Fenfluramine in CDKL5 Deficiency Disorder: Primary Efficacy and Safety Results From a Phase 3, Randomized, Double-blind, Placebo-controlled study

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Presenter Disclosures

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Introduction & Objective

- Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is an ultra-rare, drug resistant, X-linked developmental and epileptic encephalopathy (DEE) caused by *CDKL5* gene mutations[1,2]
  - Seizure freedom is rare,[3] and effective, well-tolerated antiseizure medication (ASM) options are limited[4]
- Fenfluramine differs from other DEE treatments in its mode of action
  - Modulates serotonin (5HT) release and signaling at multiple 5HT receptors and may act through other pathways, such as sigma-1 receptor signaling[5]
- Fenfluramine is approved as adjunctive treatment for the management of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients ≥2 years old in the United States[6]
- In an open-label, investigator initiated, single-center trial, fenfluramine was safe and effective in 6 patients with CDD (mean treatment duration of 5.3 months)[7]

Here we report the primary results from the randomized placebo-controlled trial (RCT) portion of the international, multicenter phase 3 study of fenfluramine (NCT05064878) in patients with CDD

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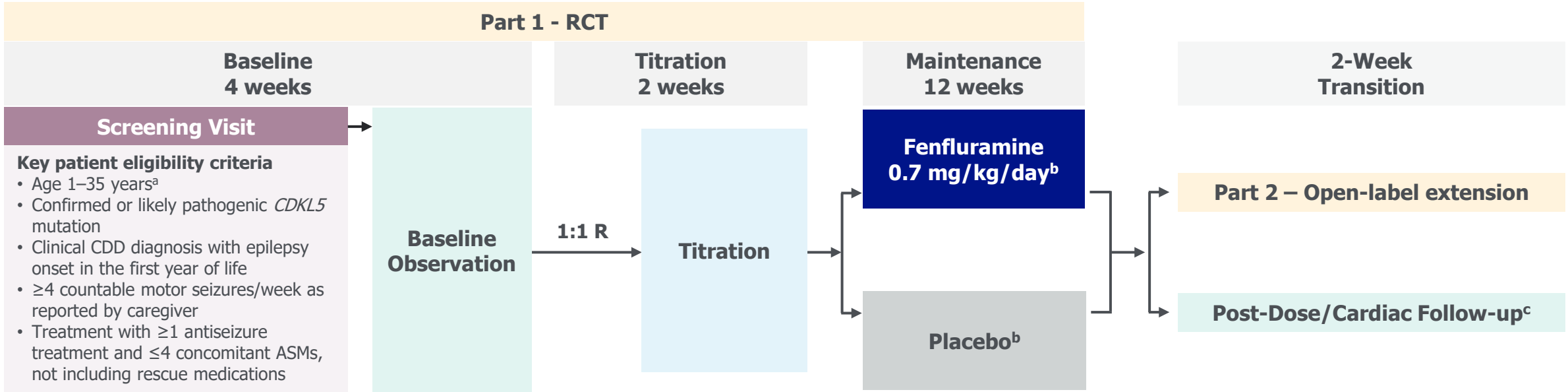
Study Design & Endpoints



[a]Enrollment of patients between 1–<2 years of age was only allowed after the DSMB reviewed safety and PK information from the first ~50% enrolled patients aged 2 to 35 years. [b]Added to existing standard of care. [c]Cardiac follow-up visit conducted 6 months after last FFA dose in patients discontinuing the trial or not continuing FFA after trial completion.

