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Fenfluramine in CDKL5 Deficiency Disorder: Phase III Primary Efficacy and Safety Results by Age

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Introduction and Objective

- CDD is an ultra-rare, drug resistant, X-linked DEE caused by pathogenic *CDKL5* variants[1,2]
  - Patients experience cognitive, motor, and speech delays, with many patients being non-verbal[2,3]
  - Other key clinical features include hypotonia, cortical vision impairment, sleep disturbances, and gastrointestinal issues[2,3]
  - Seizure freedom is rare[4]; effective, well tolerated treatment options are limited[5]
- Fenfluramine is approved for the management of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients ≥2 years old in the United States and other countries[6-8]
- Fenfluramine differs from other developmental and epileptic encephalopathy treatments in its multipronged mode of action
  - Fenfluramine modulates serotonin release and signalling at multiple 5-HT and sigma-1 receptors[9]
- The primary endpoint of the RCT part of EP0216, an international multicentre Phase III study, demonstrated a significantly greater reduction in CMSF with fenfluramine vs with placebo in all randomised patients with CDD

Here we report pre-specified and post hoc analyses stratified by age group, from the RCT part of the EP0216 trial (NCT05064878) in patients with CDD

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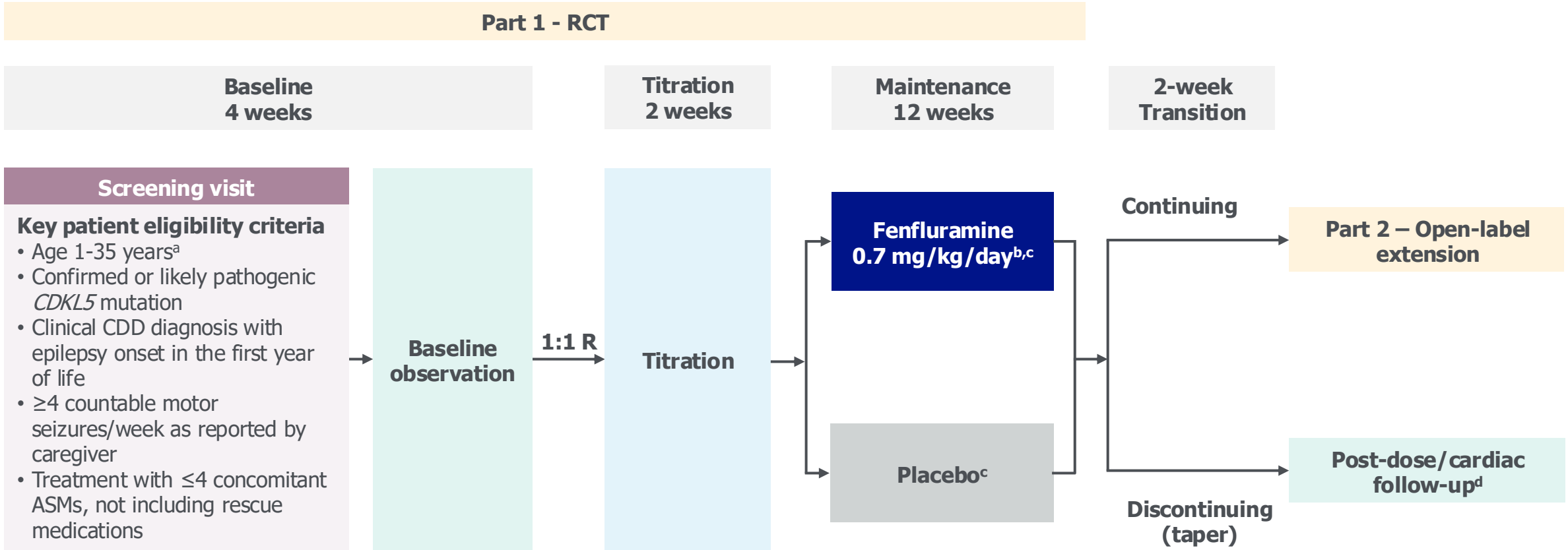
CDD, cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; CMSF, countable motor seizure frequency; DEE, developmental and epileptic encephalopathy; RCT, randomised controlled trial.

