the European Union in Jan 2024

DCCR has orphan designation from the EMA since 2017

MAA submission to EMA will be required through the centralized procedure

Initiated UK activities in addition to ongoing CT in Jan 2024

New international recognition procedure (IRP) in place at MHRA

UK submission can be based on both FDA and EMA procedures

Reimbursement & access

- EU
  - Member state (MS) specific
  - Single application to each country HTA body
  - Av. time to reimbursement in the EU for non-oncology orphan drugs ~600 days*

- UK
  - England & Wales – National I statute of Health & Care Excellence (NICE)
  - Scotland – Scottish Medicines Consortium (SMC)

* https://www.efpia.eu/media/s4qf1eqo/efpia_patient_wait_indicator_final_report.pdf