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Supplementary Material

Article Title: Effects of Gepirone-ER on Sexual Function in Patients with Major Depressive Disorder

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

Supplementary Table 1. Trial design details.

Study No.	Design Overview	Control Drug (s)	Duration	Dose Regimen and Route	Trial Center Locations
134001	8-week randomized, double-blind, placebo-controlled, parallel group trial in subjects with moderate-severe MDD	Placebo	Acute (8 weeks)	Oral tablets taken once each morning with food. After an initial dose of 20 mg/day, patients were titrated to 40 mg/day on Day 4 of treatment. Dose could be increased to 60 mg/day after 7 days, and to 80 mg/day after 14 days.	Newport Beach, CA; Wheat Ridge, CO; New York, NY; Portland, OR; King of Prussia, PA
134002	8-week randomized, double-blind, placebo-controlled, parallel group trial in subjects with moderate-severe MDD	Placebo	Acute (8 weeks)	Oral tablets taken once each morning with food. Flexible-dose design with one forced titration from 20 to 40 mg/day on Day 4. Minimum dose 40 mg/day.	Newport Beach, CA; Wheat Ridge, CO; New York, NY; Portland, OR; King of Prussia, PA
134004	3-arm, double-blind, randomized, placebo- and active-controlled study in subjects with moderate-severe MDD with atypical features	Placebo and Fluoxetine	Acute (8 weeks)	Oral tablets taken once each morning with food. Dose range 20-80 mg/day with a forced titration to 40 mg/day during the first week of treatment. For fluoxetine, dose 20 mg for the first 4 weeks which could be titrated to 40 mg.	Berkeley, CA; Beverley Hills, CA; Denver, CO; Atlanta, GA; Belmont, MA; Clementon, NJ; New York; NY; Philadelphia, PA; Dallas, TX; Salt Lake City, UT
134502	Extension of 134004; Double-blind, placebo-and active-controlled, parallel group study in subjects with moderate-severe MDD with atypical features	Placebo and Fluoxetine	Extension (44 weeks) for patients completing 134004	Subjects continued into the extension with the same treatment used in the short-term trial or switched; switchers followed a similar titration schedule as in 134004.	Beverley Hills, CA; San Diego, CA; Denver, CO; Atlanta, GA; Belmont, MA; Clementon, NJ; New York, NY; Philadelphia, PA; Dallas, TX; Salt Lake City, UT
134006	8-week randomized, double-blind, placebo-and active-controlled, parallel group trial in subjects with moderate-severe MDD with atypical features	Placebo and Paroxetine	Acute (8 weeks)	Subjects took one 20 mg tablet of gepirone-ER once each morning with food on Days 1-3. Day 4, there was a mandatory increase in dose to 40 mg/day. Dose could be increased to 60 mg after 7 days and to 80 mg after 14 days. Dose could be titrated between 40 mg and 80 mg. Subjects in the paroxetine group received 10 to 40 mg based on tolerability.	San Diego, CA; Boca Raton, FL; Atlanta, GA; Libertyville, IL; Boston MA; Farmington Hills, MI; Chapel Hill, NC; Durham, NC; New York, NY; Toronto, ON; Philadelphia PA; Seattle, WA; West Allis, WI
134503	Extension of 134006; Double-blind, placebo-and active-controlled, parallel group study in subjects with moderate-severe MDD with atypical features	Placebo and Paroxetine	Extension (16 weeks) for patients completing 134006	Subjects continued with their treatment and dosing regimen as used in the short-term treatment. During the extension, dose could be adjusted to improve tolerability.	San Diego, CA; Boca Raton, FL; Atlanta, GA; Libertyville, IL; Boston MA; Farmington Hills, MI; Chapel Hill, NC; Durham, NC; New York, NY; Toronto, ON; Philadelphia PA; Seattle, WA; West Allis, WI
134017	8-week randomized, double-blind, placebo-and active-controlled, parallel group trial in subjects with moderate-severe MDD	Placebo and Fluoxetine	Acute (8 weeks)	Subjects in the gepirone-ER group received 20 to 40 mg/day from Days 1 through 7 and 40 to 80 mg from Day 8 until discontinuation or the end of treatment. Subjects in the fluoxetine group received 20 mg/day from Days 1 through 27 and between 20 to 40 mg/day from Day 28 until discontinuation or the end of treatment.	Burbank, CA; Upland, CA; Atlanta; GA; Edwardsville, IL; Okemos, MI; Conshohocken, PA; Portland, OR; Charleston, SC; Seattle WA
134506	Extension of 134017; Double-blind, placebo-and active-controlled, parallel group study in subjects with moderate-severe MDD	Placebo and Fluoxetine	Extension (16 weeks) for patients completing 134017	Subjects continued with their treatment and dosing regimen as used in the short-term treatment. During the extension, dose could be adjusted to improve tolerability. Minimum doses were 40 mg gepirone or 20 mg fluoxetine; maximum doses were 80 mg gepirone or 40 mg fluoxetine.	Perioa, AZ; Glendale, CA; San Diego, CA; Wheat Ridge, CO; Smyrna, GA; Clementon, NJ; Brooklyn, NY; Cleveland, OH; Bellevue, WA