Study Design



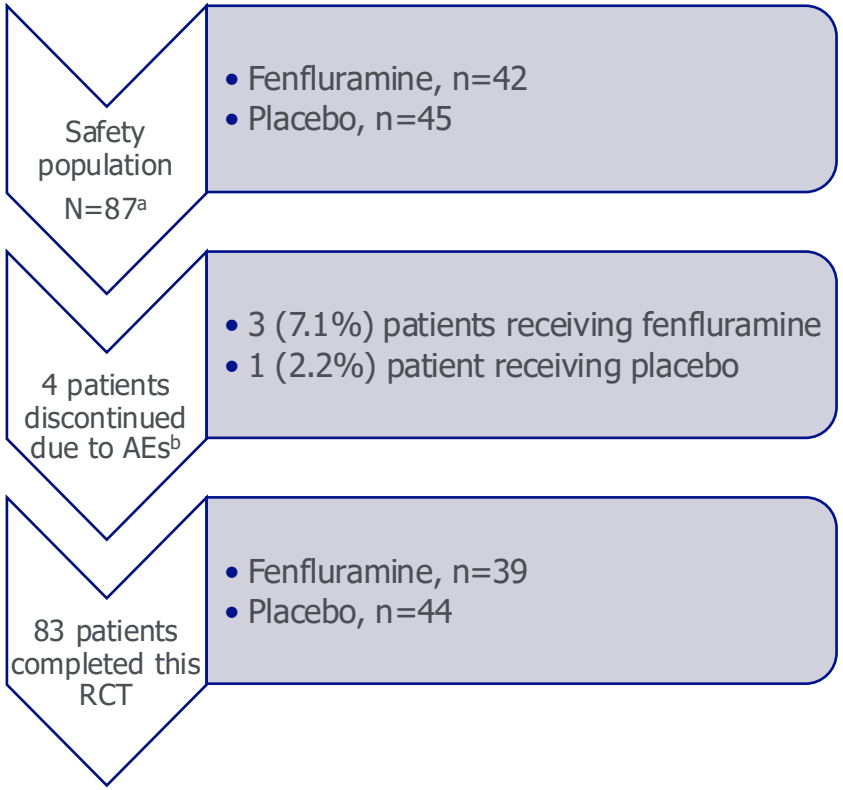
[a]Enrolment of patients between 1-<2 years of age was only allowed after the DSMB reviewed safety and PK information from the first ~50% enrolled patients aged 2-35 years; [b]Maximum 26 mg/day; [c]Added to existing standard of care; [d]Cardiac follow-up visit conducted 6 months after last fenfluramine dose in patients discontinuing the trial or not continuing fenfluramine after trial completion.
ASMs, antiseizure medications; CDD, cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder; DSMB, data and safety monitoring board; PK, pharmacokinetics; R, randomisation; RCT, randomised controlled trial.

Analyses of Study Endpoints by Age Group

- Efficacy and safety endpoints over the 14-week T+M period were analysed by patient age group: 1 to <2, 2 to ≤6, and >6 to ≤35 years of age
- In a pre-specified analysis, the primary endpoint (percentage change from baseline in CMSF) was evaluated by age group
- Post hoc age-stratified analyses were conducted for the following secondary efficacy endpoints:
  - Achievement of ≥50% reduction in CMSF
  - Achievement of a CGI–I rating of "much improved" or "very much improved", as assessed by investigators
  - Achievement of a CGI–I rating of "much improved" or "very much improved", as assessed by caregivers
  - Percentage change from baseline in GTCS frequency
  - Percentage change from baseline in frequency of all seizure types
- Pre-specified safety analyses included assessment of TEAE incidence by age group

CGI–I, Clinical Global Impression–Improvement; CMSF, countable motor seizure frequency; GTCS, generalised tonic-clonic seizure; TEAE, treatment-emergent adverse event; T+M, titration and maintenance.

