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

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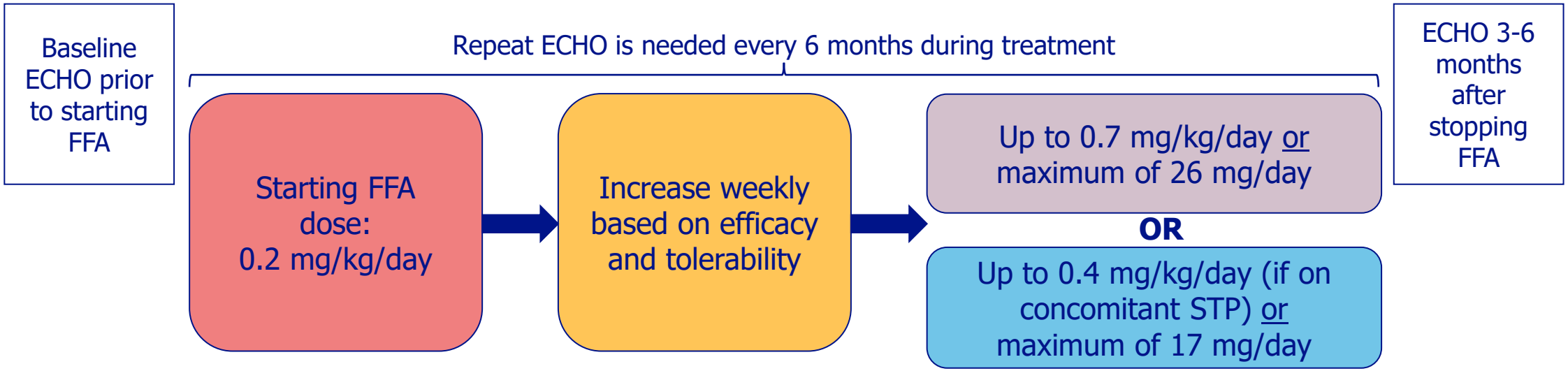
American Academy of Neurology (AAN) Annual Meeting, April 5-9, 2025

Disclosures & Acknowledgements

- All authors are employees of UCB with stock ownership
- UCB-sponsored
- The authors acknowledge Tom Grant, PhD (UCB) and Bobby Jacob, PharmD (UCB), for managing the development of this poster and Sandra M Aguero, PharmD, BCPS, and Scott Bergfeld, PhD, of PharmaWrite, LLC (Princeton, NJ, USA), for writing and editorial assistance, funded by UCB
- This work was previously presented at the American Epilepsy Society 78th Annual Meeting
Los Angeles, CA, USA | December 6—10, 2024

Background

- Fenfluramine (FFA oral solution) is FDA-approved for the treatment of seizures associated with DS and LGS in patients ≥2 years old[1]
- Due to VHD and PAH identified when the FFA oral tablet formulation was used as a weight loss agent (at 60-120 mg/day), FFA oral solution is only available in the US through a **Risk Evaluation and Mitigation Strategy (REMS)**[1]
  - Prescribers and dispensing pharmacies must be certified through REMS and patients must also be enrolled in REMS to receive FFA

