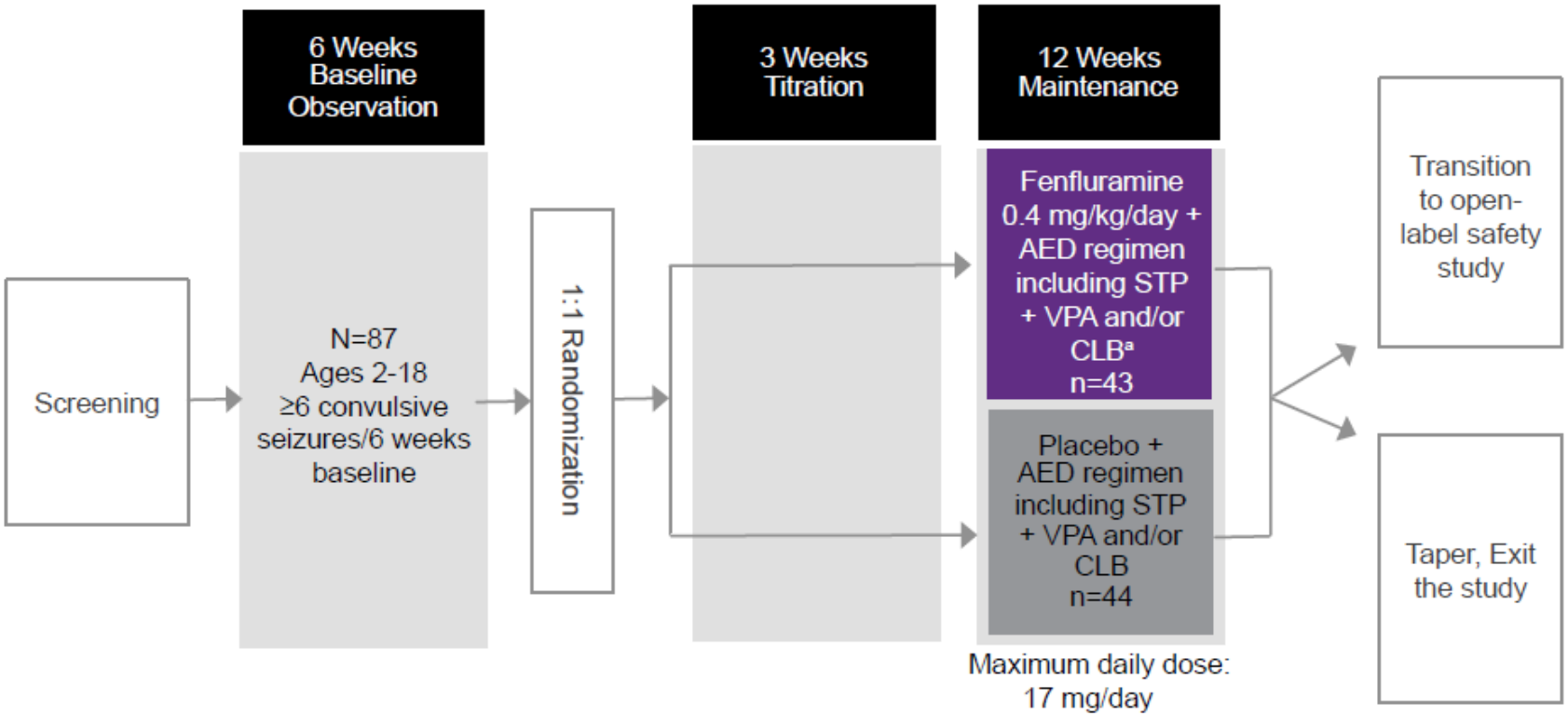
Supplementary Online Content

Nabbout R, Mistry A, Zuberi S, et al; for the FAiRE, DS Study Group. Fenfluramine for treatment-resistant seizures in patients with Dravet syndrome receiving stiripentol-inclusive regimens: a randomized clinical trial. *JAMA Neurol*. Published online December 2, 2019. doi:10.1001/jamaneurol.2019.4113