Study endpoints
over the 14-week titration and maintenance period vs placebo

Primary
- Percentage change from baseline in CMSF

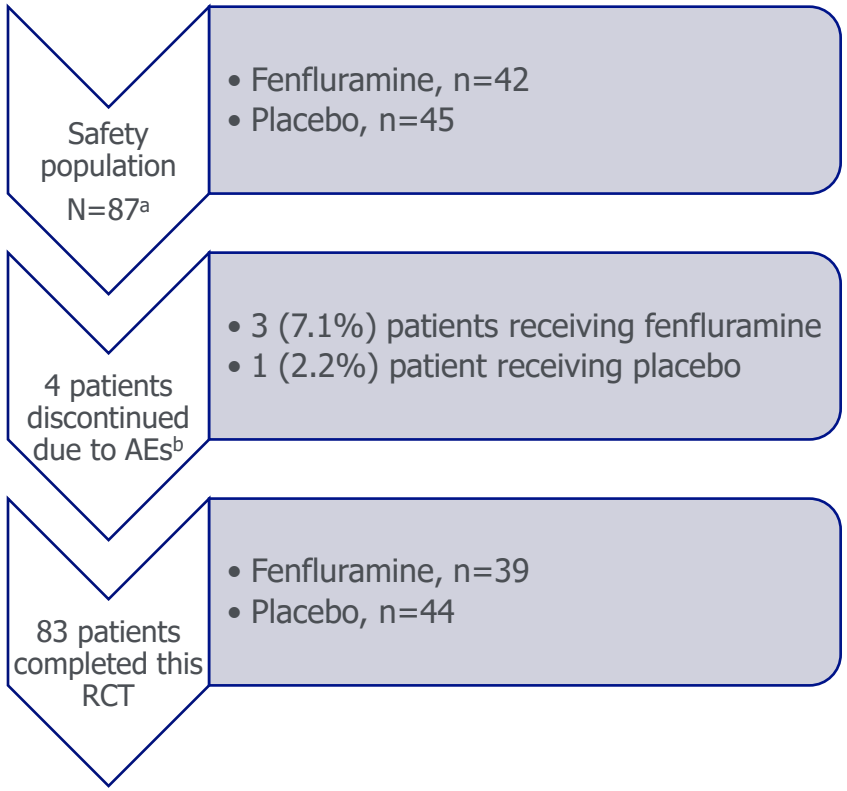
Key secondary:
- Achievement of ≥50% reduction in CMSF
- Achievement of CGI–I rating of "much improved" or "very much improved" by investigator
- Percentage change from baseline in generalized tonic-clonic seizure frequency

Other secondary:
- Achievement of ≥25%, ≥75%, and 100% reduction in CMSF
- Achievement of CGI–I rating of "much improved" or "very much improved" by caregiver
- Percentage change from baseline in all seizures
- Mean change from baseline in monthly frequency of countable motor seizure-free days

- For the primary and key secondary endpoints, a serial gatekeeper strategy was used to maintain the Type 1 error rate at α=0.05 across the family of analyses; this specified a hierarchy of significance tests where each test acted as a gatekeeper to the tests below it

ASMs, antiseizure medications; CDD, Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; CGI–I, Clinical Global Impression–Improvement; CMSF, countable motor seizure frequency; DSMB, data and safety monitoring board; FFA, fenfluramine; PK, pharmacokinetics; R, randomization; RCT, randomized-controlled trial.

Patient Disposition & Characteristics



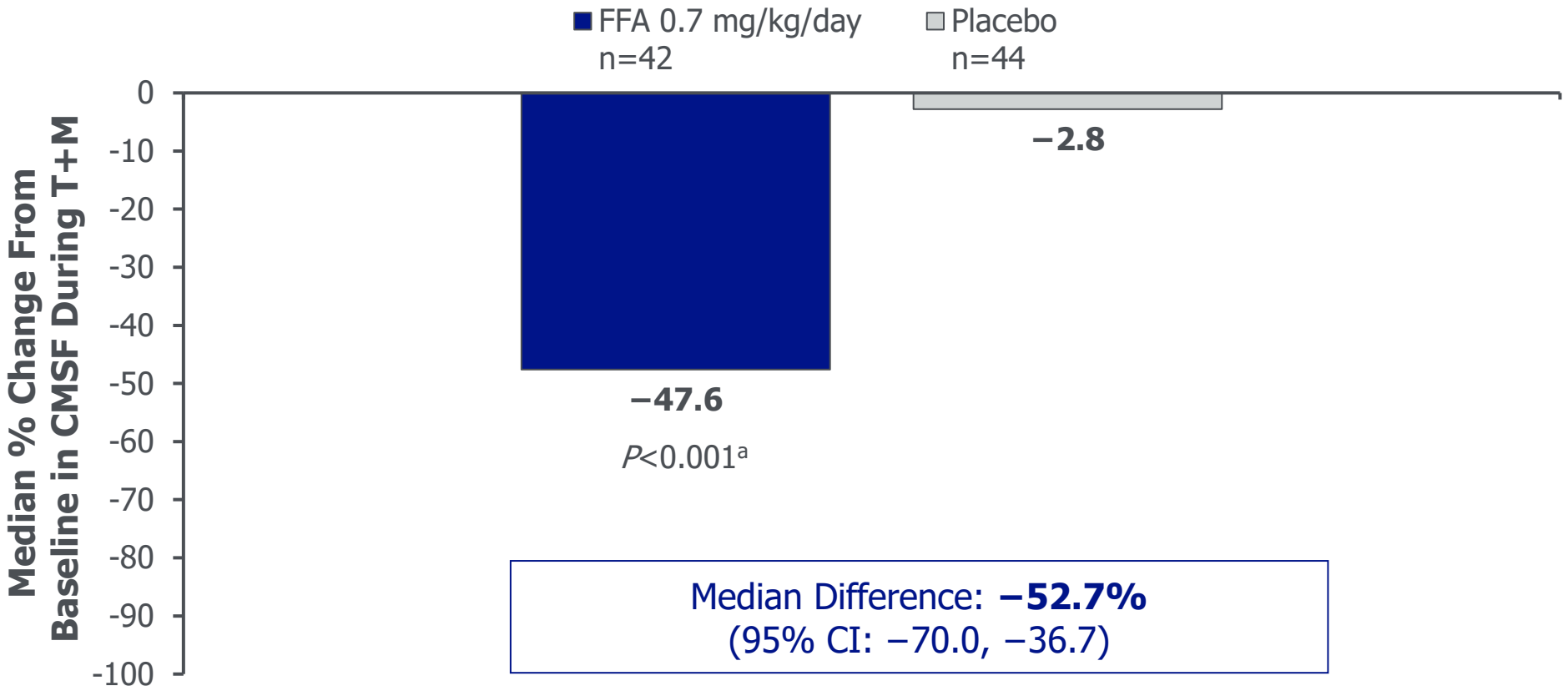
- Baseline characteristics were similar among both groups; most patients were female and pediatric

