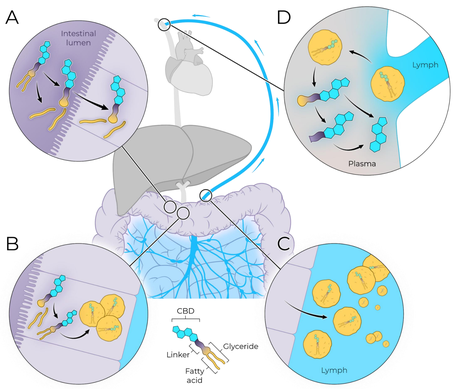
# GlyphCBD (SPT-310), a Lymphatic-Targeting Prodrug of Cannabidiol, Significantly Inhibits Seizure Activity in the Maximal Electroshock Seizure Model

Daniel K. Bonner[1], Alyssa DiLeo[1], Jamie S. Simpson[1], Jeff Jewell[1], Michael C. Chen[1]
[1]Seaport Therapeutics, Boston, MA

SEAPORT THERAPEUTICS

## Introduction

- The Glyph™ platform is a proprietary prodrug technology which reversibly conjugates a drug of interest to a dietary lipid molecule to direct absorption toward the lymphatic system; it can be widely applied to therapeutic molecules to address previous limitations (e.g., oral bioavailability)
- Cannabidiol (CBD) is approved to treat seizures in patients with Dravet syndrome, Lennox-Gastaut syndrome, and tuberous sclerosis complex in the U.S. and European Union
- Due to low oral bioavailability, CBD is dosed as a large volume, sesame seed oil-based oral solution, which carries risk for hepatotoxicity and gastrointestinal (GI) adverse events[1,2]
- GlyphCBD™ (SPT-310 or Glyph Cannabidiol), an oral prodrug of cannabidiol, is enabled by Glyph to address these challenges around oral bioavailability & adverse events
- **Objective:** Here, we evaluate the potential anti-convulsant activity of GlyphCBD in the maximal electroshock seizure (MES) model in rodents, a validated and translatable preclinical model for anti-seizure drugs




(A) Glyph prodrug enters the intestinal lumen where it is hydrolyzed. (B) The hydrolyzed prodrug is then re-esterified and assembled into chylomicrons. (C) The chylomicrons exit enterocytes and are taken up into the lymph for transport to the circulation via mesenteric and thoracic lymph. (D) Once the chylomicrons reach the plasma, the active pharmaceutical ingredient is released along with prodrug intermediates.

## Methods

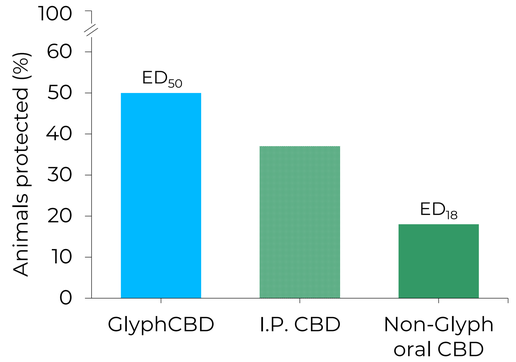
- Male Sprague Dawley rats (aged 6-8 weeks) were randomly assigned to one of the following groups:

| Non-Glyph oral CBD (N=12/group) | | GlyphCBD (N=12/group) | | |
|---|---|---|---|---|
| **Treatment** | **Dose** | **Treatment** | **Dose** | **CBD Equivalent** |
| Vehicle | 5 mL/kg | Vehicle | 5 mL/kg | NA |
| Valproate | 250 mg/kg | Valproate | 250 mg/kg | NA |
| CBD | 50 mg/kg | GlyphCBD | 100 mg/kg | 36 mg/kg |
| | 100 mg/kg | | 150 mg/kg | 54 mg/kg |
| | 150 mg/kg | | 200 mg/kg | 72 mg/kg |
| | 200 mg/kg | | 250 mg/kg | 90 mg/kg |
| | 250 mg/kg | | 300 mg/kg | 110 mg/kg |
| | | | 350 mg/kg | 130 mg/kg |

- Dosing of non-Glyph oral CBD and GlyphCBD was completed in two separate experiments with each experiment including a vehicle group & valproate group as a positive control
- Rats were assessed for the presence or absence of a tonic hindlimb extensor seizure following an electroshock (150 mA; 50 Hz; 0.3 second duration)
- Significant differences between treatment groups were determined by a two-sided Fisher's exact test versus vehicle

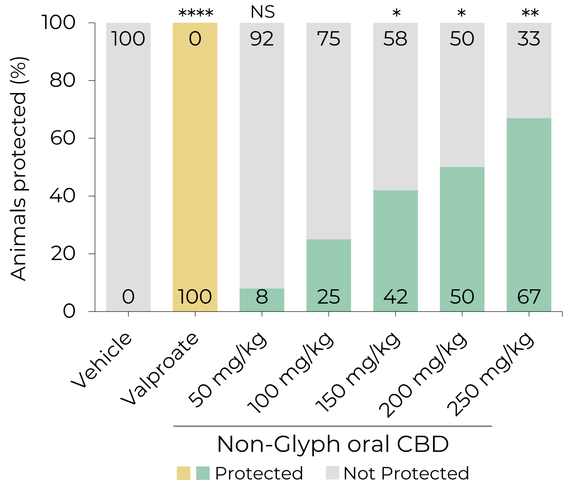
## Results

- To verify model reproducibility and validity, we evaluated intraperitoneal (I.P) CBD in this model which produced an $ED_{50}$ of 91 mg/kg, similar to previously reported values (89 mg/kg)[3]

