Interim Five-Year Results From the Cardiovascular Safety Registry Study of Fenfluramine Oral Solution Exposure in the United States

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Background

- Cardiovascular events in patients with Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS) may arise from multiple factors, including underlying cardiac conditions, comorbidities, use of antiseizure medications, and chronic seizures, causing structural, electrical, and/or mechanical dysfunction.[1-3]
- In the United States, fenfluramine is approved for the management of seizures associated with DS and LGS in patients ≥2 years of age, with a maximum dose of 26 mg/day (17 mg/day in patients taking concomitant stiripentol plus clobazam).[4]
- Cardiovascular risks, specifically valvular heart disease (VHD) and pulmonary arterial hypertension (PAH), were previously identified when fenfluramine tablet formulations were used at high doses (60-120 mg/day) as an anorectic agent; therefore, fenfluramine is available in the United States only through a Risk Evaluation and Mitigation Strategy (REMS).[4]
  - Prescribers and dispensing pharmacies must be certified through the REMS programme, and patients must be enrolled to receive fenfluramine.
  - To evaluate for VHD and/or PAH, an echocardiogram (ECHO) is required prior to fenfluramine initiation, every 6 months during treatment, and once 3-6 months after discontinuation of fenfluramine.
- The US Food and Drug Administration (FDA) has mandated a post-marketing cardiovascular safety registry study that includes all patients enrolled in the fenfluramine REMS.

Objective

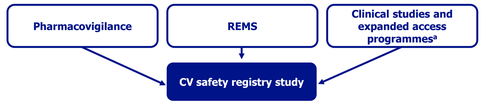
- To report interim results from the FDA-required post-marketing cardiovascular safety registry study, designed to characterise the risk of potential VHD and/or PAH in patients exposed to fenfluramine.

Methods

STUDY OVERVIEW

- The cardiovascular safety registry study is an ongoing, 10-year, prospective, observational cohort study of patients treated with fenfluramine in the United States.

Components of the fenfluramine CV safety registry study



[a]For pre-REMS exposure data only. CV, cardiovascular; REMS, Risk Evaluation and Mitigation Strategy.

DATA COLLECTION

- Data are collected from REMS enrolment (pre-treatment baseline), with assessments every 6 months during fenfluramine treatment and 3-6 months after the final dose.

Overview of data sources and data collected

DATA SOURCE		REPORTER(S)	TIMING OF COMPLETION	DATA COLLECTED
REMS form	Patient enrolment form	Patient/caregiver and prescriber	Enrolment	Registration info Demographics
	Patient status form	Prescriber	Before start of FFA Every 6 months during FFA treatment 3-6 months after final FFA dose	Height and weight FFA exposure info[a] ECHO results
	CVAE reporting form	Prescriber	At/immediately after CVAE reported	CVAE info FFA exposure info (including STP use)
Pharmacovigilance targeted follow-up form		Prescriber and/or other healthcare provider involved in integrative care of the patient	After CVAE reported/ when CVAE form received	Info regarding CVAE[b] Other exposure info[c] Medical comorbidities Concomitant medications Family history
Clinical studies/expanded access programmes		Patient/caregiver and prescriber	Enrolment	Pre-REMS exposure

[a]Start/end date of FFA, whether FFA was continued, and reasons for discontinuation. [b]Whether the CVAE was reviewed by a patient's cardiologist, if a VHD/PAH diagnosis was made, and other information that may assist in evaluating the events. [c]Medical history, concomitant medications, recreational drug exposure, and laboratory test results. CVAE, cardiovascular adverse event; ECHO, echocardiogram; FFA, fenfluramine; PAH, pulmonary arterial hypertension; REMS, Risk Evaluation and Mitigation Strategy; STP, stiripentol; VHD, valvular heart disease.

Overview

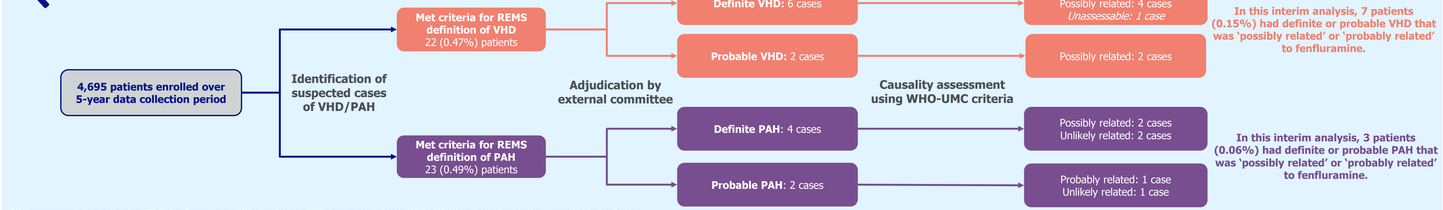
QUESTION

What is the risk of the potential development of valvular heart disease (VHD) and/or pulmonary arterial hypertension (PAH) in patients who are exposed to fenfluramine?