	Fenfluramine 0.7 mg/kg/day n=42	Placebo n=45
Median age, years (range)	6.5 (1–29)	7.0 (1–35)
Age group, <18 years, n (%)	37 (88)	40 (89)
Female, n (%)	36 (86)	40 (89)
Weight, kg, mean (SD)	23.7 (12.9)	23 (10.2)
Tried ASMs, n (%)		
1–2	6 (14)	8 (18)
3–4	21 (50)	16 (36)
5–6	6 (14)	3 (7)
≥7	9 (21)	18 (40)
Concomitant ASMs, n (%)		
1	6 (14)	4 (9)
2	9 (21)	13 (29)
3	15 (36)	19 (42)
4	12 (29)	7 (16)
≥5[c]	0 (0)	2 (4)
Prior select surgical procedures, n (%)		
Epilepsy surgery	1 (2)	0 (0)
Corpus callosotomy	1 (2)	3 (7)
Gastrostomy	4 (10)	10 (22)
Vagal nerve stimulator implantation	1 (2)	7 (16)
CMSF per 28 days, median (range)	44 (16–290)	49 (0–1382)

[a]One patient had no countable motor seizures during the baseline period and thus, 86 patients made up the mITT population (fenfluramine, n=42; placebo, n=44).
[b]Three patients receiving fenfluramine discontinued the trial due to somnolence (n=2) and dyskinesia (n=1); one patient receiving placebo discontinued due to GTCS, seizure, and irritability.
[c]Per protocol, patients could not be on >4 concomitant ASMs; two patients were on concomitant benzodiazepines for other indications.
AEs, adverse events; ASMs, antiseizure medications; CMSF, countable motor seizure frequency; GTCS, generalized tonic-clonic seizures; mITT, modified intent-to-treat; RCT, randomized-controlled trial; SD, standard deviation.

Primary Endpoint: Median Percentage Change in CMSF From Baseline During 14-Week T+M vs Placebo (mITT Population)