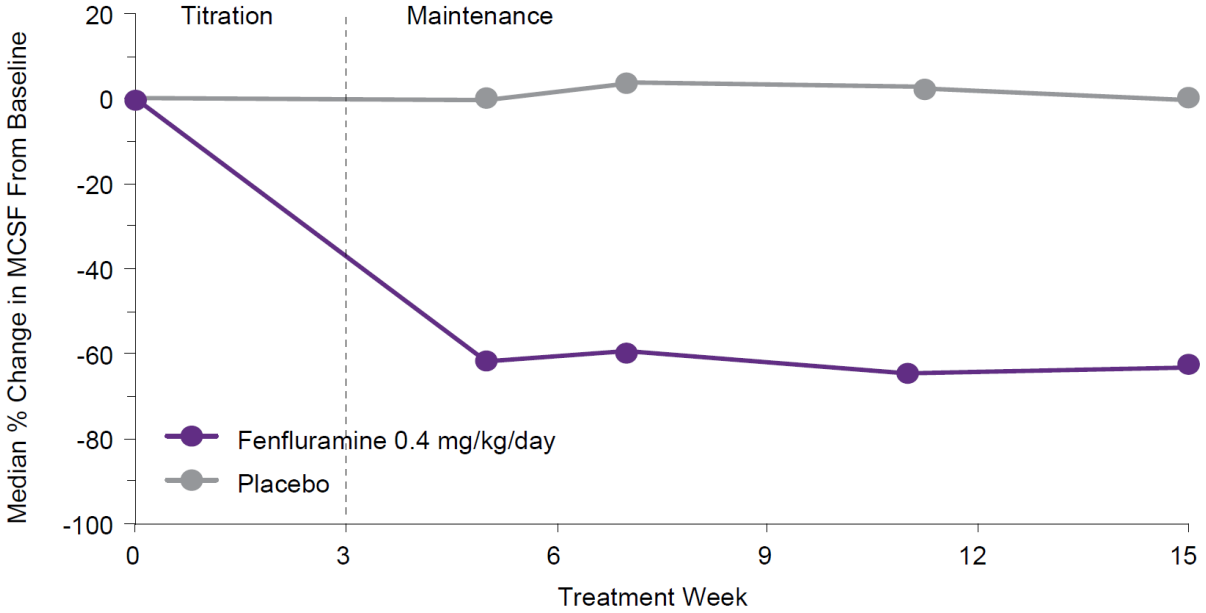
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Study Design



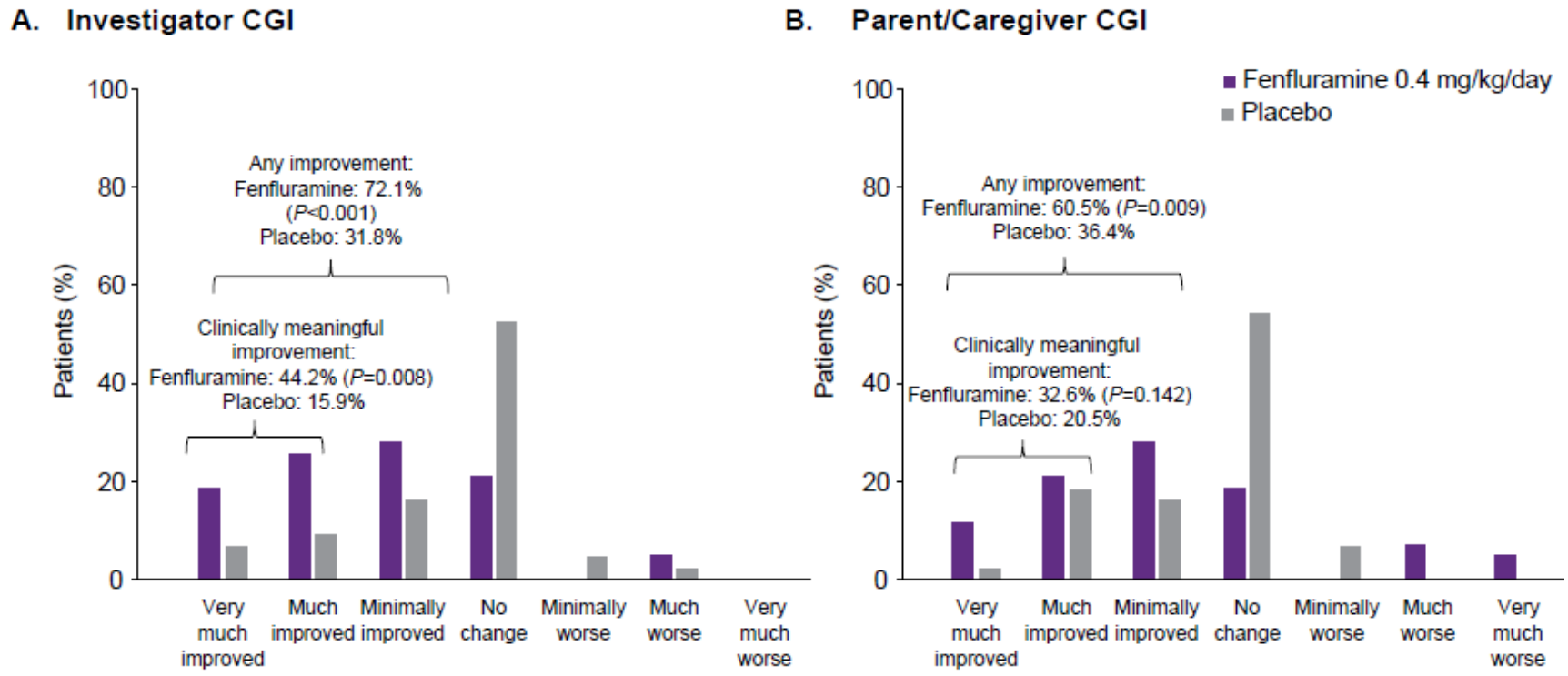
AED, antiepileptic drug; CLB, clobazam; STP, stiripentol; VPA, valproate.
[a]Protocol required, at a minimum, STP plus CLB or VPA. Initially, protocol required STP plus both CLB and VPA, but many patients could not tolerate or would not take the full regimen.