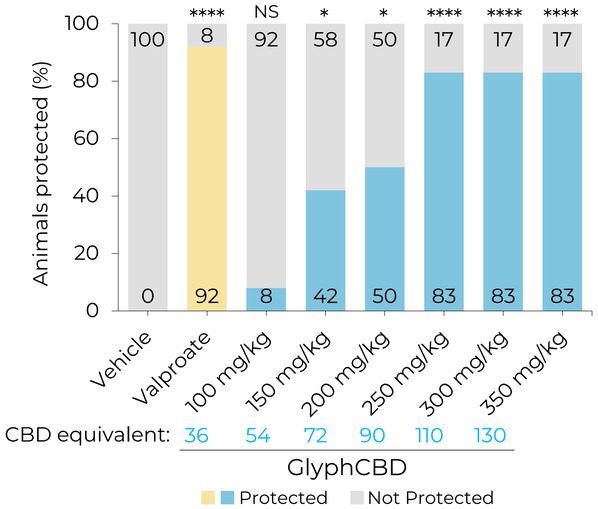



- GlyphCBD was more effective at preventing seizures at a dose 3x lower than a non-Glyph oral CBD formulation
- The $ED_{50}$ for the CBD equivalent dose of GlyphCBD (65 mg/kg) corresponds to an $ED_{18}$ for non-Glyph oral CBD
- Over 85% (19 of 21) of the approved anti-seizure medications for focal seizures were active in MES[4]

**Non-Glyph oral CBD reduces seizures starting at 150 mg/kg dose with an $ED_{50}$ of 180 mg/kg.**



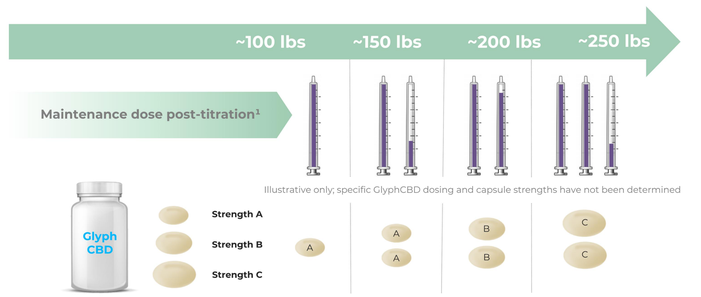

**GlyphCBD is more effective in reducing seizures at a lower CBD equivalent dose than non-Glyph oral CBD.**




*P < 0.05, **P < 0.01, ****P < 0.0001 vs vehicle. CBD, cannabidiol; $ED_{50}$, median effective dose; I.P., intraperitoneal; NS, not significant.

## Discussion

- Non-Glyph oral CBD and GlyphCBD both inhibited tonic hindlimb extensor seizures in a rodent MES model compared to vehicle, however GlyphCBD offered higher seizure protection with a lower CBD equivalent $ED_{50}$ dose
- These data suggest that GlyphCBD enhances oral bioavailability of CBD while achieving better seizure protection at lower doses, enabling oral dosing at a reduced volume
- Administration of CBD in its existing formulation is associated with the risk of GI adverse events and, in some cases, hepatotoxicity; GlyphCBD has the potential to improve the overall safety drug profile of CBD while retaining therapeutic efficacy and expanding the clinical use to broad patient populations, including focal onset seizures
- The development of GlyphCBD provides an additional proof-of-concept for the Glyph platform and its potential to be widely applied to therapeutic molecules with previous limitations




[1]Based on maintenance dose of 10 mg/kg for Dravet and LGS patients; Patients start on 2.5 mg/kg BID and increase to 5 mg/kg BID after one week and again to maximum recommended maintenance dose of 10 mg/kg BID. BID, twice a day; LGS, Lennox-Gastaut Syndrome.

**Acknowledgements and funding sources:** This study was supported by Seaport Therapeutics and, previously, Seaport Therapeutics' predecessor, PureTech Health. The authors would like to thank and acknowledge Pabitra H. Patra of Transpharmation, Ltd for contributing to the data analysis in this study.
**References:** 1. Huestis MA et al. Current Neuropharmacology. 2019;17(10). 2. Epidiolex. Prescribing information. Jazz Pharmaceuticals. 2025. 3. Klein BD et al. Neurochem Res. 2017;42(7):1939-1948. 4. Barker-Haliski et al., Neuropharmacology (2020) 167:107750.
**Disclosures:** DKB, AD, JSS, and MCC are currently employed by and hold stock in Seaport Therapeutics; JSS is also a coinventor of the Glyph platform that has been exclusively licensed to Seaport Therapeutics. JJ was a former consultant with PureTech Health at the time of this study.

*Presented at the American Epilepsy Society (AES 2025); December 5-9, 2025; Atlanta, Georgia.*