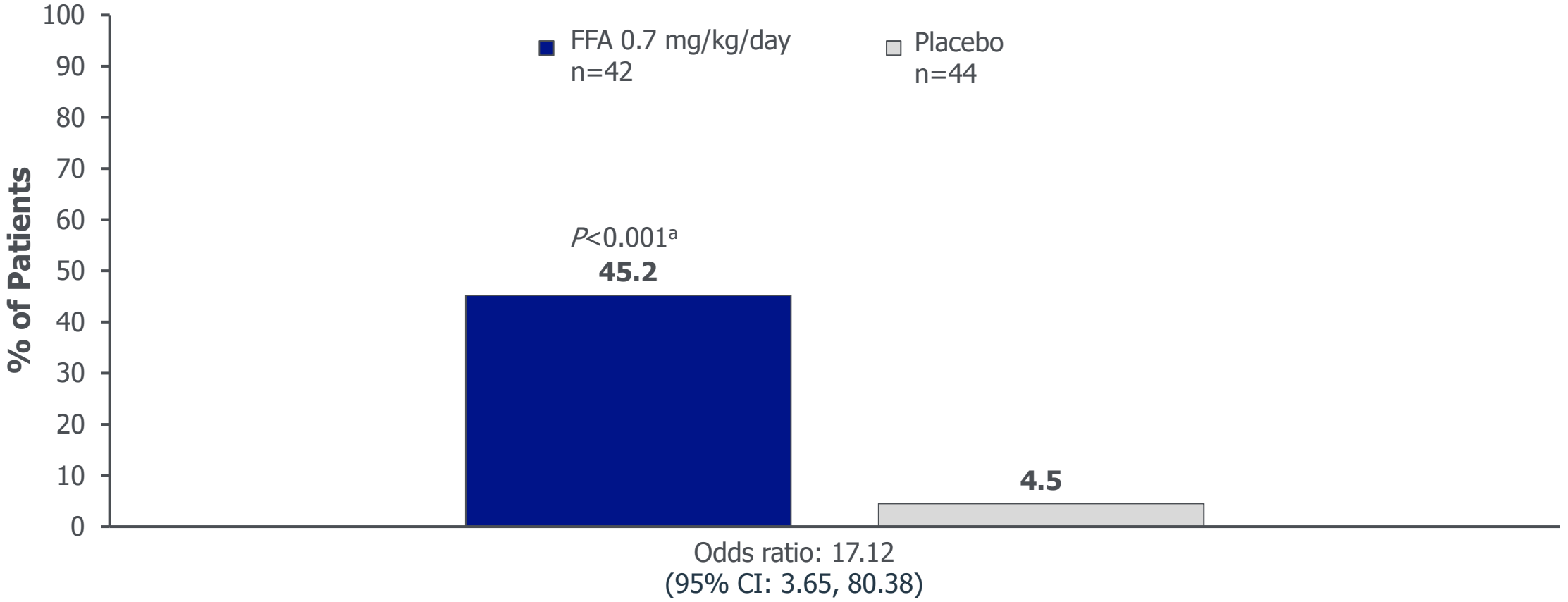
- **Primary endpoint was met**: a statistically significant difference in the median percentage change in CMSF from baseline for fenfluramine vs placebo over 14-week T+M was observed



[a] *P* values for the differences in CMSF between fenfluramine and placebo were calculated using nonparametric ANCOVA; the magnitude of differences were estimated using Hodges-Lehmann method.
CI, confidence interval; CMSF, countable motor seizure frequency; FFA, fenfluramine; mITT, modified intent-to-treat; T+M, titration and maintenance.

Key Secondary Endpoint: Proportion of Patients Who Achieved ≥50% Reductions in CMSF Over T+M (mITT)

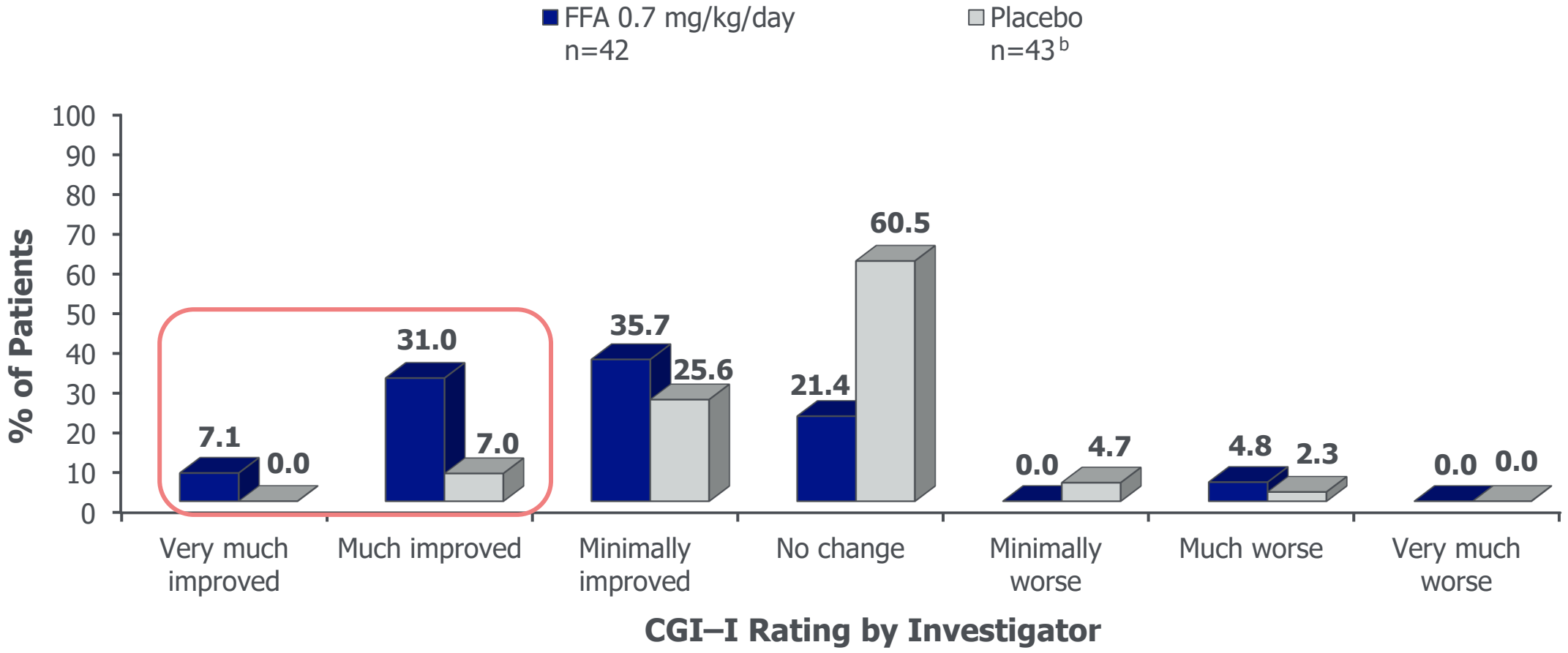
- A statistically significant difference in the key secondary endpoint of proportion of patients to achieve ≥50% reduction in CMSF over T+M was observed with fenfluramine versus placebo



