Caregiver Versus Investigator Clinical Global Impression-Improvement Ratings in Fenfluramine Clinical Trials

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QUESTION

What do the Clinical Global Impression-Improvement (CGI-I) scale ratings from the fenfluramine (FFA) clinical trial program demonstrate and are caregivers and investigators generally aligned in their evaluations?

INVESTIGATION

- In the Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) clinical trials, at each study visit, caregivers and investigators were asked to compare the patient's current condition to baseline and provide a CGI-I rating based on the 7-point Likert-like scale[1-6]
  - Ratings of 1 ("very much improved") and 2 ("much improved") are consistent with "clinically meaningful improvement"
- This analysis reviews the caregiver and investigator CGI-I scale ratings obtained at last visit from the DS and LGS clinical trials
  - The proportion of "clinically meaningful improvement" ratings in relation to reductions in frequency of monthly convulsive seizures (DS) or seizures associated with a drop (LGS) were also reported
  - CGI-I ratings for a cohort of adults who enrolled in the DS open-label extension (OLE) *de novo* were evaluated post-hoc and presented separately from the overall DS OLE data[7]

RESULTS

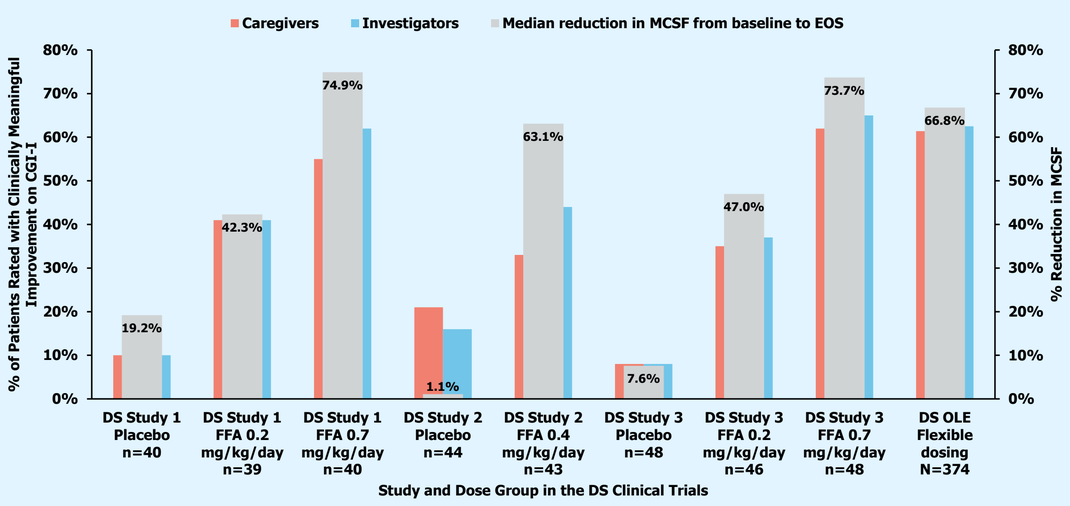
Proportion of Patients Rated as Demonstrating Clinically Meaningful Improvement on CGI-I at Last Visit

	DS Study 1 (RCT)[1]			DS Study 2 (RCT)[2]		DS Study 3 (RCT)[3]			LGS RCT[4]			DS OLE[7]	LGS OLE[6]
	Placebo n=40	FFA 0.2 mg/kg/day n=39	FFA 0.7 mg/kg/day n=40	Placebo n=44	FFA 0.4 mg/kg/day n=43	Placebo n=48	FFA 0.2 mg/kg/day n=46	FFA 0.7 mg/kg/day n=48	Placebo n=87	FFA 0.2 mg/kg/day n=89	FFA 0.7 mg/kg/day n=87	Flexible dosing N=374[a]	Flexible dosing N=247[a]
Caregivers, N	40	39	40	44	43	48	46	48	81	85	80	308	230
% of CGI-I ratings	10	41	55	21	33	8	35	63	5	27	34	61	35
Investigators, N	40	39	40	44	43	48	46	48	80	85	80	323	237
% of CGI-I ratings	10	41	63	16	44	8	37	65	6	20	26	63	38

[a]The OLEs included patients who had completed a phase 3 RCT, which could have included patients initially randomized to the placebo arm.
CGI-I, Clinical Global Impression-Improvement; DS, Dravet syndrome; FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; RCT, randomized controlled trial.