Patient Disposition and Characteristics



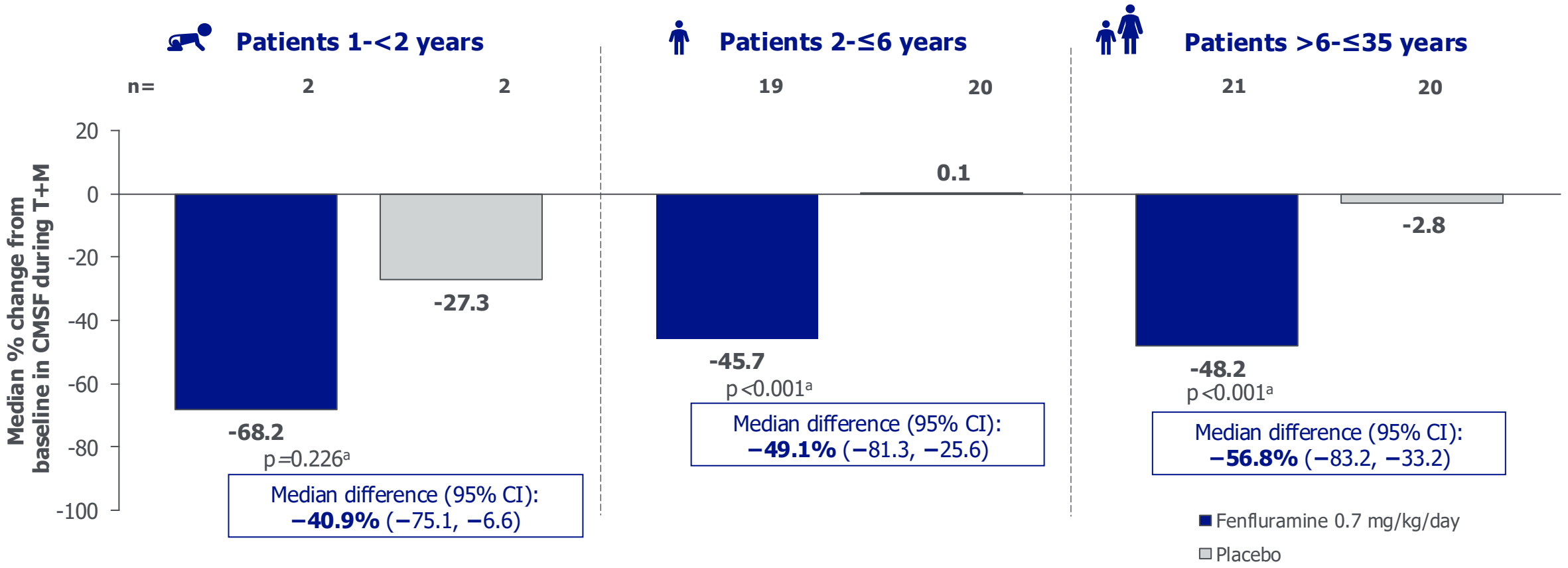
- Baseline characteristics were similar among both groups; most patients were female and paediatric

	FENFLURAMINE 0.7 mg/kg/day (n=42)	PLACEBO (n=45)
Median age, years (range)	7 (1-29)	7 (1-35)
Patients ≤18 years of age, n (%)	38 (90.5)	41 (91.1)
Age group for randomisation, years, n (%)		
1-<2	2 (5)	2 (4)
2-≤6	19 (45)	20 (44)
>6-≤35	21 (50)	23 (51)
Female, n (%)	36 (86)	40 (89)
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)
Baseline CMSF by age group, median (range)		
1-<2	122 (16-228)	19 (18-19)
2-≤6	44 (16-262)	42 (17-187)
>6-≤35	44 (17-290)	64 (23-1382)[d]

[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 receive >4 concomitant ASMs; two patients received concomitant benzodiazepines for other indications; [d]n=22.
AEs, adverse events; ASMs, antiseizure medications; CMSF, countable motor seizure frequency; GTCS, generalised tonic-clonic seizures; mITT, modified intent-to-treat; RCT, randomised controlled trial.