[a]*P* value, odds ratio, and confidence interval for the differences between fenfluramine and placebo were obtained via logistic regression.
CI, confidence interval; CMSF, countable motor seizure frequency; FFA, fenfluramine; mITT, modified intent-to-treat; T+M, titration and maintenance.

Key Secondary Endpoint: CGI–I Ratings at End of T+M by Investigator (mITT Population)

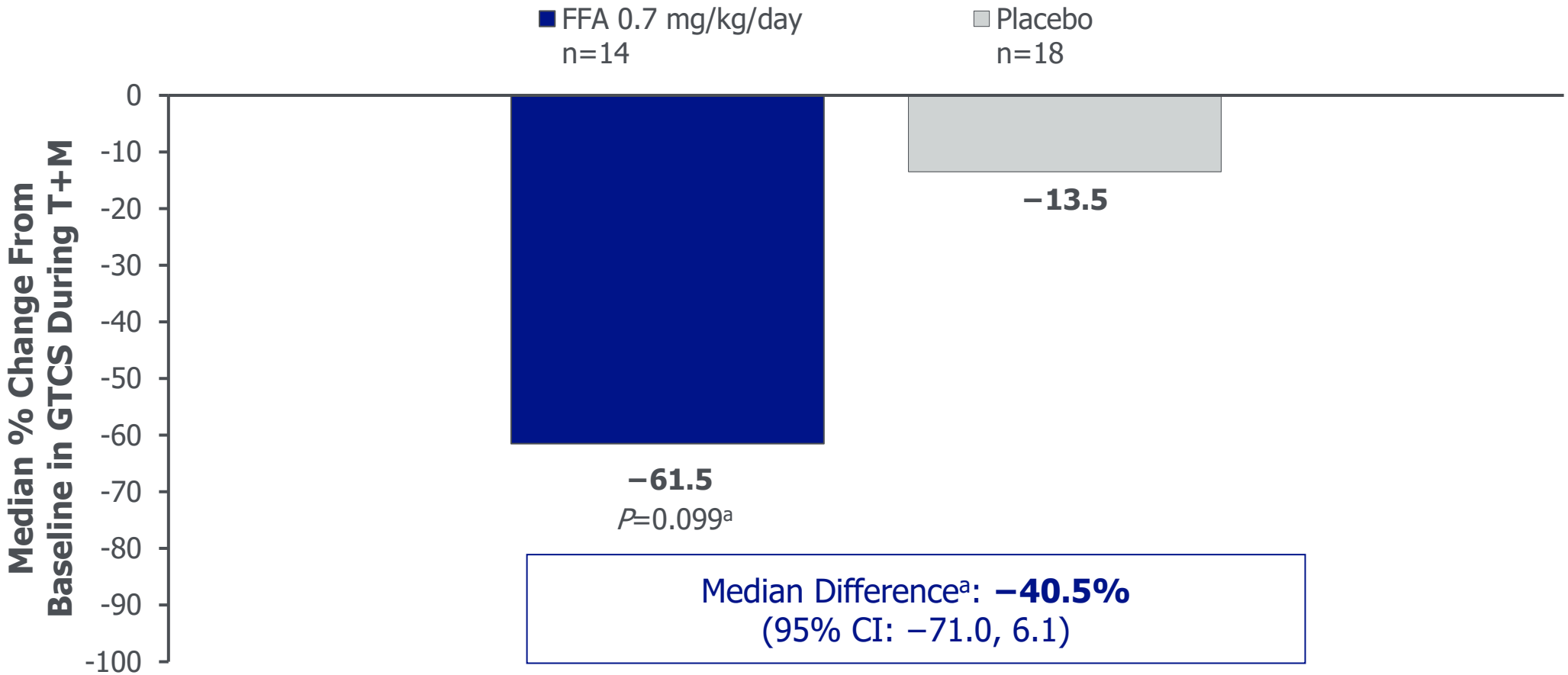
- 38.1% (fenfluramine) vs 6.8% (placebo) of patients achieved a CGI–I rating of "much improved" or "very much improved" as assessed by the investigator (*P*<0.001)[a]



