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EMPEROR Phase 3 study design: Evaluation of zorevunersen as a potential disease-modifying therapy for Dravet syndrome

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Key Findings

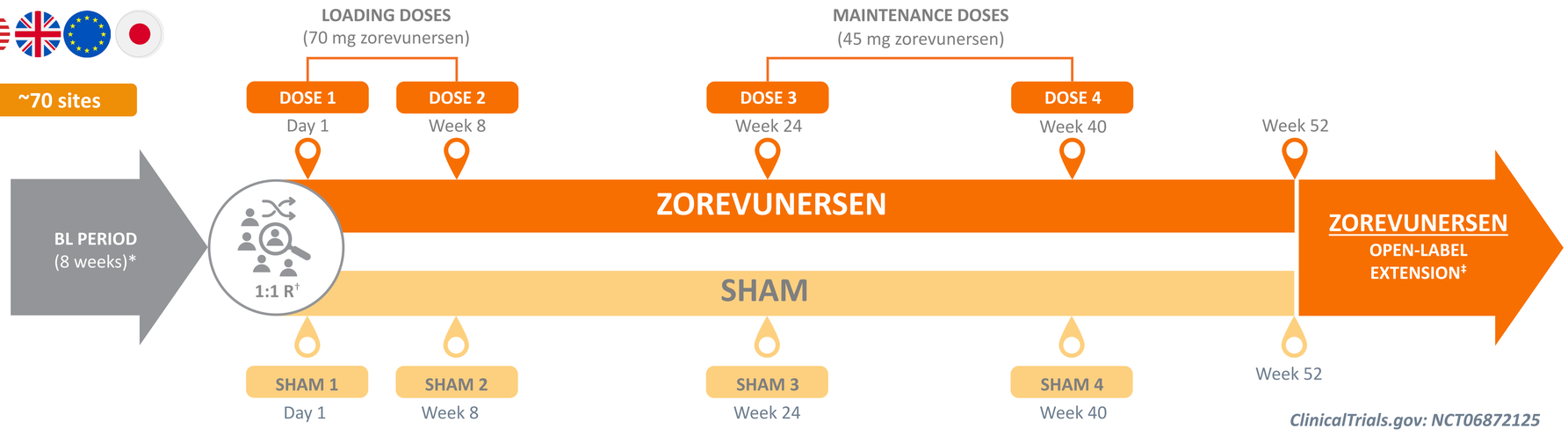
1. **EMPEROR will be the first global Phase 3 study to assess the effects of a potential disease-modifying therapy on seizures and multiple aspects of cognition and behavior in patients with Dravet syndrome.**
2. **The study builds on previous Phase 1/2a and open-label extension studies of zorevunersen in patients with Dravet syndrome that demonstrated substantial and durable reductions in seizure frequency and improvements in cognition and behavior on top of standard of care.**
3. **The study duration and endpoints in EMPEROR are designed to comprehensively evaluate the potential of zorevunersen for disease modification in Dravet syndrome.**
4. **Vineland-3 will be used in EMPEROR and its open-label extension to measure changes in cognition and behavior over time, providing insight into the potential disease-modifying impacts of zorevunersen.**

Introduction

- Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy characterized by prolonged refractory seizures as well as significant cognitive and behavioral impairments.[1–3]
- Despite standard of care treatment with the best antiseizure medications (ASMs), patients with DS enrolled in the BUTTERFLY natural history study continued to experience frequent seizures and widening cognitive and behavioral gaps relative to their neurotypical peers over 24 months.[4]
- Disease-modifying therapies targeting the etiology of DS are needed to improve short- and long-term outcomes. While current treatments for DS focus on seizure control, disease-modifying therapies aim to treat the underlying cause of the disease.[5]
- Zorevunersen is an investigational antisense oligonucleotide (ASO) designed to target the underlying genetic cause of DS, voltage-gated sodium channel α subunit 1 (*SCN1A*) gene haploinsufficiency, which results in reduced expression of $Na_V1.1$ channels.[6]
- Phase 1/2a and open-label extension studies of zorevunersen in patients with DS have demonstrated substantial and durable reductions in seizure frequency and continuing improvements in cognition and behavior.[7]
- EMPEROR is a global, multicenter, randomized, double-blind, Phase 3 study that aims to evaluate the efficacy, safety, and tolerability of zorevunersen in patients with DS. **(Figures 1–3)**

Study Design

Figure 1. EMPEROR study design



EMPEROR was designed to evaluate changes across multiple aspects of DS, including seizures, cognition and behavior, to understand the impact of zorevunersen as a potential disease-modifying therapy.