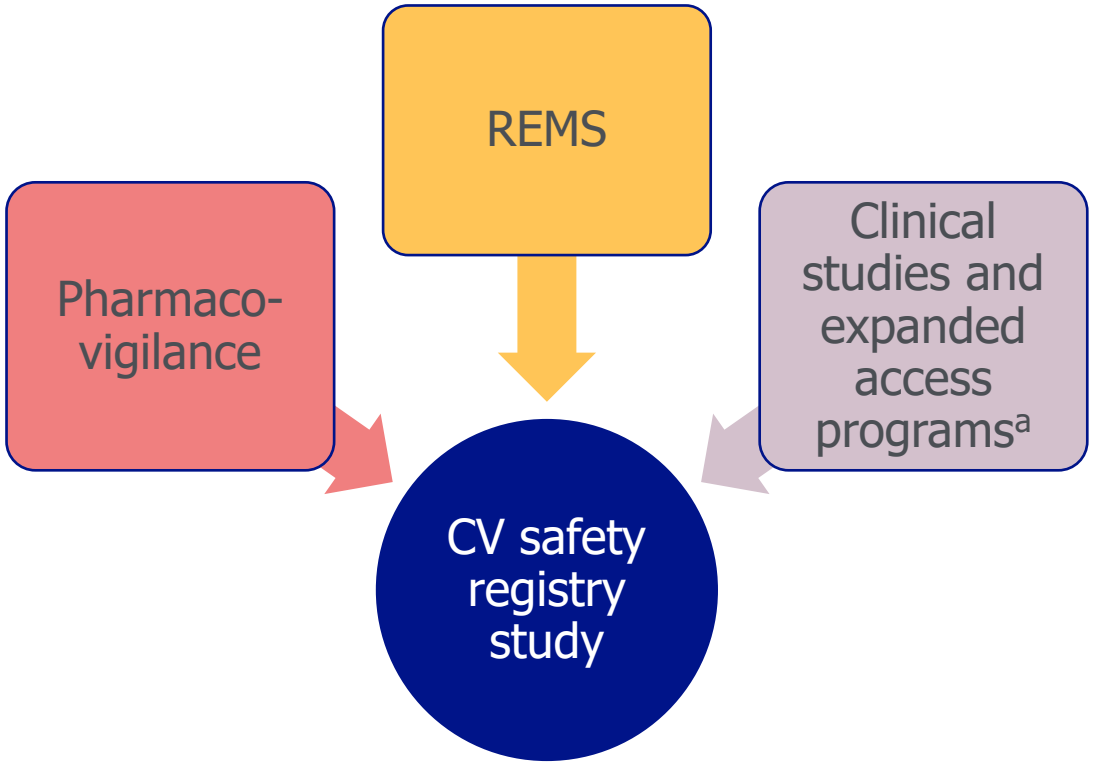


1. UCB, Inc. FINTEPLA® (fenfluramine) oral solution [prescribing information]. Smyrna, GA; March 2023.

DS, Dravet syndrome; ECHO, echocardiogram; LGS, Lennox-Gastaut syndrome; PAH, pulmonary arterial hypertension; STP, stiripentol; VHD, valvular heart disease.

Objective

- The FDA has required a post-marketing CV safety registry study to continue monitoring, evaluating, and reporting VHD, PAH, and/or other CVAEs in patients on FFA
- Here, we provide interim results from the CV safety registry study, since FDA approval of FFA oral solution (June 2020)



Definitions as agreed with FDA:	
REMS-defined VHD	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	Elevated PASP >35 mmHg

Objective:
To characterize the risk of potential development of VHD and/or PAH in patients exposed to FFA in the US.

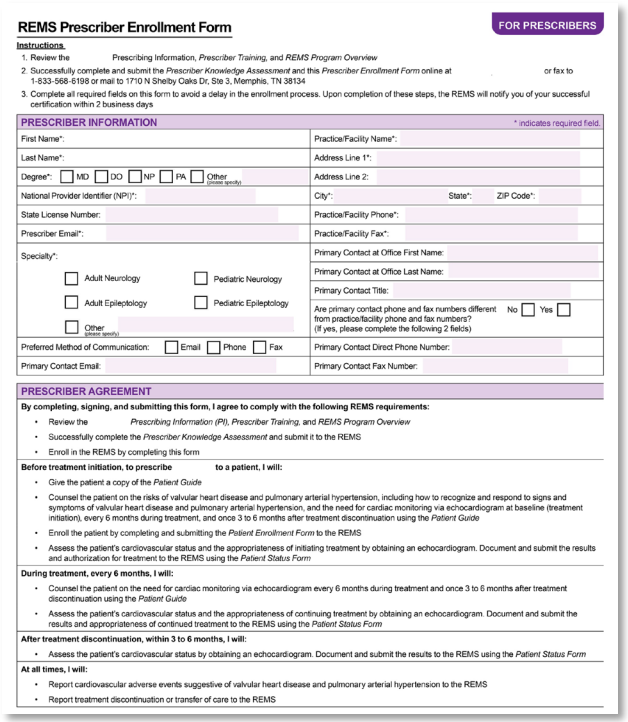
[a]For Pre-REMS exposure data only.

CV, cardiovascular; CVAEs, cardiovascular adverse events; FDA, Food and Drug Administration; FFA, fenfluramine; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; REMS, Risk Evaluation and Mitigation Strategy; VHD, valvular heart disease.

Methods – Data Collection

- Ongoing prospective, observational, cohort study of patients treated with FFA in the US
- Data collection period: June 25, 2020, through June 24, 2024
  - From REMS[1] specifically, data were collected from various forms

REMS Prescriber Enrollment Form



REMS Prescriber Enrollment Form

FOR PRESCRIBERS

Instructions

1. Review the Prescribing Information, *Prescriber Training*, and *REMS Program Overview*
2. Successfully complete and submit the *Prescriber Knowledge Assessment* and this *Prescriber Enrollment Form* online at or fax to 1-833-568-6198 or mail to 1710 N Shelby Oaks Dr, Ste 3, Memphis, TN 38134
3. Complete all required fields on this form to avoid a delay in the enrollment process. Upon completion of these steps, the REMS will notify you of your successful certification within 2 business days

PRESCRIBER INFORMATION — * indicates required field.

First Name*: | Practice/Facility Name*:
Last Name*: | Address Line 1*:
Degree*: ☐ MD ☐ DO ☐ NP ☐ PA ☐ Other (please specify) | Address Line 2:
National Provider Identifier (NPI)*: | City*: State*: ZIP Code*:
State License Number: | Practice/Facility Phone*:
Prescriber Email*: | Practice/Facility Fax*:
Specialty*: | Primary Contact at Office First Name:
☐ Adult Neurology ☐ Pediatric Neurology | Primary Contact at Office Last Name:
☐ Adult Epileptology ☐ Pediatric Epileptology | Primary Contact Title:
☐ Other (please specify) | Are primary contact phone and fax numbers different from practice/facility phone and fax numbers? (If yes, please complete the following 2 fields) No ☐ Yes ☐
Preferred Method of Communication: ☐ Email ☐ Phone ☐ Fax | Primary Contact Direct Phone Number:
Primary Contact Email: | Primary Contact Fax Number:

PRESCRIBER AGREEMENT

By completing, signing, and submitting this form, I agree to comply with the following REMS requirements:

- Review the *Prescribing Information (PI)*, *Prescriber Training*, and *REMS Program Overview*
- Successfully complete the *Prescriber Knowledge Assessment* and submit it to the REMS
- Enroll in the REMS by completing this form

Before treatment initiation, to prescribe to a patient, I will:

- Give the patient a copy of the *Patient Guide*
- Counsel the patient on the risks of valvular heart disease and pulmonary arterial hypertension, including how to recognize and respond to signs and symptoms of valvular heart disease and pulmonary arterial hypertension, and the need for cardiac monitoring via echocardiogram at baseline (treatment initiation), every 6 months during treatment, and once 3 to 6 months after treatment discontinuation using the *Patient Guide*
- Enroll the patient by completing and submitting the *Patient Enrollment Form* to the REMS
- Assess the patient's cardiovascular status and the appropriateness of initiating treatment by obtaining an echocardiogram. Document and submit the results and authorization for treatment to the REMS using the *Patient Status Form*

During treatment, every 6 months, I will:

- Counsel the patient on the need for cardiac monitoring via echocardiogram every 6 months during treatment and once 3 to 6 months after treatment discontinuation using the *Patient Guide*
- Assess the patient's cardiovascular status and the appropriateness of continuing treatment by obtaining an echocardiogram. Document and submit the results and appropriateness of continued treatment to the REMS using the *Patient Status Form*

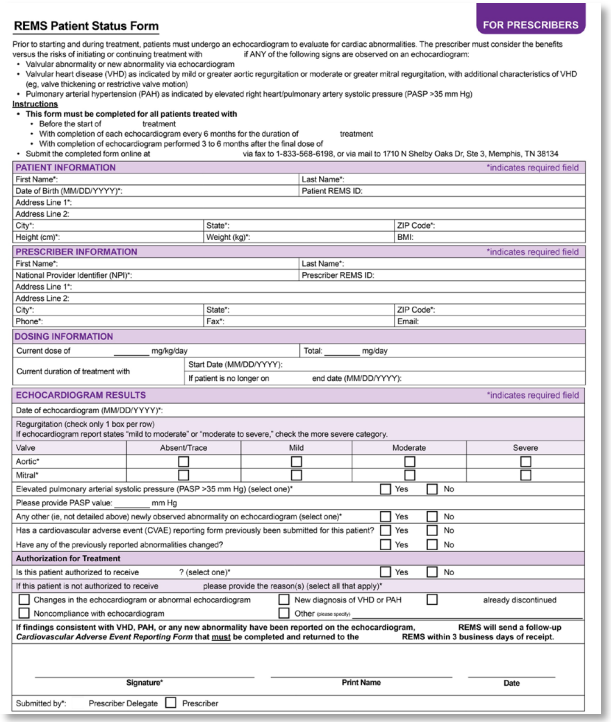
After treatment discontinuation, within 3 to 6 months, I will:

- Assess the patient's cardiovascular status by obtaining an echocardiogram. Document and submit the results to the REMS using the *Patient Status Form*

At all times, I will:

- Report cardiovascular adverse events suggestive of valvular heart disease and pulmonary arterial hypertension to the REMS
- Report treatment discontinuation or transfer of care to the REMS

REMS Patient Status Form



REMS Patient Status Form

FOR PRESCRIBERS

Prior to starting and during treatment, patients must undergo an echocardiogram to evaluate for cardiac abnormalities. The prescriber must consider the benefits versus the risks of initiating or continuing treatment with if ANY of the following signs are observed on an echocardiogram:

- Valvular abnormality or new abnormality via echocardiogram
- Valvular heart disease (VHD) as indicated by mild or greater aortic regurgitation or moderate or greater mitral regurgitation, with additional characteristics of VHD (eg, valve thickening or restrictive valve motion)
- Pulmonary arterial hypertension (PAH) as indicated by elevated right heart/pulmonary artery systolic pressure (PASP >35 mm Hg)

Instructions

- **This form must be completed for all patients treated with**
  - Before the start of treatment
  - With completion of each echocardiogram every 6 months for the duration of treatment
  - With completion of echocardiogram performed 3 to 6 months after the final dose of
- Submit the completed form online at via fax to 1-833-568-6198, or via mail to 1710 N Shelby Oaks Dr, Ste 3, Memphis, TN 38134

PATIENT INFORMATION — *indicates required field

First Name*: | Last Name*:
Date of Birth (MM/DD/YYYY)*: | Patient REMS ID:
Address Line 1*:
Address Line 2:
City*: | State*: | ZIP Code*:
Height (cm)*: | Weight (kg)*: | BMI:

PRESCRIBER INFORMATION — *indicates required field

First Name*: | Last Name*:
National Provider Identifier (NPI)*: | Prescriber REMS ID:
Address Line 1*:
Address Line 2:
City*: | State*: | ZIP Code*:
Phone*: | Fax*: | Email:

DOSING INFORMATION

Current dose of _____ mg/kg/day | Total: _____ mg/day
Current duration of treatment with | Start Date (MM/DD/YYYY):
If patient is no longer on end date (MM/DD/YYYY):

ECHOCARDIOGRAM RESULTS — *indicates required field

Date of echocardiogram (MM/DD/YYYY)*:

Regurgitation (check only 1 box per row)
If echocardiogram report states "mild to moderate" or "moderate to severe," check the more severe category.

Valve	Absent/Trace	Mild	Moderate	Severe
Aortic*	☐	☐	☐	☐
Mitral*	☐	☐	☐	☐

Elevated pulmonary arterial systolic pressure (PASP >35 mm Hg) (select one)* ☐ Yes ☐ No
Please provide PASP value: _____ mm Hg
Any other (ie, not detailed above) newly observed abnormality on echocardiogram (select one)* ☐ Yes ☐ No
Has a cardiovascular adverse event (CVAE) reporting form previously been submitted for this patient? ☐ Yes ☐ No
Have any of the previously reported abnormalities changed? ☐ Yes ☐ No

Authorization for Treatment

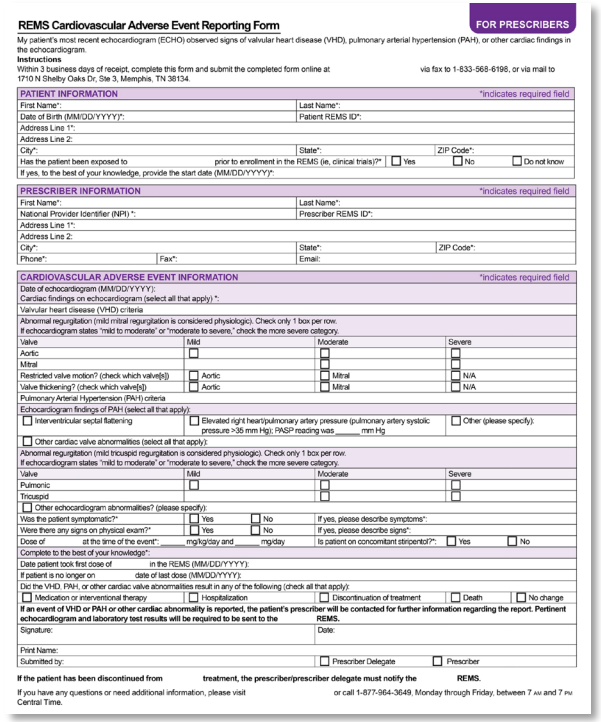
Is this patient authorized to receive ? (select one)* ☐ Yes ☐ No
If this patient is not authorized to receive please provide the reason(s) (select all that apply)*
☐ Changes in the echocardiogram or abnormal echocardiogram ☐ New diagnosis of VHD or PAH ☐ already discontinued
☐ Noncompliance with echocardiogram ☐ Other (please specify) _____

If findings consistent with VHD, PAH, or any new abnormality have been reported on the echocardiogram, *Cardiovascular Adverse Event Reporting Form* that must be completed and returned to the REMS will send a follow-up REMS within 3 business days of receipt.

Signature* | Print Name | Date

Submitted by*: Prescriber Delegate ☐ Prescriber

REMS CVAE Reporting Form



REMS Cardiovascular Adverse Event Reporting Form

FOR PRESCRIBERS

My patient's most recent echocardiogram (ECHO) observed signs of valvular heart disease (VHD), pulmonary arterial hypertension (PAH), or other cardiac findings in the echocardiogram.

Instructions

Within 3 business days of receipt, complete this form and submit the completed form online at via fax to 1-833-568-6198, or via mail to 1710 N Shelby Oaks Dr, Ste 3, Memphis, TN 38134.

PATIENT INFORMATION — *indicates required field

First Name*: | Last Name*:
Date of Birth (MM/DD/YYYY)*: | Patient REMS ID*:
Address Line 1*:
Address Line 2:
City*: | State*: | ZIP Code*:
Has the patient been exposed to prior to enrollment in the REMS (ie, clinical trials)?* ☐ Yes ☐ No ☐ Do not know
If yes, to the best of your knowledge, provide the start date (MM/DD/YYYY)*:

PRESCRIBER INFORMATION — *indicates required field

First Name*: | Last Name*:
National Provider Identifier (NPI) *: | Prescriber REMS ID*:
Address Line 1*:
Address Line 2:
City*: | State*: | ZIP Code*:
Phone*: | Fax*: | Email:

CARDIOVASCULAR ADVERSE EVENT INFORMATION — *indicates required field

Date of echocardiogram (MM/DD/YYYY):
Cardiac findings on echocardiogram (select all that apply) *:
Valvular heart disease (VHD) criteria
Abnormal regurgitation (mild) mitral regurgitation is considered physiologic). Check only 1 box per row.
If echocardiogram states "mild to moderate" or "moderate to severe," check the more severe category.

Valve	Mild	Moderate	Severe
Aortic	☐	☐	☐
Mitral		☐	☐
Restricted valve motion? (check which valve[s])	☐ Aortic	☐ Mitral	☐ N/A
Valve thickening? (check which valve[s])	☐ Aortic	☐ Mitral	☐ N/A

Pulmonary Arterial Hypertension (PAH) criteria
Echocardiogram findings of PAH (select all that apply):
☐ Interventricular septal flattening ☐ Elevated right heart/pulmonary artery pressure (pulmonary artery systolic pressure >35 mm Hg); PASP reading was _____ mm Hg ☐ Other (please specify):
☐ Other cardiac valve abnormalities (select all that apply):
Abnormal regurgitation (mild tricuspid regurgitation is considered physiologic). Check only 1 box per row.
If echocardiogram states "mild to moderate" or "moderate to severe," check the more severe category.

Valve	Mild	Moderate	Severe
Pulmonic	☐	☐	☐
Tricuspid		☐	☐

☐ Other echocardiogram abnormalities? (please specify):
Was the patient symptomatic?* ☐ Yes ☐ No | If yes, please describe symptoms*:
Were there any signs on physical exam?* ☐ Yes ☐ No | If yes, please describe signs*:
Dose of at the time of the event*: _____ mg/kg/day and _____ mg/day | Is patient on concomitant stiripentol?*: ☐ Yes ☐ No
Complete to the best of your knowledge*:
Date patient took first dose of in the REMS (MM/DD/YYYY):
If patient is no longer on date of last dose (MM/DD/YYYY):
Did the VHD, PAH, or other cardiac valve abnormalities result in any of the following (check all that apply):
☐ Medication or interventional therapy ☐ Hospitalization ☐ Discontinuation of treatment ☐ Death ☐ No change

If an event of VHD or PAH or other cardiac abnormality is reported, the patient's prescriber will be contacted for further information regarding the report. Pertinent echocardiogram and laboratory test results will be required to be sent to the REMS.

Signature: | Date:
Print Name:
Submitted by: ☐ Prescriber Delegate ☐ Prescriber

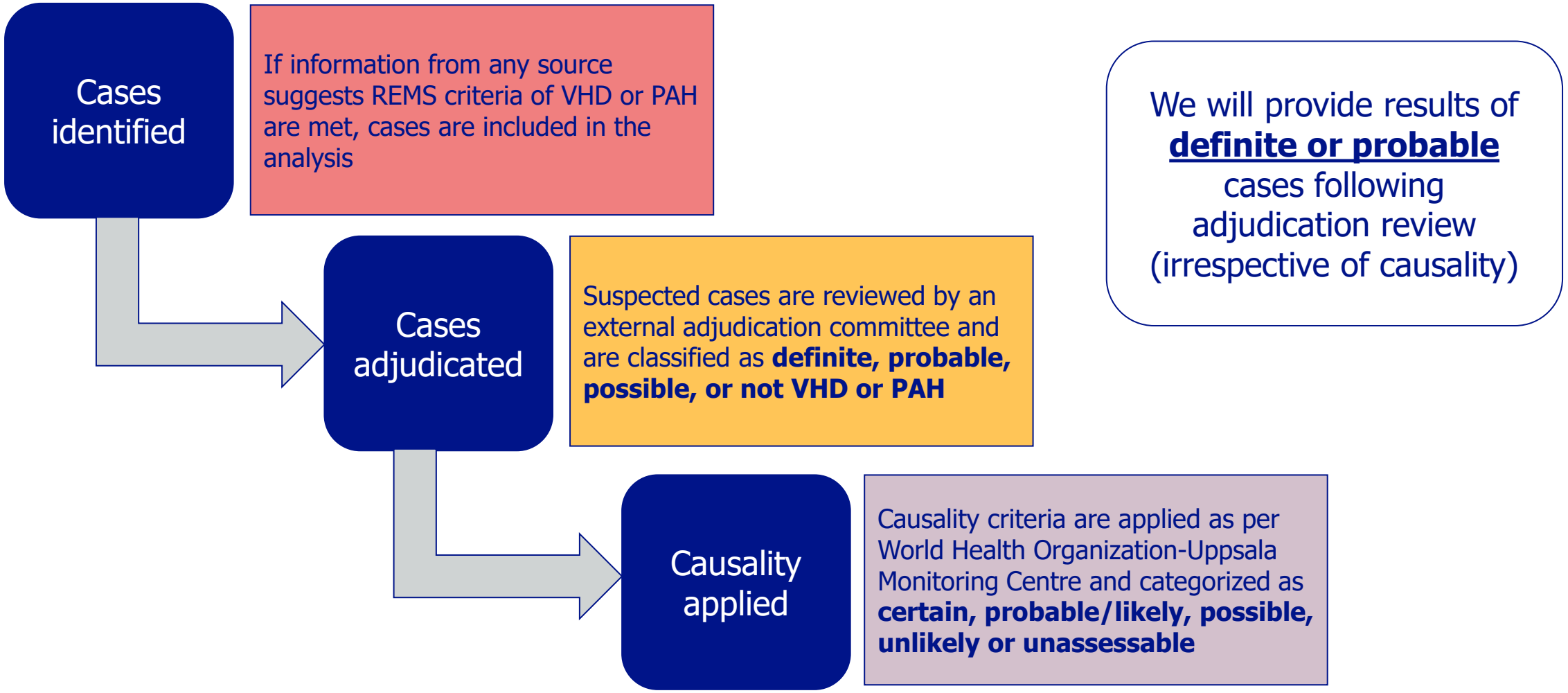
If the patient has been discontinued from treatment, the prescriber/prescriber delegate must notify the REMS.

If you have any questions or need additional information, please visit or call 1-877-964-3649, Monday through Friday, between 7 AM and 7 PM Central Time.

1. https://www.finteplarems.com/

CVAE, cardiovascular adverse event; FFA, fenfluramine; REMS, Risk Evaluation and Mitigation Strategy.

Methods – Outcomes



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

Patients Enrolled & Duration of Exposure

	Enrolled Set N=3563	Patients With CV Events at Enrollment n=216
Age, years		
Mean±SD	14±10.8	17.4±13.1
Range	0.1-70.1	0.1-62.4
Sex, 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/m^2)		
n	3115	196
Mean±SD	21.3±6.6	21.2±6.9

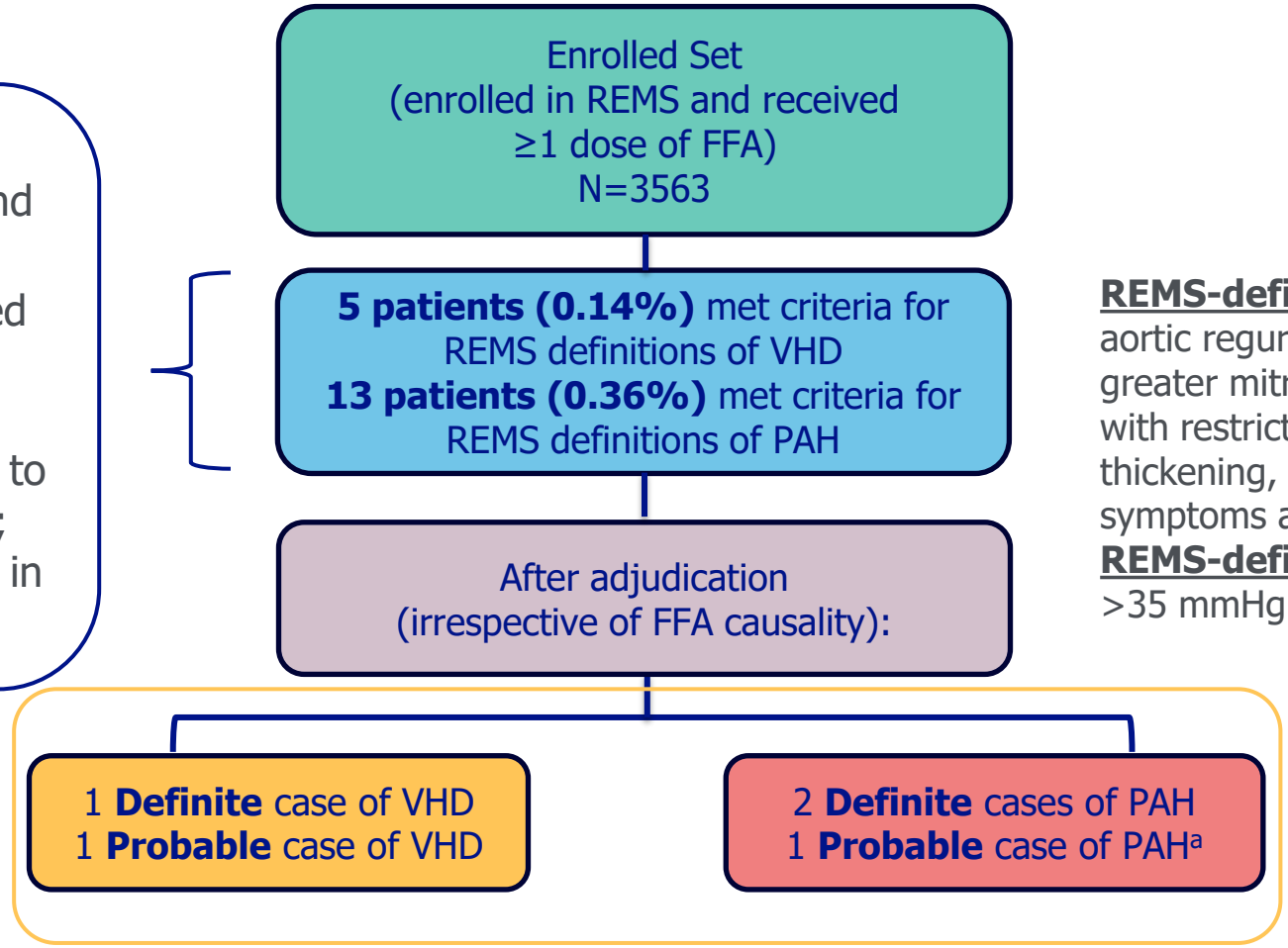
Of the enrolled set, mean±SD FFA daily dose was 0.5±0.3 mg/kg/day or 17.6±9.3 mg/day

	Enrolled Set N=3563
Patients initiating FFA 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 FFA from REMS enrollment, patient-years	4588.8
Total duration of exposure, patient-years	5611.4

[a]Includes FFA exposure from participation in clinical trials or expanded access programs.
BMI, body mass index; CV, cardiovascular; FDA, Food and Drug Administration; FFA, fenfluramine; PAH, pulmonary arterial hypertension; REMS, Risk Evaluation and Mitigation Strategy; SD, standard deviation.

Reports of REMS-Defined VHD and REMS-Defined PAH Cases and Results of Definite or Probable Adjudication

- No patient had both REMS-defined VHD and REMS-defined PAH
- No patient experienced symptomatic VHD or PAH
- There was no change to FFA in 14/18 patients; FFA was discontinued in the remaining 4

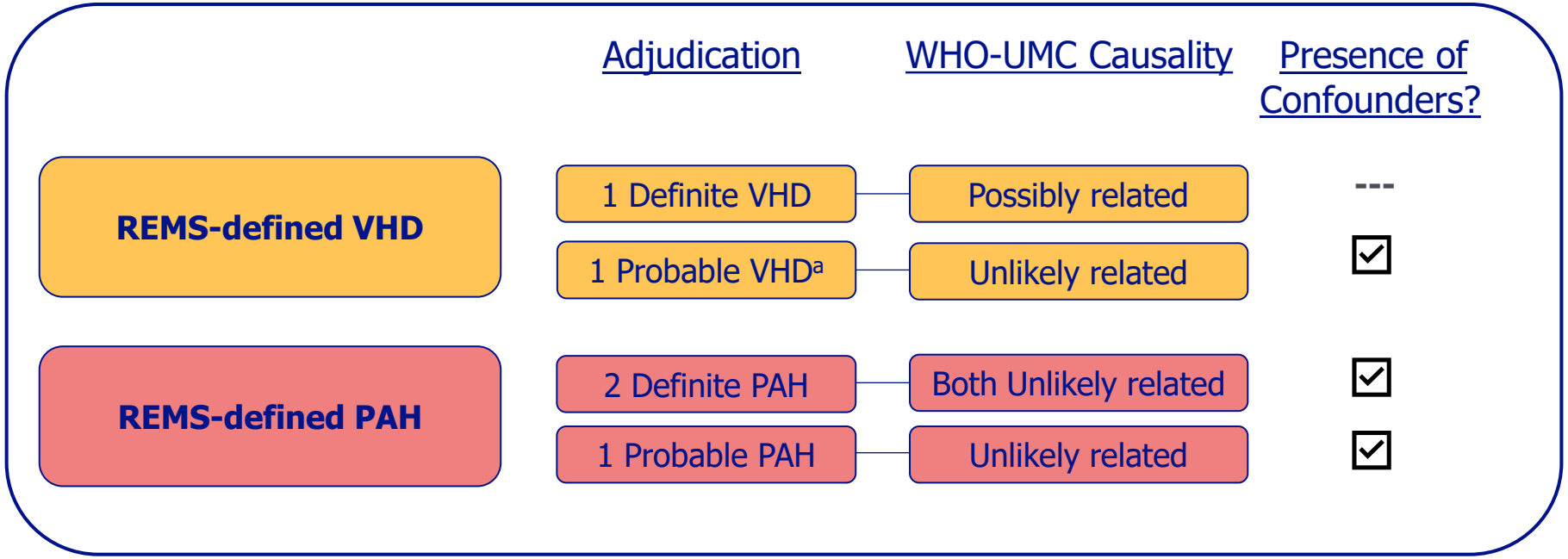


REMS-defined VHD: Mild or greater aortic regurgitation or moderate or greater mitral regurgitation associated with restricted valve motion, valve thickening, and/or physical signs or symptoms attributable to valve disease
REMS-defined PAH: Elevated PASP >35 mmHg

[a]One case that did not meet criteria for REMS definition of PAH (PASP=35 mmHg) was adjudicated as a probable PAH. This patient was likely developing PAH that resolved after discontinuation of FFA. There were no confounding factors and was likely related to FFA.

FFA, fenfluramine; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; REMS, Risk Evaluation and Mitigation Strategy; VHD, valvular heart disease.

Adjudication and Causality of Definite and Probable Cases



[a]After completion of the interim report, this case was re-adjudicated as "definite VHD" but remained unlikely related to FFA.

REMS-defined VHD: 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: Elevated PASP >35 mmHg

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

Conclusions

- As of data cutoff date, **3563 patients** have been enrolled in the FFA REMS representing **5611 patient-years** of FFA exposure in the US
- No patients experienced symptomatic VHD or PAH were reported
- The adjudication committee classified 2 cases (0.06%) as definite or probable VHD and 3 cases (0.08%) as definite or probable PAH
  - One of these (definite VHD) was considered possibly related to FFA
- 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 FFA and help to inform patients, caregivers, and healthcare providers of the incidence of CVAEs
- FFA's 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 FFA
- Ongoing treatment in any patient, including the decision to continue or discontinue FFA, involves the benefit-risk assessment by the healthcare provider in consultation with patient and caregiver

AEs, adverse events; CV, cardiovascular; CVAEs, cardiovascular adverse events; DS, Dravet syndrome; ECHO, echocardiogram; FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; PAH, pulmonary arterial hypertension; REMS, Risk Evaluation and Mitigation Strategy; VHD, valvular heart disease.

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 FFA • Every 6 months during FFA treatment • 3-6 months after final FFA dose	• Height, weight • FFA exposure information[a] • ECHO results
	REMS CVAE reporting form	Prescriber	• At or immediately after CVAE reported	• CVAE information • FFA exposure information[a] (including STP use)
Pharmacovigilance targeted follow-up form		Prescriber and/or other HCP 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 early access programs		Patient or caregiver and prescriber	• Enrollment	• Pre-REMS exposure

[a]Includes start/end date of FFA, and whether FFA 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; FFA, fenfluramine; HCP, healthcare provider; PAH, pulmonary arterial hypertension; REMS, Risk Evaluation and Mitigation Strategy; STP, stiripentol; VHD, valvular heart disease.

Reports *not* adjudicated as definite or probable (n=13)

- Of the REMS-defined VHD or REMS-defined PAH reports that were *not* classified as definite or probable (n=13):
  - **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)
    - **1 case** requires additional information for complete adjudication
  - 12 of the 13 cases had confounding factors

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