Impact on Body Composition in Individuals With Prader-Willi Syndrome Receiving Diazoxide Choline Extended-Release Tablets in the Phase 3 Clinical Program

SOLENO THERAPEUTICS

- Diazoxide choline extended-release tablets (**diazoxide choline**) are once-daily oral tablets indicated for the treatment of hyperphagia in adults and pediatric patients 4 years of age and older with Prader-Willi syndrome (PWS)[1]
- Hyperphagia, as assessed using the change from baseline in the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) total score, was the primary efficacy endpoint in the Phase 3 PWS clinical trials of diazoxide choline[1-3]
  - Results from the Phase 3 C602-randomized withdrawal period (C602-RWP) trial showed a statistically significant worsening of hyperphagia in the placebo group, compared with the diazoxide choline group, and was the basis for US Food and Drug Administration (FDA) approval[1,4]
- Diazoxide choline improved certain measures of body composition in clinical study participants with PWS.[2,3,5,6] **Diazoxide choline is not indicated for weight reduction or body composition improvements in PWS**

Atypical Body Composition in PWS

- PWS represents the most common form of syndromic obesity and is characterized by distinctive atypical body composition with patterns that evolve over the developmental stages.[7,8] Infants and children with PWS, even those with normal body mass index (BMI), display reduced lean body mass (LBM) and increased fat mass[7-9]
  - These patterns also differ clinically from those observed in non-syndromic obesity[8-10]
- **Hyperphagia, as well as obesity,** are among the clinical features of PWS that may typically develop in childhood and, if present, can each further impact body composition. **Not all individuals with PWS are obese** - excessive weight or obesity affects ~40% of children and adolescents and ~80-90% of adults, yet body composition remains distinct from non-syndromic obesity[9]

Hyperphagia is the hallmark symptom of PWS that can start as early as age 4 years. It is characterized by extreme hunger, constant thoughts about food, and a constant urge to eat that cannot be satisfied with food[11]

- Compared with individuals who have non-syndromic obesity, individuals with PWS have increased subcutaneous adiposity with relatively lower visceral adiposity. Individuals have reduced LBM and muscle tone (hypotonia), decreased basal metabolic rate, and lower energy expenditure[9,10]
- Despite timely initiation of growth hormone therapy in children with PWS, atypical body composition, such as increased fat mass and reduced LBM, can still persist[9]

Natural History of Body Composition Changes in People With PWS[12-14]

Infants

- **Decreased birth weight, length, and BMI,** although birth weight, length, and BMI may remain in the normal range[8]
- **Increased body fat percentage**[10]

Children

- **Progressive weight gain**, which can lead to childhood obesity[8]
- **Decrease in LBM** becomes evident[8]

Adolescents and adults

- **Severe and progressive obesity**[9,18]
- **Significantly decreased total lean mass** for arms, legs, and trunk[9]
- **High ratio of body fat mass to LBM**, especially in the in arms and legs[9]
- **Decreased bone density**[8]

Measuring Body Composition in People With PWS

- Anthropometric indicators like weight and BMI may not be accurate assessments of body composition in people with PWS, particularly for children and adolescents, who experience natural weight gain during growth periods
- Measuring additional parameters, including LBM, lean-to-fat mass ratio, and fat mass, may provide a more comprehensive clinical context regarding the patterns across development and qualitative shifts in body composition in patients with PWS

BMI z-score can more appropriately be used to assess changes in body composition in children and adolescents with PWS, compared with BMI alone[10,15]

- BMI z-score indicates how much a person's BMI deviates from the average BMI for individuals of the same age and sex, relative to a reference population (BMI z-score of 0 represents the average BMI for age and sex; >0 = higher than average BMI, and <0 = lower than average BMI)[10,15]

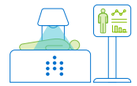
LBM, **body fat mass**, and **lean-to-fat mass ratio** are important parameters to measure body composition changes in people with PWS, who typically have reduced LBM and increased adiposity even if they have normal body weight[10,14]

Trunk fat mass is also a relevant measure as people with PWS can have significantly decreased total lean mass in the arms, legs, and trunk[13,14]

Diazoxide Choline Extended-Release Phase 3 Clinical Trial Program in Individuals With PWS