Median Percentage Change From Baseline in CMSF (mITT)

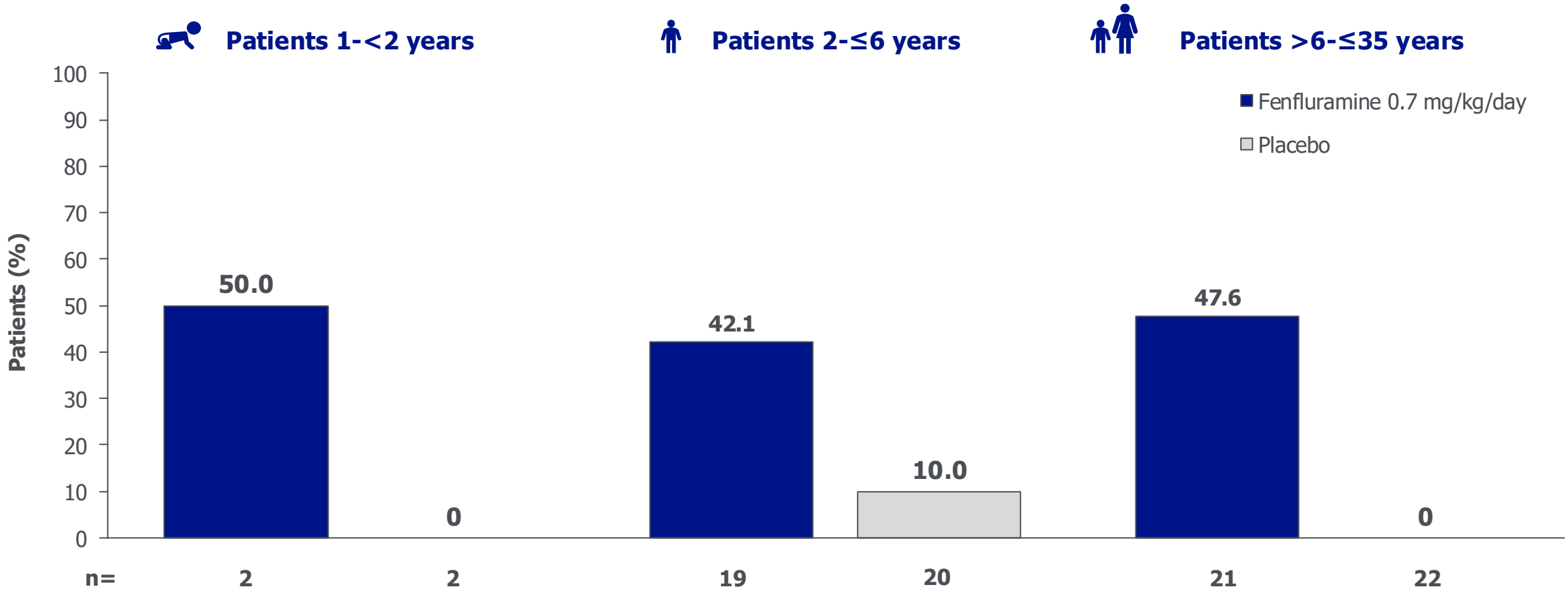
- Patients experienced a **reduction in CMSF** when treated with fenfluramine vs placebo in all age groups
  - Results in patients 1-<2 years of age should be interpreted with caution due to the reduced sample size



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

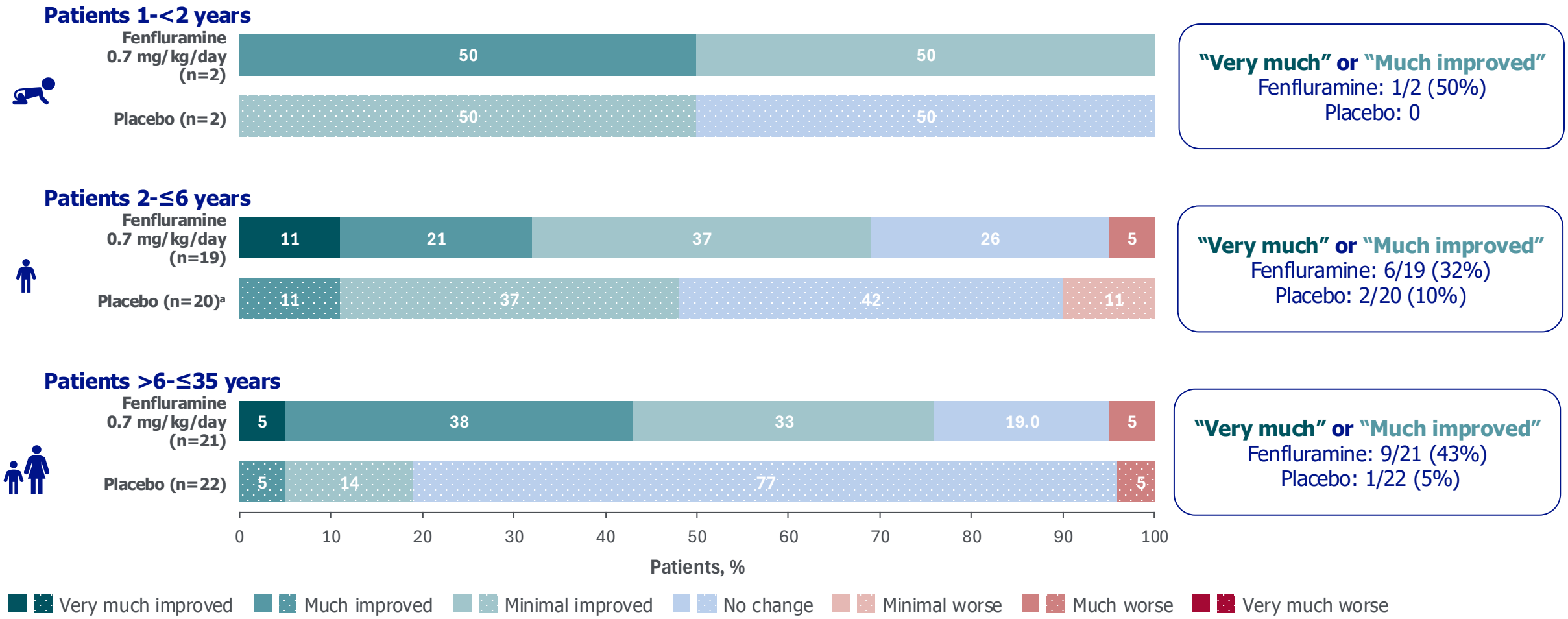
Achievement of 50% Reduction in CMSF (mITT)

- A **higher proportion** of patients achieved **≥50% reduction in CMSF** over T+M with fenfluramine vs placebo in all age groups



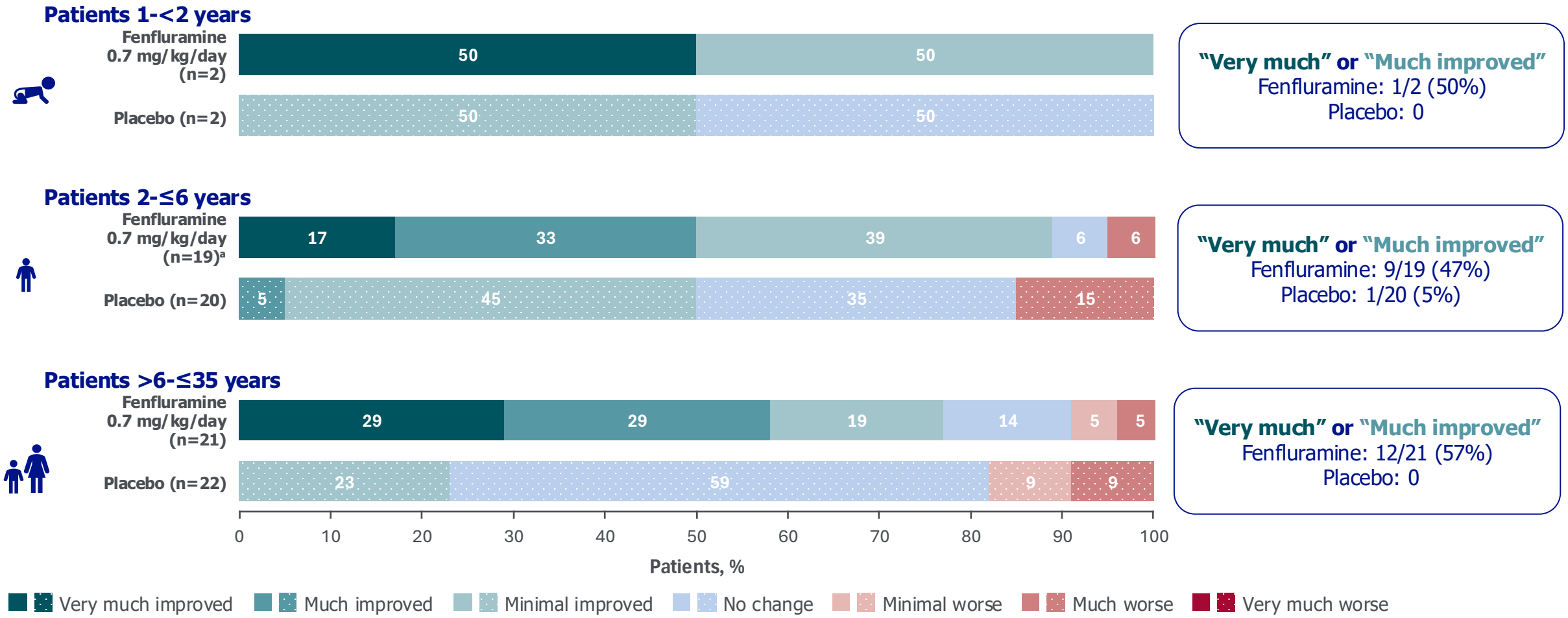
CMSF, countable motor seizure frequency; mITT, modified intent-to-treat; T+M, titration and maintenance.

CGI–I Ratings at End of T+M, as Assessed by the Investigator (mITT)



[a]Data were missing for 1 patient in the 2-≤6 year age group, who received placebo.
CGI–I, Clinical Global Impression–Improvement; mITT, modified intent-to-treat; T+M, titration and maintenance.

CGI–I Ratings at End of T+M, as Assessed by the Caregiver (mITT)



"Very much" or "Much improved"
Fenfluramine: 1/2 (50%)
Placebo: 0

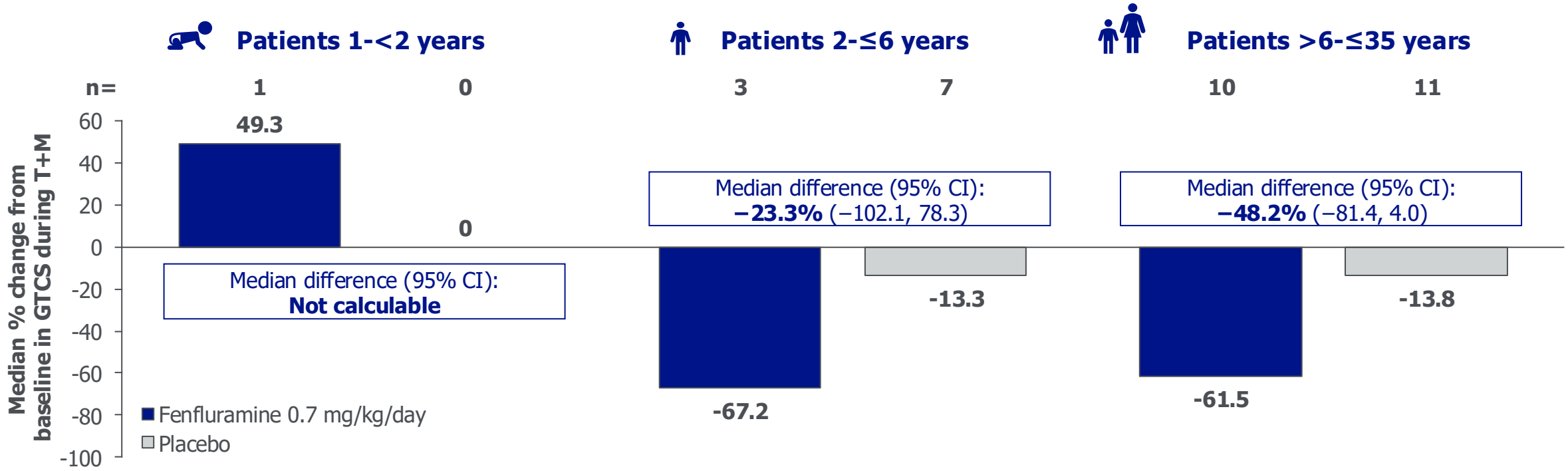
"Very much" or "Much improved"
Fenfluramine: 9/19 (47%)
Placebo: 1/20 (5%)

