Interim Results of the US Fenfluramine Oral Solution Cardiovascular Safety Registry Study

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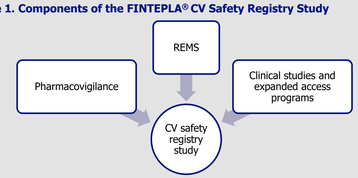
Introduction

- In the United States (US), fenfluramine (FFA oral solution, FINTEPLA®) is FDA-approved for the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients ≥2 years old[1]
- Due to cardiovascular (CV) risks, namely valvular heart disease (VHD) and pulmonary arterial hypertension (PAH), originally identified when in the past the FFA oral tablet formulation was used at high doses as an anorectic agent (at 60-120 mg/day), FINTEPLA® is only available in the US through a Risk Evaluation and Mitigation Strategy (REMS)[1]
  - Starting dose is 0.1 mg/kg twice daily (0.2 mg/kg/day), increased weekly based on efficacy and tolerability up to 0.35 mg/kg twice daily (0.7 mg/kg/day) or 0.2 mg/kg/day twice daily (0.4 mg/kg/day) if on concomitant stiripentol (STP)
  - Doses not to exceed 26 mg/day or 17 mg/day if on concomitant STP
- Prescribers and dispensing pharmacies must be certified through REMS and patients must also be enrolled in REMS to receive the medication
- To evaluate for VHD and/or PAH, a baseline echocardiogram (ECHO) must be obtained before starting treatment with FINTEPLA® and a repeat ECHO is then needed every 6 months and once 3-6 months after stopping FINTEPLA®
- The FDA has required a post-marketing CV safety registry study in the US, including all patients who enrolled in the FINTEPLA® REMS, to continue monitoring, evaluating, and reporting VHD, PAH, and/or other CV adverse events (CVAEs); the study includes data obtained from REMS, pharmacovigilance processes, and clinical studies/expanded access programs (**Figure 1**)
- In a large prospective cohort of middle-aged patients with epilepsy, VHD, hypertension, coronary artery disease, heart failure, and congenital heart disease were more prevalent in patients with epilepsy versus comparators without epilepsy ($P<0.001$)[2]
- As with all patients with epilepsy, CV events in patients with DS or LGS may be due to various factors
  - These include underlying cardiac conditions, comorbidities, use of antiseizure medications, and chronic seizures causing structural, electrical and/or mechanical dysfunction[3-5]

Figure 1. Components of the FINTEPLA® CV Safety Registry Study

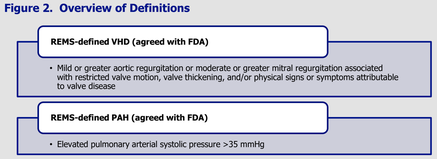


CV, cardiovascular; REMS, Risk Evaluation and Mitigation Strategy.

Objective

To provide interim results from the CV safety registry study, since launch of FINTEPLA® (June 2020), whose objective is to characterize the risk of potential development of VHD and/or PAH (**Figure 2**) in patients exposed to FINTEPLA® in the US.

Figure 2. Overview of Definitions



FDA, Food and Drug Administration; PAH, pulmonary arterial hypertension; REMS, Risk Evaluation and Mitigation Strategy; VHD, valvular heart disease.

Methods

- The CV safety registry study is an ongoing prospective, observational, cohort study of patients treated with FINTEPLA® in the US
- Data are collected from REMS, pharmacovigilance processes, and clinical studies/expanded access programs from patients enrolled in the FINTEPLA® REMS (**Figure 1**)
  - An overview of the data collection process is provided in **Table 1**
  - Data are collected from REMS enrollment (pre-treatment baseline), through follow-up during FINTEPLA® treatment, at study end, or when patients are lost to follow-up
    - During FINTEPLA® treatment, data are collected via REMS every 6 months and 3-6 months after the last FINTEPLA® dose
  - If information from any source suggests REMS criteria of VHD or PAH are met, the cases are included in the analysis
- Cases of suspected VHD or PAH are reviewed by an external adjudication committee to support the correct diagnosis of the event
  - The committee consists of three cardiologists with expertise in adult and pediatric cardiology and knowledge of FINTEPLA®
  - The adjudication committee reviews all medical information reported for the cases (including but not limited to ECHO imaging and results, clinical course, co-medication, and comorbidities) and makes a clinical judgment to classify them as definite, probable, possible, or not VHD/PAH
- Data collection period for this interim report was June 25, 2020, through June 24, 2024