[a]*P* values for the CGI–I rating comparisons were calculated with Fisher's exact test. [b]Data missing for one patient.
CGI–I, Clinical Global Impression–Improvement; FFA, fenfluramine; mITT, modified intent-to-treat; T+M, titration and maintenance.

Key Secondary Endpoint: Median Percentage Change in GTCS From Baseline During 14-Week T+M vs Placebo (mITT Population)

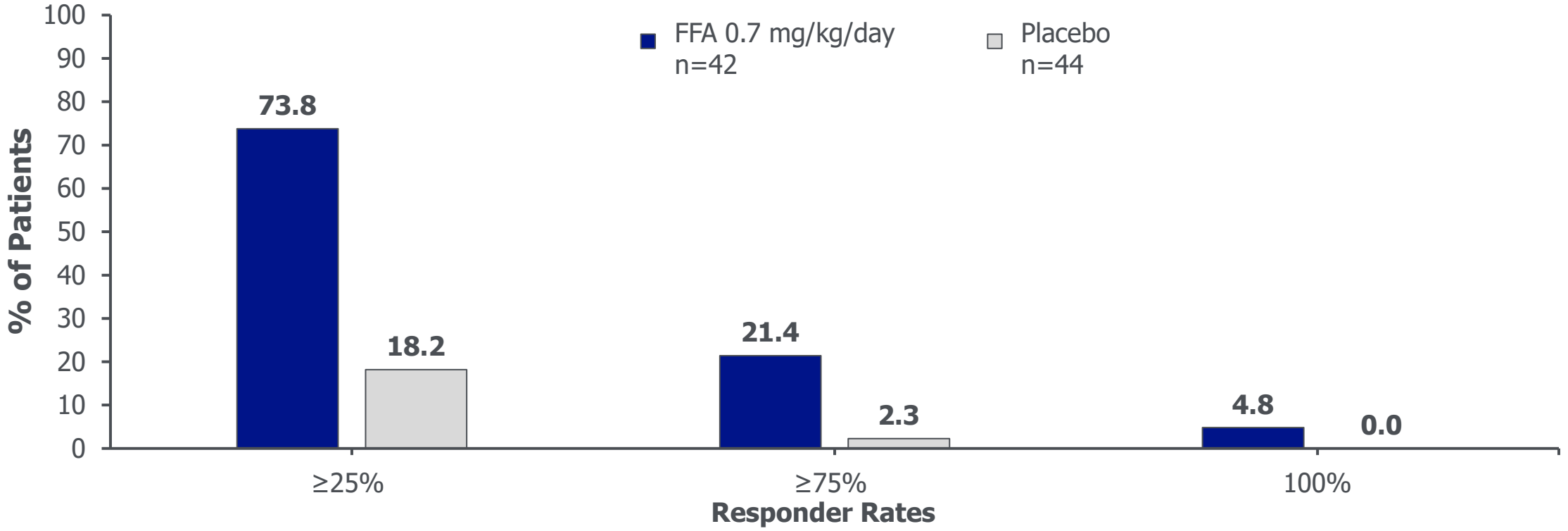
- Fenfluramine was associated with a numerically greater reduction in GTCS compared with placebo
  - This result did not achieve statistical significance; this analysis was conducted in the subset of patients with GTCS at baseline (n=32/87)



[a]*P* values for the differences in GTCS between fenfluramine and placebo were calculated using nonparametric ANCOVA; the magnitude of differences were estimated using Hodges-Lehmann method.
CI, confidence interval; FFA, fenfluramine; GTCS, generalized tonic-clonic seizure; mITT, modified intent-to-treat; T+M, titration and maintenance.