INVESTIGATION

Ongoing 10-year, prospective, observational cardiovascular safety study of patients treated with fenfluramine in the United States. Cases of suspected VHD or PAH are adjudicated by an external committee of independent cardiologists, and causality is assessed. Data are reported for patients who received ≥1 dose of fenfluramine from 25 June 2020 through 24 June 2025.

RESULTS



PAH, pulmonary arterial hypertension; REMS, Risk Evaluation and Mitigation Strategy; VHD, valvular heart disease; WHO-UMC, World Health Organization-Uppsala Monitoring Centre.

CONCLUSIONS

These interim findings further characterise the cardiovascular safety profile of fenfluramine.
The cases during the reporting interval do not change the overall risk assessment of VHD and PAH for the ongoing conduct of the fenfluramine REMS, and at this time, no additional clinical monitoring measures are recommended.

For a copy of the poster, scan:

ADJUDICATION OF SUSPECTED VHD OR PAH CASES

Overview of definitions

REMS-defined VHD (agreed with the FDA)

Mild or greater aortic regurgitation or moderate or greater mitral regurgitation associated with restricted valve motion, valve thickening, and/or physical signs or symptoms attributable to valve disease

REMS-defined PAH (agreed with the FDA)

Elevated pulmonary arterial systolic pressure >35 mmHg

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

- If information from any source suggests that REMS criteria of VHD or PAH are met, the case is included in the adjudication analysis.
- Suspected VHD or PAH cases are adjudicated by an external committee comprising 3 independent cardiologists with expertise in adult and paediatric cardiology and knowledge of fenfluramine.
- The committee reviews all available medical information for each case (including but not limited to ECHO imaging and findings, clinical course, concomitant medications, and comorbidities) and applies clinical judgement to classify cases as definite, probable, possible, or not VHD/PAH.
- In addition, causality is assessed by the sponsor in accordance with World Health Organization-Uppsala Monitoring Centre (WHO-UMC) guidance, considering clinical-pharmacological aspects of the case history and the quality of documentation.
- Cases are categorised as definitely, probably/likely, possibly, or unlikely related to fenfluramine, or as unassessable.

Results

PATIENTS

- Over the 5-year data collection period (25 June 2020 through 24 June 2025), 4,695 patients were enrolled in the REMS and received ≥1 dose of fenfluramine.
- Of these, 273 (5.8%) patients had an abnormality on baseline ECHO.
  - These included: FDA-defined mild and moderate aortic valvulopathy, FDA-defined moderate mitral valvulopathy, and REMS-defined PAH.

Patient demographics

	ENROLLED SET (N=4,695)	PATIENTS WITH CV EVENTS AT ENROLMENT (n=273)	PATIENTS WITHOUT CV EVENTS AT ENROLMENT (n=4,422)
Age, years			
Mean (SD)	15.8 (11.6)	18.2 (13.0)	15.6 (11.5)
Range	0.1, 70.7	0.1, 62.4	0.3, 70.7
Sex, n (%)			
Male	2,456 (52.3)	145 (53.1)	2,311 (52.3)
Female	2,237 (47.6)	128 (46.9)	2,109 (47.7)
Missing	2 (0.04)	0 (0.00)	2 (0.05)
Weight at enrolment, kg	n=4,688	n=273	n=4,415
Mean (SD)	44.1 (25.8)	45.9 (24.8)	44.0 (25.8)
BMI at enrolment, kg/m²	n=4,267	n=255	n=4,012
Mean (SD)	21.3 (6.6)	21.5 (6.8)	21.3 (6.6)

BMI, body mass index; CV, cardiovascular.