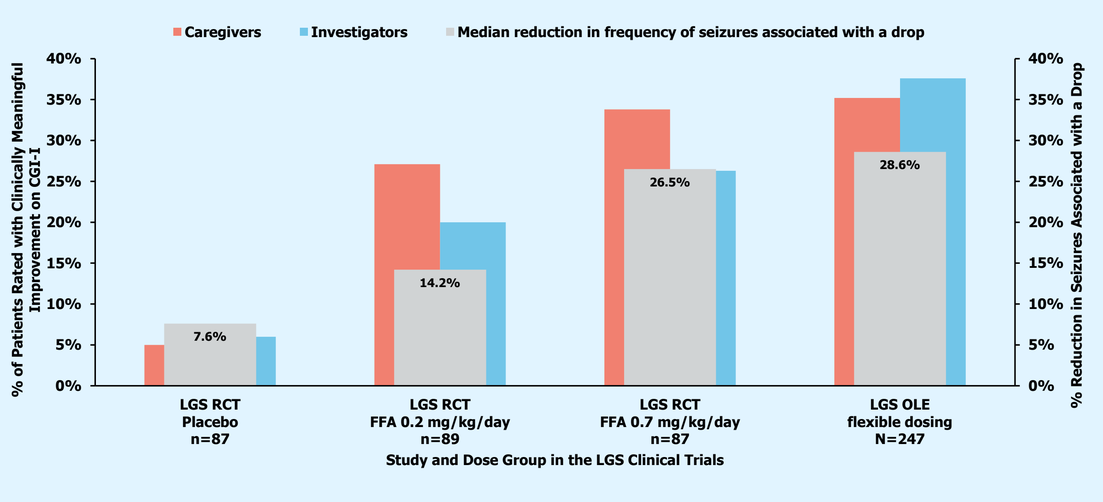
Proportion of Patients With Clinically Meaningful Ratings on CGI-I and Reductions in Seizure Frequency

A. CGI-I and MCSF Reduction in the FFA DS Clinical Trial Program[a]



Baseline MCSF/28 days:	27.3	17.5	20.7	10.7	14	12.7	18	13	14.7

B. CGI-I and Reductions in Seizures Associated With a Drop in the FFA LGS Clinical Trial Program[a]



Baseline frequency of seizures associated with a drop/28 days:	53	85	83	75

[a]N-values provided are for the number of patients evaluated for seizure reduction; N-values for CGI-I ratings are described in the table above.
CGI-I, Clinical Global Impression-Improvement; DS, Dravet syndrome; EOS, end of study; FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; MCSF, monthly convulsive seizure frequency; OLE, open-label extension; RCT, randomized controlled trial.

Proportion of Adults Enrolled in FFA DS OLE *De Novo* and Rated as Demonstrating Clinically Meaningful Improvement on CGI-I at Last Visit

Caregivers

71.4% of adult patients (n=28) were rated as "very much improved" or "much improved" by caregivers

Investigators

75% of adult patients (n=28) were rated as "very much improved" or "much improved" by investigators

CONCLUSIONS

This analysis of >800 CGI-I assessments from four RCTs and two OLE studies highlighted that caregivers and investigators were mostly aligned on CGI-I ratings of clinically meaningful improvement in the FFA clinical trial program, and the scores appeared to be associated with median reduction in seizure endpoints. As part of a more patient-centric strategy, continuing to obtain both caregiver and investigator CGI-I ratings in clinical trials and real-world studies may complement seizure reduction measures and provide insight into non-seizure outcomes.

This is a summary of the main findings.

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