"Very much" or "Much improved"
Fenfluramine: 12/21 (57%)
Placebo: 0

[a]Data were missing for 1 patient in the 2-≤6 year age group, who received fenfluramine.
CGI–I, Clinical Global Impression–Improvement; mITT, modified intent-to-treat; T+M, titration and maintenance.

Median Percentage Change From Baseline in GTCS Frequency (mITT)

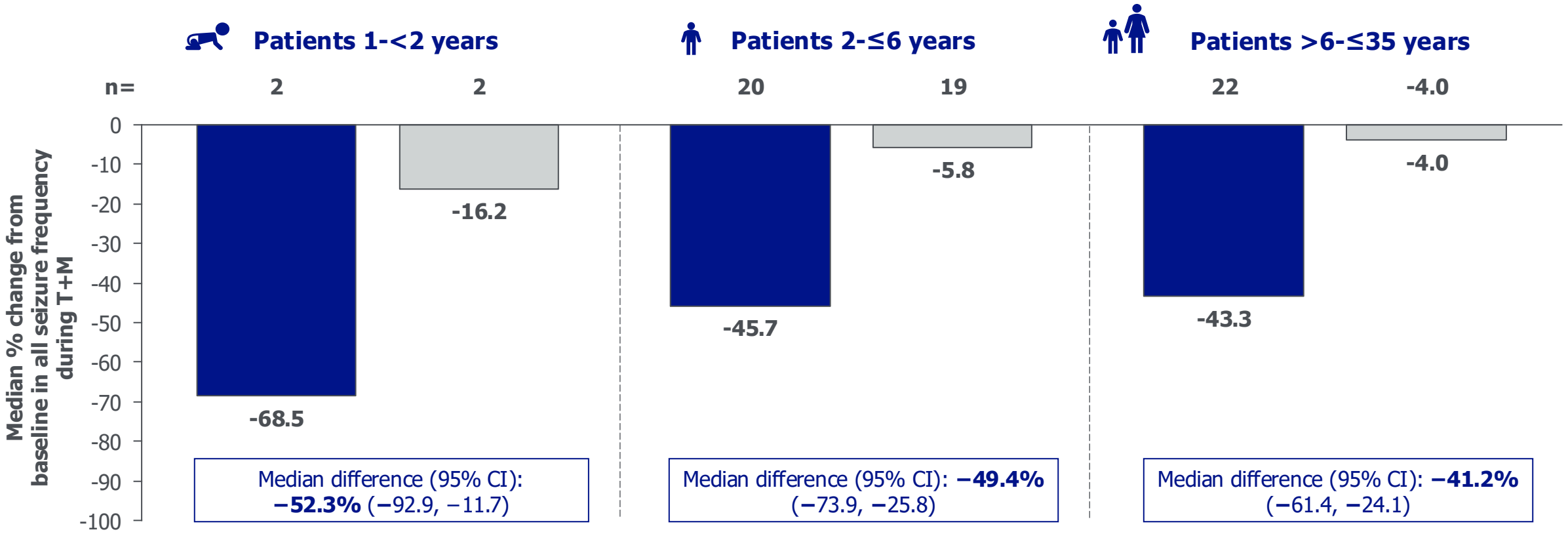
- In patients 2-≤6 and >6-≤35 years of age, fenfluramine was associated with a **greater reduction in GTCS frequency** vs placebo
  - Conclusions are difficult to draw in the 1-<2 years age group, as only 1 of the 4 patients had baseline GTCS, and no patients received placebo
- This analysis was conducted in the subset of patients with GTCS at baseline (n=32)



Median differences and confidence intervals were calculated using the Hodges-Lehmann method.
CI, confidence interval; GTCS, generalised tonic-clonic seizure; mITT, modified intent-to-treat; T+M, titration and maintenance.