Scan the QR code at the top of the poster or use the links below to learn more about the EMPEROR Phase 3 study design.

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The duration of the study is anticipated to be approximately 60 weeks, including an 8-week baseline period and a 52-week double-blind efficacy period. *The 8-week baseline period consists of screening Visit A, screening Visit B, and observation for 6 weeks. †Following eligibility confirmation, patients will be randomized in a 1:1 ratio (zorevunersen:sham). ‡Patients will have the option to receive zorevunersen in an open-label extension study if they meet eligibility criteria. BL, baseline; R, randomization.

Key Endpoints

Figure 2. Key endpoints (EU-specific)*

PRIMARY	Percent change from baseline in **major motor seizure frequency** (number per 28 days) in patients receiving zorevunersen as compared with sham	Week 16 to Week 28†
SECONDARY	Percent change from baseline in **major motor seizure frequency** (number per 28 days) in patients receiving zorevunersen as compared with sham	Week 16 to Week 52‡
	Change from baseline on a **multi-component Vineland-3 Outcome Score**§ in patients receiving zorevunersen as compared with sham at Week 52	At Week 52
	Change from baseline in **raw scores on Vineland-3 subdomains** in patients receiving zorevunersen as compared with sham at Week 52	At Week 52
SAFETY	**Safety profile of zorevunersen** compared with sham with respect to adverse events	

*Endpoints listed in the figure are for the European registration. Details for non-European endpoints are listed in the footnotes. †Week 16 to Week 28 constitutes the initial 12-week interval of anticipated steady state for reduction of major motor seizures based on exposure-response analysis of the zorevunersen Phase 1/2a and available open-label extension data. Percent change from baseline in log-transformed major motor seizure frequency will be compared with sham at Week 28 for the non-European registration. ‡For the non-European registration, this is the percent change from baseline in log-transformed major motor seizure frequency in patients receiving zorevunersen as compared with sham at Week 52. §Vineland-3 Outcome Score comprises Vineland-3 expressive communication, receptive communication, interpersonal relationships, coping skills, and personal skills subdomain raw scores. Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

Eligibility Criteria

Figure 3. Key inclusion and exclusion criteria

INCLUSION CRITERIA

- Age ≥2 and <18 years
- Clinical diagnosis of DS confirmed by the ESCI
- Presence of a documented pathogenic variant, likely pathogenic variant, or variant of uncertain significance in the *SCN1A* gene*
- Experience the required number of major motor seizures during the 6-week observation period†
- Used at least two prior interventions for seizures, which can be ongoing and include ASMs, ketogenic diet, and/or VNS
- Taking at least one ASM§
- All maintenance ASMs and seizure interventions, as well as any marijuana- or cannabinoid-based products, must have been stable (unless adjusted for weight) during the baseline period

EXCLUSION CRITERIA

- Presence of a documented variant in the *SCN1A* gene associated with gain-of-function‡
- Currently being treated with a maintenance ASM acting primarily as a sodium channel blocker, including but not limited to phenytoin, carbamazepine, oxcarbazepine, lamotrigine, lacosamide, rufinamide, or cenobamate
- Currently treated with neuromodulation techniques, with the exception of VNS
- Emergence of a new seizure type, re-emergence of a past seizure type (a type that last occurred >12 months before screening visit), or >1 hospitalizations for seizures during the baseline period

*Patients who have *SCN1A* testing results of negative (no variants identified) cannot be randomized. †Seizure types: hemiclonic, focal with motor signs, focal to bilateral tonic-clonic, generalized tonic-clonic, tonic, tonic/atonic (drop attacks with fall or risk of fall), and bilateral clonic. §Benzodiazepines or ASMs used on a standing basis (i.e., not as needed) for any indication will be considered an ASM. ASM, antiseizure medication; DS, Dravet syndrome; ESCI, Epilepsy Study Consortium, Inc.; *SCN1A*, voltage-gated sodium channel α subunit 1 gene; VNS, vagus nerve stimulation.