Table 1. Overview of Data Collection Sources and Types of Data Collected

	Data Collection Source	Data Source/ Reporter(s)	Timing of Completion	Data Collected
REMS forms	REMS patient enrollment form	Patient or caregiver and prescriber	Enrollment	• Registration information • Demographics
	REMS patient status form	Prescriber	• Before start of FINTEPLA® • Every 6 months during FINTEPLA® treatment • 3-6 months after final FINTEPLA® dose	• Height, weight • FINTEPLA® exposure information[a] • ECHO results
	REMS CVAE reporting form	Prescriber	• At or immediately after CVAE reported	• CVAE information • FINTEPLA® exposure information[a] (including STP use)
Pharmacovigilance targeted follow-up form		Prescriber and/or other healthcare provider involved in the integrative care of the patient	• After CVAE reported or when CVAE form is received	• Information re: CVAE[b] • Other exposure information[c] • Medical comorbidities • Concomitant medications • Family history
Clinical studies or expanded access programs		Patient or caregiver and prescriber	• Enrollment	• Pre-REMS exposure

[a]Includes start/end date of FINTEPLA®, and whether FINTEPLA® was continued or not and reasons for discontinuation if applicable.
[b]Includes whether the CVAE was reviewed by a patient's cardiologist, if a VHD/PAH diagnosis was made, as well as other information that may assist in evaluating the events.
[c]Includes medical history, concomitant medications, recreational drug exposure, and laboratory test results.
CVAE, cardiovascular adverse event; ECHO, echocardiogram; REMS, Risk Evaluation and Mitigation Strategy; STP, stiripentol.

Outcomes

- Variables and outcomes reported included: patient demographics, FINTEPLA® mean daily dose, duration of FINTEPLA® exposure, occurrence of potential symptomatic or asymptomatic VHD and/or PAH (regardless of FINTEPLA® causality), and results of definite or probable cases following adjudication review
  - As noted above, suspected cases undergo additional follow-ups and adjudication for confirmation of diagnosis
  - Causality criteria for potential cases of VHD and/or PAH were also applied by UCB as per World Health Organization-Uppsala Monitoring Centre (WHO-UMC) and are described in this report
    - Considers clinical-pharmacological aspects of the case history and the quality of documentation to categorize as certain, probable/likely, possibly, unlikely, and unassessable

Statistical analyses

- Descriptive statistics were used; specifically, percentages, means, standard deviations, and medians with minimum and maximum values

Results

- Over the data collection period (June 25, 2020, through June 24, 2024), 3563 patients have been enrolled in the REMS and received ≥1 dose of FINTEPLA® (Enrolled Set)
  - Of 3563, 216 (6.1%) patients had an abnormality on baseline ECHO
    - Some of these included: FDA-defined mild and moderate aortic valvulopathy, FDA-defined moderate mitral valvulopathy, and REMS-defined PAH
- Patient demographics are described in **Table 2**
- Of the enrolled set, mean ± SD FINTEPLA® daily dose was 0.5±0.3 mg/kg/day or 17.6±9.3 mg/day
- Total duration of FINTEPLA® exposure was 5611.4 patient-years (see **Table 3**)

Table 2. Patient Demographics

	Enrolled Set N=3563	Patients With CV Events at Enrollment n=216
Age, years		
Mean±SD	14.9±10.8	17.4±13.1
Range	0.1-70.1	0.1-62.4
Gender, n (%)		
Male	1883 (52.8)	124 (57.4)
Female	1678 (47.1)	92 (42.6)
Missing	2 (0.1)	0 (0.0)
Weight at enrollment (kg)		
n	3554	216
Mean±SD	43.3±25.5	44.8±25.8
BMI at enrollment (kg/m²)		
n	3115	196
Mean±SD	21.3±6.6	21.2±6.9

BMI, body mass index; CV, cardiovascular; SD, standard deviation.