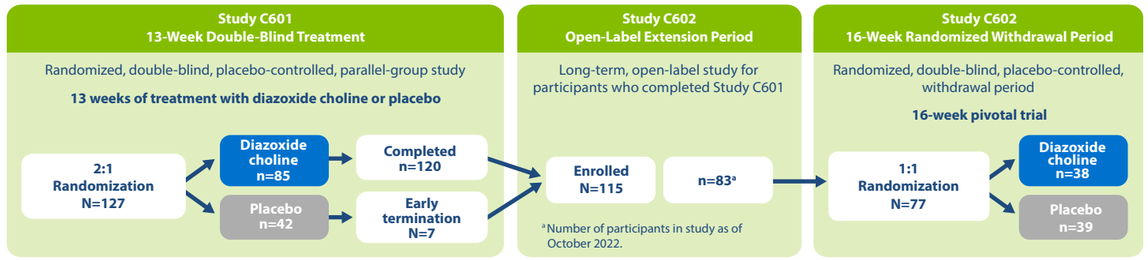
Body composition parameters, including weight, BMI, BMI z-score, LBM, and fat mass, were evaluated as secondary or exploratory efficacy endpoints in the completed Phase 3 PWS clinical trials[2,3,5,6,16]

Body composition assessments



Fat mass, LBM, and trunk fat mass were measured using dual-energy x-ray absorptiometry[2,3,5,17]

- Lean mass index (LMI) was calculated as LBM divided by height squared (kg/m^2)
- LBM was calculated from the sum of the lean mass values of the trunk, left arm, right arm, left leg, and right leg
- LBM-to-fat mass ratio was calculated by dividing the total LBM by the total fat mass

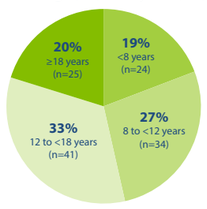


- Study **C601** (NCT03440814) was the initial 13-week, randomized, placebo-controlled trial with participants ≥4 years of age with PWS[2]
- Eligible participants subsequently enrolled in **C602** (NCT03714373), a multicenter, 2-period study consisting of an open-label extension period (**C602-OLE**), lasting up to 4.3 years, followed by a 16-week, double-blind, placebo-controlled, randomized withdrawal period (**C602-RWP**)[1,3,16]
- In **C602-RWP**, the effects of continued once-daily diazoxide choline versus diazoxide choline withdrawal (initiation of placebo) were assessed[1,16]

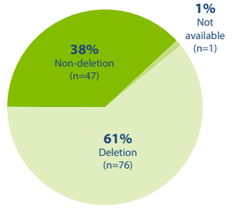
Baseline Demographics and Characteristics in Study C601 (13-week): Diazoxide Choline Versus Placebo[2,17]

Age Distribution

Mean age (SD): 13.5 years (7.0)



PWS Genetic Subgroup



Mean Weight (SD)
61.6 (30.0) kg

Mean Height (SD)
146.7 (19.0) cm

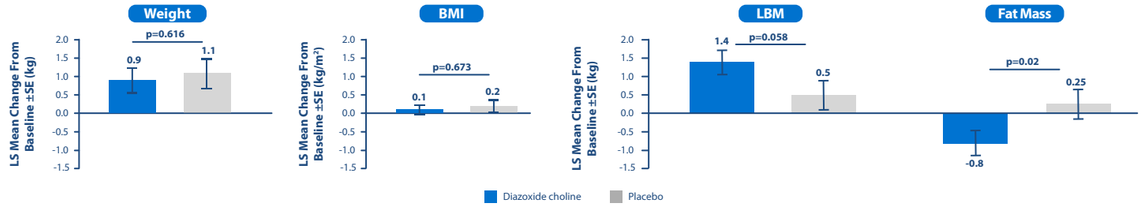
Mean BMI (SD)
27.3 (9.6)

Mean fat mass (SD)
26.5 (17.6) kg

Mean LBM (SD)
28.3 (12.5) kg

Analysis of Body Composition Changes in Study C601: Placebo-Controlled 13-Week Study (Intent-to-Treat Population)[2,17]