eFigure 2. Greater Percentage Change in MCSF Over Time in Fenfluramine vs Placebo Treatment Groups



MCSF, monthly convulsive seizure frequency.

eFigure 3. Clinical Global Impression of Improvement. Clinically meaningful improvements (Very much improved or Much improved) on Clinical Global Impression (CGI) of patient disposition scored by (A) investigators and (B) parents/caregivers at Visit 12 (combined titration and maintenance periods). CGI, clinical global impression; *P*-values by Cochran-Mantel Haenszel test (placebo vs fenfluramine).



eTable 1. Diagnostic Criteria for Inclusion in Trial

Inclusion Diagnostic Criteria	
Clinical Diagnosis	Documented medical history to support a clinical diagnosis of Dravet syndrome, where convulsive seizures were not completely controlled by current AED regimen
Patient Meets All of the Following Criteria:	1. Onset of seizures in the first year of life in an otherwise healthy infant. 2. A history of seizures that were either generalized tonic-clonic or unilateral clonic or bilateral clonic and were prolonged 3. Initial development was normal 4. History of normal brain magnetic resonance imaging without cortical brain malformation 5. Lack of alternative diagnosis
Patient Meets ≥1 of the Following Criteria:	1. Emergence of another seizure type, including myoclonic, generalized tonic-clonic, tonic, atonic, absence and/or focal had developed after the first seizure type 2. Prolonged exposure to warm temperatures induces seizures and/or seizures were associated with fevers due to illness or vaccines, hot baths, high levels of activity and sudden temperature changes and/or seizures were induced by strong natural and/or fluorescent lighting, as well as certain visual patterns 3. Genetic test results consistent with a diagnosis of Dravet syndrome (pathogenic, likely pathogenic, variant of unknown significance, or inconclusive but unlikely to support an alternative diagnosis)
Randomization Criteria	
Convulsive Seizures During Baseline	A stable Baseline with ≥ 6 convulsive seizures during the 6-week Baseline, with a ≥2 seizures in the first 3 weeks and ≥2 seizures in the second 3 weeks
Cardiovascular/ Cardiopulmonary	No cardiovascular disease based on ECHO, ECG, or physical examination, including but not limited to trace mitral or aortic valve regurgitation or signs of pulmonary hypertension; approved for study entry by central cardiac reader
Seizure Diary Compliance	Parent/Caregiver was ≥90% compliant with electronic diary completion during baseline
Approval	Approved for study inclusion by Epilepsy Study Consortium

AED, antiepileptic drug; ECG, electrocardiogram; ECHO, echocardiogram.

eTable 2: Titration and Tapering Algorithms

	Step 1	Step 2	Step 3
Titration[a,b]	**Study Days 1-7**	**Study Days 8-14**	**Study Days 15-21**
Placebo Fenfluramine 0.4 mg/kg/day	Placebo Fenfluramine 0.2 mg/kg/day	Placebo Fenfluramine 0.3 mg/kg/day	Placebo Fenfluramine 0.4 mg/kg/day
Tapering[a]	**Days 1 to 4 after study completion or early termination**	**Days 5 to 8 after study completion or early termination**	**Days 9 to 14 after study completion or early termination**
Placebo Fenfluramine 0.4 mg/kg/day	Placebo Fenfluramine 0.3 mg/kg/day	Placebo Fenfluramine 0.2 mg/kg/day	No study drug administration No study drug administration

BID, twice daily.
[a]Maximum daily dose of fenfluramine, 17 mg.
[b]The dosing regimen, BID for all doses.