Additional Secondary Endpoints: Proportion of Patients Who Achieved ≥25%, ≥75%, and 100% Reductions in CMSF Over T+M (mITT)

- A statistically significant difference in the proportion of patients to achieve ≥25% and ≥75% reduction rates in CMSF over T+M was observed with fenfluramine versus placebo

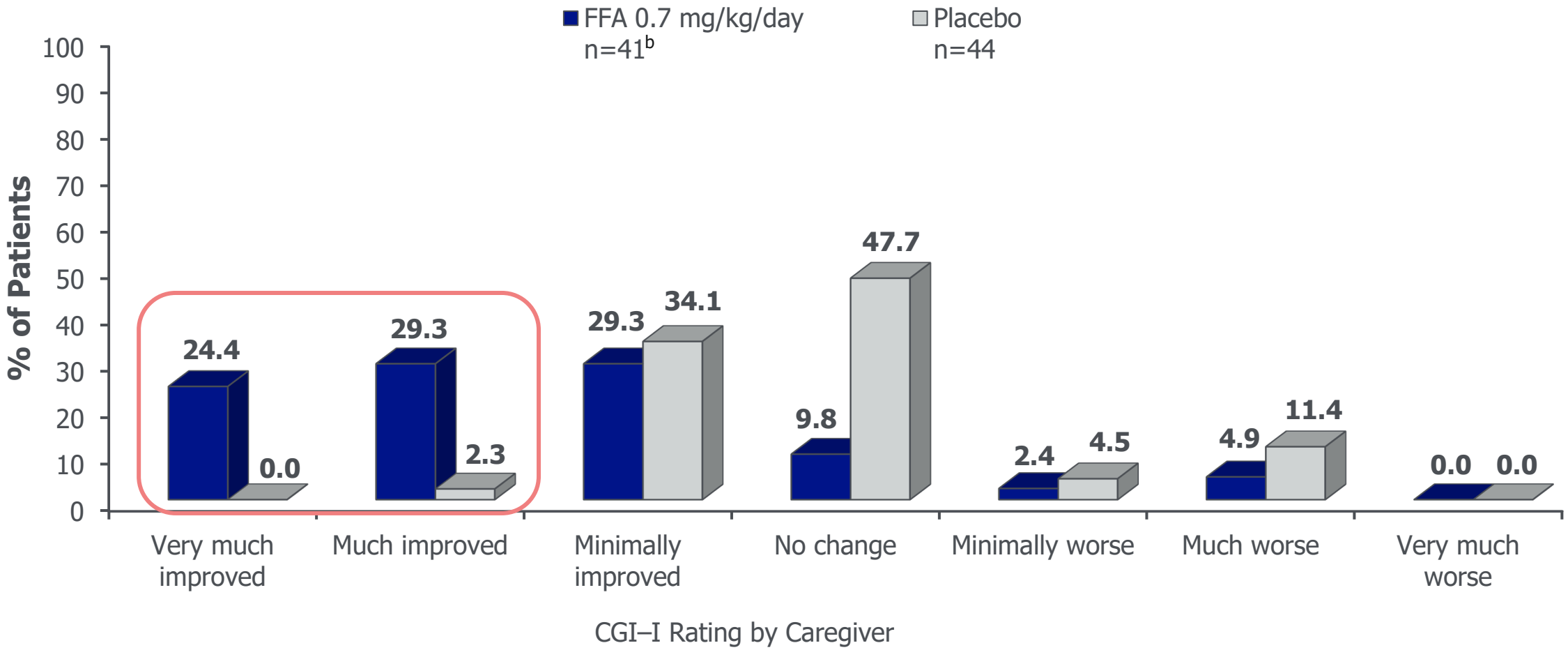


	≥25%	≥75%	100%
Odds ratio:	14.80	11.56	NE[b]
95% CI:	4.97, 44.04	1.39, 96.34	NE[b]
***P* value[a]:**	<0.001	0.024	NE[b]

[a] *P* values, odds ratios and confidence intervals for the differences between fenfluramine and placebo were obtained via logistic regression.
[b] Non-estimable due to placebo group having no patients with 100% reduction in CMSF.
CI, confidence interval; CMSF, countable motor seizure frequency; FFA, fenfluramine; mITT, modified intent-to-treat; NE, non-estimable; T+M, titration and maintenance.

Additional Secondary Endpoint: CGI–I Ratings at End of T+M by Caregiver (mITT Population)

- 52.4% (fenfluramine) vs 2.3% (placebo) achieved a CGI–I rating of "much improved" or "very much improved" (*P*<0.001)[a]



[a]*P* values for the CGI–I rating comparisons were calculated with Fisher's exact test. [b]Data missing for one patient.
CGI–I, Clinical Global Impression–Improvement; FFA, fenfluramine; mITT, modified intent-to-treat; T+M, titration and maintenance.

Additional Secondary Endpoints (mITT Population)

	Fenfluramine 0.7 mg/kg/day n=42	Placebo n=44
Percentage change in frequency of all seizures from baseline over T+M[a], median	−43.7%	−4.0%
Change in monthly frequency of countable motor seizure-free days from baseline over T+M[a,b], median	6.4	0.1

[a] *P* values not available, as statistical analysis was not performed.
[b] Baseline median monthly frequency of seizure-free days: fenfluramine group, 5.4 (range, 0–17) and placebo group, 3.9 (range, 0–17).
mITT, modified intent-to-treat; T+M, titration and maintenance.

