Swallowability and Dosing Compliance of Diazoxide Choline Extended-Release Tablets in Patients with Prader-Willi Syndrome

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Abstract #34
United in HOPE
2025 PWS Conference
June 25-26, 2025
Phoenix, AZ

INTRODUCTION

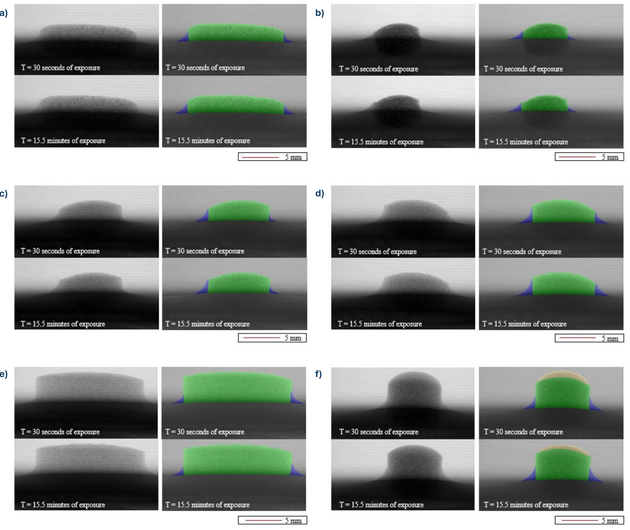
Diazoxide choline extended-release (DCCR) tablets have recently been approved by the FDA as VYKAT™ XR for the treatment of hyperphagia in adults and pediatric patients 4 years of age and older with Prader-Willi syndrome (PWS).[1]

DCCR had been evaluated in a series of three sequential Phase 3 studies in participants with PWS. The initial study, C601 or DESTINY PWS, was a double-blind, placebo controlled 13-week study.[2] This was followed by C602, which included a multi-year open-label treatment phase (C602-OLE) and a 16-week randomized withdrawal phase (C602-RWP).[3,4] The final study in the sequence was open-label extension study C614.[5] DCCR is administered orally once daily and tablets are to be taken whole, and not split, crushed or chewed. Dosing is based on weight.[1]

METHODS

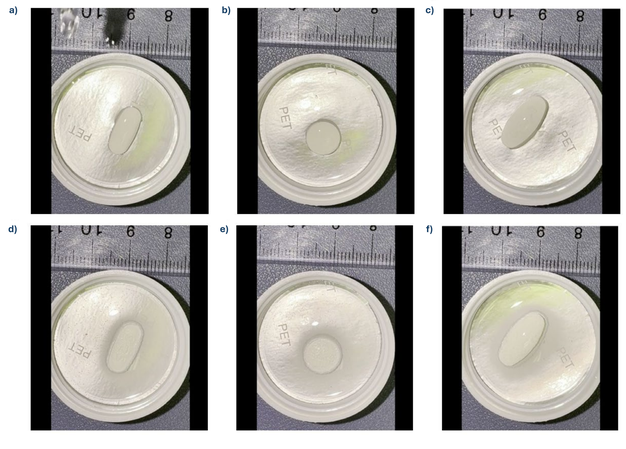
Three tablet strengths of DCCR containing 25 mg, 75 mg or 150 mg of diazoxide choline, were administered once daily to participants in the Phase 3 development program. DCCR tablets contain a polymer which, following administration, forms a hydrogel which erodes to release the active ingredient. The swelling of the tablet mass during the swallowing process was evaluated using artificial saliva and 2D x-ray radiography with AI-based data analysis **(Figure 1)** and in a separate study using calipers **(Figure 2)**. Compliance with dosing was characterized based on the unused drug on returned study medication cards or IRB/IEC-approved study drug administration diaries / logs, and adverse events (AEs) related to challenges in swallowing the tablets were reviewed.