Supplementary Table 2: Controlled gepirone-ER studies prospectively measuring sexual function

Study Identifier	Intervention(s)	Number of Participants*		
		Total	Women	Men
134001	Placebo Gepirone ER (20-80 mg)	208	126	82
134002	Placebo Gepirone ER (20-80 mg)	218	135	83
134004	Placebo Gepirone ER (20-80 mg) Fluoxetine (20-40 mg)	409	269	140
134006	Placebo Gepirone ER (20-80 mg) Paroxetine (10-40 mg)	437	331	106
134017	Placebo Gepirone ER (20-80 mg) Fluoxetine (20-40 mg)	495	315	180
	Total	1,767	1,176	591
Extension				
134502	Non-switchers: Final dosing in the last week of study 134004	114	73	41
	Switchers: Gepirone ER (20-80 mg) Fluoxetine (20-40 mg)	155	98	57
134503	Final dosing in the last week of study 134006 adjusted, Gepirone ER (40-80 mg) Paroxetine (20-40 mg)	197	154	43
134506	Final dosing in the last week of study 134017 adjusted, Gepirone ER (40-80 mg) Fluoxetine (20-40 mg)	208	142	66
	Total	674	467	207

Supplementary Table 3: Schedule of sexual function assessments in controlled gepirone-ER studies

Study/ Extension	Control(s)	Sexual Function Measure	Weeks [a]														
			----Short-term---				----------Extension Phase----------										
			B	2	4	8	12	16	20	21	24	26	28	36	40	44	52
134001	Placebo	DISF-SR	X			**ET**											
134002	Placebo	DISF-SR	X			**ET**											
134004/ 134502	Fluoxetine Placebo	DISF	X	X	X	**ET**	X	X	X				X	X		X	**ET**
134006/ 134503	Paroxetine Placebo	DISF	X	X	X	**ET**	X	X	X		X		**ET**				
134017/ 134506	Fluoxetine Placebo	CSFQ	X	X	X	**ET**	X	X	X		**ET**						

[a] Weeks are defined relative to the start of double-blind treatment
Abbreviations: B=Baseline; ET=End of Treatment Assessment

Supplementary Table 4: Participant disposition

Status	Gepirone - ER	Placebo	Fluoxetine	Paroxetine	Total [a]
Participants Randomized	660	665	304	144	1773
Participants Treated	659	662	304	142	1767
Full Analysis Set [b]	542 (82%)	558 (84%)	291 (96%)	129 (91%)	1520 (86%)
Participants Discontinued	210 (32%)	156 (24%)	65 (21%)	41 (29%)	472 (27%)
Adverse Event	67 (10%)	19 (3%)	12 (4%)	8 (6%)	106 (6%)
Lack of Efficacy	30 (5%)	25 (4%)	8 (3%)	4 (3%)	67 (4%)
Other Reason	113 (17%)	112 (17%)	45 (15%)	29 (20%)	299 (17%)

[a] *Percentage is calculated using the number of participants randomized and treated as the denominator.*
[b] *Participants with at least one post-baseline sexual function assessment.*