EXPOSURE

Duration of fenfluramine exposure

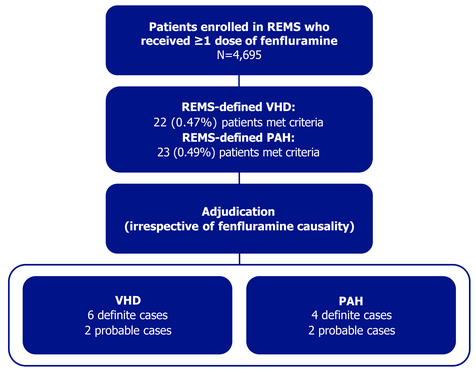
	ENROLLED SET
All patients	**N=4,695**
Total duration of exposure, patient-years	8,632.1
Patients initiating fenfluramine *prior to* REMS enrolment	**n=180**
Pre-REMS duration of exposure, patient-years[a]	529.2
REMS duration of exposure, patient-years	647.6
Total duration of exposure, patient-years	1,176.8
Patients initiating fenfluramine *from* REMS enrolment	**n=4,515**
Duration of exposure, patient-years	7,455.3

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

- Overall, 2,835 (60.4%) patients received fenfluramine treatment for ≥1 year.
- Mean (SD) fenfluramine daily dose was 0.4 (0.2) mg/kg/day (18.0 [7.4] mg/day).

REMS-DEFINED VHD AND PAH

REMS-defined VHD and PAH cases and adjudication outcomes (definite or probable), irrespective of causality



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

- One patient had both REMS-defined VHD and REMS-defined PAH, 1 patient experienced symptomatic REMS-defined VHD (tired/lethargy), and 1 patient with REMS-defined PAH had signs on physical examination (hypotension).
  - These signs/symptoms could be attributed to other concomitant conditions (eg, pneumonia with sepsis), the underlying indication for treatment, or known AEs of fenfluramine (eg, fatigue).
- Of all reports of REMS-defined VHD or PAH:
  - Six cases were pending adjudication at the time of this interim assessment.
  - One case was adjudicated as not VHD, and 3 cases as not PAH.
- Of the patients with REMS-defined VHD (n=22) or PAH (n=23):
  - Eight patients discontinued treatment with fenfluramine.
  - One additional patient with REMS-defined PAH discontinued and then re-started fenfluramine treatment.
  - No patients required medication or intervention, hospitalisation, or died due to VHD or PAH.

CAUSALITY ASSESSMENT USING WHO-UMC CRITERIA

Causality of definite/probable REMS-defined VHD and PAH

ADJUDICATION	WHO-UMC CAUSALITY ASSESSMENT
REMS-defined VHD	
6 definite VHD	1 probably related 4 possibly related 1 unassessable
2 probable VHD	2 possibly related
REMS-defined PAH	
4 definite PAH	2 possibly related 2 unlikely related
2 probable PAH	1 probably related 1 unlikely related

PAH, pulmonary arterial hypertension; REMS, Risk Evaluation and Mitigation Strategy; VHD, valvular heart disease; WHO-UMC, World Health Organization-Uppsala Monitoring Centre.

- In this interim analysis of 4,695 patients:
  - 7 (0.15%) patients had definite or probable VHD that was 'possibly related' or 'probably related' to fenfluramine.
  - 3 (0.06%) patients had definite or probable PAH that was 'possibly related' or 'probably related' to fenfluramine.
  - Of the definite or probable REMS-defined VHD/PAH cases, none had a definite fenfluramine causality.
- In at least half of definite or probable cases, patients had comorbidities or risk factors which could have caused or contributed to PAH (i.e. congenital heart diseases or pulmonary infection) or VHD (i.e. pre-existing valvulopathy, congenital heart disease or hypertension).
- Management of these comorbidities and risk factors is important to mitigate the cardiovascular risk for patients treated with fenfluramine.

Conclusions

- Following approximately 5 years of evaluation, 4,695 patients in the United States have been enrolled in the REMS, representing 8,632 patient-years of fenfluramine exposure.
- Overall, the benefit-risk balance of fenfluramine remains favourable.
  - A total of 22 cases met REMS-defined VHD criteria; 7 of 8 cases adjudicated as definite/probable VHD were considered 'possibly related' or 'probably related' to fenfluramine.
  - A total of 23 cases met REMS-defined PAH criteria; 3 of 6 cases adjudicated as definite/probable PAH were considered 'possibly related' or 'probably related' to fenfluramine.
- Echocardiographic monitoring must be performed for patients on fenfluramine before, during and after treatment.
- Ongoing treatment decisions, including whether to continue or discontinue fenfluramine, require an individualised benefit-risk assessment by the healthcare provider in consultation with the patient and caregiver.
- These interim findings further characterise the cardiovascular safety profile of fenfluramine.

References

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