Safety Summary

	Fenfluramine 0.7 mg/kg/day n=42	Placebo n=45
Patients with any TEAE, n (%)	32 (76.2)	35 (77.8)
Patients with related TEAEs[a], n (%)	17 (40.5)	13 (28.9)
Patients with serious TEAEs[b], n (%)	6 (14.3)	3 (6.7)
Patients with related serious TEAEs[a,c], n (%)	2 (4.8)	0 (0.0)
Patients with TEAEs of special interest[d], n (%)	0 (0.0)	0 (0.0)
Patients with TEAEs with outcome of death, n (%)	0 (0.0)	0 (0.0)
Patients with TEAEs leading to discontinuation of the trial[e], n (%)	3 (7.1)	3 (6.7)
TEAEs reported in ≥10% of patients in either treatment group, n (%)		
Pyrexia	8 (19.0)	7 (15.6)
Diarrhea	8 (19.0)	6 (13.3)
Somnolence	8 (19.0)	2 (4.4)
Decreased appetite	7 (16.7)	5 (11.1)
Nasopharyngitis	4 (9.5)	11 (24.4)

- TEAEs reported in ≥5 to <10% of patients in each group were:
  - **Fenfluramine:** upper respiratory tract infection (9.5%); seizure, urinary tract infection, and insomnia (each 7.1% of patients)
  - **Placebo:** seizure, insomnia, and irritability (each 8.9% of patients); upper respiratory tract infection, cough, vomiting, conjunctivitis, gastroenteritis, and viral infection (each 6.7% of patients)
- Gastrointestinal TEAEs were reported in 12 (28.6%) patients in the fenfluramine group and 12 (26.7%) patients in the placebo group
- At last visit, weight loss of ≥7% was reported in 0 and 3 (6.7%) patients in the fenfluramine and placebo groups, respectively; weight loss of ≥10% was reported in no patients receiving fenfluramine and 1 (2.2%) receiving placebo
- No cases of valvular heart disease or pulmonary arterial hypertension were observed

[a]Treatment causality is based on the investigator's assessment. [b]Serious TEAEs included urinary tract infection (n=2), metapneumovirus infection (n=1), RSV pneumonia (n=1), decreased appetite (n=1), and dyskinesia (n=1) in patients on fenfluramine, and gastroenteritis, pneumoperitoneum, and hypoxia in the 3 patients on placebo. [c]Serious TEAEs related to fenfluramine were: dyskinesia (n=1) and RSV pneumonia (n=1). [d]TEAEs of special interest included: suicidal thoughts, ideation, or gestures; valvular heart disease; pulmonary arterial hypertension.
[e]Aside from the 4 total patients who discontinued this RCT, another 2 patients had a TEAE with onset during the RCT that led to discontinuation during the open-label extension part (which is ongoing); 3 patients receiving FFA discontinued the trial due to somnolence (n=2) and dyskinesia (n=1); one patient receiving placebo discontinued due to GTCS, seizure, and irritability.
FFA, fenfluramine; GTCS, generalized tonic-clonic seizures; RCT, randomized controlled trial; RSV, respiratory syncytial virus; TEAEs, treatment-emergent adverse events.

Conclusions

- In this RCT evaluating fenfluramine in patients with CDD, fenfluramine provided significantly greater reduction in CMSF compared with placebo
- A significantly higher proportion of patients receiving fenfluramine demonstrated clinically meaningful improvement in CGI–I as rated by the investigator and caregiver
- A significant difference in the proportion of patients achieving ≥50% CMSF reduction was also observed in patients receiving fenfluramine vs placebo
- Fenfluramine was well tolerated; no new safety signals were identified in this RCT
- TEAEs reported in this RCT were consistent with those known from the DS and LGS clinical trials,[1–6] including no cases of valvular heart disease or pulmonary arterial hypertension
- The results of this trial suggest that fenfluramine may be a promising therapy for treating seizures in patients with CDD

CDD, Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; CGI–I, Clinical Global Impression–Improvement; CMSF, countable motor seizure frequency. DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; RCT, randomized-controlled trial; TEAEs, treatment-emergent adverse events.

1. Lagae L, et al. *Lancet.* 2019;394(10216):2243-54. 2. Nabbout R, et al. *JAMA Neurol.* 2020;77(3):300-8. 3. Sullivan J, et al. *Epilepsia.* 2023;64(10):2653-66.
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