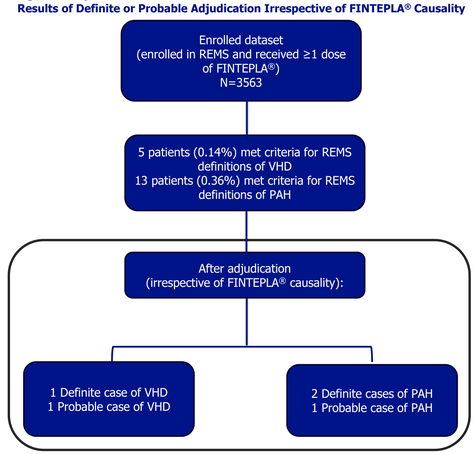
Table 3. Duration of FINTEPLA® Exposure

	Enrolled Set N=3563
Patients initiating FINTEPLA® *prior* to REMS enrollment, patient-years	
Pre-REMS duration of exposure[a]	522.8
REMS duration of exposure	499.7
Total	1022.6
Patients initiating FINTEPLA® from REMS enrollment, patient-years	4588.8
Total duration of exposure, patient-years	5611.4

[a]Includes FINTEPLA® exposure from participation in clinical trials or expanded access programs.
REMS, Risk Evaluation and Mitigation Strategy.

- Reports of REMS-defined VHD and REMS-defined PAH, as well as adjudication of those cases as definite or probable are described in **Figure 3** and **Table 4**

Figure 3. Reports of REMS-Defined VHD and REMS-Defined PAH Cases and Results of Definite or Probable Adjudication Irrespective of FINTEPLA® Causality



PAH, pulmonary arterial hypertension; REMS, Risk Evaluation and Mitigation Strategy; VHD, valvular heart disease.

- Of all reports of REMS-defined VHD or PAH (**Figure 3**):
  - 3 cases were adjudicated as not PAH
  - Due to insufficient or conflicting information to confirm the diagnosis, 9 cases were adjudicated as possible VHD (n=3) or possible PAH (n=6) and 1 case requires additional information for complete adjudication; of these, all except one had confounding factors

Table 4. Adjudication and Causality of Definite and Probable REMS-Defined VHD and REMS-Defined PAH Cases

	Adjudication	WHO-UMC Causality Assessment	Presence of Confounding Factors and/or Relevant History (Yes or No)
REMS-defined VHD	1 Definite VHD	1 Possibly related	No
	1 Probable VHD[a]	1 Unlikely related	Yes
REMS-defined PAH	2 Definite PAH	2 Unlikely related	Yes
	1 Probable PAH	1 Unlikely related	Yes

[a]After completion of the interim report, this case was re-adjudicated as "definite VHD" but remained unlikely related to FINTEPLA®.
PAH, pulmonary arterial hypertension; REMS, Risk Evaluation and Mitigation Strategy; VHD, valvular heart disease; WHO-UMC, World Health Organization-Uppsala Monitoring Centre.

- WHO-UMC causality assessment of cases adjudicated as definite or probable are described in **Table 4**
  - Of the reports of REMS-defined VHD cases:
    - 2 were adjudicated as definite or probable VHD and one of those was possibly related to FINTEPLA® with no confounding factors
  - Of the reports of REMS-defined PAH cases:
    - 3 were adjudicated as definite (n=2) or probable (n=1) PAH; all were likely caused by pre-existing cardiac abnormalities and concurrent respiratory infections and, thus, unlikely related to FINTEPLA®
- No patient had both REMS-defined VHD and REMS-defined PAH and no patient experienced symptomatic VHD or PAH
- There was no change to FINTEPLA® treatment in 14/18 patients; in the 4 remaining patients (2 REMS-defined VHD and 2 REMS-defined PAH), FINTEPLA® was discontinued
- One additional case that did not meet the REMS definition of PAH (pulmonary arterial systolic pressure = 35 mmHg) was adjudicated as a probable PAH based on information available
  - This patient was likely developing PAH which appeared to resolve after discontinuation of FINTEPLA®; this case was not associated with any confounding factors and likely related to FINTEPLA®

Conclusions

- As of data cutoff date and approximately 4 years of evaluation for this interim report, 3563 patients have been enrolled in the FINTEPLA® REMS representing 5611 patient-years of FINTEPLA® exposure in the US
- The adjudication committee classified 2 cases (0.06%) as definite or probable VHD and 3 cases (0.08%) as definite or probable PAH, with one patient not having additional confounding factors; thus, only one case possibly related to FINTEPLA®
- No cases of symptomatic VHD or PAH were reported and regular ECHO monitoring enabled early identification of CV events
- Results of this interim report add to the current understanding of the CV safety profile of FINTEPLA® and help to inform patients, caregivers, and healthcare providers of the incidence of CVAEs
- The benefit-risk balance is favorable for patients with DS or LGS
- Timely reporting of AEs with high quality information from healthcare providers is important for assessing the safety profile of medications
- Ongoing treatment in any patient, including the decision to continue or discontinue FINTEPLA®, involves the benefit-risk assessment by the healthcare provider in consultation with patient and caregiver

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Disclosures

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