Median Percentage Change From Baseline in Frequency of All Seizure Types (mITT)

- Across all age groups, fenfluramine was associated with a **greater reduction in frequency of all seizure types** compared with placebo



Median differences and confidence intervals were calculated using the Hodges-Lehmann method.
CI, confidence interval; mITT, modified intent-to-treat; T+M, titration and maintenance.

Safety (Safety population)

PATIENTS, n (%)	1–<2 years (n=4)		2–≤6 years (n=39)		6–≤35 years (n=44)	
	FENFLURAMINE 0.7 mg/kg/day n=2	PLACEBO n=2	FENFLURAMINE 0.7 mg/kg/day n=20	PLACEBO n=19	FENFLURAMINE 0.7 mg/kg/day n=21	PLACEBO n=23
Any TEAEs	2 (100)	2 (100)	14 (73.7)	17 (85.0)	16 (76.2)	16 (69.6)
Related TEAEs[a]	0	1 (50.0)	9 (47.4)	7 (35.0)	8 (38.1)	5 (21.7)
Serious TEAEs[b]	0	0	3 (15.8)	3 (15.0)	3 (14.3)	0
Related serious TEAEs[a,c]	0	0	0	0	2 (9.5)	0
TEAEs of special interest	0	0	0	0	0	0
Deaths due to TEAEs	0	0	0	0	0	0
Discontinuations due to TEAEs[d]	0	0	2 (10.5)	2 (10.0)	1 (4.8)	1 (4.3)

- Incidences of TEAEs were generally similar across age and treatment groups
- **TEAEs of special interest:** No cases of suicidal thoughts, ideation, or gestures; valvular heart disease; or pulmonary arterial hypertension were observed in the RCT

[a]Treatment causality is based on the investigator's assessment; [b]Serious TEAEs were: urinary tract infection (n=2), metapneumovirus infection (n=1), 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 deemed related to fenfluramine were: dyskinesia (n=1) and Respiratory syncytial virus pneumonia (n=1); [d]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 OLE (ongoing); three patients receiving fenfluramine discontinued the study due to somnolence (n=2) and dyskinesia (n=1); one patient receiving placebo discontinued due to GTCS.
GTCS, generalised tonic-clonic seizure; OLE, open-label extension; RCT, randomised controlled trial; TEAE, treatment-emergent adverse event.

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Conclusions

- In this post hoc analysis of an RCT, fenfluramine provided **greater reduction in CMSF** compared with placebo (nominal p<0.001), among patients with CDD aged 2-<6 and 6-<35 years of age
  - The sample size was too small to allow meaningful interpretation in the 1-<2 years of age group
- A **higher proportion** of patients achieved a **≥50% reduction in CMSF** with fenfluramine vs placebo (2-≤6 years, 42.1%/10%; >6-≤35 years, 47.6%/0%)
- A **higher proportion** of patients receiving fenfluramine vs placebo demonstrated **clinically meaningful improvement** in CGI–I (very much/much improved), as assessed by investigators and caregivers
  - Investigator assessments (fenfluramine/placebo): 2-≤6 years, 32%/10%; >6-≤35 years, 43%/5%
  - Caregiver assessments (fenfluramine/placebo): 2-≤6 years, 47%/5%; >6-≤35 years, 57%/0%
- Fenfluramine was **well tolerated**, with no new safety signals identified in this RCT; TEAEs were consistent with those reported in DS and LGS clinical trials[1–6]
- The results of this post hoc analysis suggest that **fenfluramine may be a promising therapy** for adult and paediatric patients with CDD, irrespective of age

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