Supplementary Table 5: Demographic and baseline characteristics of participants with sexual function data in 5 pooled studies, grouped by treatment

Variable Statistic/Category	Treatment Groups – Full Analysis Set [a]		
	Gepirone - ER (N = 542)	Placebo (N = 558)	SSRI [b] (N = 420)
Age (years)			
n	542	558	420
Mean	39.0	38.7	39.0
Standard Deviation	11.47	11.35	11.42
Median	38.0	38.0	39.0
Range	18, 69	18, 69	18, 65
Gender (n, %)			
Men	177 (32.7)	192 (34.4)	137 (32.6)
Women	365 (67.3)	366 (65.6)	283 (67.4)
Race (n, %)			
White	449 (82.8)	455 (81.5)	339 (80.7)
Black	51 (9.4)	59 (10.6)	39 (9.3)
Asian	7 (1.3)	9 (1.6)	11 (2.6)
Other	35 (6.5)	35 (6.3)	31 (7.4)
Baseline Level of Depression (n, %)			
Mild	112 (20.7)	123 (22.0)	128 (30.5)
Moderate	224 (41.3)	221 (39.6)	137 (32.6)
Severe / Extreme	206 (38.0)	214 (38.4)	155 (36.9)
Age at first episode (years)			
n	334	350	280
Mean	25.0	24.5	24.8
Standard Deviation	11.49	10.96	12.10
Median	23.0	22.0	22
Range	4, 60	4, 60	4, 58
Duration of present episode < 1 year (n, %)			
Yes	272 (50.2)	291 (52.2)	210 (50.0)
No	270 (49.8)	267 (47.8)	210 (50.0)
Baseline HAMD-17 Total Score			
N	542	558	420
Mean	21.36	21.34	20.95
Standard Deviation	3.693	3.912	3.986
Median	22.00	22.00	22
Range	10.0, 31.0	9.0, 33.0	10.0, 32.0

[a] *All treated participants with at least one post-baseline assessment of sexual function.*
[b] *Fluoxetine (N=291) and Paroxetine (N=129).*

Supplementary Table 6: Sexual function (mean total score) at baseline

Study/ Scale	Participants	N	Gepirone-ER	Placebo	SSRI [a]
134001 DISF-SR	All	148	42.4	44.9	--
	Women	94	42.5	36.7	--
	Men	54	42.4	56.6	--
134002 DISF-SR	All	93	49.2	44.4	--
	Women	62	42.7	31.7	--
	Men	31	62.0	70.0	--
134004 DISF	All	372	56.3	54.9	53.9
	Women	241	45.3	46.6	47.0
	Men	131	74.8	71.9	66.4
134006 DISF	All	403	50.4	53.7	50.0
	Women	304	42.7	44.5	45.2
	Men	99	73.5	77.8	68.2
134017 CSFQ	All	456	48.3	50.6	48.7
	Women	290	45.4	47.4	45.7
	Men	166	54.2	56.1	53.1
4 Pooled Studies (DISF/DISF-SR) [b]	All	1016	50.6	51.2	52.0
	Women	701	43.4	42.3	46.0
	Men	315	66.7	69.5	67.1

[a] *Active Control = Fluoxetine in studies 134004 and 134017, Paroxetine in study 134006.*
[b] *Higher scores denote better sexual function*

Abbreviations: CSFQ: Changes in Sexual Function Questionnaire; DISF: Derogatis Interview for Sexual Functioning; SR: Self Report

Supplementary Table 7: Incidence of treatment-emergent sexual dysfunction (per DSM-IV criteria) in participants without sexual dysfunction at baseline [Pooled studies 134004, 134006, and 134017]

DSM-IV Diagnosis Incidence [a]	Gepirone-ER (N [b]=331-389)	Placebo (N=346-405)	SSRI (N=347-404)
Any Sexual Dysfunction	9%	10%	27%**
Sexual Desire Disorder	7%	8%	16%**
Sexual Arousal Disorder	2%	2%	4%
Orgasmic Disorder	4%	5%	18%**

[a] Incidence = Number of patients with sexual dysfunction during the study, as a percentage of those without sexual dysfunction at baseline. Sexual dysfunction was diagnosed by the investigator according to established DSM-IV criteria.

