

**Psychopharmacological
Drugs Advisory Committee
November 3, 1999**

**Fluoxetine in the
Treatment of PMDD**

**Gregory T. Brophy PhD
Director, US Regulatory Affairs
Eli Lilly and Company
Indianapolis, IN**

Introduction

Jean Endicott, PhD

Columbia University, New York, New York

**The Efficacy and Safety of Fluoxetine in
Premenstrual Dysphoric Disorder**

Conclusions

Rajinder Judge, MD

Eli Lilly and Company, Indianapolis, Indiana

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JE-L-1

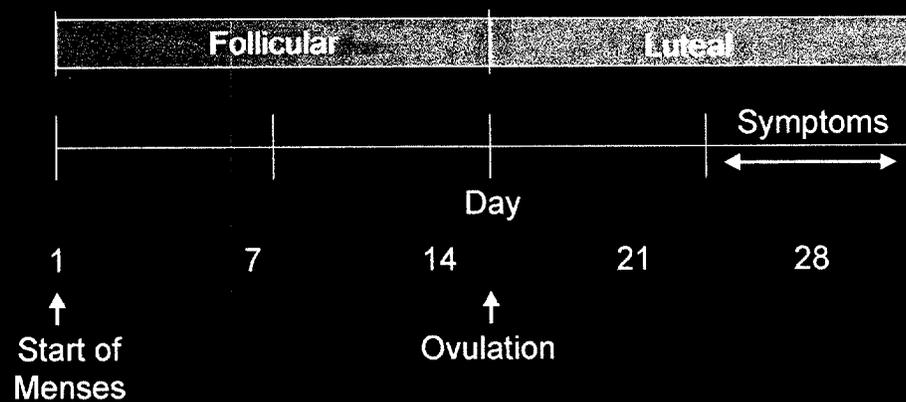
Introduction

Jean Endicott, PhD

Department of Psychiatry
College of Physicians and Surgeons
Columbia University, New York, New York

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The Menstrual Cycle



JE-L-2

History

- Ancient history
 - Literature described severe changes in mood and behavior that occurred just prior to the onset menses
- 1930s
 - "Premenstrual tension syndrome" was used to describe problems experienced by 15 women (R.T. Frank, Archives of Neurology and Psychiatry)
- 1950s
 - "Premenstrual syndrome" came into more common usage

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History

- 1983
 - Workshop on premenstrual syndrome held under the co-sponsorship of the NIMH yielded some suggestions for criteria for premenstrual "changes" and "syndrome".¹
- 1987
 - DSM III-R included specific criteria for late luteal phase dysphoric disorder in the appendix as a "proposed diagnostic category needing further study". (Content almost identical to DSM-IV criteria)

¹Blume E, JAMA 249:2866, 1983

JE-L-3

History

- Early 90s
 - DSM-IV premenstrual dysphoric disorder work group reviewed available literature (up to 1993):
 - Agreement on the suggested criteria and name
 - Agreement on summary of evidence
 - Lack of consensus regarding recommendations on placement of condition
- 1994
 - PMDD was included in DSM-IV (criteria in the appendix)

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Premenstrual Symptomatology

A Spectrum of Mood and Physical Symptoms



Premenstrual Dysphoric Disorder

Mood symptoms are prominent and severe

- Irritability, low mood, anxiety

Functional impairment

Physical symptoms

- breast tenderness, bloating

Prevalence 3-5%

Premenstrual Syndrome

Physical symptoms are prominent

- breast tenderness, bloating,

Mood symptoms may be less severe

Little or no functional impairment

Prevalence 20-80%

Symptoms appear regularly during the week before menses (the luteal phase of the menstrual cycle) and remit following the onset of menses

JE-L-4

Premenstrual Symptomatology

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JE-R-4

PMDD DSM-IV Criteria

- Symptoms occur in the late luteal phase of most menstrual cycles during the past year and remit within a few days of menses
- At least 5 of these symptoms have been present most of the time during each symptomatic phase, at least one of those being either items 1, 2, 3 or 4:
 - 1- markedly depressed mood, feelings of hopelessness, or self-depreciating thoughts
 - 2- marked anxiety, tension, feelings of being 'keyed up,' or 'on edge'
 - 3- marked affective lability
 - 4- persistent and marked anger, irritability, or increased interpersonal conflicts

from DSM-IV, 1994

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PMDD DSM-IV Criteria

- 5 - decreased interest in usual activities
- 6 - subjective sense of difficulty in concentrating
- 7 - lethargy, easy fatigability, or lack of energy
- 8 - marked change in appetite
- 9 - hypersomnia or insomnia
- 10* - subjective sense of being overwhelmed or out of control
- 11- other physical symptoms

*symptom added to the DSM-III-R diagnosis of late luteal phase dysphoric disorder (LLPDD)

from DSM-IV, 1994

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PMDD: DSM-IV Criteria

- Markedly interferes with work, school or usual social activities and relationships
- Not merely an exacerbation of the symptoms of another disorder, such as Major Depressive Disorder
- Criteria must be confirmed by prospective daily ratings during at least 2 consecutive symptomatic cycles

from DSM-IV, 1994

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JE-R-6

PMDD: Impact on Functioning

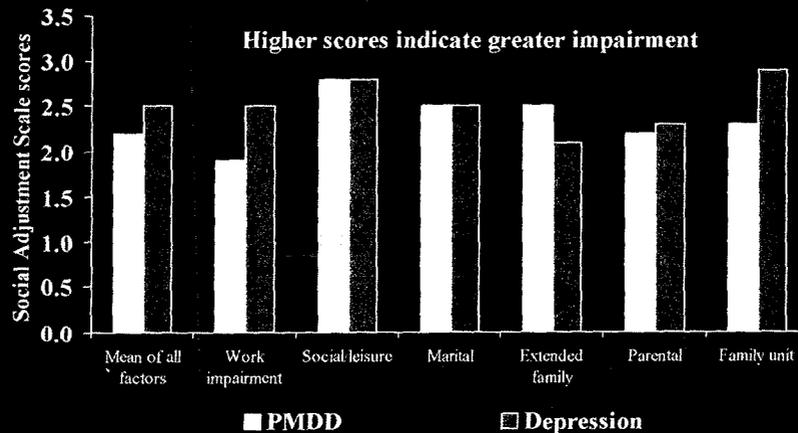
- A woman who develops the disorder at age 26 may experience more than 200 symptomatic cycles or 1,400-2,800 symptomatic days¹
- DSM-IV criteria for PMDD: symptoms are severe enough to have a significant impact on social, home, and occupational functioning^{1,2}
- Social functioning is affected more than vocational functioning
- Women with PMDD may report impairment of family and social activities at a level similar to that of depression^{1,2}

¹Yonkers et. al., *JAMA*, 1997;278(12):983-988

²Steiner et. al., *N Engl J Med*, 1995;332(23):1529-1534

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Impairment in Functioning PMDD vs. Depression



Yonkers et al., *JAMA*, 1997;278(12):983-988

JE-R-7

Etiology

- Pathophysiology of PMS/PMDD is not fully understood
- Most likely theory based on observation that cyclic changes in ovarian steroids cause dramatic changes in brain neurotransmitter systems
- In women sensitive or otherwise predisposed to mood instability, the normal events of the ovarian cycle may trigger severe mood changes

Mortola et al., *Trends Endocrinol Metab*, 1996;7:184-89
Rubinow and Schmidt, *N Engl J Med*, 1995, 332:1574-75

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PMDD: Distinct From Other Depressive Disorders

- Mood disturbance is cyclical; tightly linked to phases of menstrual cycle with predictable onset and offset
- Most common chief complaint is irritability
- Cyclical occurrence of symptoms cease during pregnancy and post-menopause
- Prevention or suppression of cycling gonadal hormones relieves symptoms

JE-L-9

PMDD: Distinct From Other Depressive Disorders

- HRT can provoke cyclical dysphoric mood changes in women with history of PMDD
- HPA Axis functions normally in PMDD, unlike documented disturbances in major depression
- Symptom stability is seen across cycles
- The genetic and environmental risk factors for premenstrual-related symptoms and lifetime major depression are not closely related¹

¹Kendler et al., *Am J Psychiatry*, 1998

JE-R-9

PMDD: Distinct From Other Depressive Disorders

- PMDD is more likely to respond to serotonergic antidepressants than to other antidepressants
- Upon treatment, symptom improvement is rapid (within first treatment cycle)
- Physical symptoms of PMDD are unique (eg, breast tenderness and bloating are most common)
- Upon treatment cessation, symptoms return rapidly and re-emergence is more predictable

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Re-emergence of Symptoms After Stopping Treatment

Pearlstein, 1994

After 1 year of successful fluoxetine treatment, 31 women discontinued treatment. PMDD symptoms returned within 2 cycles in 30 women.

Yonkers, 1997

Following double-blind randomization from sertraline to placebo, rates of recurrence were 66%, 66%, and 60% after 3, 6, and 9 cycles, respectively.

JE-R-10

Treatments Studied for PMDD/PMS

Psychotropics:

- Selective serotonin reuptake inhibitors (SSRIs)
- Tricyclic antidepressants (TCAs)
- Alprazolam
- Buspirone

Other Interventions:

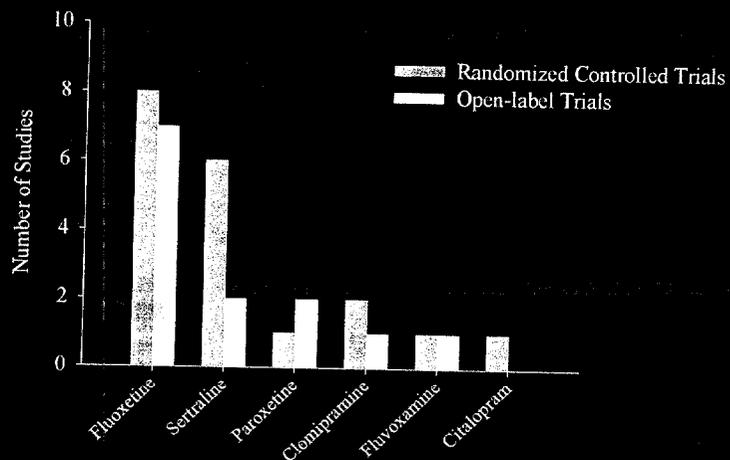
- Lifestyle alterations
- Over the counter/Nutritional supplements

Other Pharmacotherapies:

- