

Design of a Phase III Randomised, Double-Blind, Placebo-Controlled Trial With an Open-Label Extension Evaluating the Efficacy and Safety of Fenfluramine in Patients With Rett Syndrome

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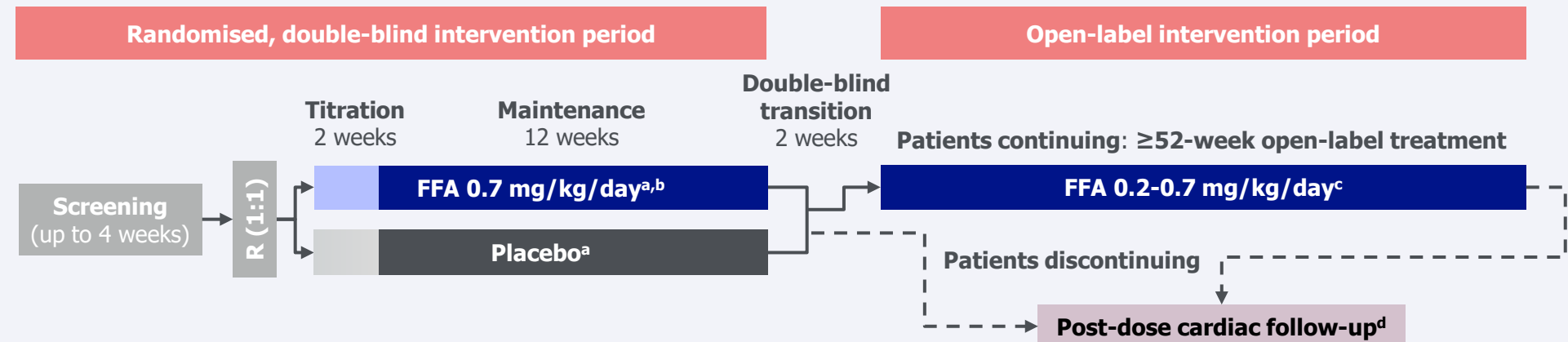
QUESTION

How are the efficacy and safety of fenfluramine being evaluated in patients with Rett syndrome (RTT) in an ongoing Phase III study (NCT07503444)?

INVESTIGATION

- Randomised, double-blind, placebo-controlled trial of fenfluramine.
- ≥52-week open-label extension evaluating long-term fenfluramine treatment with flexible dosing.

TRIAL DESIGN AND ENDPOINTS



^aMay be added to concomitant trofinetide; ^bMaximum 26 mg/day; ^cFlexible-dose FFA (0.2-0.7 mg/kg/day; maximum 26 mg/day); ^dCardiac follow-up visit conducted 6 months after last FFA dose in patients discontinuing the trial or not continuing FFA after study completion. CaGIC-Seizure, Caregiver Global Impression of Change-Seizure; CGIC, Clinical Global Impression of Change; ECG, electrocardiogram; FFA, fenfluramine; ORCA, Observer-Reported Communication Ability; PAH, pulmonary arterial hypertension; PROMIS-SD, Patient-Reported Outcomes Measurement Information System-Sleep Disturbance; QTcF, QT interval corrected using Fridericia's formula; R, randomisation; RSBQ, Rett Syndrome Behaviour Questionnaire; TEAE, treatment-emergent adverse event; VHD, valvular heart disease.

CONCLUSIONS

- ▶ This ongoing trial will characterise the short- and long-term efficacy and safety of fenfluramine in patients with RTT, a severe neurodevelopmental disorder with significant unmet medical needs.
- ▶ Efficacy of fenfluramine is being assessed across a range of RTT outcomes (eg, behaviour, sleep, communication, and seizures) using the Rett Syndrome Behaviour Questionnaire and Clinical Global Impression of Change as co-primary efficacy endpoints.

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Background

- Rett syndrome (RTT) is a rare neurodevelopmental disorder characterised by early regression, which may begin as early as 6 months of age and typically ends before 3 years of age.¹
 - Key clinical features include regression of hand use, regression of speech, impaired motor coordination, seizures, and breathing abnormalities.¹
 - RTT predominantly presents in females; however, males can also be affected.¹
- Fenfluramine is approved for the treatment of seizures in patients (≥2 years of age) with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in the European Union, United States, and many other countries worldwide.^{2,3}
- Fenfluramine has a multimodal mechanism of action, modulating serotonin release and signalling across multiple 5-hydroxytryptamine (5-HT) receptor subtypes and sigma-1 receptors.⁴
 - As both pathways are implicated in RTT pathophysiology, fenfluramine has the potential to induce sustained and meaningful effects on RTT outcomes such as behaviour, sleep, respiration, and seizures.^{4,5}
 - Consequently, there is a long-standing interest among RTT specialists in clinically evaluating fenfluramine.⁶
- Preliminary evidence from small pilot studies suggests that fenfluramine may provide benefits across multiple disease domains in patients with RTT,^{6,7} with effects that may be independent of its antiseizure efficacy.
 - These data support further investigation in randomised clinical trials.

Objective

- To describe the design of EP0247 (NCT07503444), an ongoing Phase III study evaluating the efficacy and safety of fenfluramine in patients with RTT.

Methods

STUDY DESIGN

- EP0247 is an ongoing Phase III, randomised, double-blind, placebo-controlled, parallel-group, multicentre trial with an open-label extension.^{8,9}
- In the double-blind intervention period, eligible patients are randomised (1:1) to fenfluramine 0.7 mg/kg/day (maximum 26 mg/day) or placebo.
 - Randomisation is performed using minimisation to maximise balance across region (North America, Europe, Asia, rest of world), Rett Syndrome Behaviour Questionnaire severity (total score </≥35), presence/absence of baseline seizures, age groups (≥5 to ≤11, ≥12 to ≤15, ≥16 to ≤20, ≥21 to ≤35 years), and concomitant trofinetide use (yes/no).
- Patients who complete the 14-week double-blind intervention period (2-week titration; 12-week maintenance) enter a 2-week double-blind transition period.
 - Patients receiving placebo transition to fenfluramine, while those already receiving fenfluramine continue at a dose of 0.7 mg/kg/day.
- In the open-label intervention period, patients receive flexible-dose fenfluramine for ≥52 weeks, or until study discontinuation, access to an alternative form of fenfluramine becomes available, or regulatory approval of fenfluramine for RTT.
 - Doses may be adjusted in ≤0.2 mg/kg/day increments every 4 days (range 0.2-0.7 mg/kg/day; maximum 26 mg/day).
- Patients who discontinue the study undergo a taper and safety follow-up, including electrocardiogram (ECG) and 2D colour Doppler echocardiogram (ECHO) assessments 26 weeks after the final dose.

PATIENT ELIGIBILITY CRITERIA

Key inclusion criteria

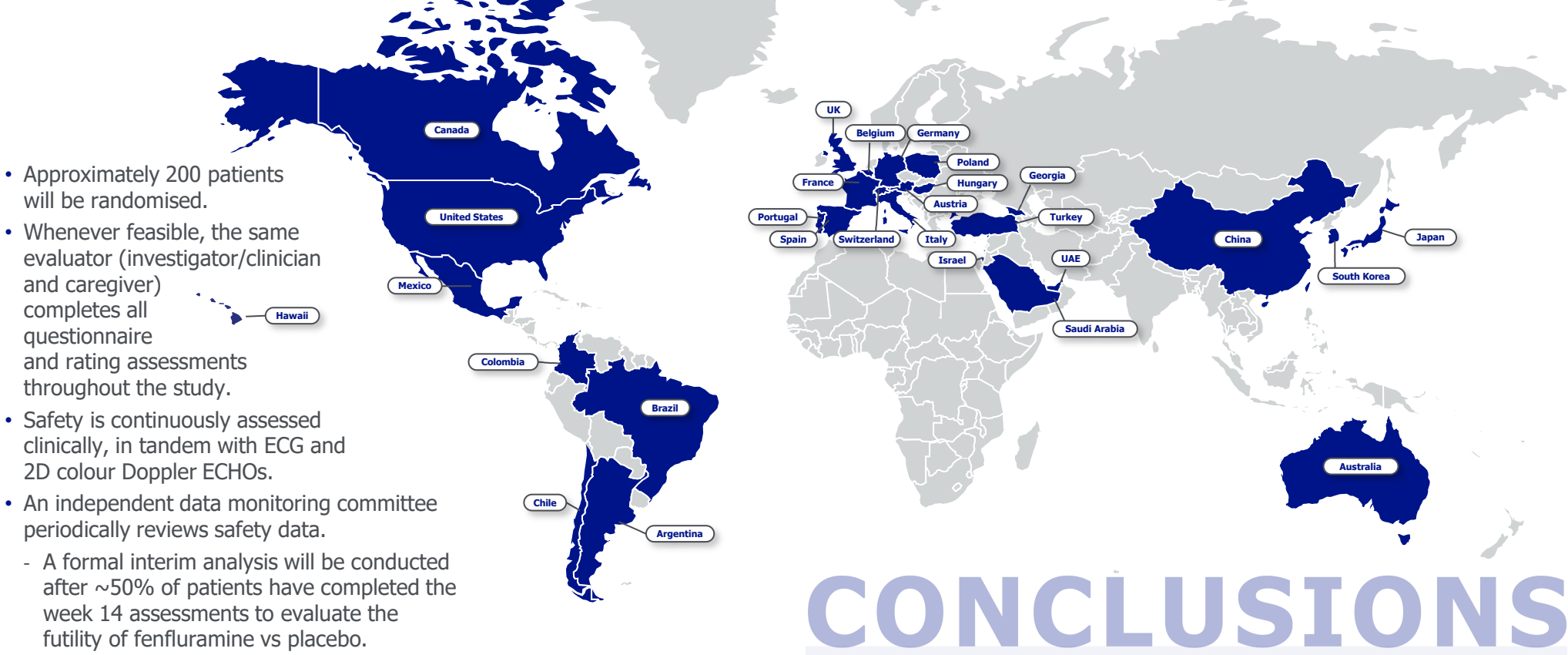
- ✓ Females and males 5-35 years of age
- ✓ Diagnosis of typical/classic RTT (RettSearch Consortium 2010 revised criteria)⁹
- ✓ A documented pathogenic *MECP2* variant
- ✓ RTT-Clinical Severity Scale rating of 10-36
- ✓ Clinical Global Impression-Severity score ≥4
- ✓ Meet defined post-regression criteria for ≥6 months prior to screening (no loss/degradation of ambulation, hand function, speech, non-verbal communication, or social skills)

Key exclusion criteria

- ✗ Previous fenfluramine use
- ✗ Clinically significant cardiovascular or cardiopulmonary abnormality based on ECHO, ECG, or physical examination
- ✗ Mild, moderate, or severe hepatic impairment
- ✗ Moderate or severe renal impairment
- ✗ Any clinically significant medical condition
- ✗ Receiving treatment with >4 concomitant antiseizure medications
- ✗ Current or previous participation (within 3 months before screening) in any other interventional clinical study, or previous participation in a gene therapy study for RTT

Planned results

PLANNED STUDY LOCATIONS



- Approximately 200 patients will be randomised.
- Whenever feasible, the same evaluator (investigator/clinician and caregiver) completes all questionnaire and rating assessments throughout the study.
- Safety is continuously assessed clinically, in tandem with ECG and 2D colour Doppler ECHOs.
- An independent data monitoring committee periodically reviews safety data.
 - A formal interim analysis will be conducted after ~50% of patients have completed the week 14 assessments to evaluate the futility of fenfluramine vs placebo.

ENDPOINTS

Primary and secondary endpoints

Objective	Endpoint
Co-primary efficacy	
To investigate the efficacy of FFA vs PBO	Change from baseline to week 14 in caregiver completed RSBQ total score
	Investigator-completed CGIC score at week 14
Secondary efficacy	
To investigate the efficacy of FFA vs PBO as assessed by the caregiver:	
On sleep	Change from baseline to week 14 in PROMIS-SD
On the ability to communicate	Change from baseline to week 14 in ORCA score
On seizures ^a	CaGIC-Seizure score at week 14
Secondary safety and tolerability	
To investigate safety and tolerability of FFA vs PBO	Incidence of TEAEs, serious TEAEs, TEAEs leading to discontinuation, related TEAEs
	Change from baseline in QTcF (12-lead ECG) at week 14
	Treatment-emergent Doppler ECHO results meeting FDA case definitions for drug-associated VHD ^b or PAH ^c

^aAssessed for patients with seizures at baseline; ^bAortic regurgitation ≥mild and/or mitral regurgitation ≥moderate with restricted valve motion, valve thickening, and/or physical signs or symptoms attributable to valve disease; ^cPASP >35 mmHg. CaGIC-Seizure, Caregiver Global Impression of Change-Seizure; CGIC, Clinical Global Impression of Change; ECG, electrocardiogram; ECHO, echocardiogram; FDA, US Food and Drug Administration; FFA, fenfluramine; ORCA, Observer-Reported Communication Ability; PAH, pulmonary arterial hypertension; PASP, pulmonary artery systolic pressure; PBO, placebo; PROMIS-SD, Patient-Reported Outcomes Measurement Information System-Sleep Disturbance; QTcF, QT interval corrected using Fridericia's formula; RSBQ, Rett Syndrome Behaviour Questionnaire; TEAE, treatment-emergent adverse event; VHD, valvular heart disease.

CONCLUSIONS

- ▶ There is a strong scientific rationale for continued investigation of fenfluramine in patients with RTT, a severe neurodevelopmental disorder with a significant unmet medical need.
- ▶ The EP0247 study is designed to evaluate the short- and long-term efficacy and the safety profile of fenfluramine in children and adults with RTT.
- ▶ By enrolling males and females 5-35 years of age, the EP0247 study expands the RTT population beyond that represented in most prior and ongoing clinical studies.¹¹⁻¹⁴
- ▶ Efficacy of fenfluramine is being assessed across a range of RTT outcomes (eg, behaviour, sleep, communication, and seizures) using the Rett Syndrome Behaviour Questionnaire and Clinical Global Impression of Change as co-primary efficacy endpoints.

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- UCB-sponsored. UCB was involved in the design of the study and review of the poster. The authors thank the patients and their caregivers in addition to the investigators and their teams who are contributing to this trial. The authors acknowledge Katerina Kumpan, PhD, CHPP (UCB, Slough, UK) for managing the development of the poster, and Hannah Carney, PhD (Envision Spark, an Envision Medical Communications agency, a part of Envision Pharma Group, Glasgow, UK) for writing assistance, which was funded by UCB. Author contributions: All authors designed the study, critically reviewed the poster, and approved the final version for presentation. Author disclosures: E González-Alguacil, V Soto-Insuga, and N Lamagrande Casanova have received funding for research and educational activities from Biocodex, Eisai, Jazz, Nutricia, Takeda, and UCB. B Moseley, L Heinzen, T Vaux, S Pilla, S Patel, B Tugaut, C McClung, and D Morita are salaried employees of UCB and receive stock or stock options from their employment.

16th European Epilepsy Congress
Athens, Greece | 5-9 September 2026

Originally presented at 2026 Epilepsy Foundation Pipeline Conference
Leesburg, VA | 18-19 June 2026