[b] N = Number of patients without sexual dysfunction at baseline; specific Ns for each diagnosis vary as shown.
***Statistically significantly higher than Placebo (p<0.001) and Gepirone-ER (p<0.001)*

Supplementary Table 8: Incidence of Treatment Emergent Sexual Dysfunction (per DSM-IV criteria), by Gender [Pooled Studies 134004, 134006, and 134017]

Incidence by Gender [a]	Gepirone-ER N=218:113 [b]	Placebo N=227:119	SSRI N=232:115
Women	11%	8%	26%**
Men	5%*	15%	30%**

[a] Incidence = Number of patients with sexual dysfunction during study, as a percentage of those without sexual dysfunction at baseline.
[b] Size for group is the number of patients (women: men) without sexual dysfunction at baseline.
**Statistically significantly lower than Placebo (p<0.05).*
***Statistically significantly higher than Placebo (p<0.01) and Gepirone-ER (p<0.001).*

Supplementary Table 9: Change in DISF domain scores from baseline at each visit (Pooled studies 134004 and 134006)

DISF Domain		Gepirone - ER (N [a]=257)	Placebo (N=267)	SSRI (N=261)	Treatment Difference		
					Gepirone - Placebo	SSRI - Placebo	SSRI - Gepirone
Arousal							
Week 2	**n**	230	250	244			
	Mean [b]	0.6	0.1	-1.1	**0.5**	**-1.2**	**-1.6**
	95% CI				-0.37, 1.27 [c]	-2.00, -0.39	-2.47, -0.82
	p-value [b]				0.2789	**0.0038** [d]	**<0.0001**
Week 4	**n**	207	234	227			
	Mean	1.2	0.8	-0.9	**0.4**	**-1.7**	**-2.1**
	95% CI				-0.54, 1.37	-2.66, -0.78	-3.10, -1.17
	p-value				0.3940	**0.0003**	**<0.0001**
Week 8	**n**	185	212	208			
	Mean	1.3	1.1	-0.0	**0.2**	**-1.1**	**-1.3**
	95% CI				-0.84, 1.30	-2.12, -0.04	-2.39, -0.24
	p-value				0.6693	**0.0418**	**0.0166**
Overall*	**n**	234	256	248			
	Mean	1.2	0.8	-0.4	0.3	-1.3	-1.6
	95% CI				-0.56, 1.19	-2.14, -0.42	-2.48, -0.71
	p-value				0.4800	**0.0036**	**0.0004**
Behavior							
Week 2	**n**	228	249	244			
	Mean	0.4	-0.2	-1.0	**0.6**	**-0.8**	**-1.4**
	95% CI				-0.08, 1.34	-1.47, -0.07	-2.12, -0.68
	p-value				**0.0817**	**0.0313**	**0.0001**
Week 4	**n**	208	235	227			
	Mean	0.8	0.1	-0.3	**0.7**	**-0.4**	**-1.1**
	95% CI				-0.16, 1.49	-1.24, 0.37	-1.93, -0.27
	p-value				0.1128	0.2863	**0.0093**
Week 8	**n**	183	212	209			
	Mean	1.0	0.4	0.4	**0.7**	**0.0**	**-0.6**
	95% CI				-0.28, 1.62	-0.90, 0.95	-1.61, 0.31
	p-value				0.1684	0.9616	0.1858
Overall*	**n**	233	256	248			
	Mean	0.9	0.2	-0.0	**0.7**	**-0.2**	**-0.9**
	95% CI				-0.10, 1.43	-0.97, 0.53	-1.66, -0.11
	p-value				**0.0895**	0.5602	**0.0246**
Sexual Desire							
Week 2	**n**	229	253	244			
	Mean	0.9	-0.2	-1.2	**1.1**	**-0.9**	**-2.0**
	95% CI				-0.15, 2.35	-2.17, 0.28	-3.30, -0.79
	p-value				**0.0833**	0.1313	**0.0015**
Week 4	**n**	208	237	228			
	Mean	1.5	-0.2	-1.0	**1.8**	**-0.8**	**-2.5**
	95% CI				0.36, 3.17	-2.16, 0.59	-3.96, -1.12
	p-value				**0.0140**	0.2653	**0.0005**
Week 8	**n**	186	215	210			
	Mean	1.8	-0.0	0.7	**1.9**	**0.7**	**-1.1**
	95% CI				0.29, 3.42	-0.78, 2.26	-2.69, 0.46