- Body composition changes from Study C601 provide important baseline context for the Phase 3 PWS program
- Participants were treatment naive at enrollment and the active-treatment arm represented first exposure to diazoxide choline and was compared against a placebo group



Changes in **weight** and **BMI** after 13 weeks of treatment with diazoxide choline were **not significant** compared with placebo

Following 13 weeks of treatment, **body fat mass decreased significantly**, with a trend toward an **increase** in **LBM** from baseline compared with that of placebo

- There were significant improvements in the **lean-to-fat mass ratio** (LS mean [SE]: 0.1 [0.03] vs. 0.0 [0.03]; p=0.001) and **trunk fat mass** in the diazoxide choline group compared to placebo (LS mean [SE]: -0.3 kg [0.31] vs. 0.5 kg [0.36], respectively; p=0.047).

Note, in Study C601, diazoxide choline was not associated with a statistically significant reduction in hyperphagia as measured by the HQ-CT total score, compared with placebo in the intent-to-treat population

Analysis of Body Composition Changes With Long-Term Diazoxide Choline Treatment

- The following analyses include long-term exposure data from participants in Studies C601 and/or C602 who received at least 1 dose of diazoxide choline

Impact of Diazoxide Choline Treatment on LBM and Fat Mass: C601/C602-OLE Over 156 Weeks[5,17]

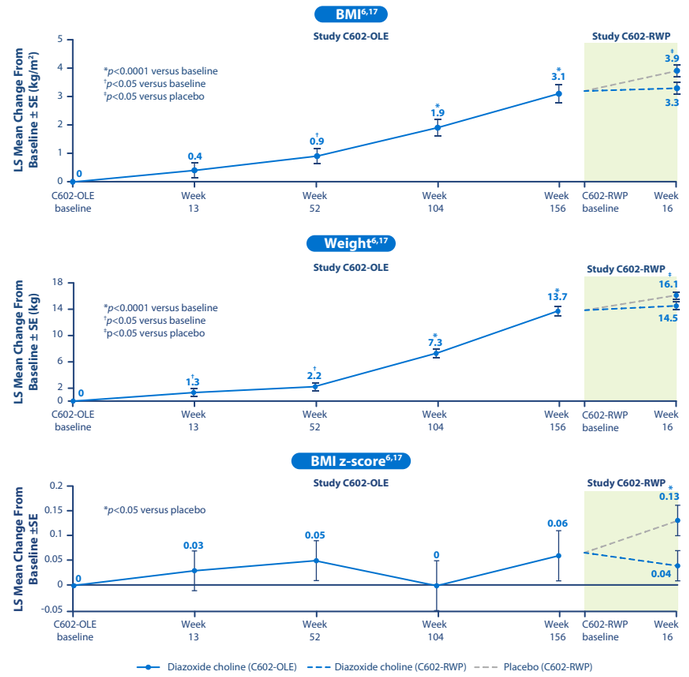
LBM, lean body mass; LS, least-squares; SE, standard error.

- **LBM** increased significantly from baseline at all time points
- **Fat mass** showed no significant changes during the first year of treatment but increased significantly at later time points
- After 156 weeks of treatment, **LBM** and **fat mass increased significantly** from baseline measurements

- **LBM** (percent change from baseline): progressive increases from baseline in LBM were observed at all time points with continued diazoxide choline treatment, with sustained improvements continued in Week 156 (+40.3% increase from baseline)[5]
- In **weight and age subgroup analyses** (C601/C602-OLE safety population; N=125), LBM improvements were more pronounced in obese participants, and LMI improvements were greatest in the youngest participants following long-term treatment with diazoxide choline[5]
  - **At Week 156, LBM** had increased by 50.7% ± 24.2 from baseline in participants (n=12) who were **overweight or obese** at baseline and by 53.7% ±29.2 from baseline in participants (n=8) who were **obese** at baseline, compared to the lean mass increase from baseline in the overall safety population (n=29) of 40.3% (±25.8%)[5]
  - The **LMI** increase from baseline was statistically significant in participants who were <8 years of age (1.38 kg/m^2 ± 0.39; p=0.0029) and participants 8 to <12 years of age (0.85 kg/m^2 ± 0.28; p=0.006), following 1 year of treatment[5]