Figure 1. DCCR 2D X-Ray Radiograph



One 2D x-ray radiograph taken after **thirty seconds** of media exposure (**top image**) and after **15.5 minutes** of media exposure (**bottom image**). Segmentation results are overlaid on the greyscale data next to each respective radiograph **(a, c, e)**. Radiographs focusing on the tablet length x height dimensions **(b, d, f)**. Radiographs focusing on the tablet width x height dimensions. 25 mg **(a, b)**, 75 mg **(c, d)**, and 150 mg **(e, f)**.

Figure 2. DCCR Exposure to Artificial Saliva - Caliper Measurements



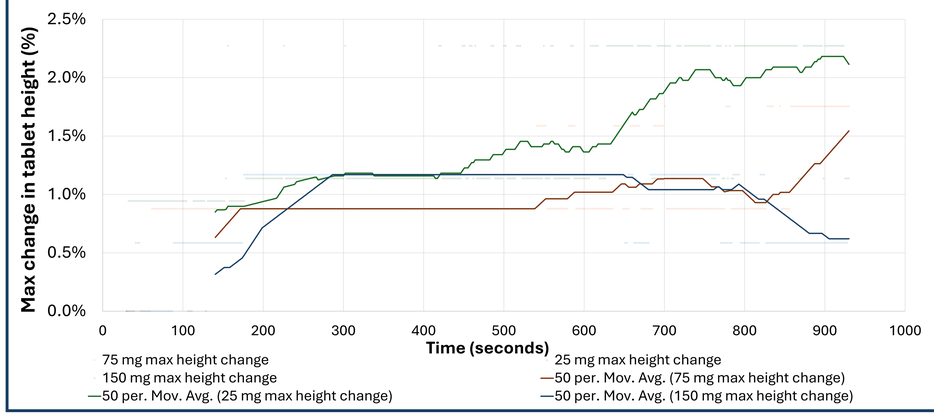
a-c. Optical images taken **immediately** after coating the sample with artificial saliva

d-f. Optical images taken **after 15 minutes** of exposure to artificial saliva 25 mg **(a, d)**, 75 mg **(b, e)**, and 150 mg **(c, f)**.

RESULTS

- During the simulated swallowing process there were small changes in tablet dimensions associated with the initial hydration of the tablet mass.
- The 25 mg tablet exhibited 1% increase in tablet length, 5% increase in tablet width, and 2.5% increase in tablet height; height results provided as an example in **Figure 3**.
- Both the 75 mg and 150 mg tablets increased by less than 2% in length, width, and height planes.

Figure 3. Maximum Percent Change in Tablet Height



Maximum percent change in tablet height evaluated from each tablet strength time lapse. The light green, orange, and blue data points represent each measurement collected from individual radiographs on the 25 mg, 75 mg, and 150 mg tablet strength, respectively. The solid dark green, orange, and blue lines represent a moving average over 50 data points for the 25 mg, 75 mg, and 150 mg tablet strength, respectively.

- During the Phase 3 Program, a very high degree of compliance was observed across all studies **(Table 1)** and age categories, including the youngest age category (4 to <6 years).
- Mean compliance ranged from 94.2% to 99.5%.
- No AEs of dysphagia, choking, or other problems related to swallowability were reported.

Table 1. Dosing Compliance by Study and Treatment

	ACTIVE			PLACEBO		
Study	N	Mean (%)	Median (%)	N	Mean (%)	Median (%)
C601	84	97.2	98.9	42	98.2	99.5
C602-OLE	115	94.2	98.3	-	-	-
C602-RWP	38	99.5	100	39	98.8	100
C614	77	95.2	99.8	-	-	-

Abbreviations: OLE, open-label extension; RWP, randomized withdrawal phase.

CONCLUSIONS

- **During the simulated swallowing process there were small changes in tablet dimensions associated with the initial hydration of the tablet mass.**
- **There was no evidence of issues with swallowability of DCCR tablets in children as young as 4 years as determined by dosing compliance in the Phase 3 development program and the lack of AEs that might reflect challenges with swallowability.**
- **DCCR tablets can be readily used to dose patients with PWS as young as 4 years old.**

REFERENCES

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