EPH71

Expected vs Observed Mortality Rates, Expressed as Number Needed to Treat, From a Phase 3 Clinical Trial Program of Patients With Hyperphagia and Prader-Willi Syndrome Treated With Diazoxide Choline Extended-Release (DCCR)

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INTRODUCTION

Prader-Willi syndrome (PWS) is a complex developmental genetic disorder characterized by hyperphagia, a chronic and life-threatening condition, characterized by constant thoughts about consumption, and a pathological urge to consume non-food and food items that cannot be satisfied.[1,2] Hyperphagia-related complications is a leading cause of death due to choking, gastrointestinal perforation, and accidents, and contributes to ~one third of all deaths and half of deaths in children, according to a U.S. cause-of-death PWS analysis.[2]

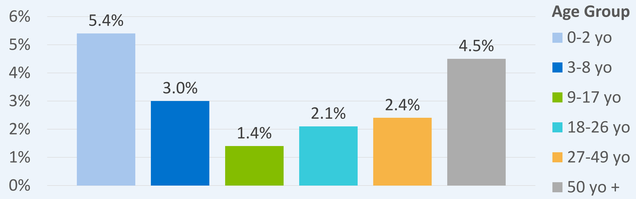
In 2025, **diazoxide choline** extended-release tablets was approved by the U.S. Food and Drug Administration for the treatment of hyperphagia in individuals with PWS aged ≥4 years. This analysis draws from the Phase 3 C601 trial, followed by the long-term extension, C602-OLE, to evaluate the potential impact of treatment on mortality outcomes.

This analysis examines observed mortality during the combined duration of C601 and C602-OLE studies with diazoxide choline treatment to calculate the NNT to avoid one death in PWS.

BACKGROUND

PWS is associated with shortened life span; the median age of death is 23 years.[1] A 2020 study by McCandless et al. revealed that annual mortality rates in individuals with PWS are substantially higher than in the general U.S. population, with rates ≥3 times higher across all age groups (2.7% vs 0.8%).[1]

Figure 1. Real-World PWS Mortality Rate By Age (2018)[1]



METHODS

- This post-hoc analysis assessed **observed mortality** from the combined Phase 3 C601 and C602-OLE studies (Figure 2).
  - All patient-time exposure to diazoxide choline for individuals in C601 and C602-OLE was examined.
- **Expected mortality** for control PWS population was computed based on age match with a real-world epidemiology study.[1]
  - Rates were further adjusted to reflect the patient-year captured in C601/C602-OLE using patient's age.
- Both event rates were recorded to calculate the absolute risk reduction (**ARR**) and Number Needed to Treat (**NNT**).

Figure 2. C601 and C602-OLE Study Design

C601
NCT03440814: A 13-week, randomized, double-blind, placebo-controlled parallel-group study

C602-OLE
NCT03714373: A long-term, open-label study of up to 5 years for participants completing Study C601

NNT Number Needed to Treat $= \frac{1}{ARR}$

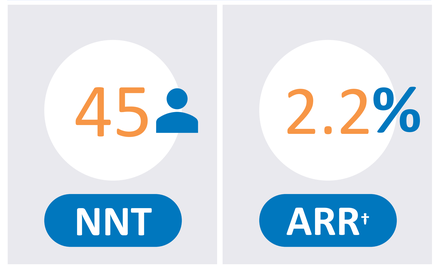
RESULTS

Figure 3. Comparison of Expected vs. Observed Mortality Over a Matched Exposure Duration

7 Expected Deaths[1] during Matched Duration Period — Event Rate = 2.2%

No Deaths — **0** Observed Deaths during the Study Period with Diazoxide Choline — Event Rate = 0%

Figure 4. Number Needed to Treat and Absolute Risk Reduction



†The difference in Event Rates (ER): 7 expected deaths[1] (ER = 2.2%) minus 0 observed deaths (ER = 0.0%), resulting in an ARR of 2.2%.

- 115 patients, age 4-44 years, exposed to **diazoxide choline** in C601 and C602-OLE were included in the analysis representing 313.4 patient-years (max exposure 4.5 years) and matched against real-world PWS mortality rate (Figure 1).
- There were **no deaths reported with diazoxide choline** treatment through median of 3 years of exposure. Based on real-world PWS mortality rates[1], 7 deaths would be expected in an age-matched population (Figure 3).
  - **Expected Deaths** were estimated using published event rates from individuals with PWS.[1]
  - **Observed Deaths** reflect mortality outcomes in participants receiving diazoxide choline in Studies C601/C602-OLE.
- An estimated 45 individuals with PWS would need to be treated with diazoxide choline to prevent one death, based on a median exposure duration of 3.0 years (see Figure 4).

CONCLUSIONS

- PWS is a rare genetic condition associated with elevated mortality rate.
- No deaths were observed in individuals treated with diazoxide choline during the sequential C601 and C602-OLE trials; when benchmarked against real-world PWS mortality rates, this corresponds to a NNT of 45 to potentially prevent one death.
- This is the first analysis to explore the potential association between diazoxide choline treatment and reduced mortality risk in individuals with PWS.
- The NNT was calculated based on a median diazoxide choline exposure of 3 years with zero deaths observed; of note, as of latest data refresh, no deaths have occurred through >5 years of continuous diazoxide choline exposure.

ACKNOWLEDGEMENTS

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REFERENCES

1. McCandless SE, et al. *J Endocr Soc.* 2020; 4(Suppl 1): SUN-604.
2. Butler MG. Et al. *Genet Med.* 2017; 19(6): 635-642.

Abbreviations: ARR, absolute risk reduction; ER, event rate; PWS, Prader-Willi syndrome; NNT, number needed to treat; OLE, open-label extension; Yo, years old; max, maximum.

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