DISF Domain		Gepirone - ER (N [a]=257)	Placebo (N=267)	SSRI (N=261)	Treatment Difference		
					Gepirone - Placebo	SSRI - Placebo	SSRI - Gepirone
	p-value				**0.0200**	0.3413	0.1637
Overall*	**n**	233	258	248			
	Mean	1.6	-0.1	-0.1	**1.7**	**0.1**	**-1.7**
	95% CI				0.46, 2.99	-1.17, 1.30	-2.94, -0.38
	p-value				**0.0078**	0.9193	**0.0111**
Orgasm							
Week 2	**n**	225	239	231			
	Mean	0.6	0.4	-2.0	**0.2**	**-2.4**	**-2.6**
	95% CI				-0.69, 1.15	-3.30, -1.47	-3.55, -1.68
	p-value				0.6264	**<0.0001**	**<0.0001**
Week 4	**n**	204	222	216			
	Mean	1.2	1.2	-2.1	**-0.1**	**-3.3**	**-3.3**
	95% CI				-1.10, 0.95	-4.35, -2.32	-4.29, -2.23
	p-value				0.8872	**<0.0001**	**<0.0001**
Week 8	**n**	181	199	197			
	Mean	1.5	1.5	-1.5	**0.0**	**-3.0**	**-3.0**
	95% CI				-1.11, 1.17	-4.08, -1.84	-4.14, -1.85
	p-value				0.9547	**<0.0001**	**<0.0001**
Overall*	**n**	230	244	238			
	Mean	1.3	1.2	-1.7	**0.0**	**-3.0**	**-3.0**
	95% CI				-0.89, 0.95	-3.89, -2.08	-3.94, -2.10
	p-value				0.9481	**<0.0001**	**<0.0001**
Drive							
Week 2	**n**	227	247	240			
	Mean	1.0	0.5	-0.5	**0.5**	**-1.0**	**-1.5**
	95% CI				-0.10, 1.05	-1.55, -0.42	-2.04, -0.89
	p-value				0.1023	**0.0006**	**<0.0001**
Week 4	**n**	207	231	223			
	Mean	1.6	1.2	-0.3	**0.4**	**-1.5**	**-1.9**
	95% CI				-0.22, 1.01	-2.12, -0.91	-2.54, -1.29
	p-value				0.2076	**<0.0001**	**<0.0001**
Week 8	**n**	186	207	204			
	Mean	1.8	1.4	0.2	**0.4**	**-1.1**	**-1.6**
	95% CI				-0.28, 1.17	-1.84, -0.42	-2.31, -0.85
	p-value				0.2277	**0.0018**	**<0.0001**
Overall*	**n**	232	252	245			
	Mean	1.6	1.2	-0.0	**0.4**	**-1.2**	**-1.7**
	95% CI				-0.15, 1.02	-1.80, -0.65	-2.25, -1.07
	p-value				0.1437	**<0.0001**	**<0.0001**

[a] N = Participants with DISF total scores at baseline and at least one post-baseline visit; N for other domains may vary.

[b] Least square means and p-values from a mixed model with fixed effects for treatment, study, gender, and treatment by week interaction term, with week as the repeating factor, patient as a random effect, and baseline score as a covariate. Positive mean change denotes improvement in sexual function.

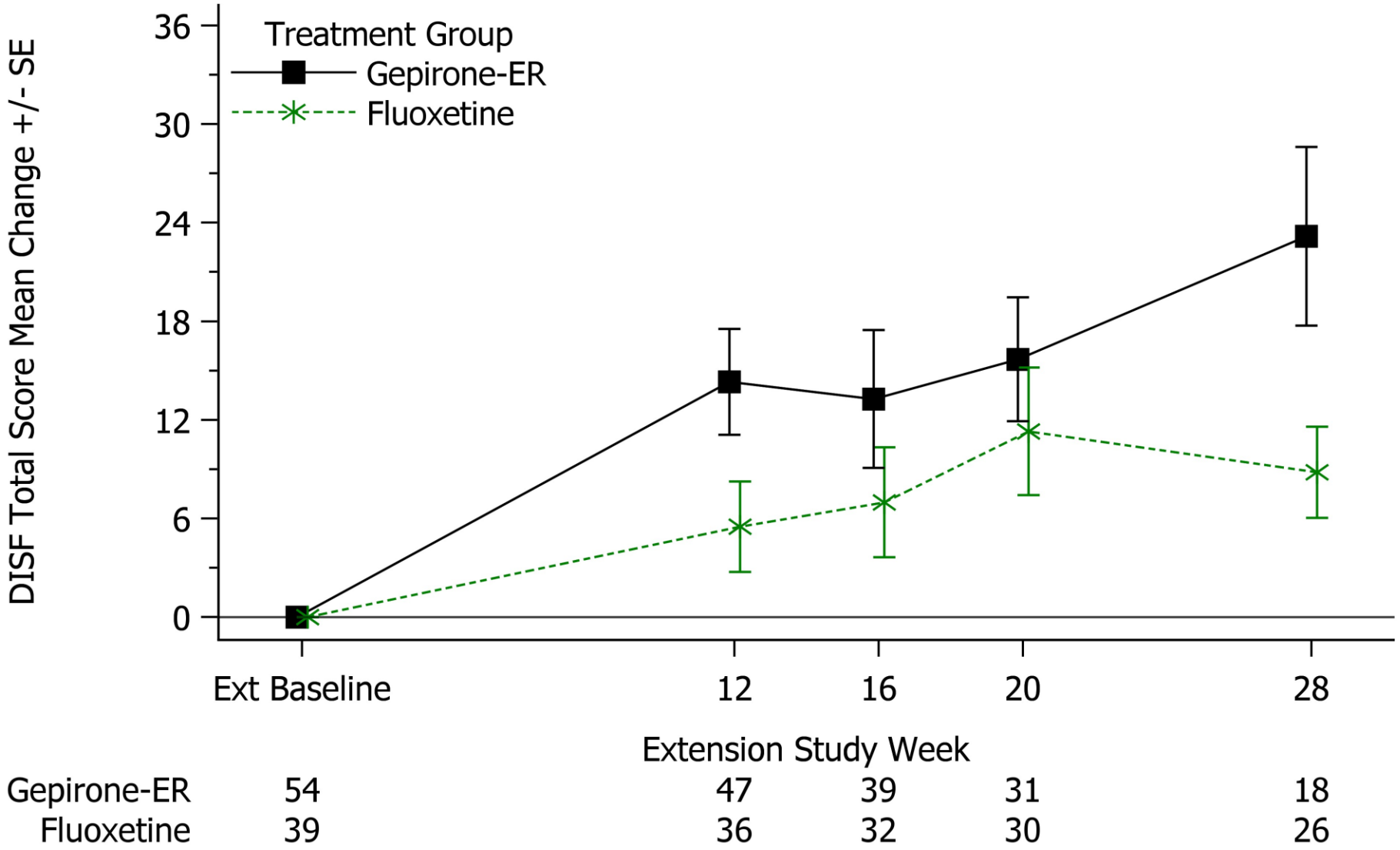
[c] Yellow highlighted cells indicate that the lower limit of the 95% CI is above -1.0.

[d] *P-values ≤ 0.10 (two-sided) are in bold font.*

**Based on contrasts of the least squares means weighted across weeks for each treatment pair.*

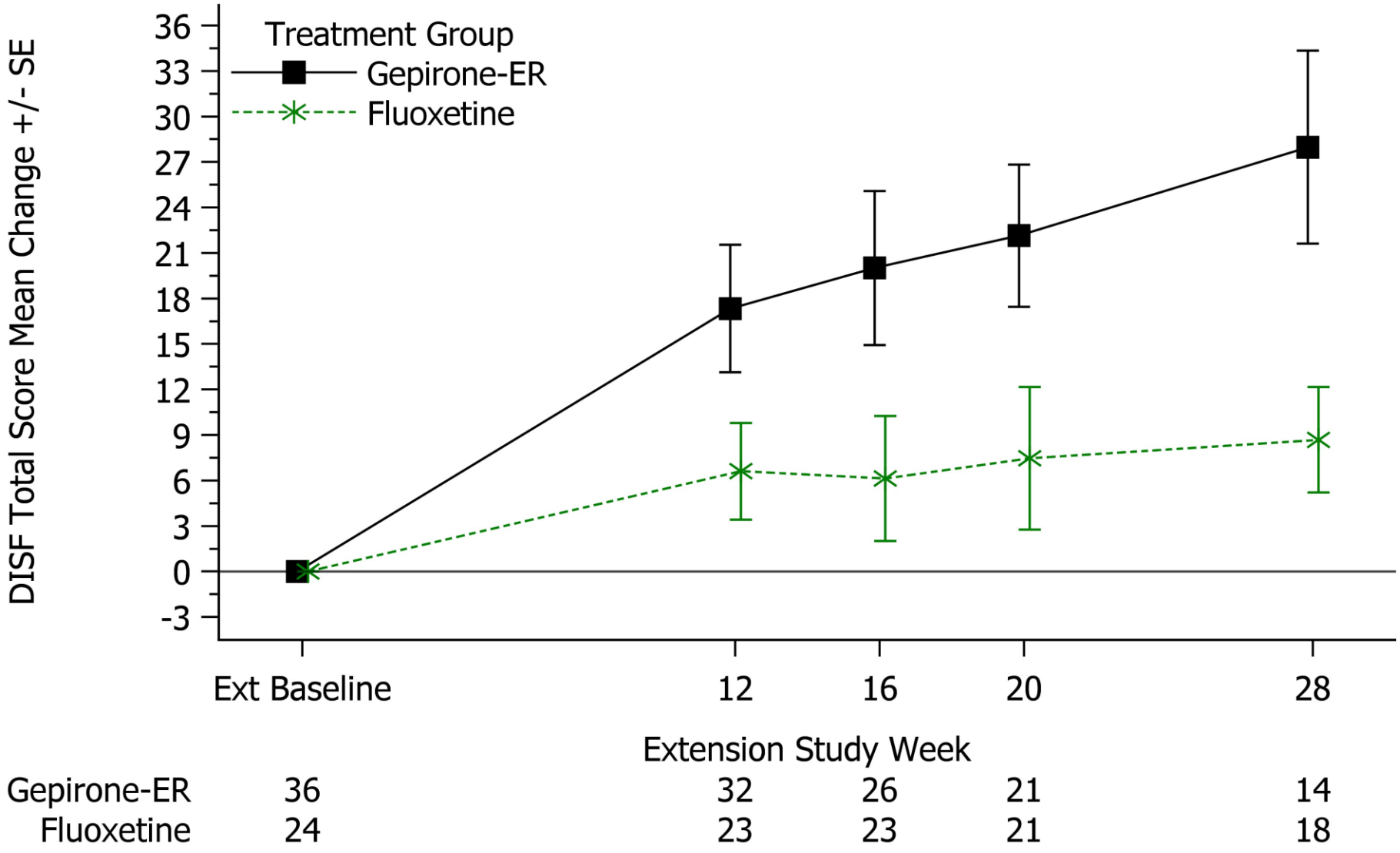
Abbreviations: CI=confidence interval; Derogatis Interview for Sexual Functioning; LS=least squares

Supplementary Figure 1: Change in sexual functioning among participants on SSRI in prior study (Study 134502 data only)



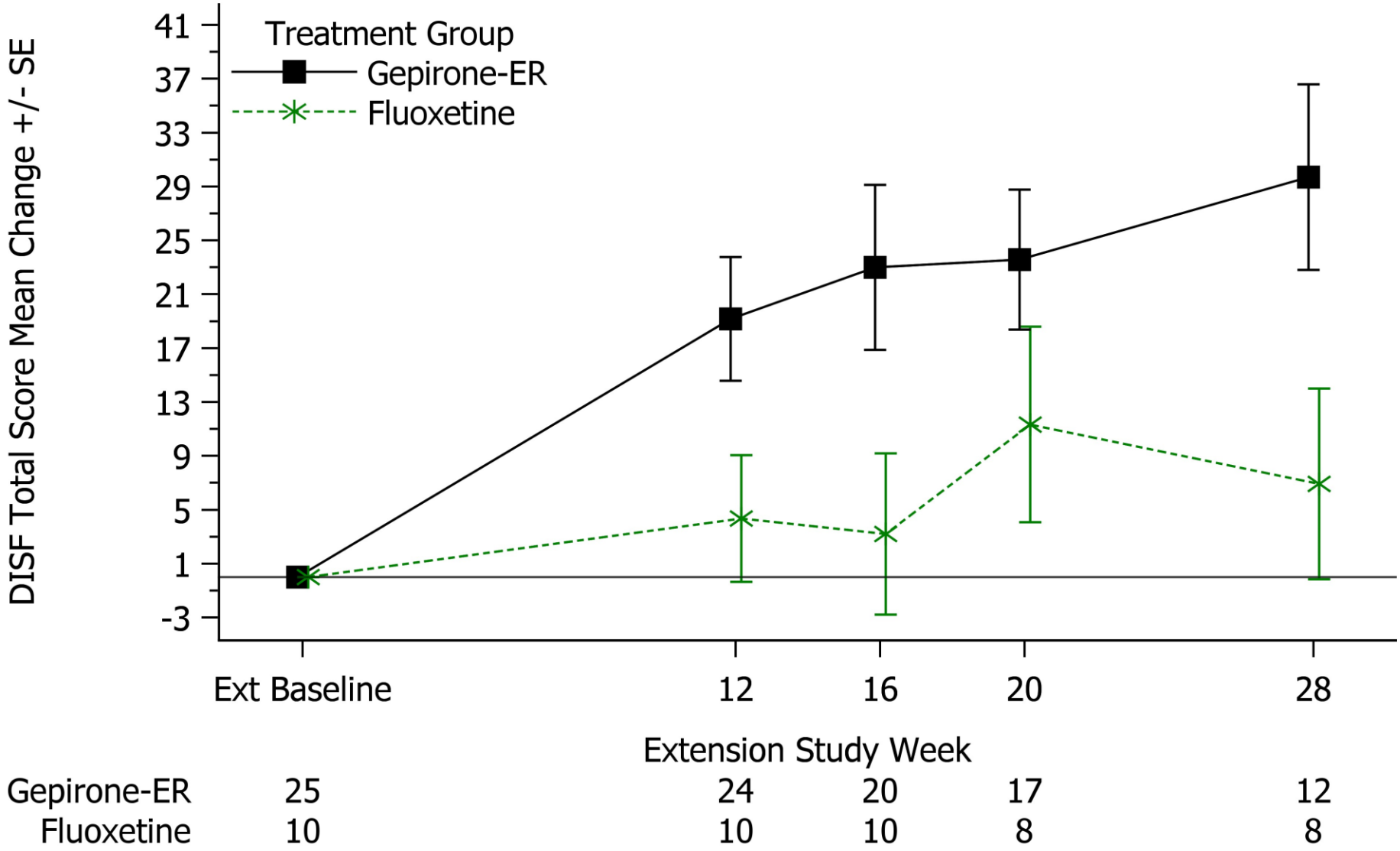
Abbreviations: Derogatis Interview for Sexual Functioning; ER: Extended Release; SE: Standard Error

Supplementary Figure 2: Average change in sexual functioning from baseline among women on SSRI in prior study (Study 134502 data only)



Abbreviations: Derogatis Interview for Sexual Functioning; ER: Extended Release; SE: Standard Error

Supplementary Figure 3: Average change in sexual functioning from baseline among women with treatment-emergent sexual dysfunction in prior study (Study 134502 data only)



Abbreviations: DISF: Derogatis Interview for Sexual Functioning; ER: Extended Release; SE: Standard Error