Impact of Diazoxide Choline Treatment on Weight, BMI, and BMI Z-score: C602-OLE and C602-RWP[6,17]

- Data on longitudinal exposure to diazoxide choline for both **C602-OLE** and **C602-RWP** are presented here for BMI, BMI z-score, and absolute weight to provide context with a withdrawal/placebo arm (RWP) after C602-OLE
  - LBM and fat mass were not exploratory or additional endpoints for C602-RWP
- Note, the LS means presented below were adjusted for baseline and were not adjusted for age, sex, or growth hormone use



- **C602-OLE:** After 156 weeks of treatment, BMI **increased significantly** compared with baseline measurements[17]
- **C602-RWP:** Following the 16-week withdrawal period, BMI **increased significantly** in the group that switched to placebo compared with the group that continued taking diazoxide choline[6,17]

- **C602-OLE:** After 156 weeks of treatment, weight **increased significantly** compared with baseline measurements[17]
- **C602-RWP:** Following the 16-week withdrawal period, weight **increased significantly** in the group that switched to placebo compared with the group that continued taking diazoxide choline[6,17]

- **C602-OLE:** After 156 weeks of treatment, BMI z-score **increased** compared with baseline measurements[17]
- **C602-RWP:** Following the 16-week withdrawal period, BMI z-score **increased significantly** in the group that switched to placebo compared with a decrease in the group that continued taking diazoxide choline[6,17]

- In Study C602-OLE, increases in weight, BMI, and BMI z-score were expected over the 3-year treatment period, consistent with the natural growth trajectory of children and adolescents (who made up approximately 80% of the study population; mean age, 13.5 years)
- During the 16-week C602-RWP study, participants who switched to placebo had greater increases in weight and BMI than those who continued diazoxide choline, indicating that ongoing treatment may slow the expected upward trajectory of weight and BMI in patients with PWS

Key Results

- Treatment with diazoxide choline was associated with improved and durable changes in key body composition outcomes in participants with PWS in Phase 3 trials
- Most participants (~80%) were children and adolescents, who were expected to gain weight with age-sex-appropriate growth, yet changes in **BMI z-score**, **LBM**, and **fat mass** were observed that were not apparent from weight or BMI alone
- The **placebo-controlled trials/periods** showed that, compared with placebo groups
  - **C601:** Diazoxide choline-treated individuals had significantly improved **body fat mass** and **nonsignificant increase in LBM** but no significant improvements in weight or BMI over a 13-week period (C601 Intent-to-Treat population)
  - **C602-RWP:** Participants who remained on diazoxide choline experienced comparatively smaller increases in BMI, BMI z-score, and absolute weight than those who were switched to placebo for a 16-week period
- **Long-term exposure of diazoxide choline (C601/C602-OLE safety population) from baseline to Week 156** showed significant increases in **LBM** at all time points, with a 40.3% increase from baseline by Week 156. Subgroup analyses showed the most pronounced LBM gains occurred in overweight/obese participants and the greatest improvements in LMI were observed in younger participants (**aged <8 years and 8-11 years**)

Indication[1]

- VYKAT XR (diazoxide choline extended-release tablet) is indicated for the treatment of hyperphagia in adults and pediatric patients 4 years of age and older with PWS
- VYKAT XR is **not indicated for the management or treatment of obesity** or for **improvements in body composition parameters** (eg, weight, BMI, fat mass, or LBM)

Warnings and Precautions[1]

see PI for full details

- **Hyperglycemia:** Hyperglycemia, including diabetic ketoacidosis, has been reported. Monitor fasting glucose and hemoglobin A1c during treatment; monitor fasting glucose more frequently during the first few weeks in patients with risk factors
- **Risk of fluid overload:** Edema, including severe reactions associated with fluid overload, has been reported. Monitor for signs or symptoms of edema or fluid overload

Adverse Reactions[1]

- The most common adverse reactions (≥10% and ≥2% more frequent than placebo) with diazoxide choline were: hypertrichosis (36% vs 14%), edema (27% vs 12%), hyperglycemia (17% vs 5%), and rash (12% vs 2%)
- Serious adverse reactions included erythema multiforme (1 participant, C601) and diabetic ketoacidosis (1 participant, C614)

References

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