Vineland-3

Measuring Functional Impact with Vineland-3

- Vineland Adaptive Behavior Scales – Third edition (Vineland-3) is a clinician-administered standardized assessment that uses a semi-structured interview with a parent or caregiver to assess adaptive behavior across a wide range of ages.[8]
- Adaptive behavior is the collection of conceptual, social, and practical skills that help people function in their everyday lives.
- These skills can be assessed across domains including Communication, Daily Living Skills, and Socialization. **(Figure 4)**
- Small improvements in Vineland-3 are considered meaningful by caregivers of DS, underscoring Vineland's relevance for capturing functional change.[8]

93% of children with DS have significant deficits in adaptive behavior, contributing to challenges in everyday functioning[9]

Figure 4. Vineland-3 domains, subdomains, and scoring

	DOMAINS (functions assessed)	SUBDOMAINS (examples of tasks)
Core Domains	COMMUNICATION	**Receptive** — Responds upon hearing name called **Expressive** — Says "Dada", "Mama", or caregiver name **Written** — Writes alphabet letters using correct orientation
Core Domains	DAILY LIVING SKILLS	**Personal** — Cooperates in dressing and undressing **Domestic** — Puts away books, toys, etc. when done **Community** — Talks with a familiar person using a phone
Core Domains	SOCIALIZATION	**Interpersonal Relationships** — Tries to interact with others **Play and Leisure** — Responds when parent/caregiver is playful **Coping Skills** — Transitions easily from one activity to another
Optional Domains	MOTOR SKILLS	**Gross Motor** — Moves, scoots, or crawls across the floor **Fine Motor** — Picks up small objects with thumb and fingers
Optional Domains	MALADAPTIVE BEHAVIOR	**Internalizing** — Experiences extreme anxiety or lacks energy or interest **Externalizing** — Has temper tantrums or is overly active or restless **Critical Items** — Engages in repetitive behaviors or self-harm

SCORING*

Raw scores

- Vineland-3 uses a Likert-based format that reflects how often a behavior is observed without help or prompting
- Most items use a 3-point scale:
  - 0 = never
  - 1 = sometimes
  - 2 = usually or often
- Other items require a yes/no answer:
  - 0 = no
  - 2 = yes

*Maladaptive Behavior scores are optional and use a different scoring metric from the other domains. Vineland-3, Vineland Adaptive Behavior Scales – Third Edition.

References: 1. Steel D *et al*. *Epilepsia* 2017; 58 (11): 1807–1816; 2. Zuberi SM *et al*. *Epilepsia* 2022; 63 (6): 1349–1397; 3. Villas N *et al*. *Epilepsy Behav* 2017; 74: 81–86; 4. Sullivan J *et al.* Poster P788 presented at EEC 2024; Rome, Italy, 7–11 September 2024; 5. Wirrell EC *et al*. *Epilepsia* 2022; 63 (7): 1761–1777; 6. Lim KH *et al*. *Nat Commun* 2020;11 (1): 3501; 7. Laux L *et al*. Poster 2.379 presented at AES 2024; Los Angeles, CA, USA, 6–10 December 2024; 8. Condon C *et al*. *Eplispey Behav* 2025; 167: 110381; 9. Reilly C *et al*. *Dev Med Child Neurol* 2023; 65 (6): 831–837. **Acknowledgments:** This study was supported by Stoke Therapeutics Inc. We thank investigators, healthcare providers, research staff, patients, and caregivers who participated. Writing support was provided by Porterhouse Medical US and was funded by Stoke Therapeutics Inc. according to Good Publication Practice guidelines.

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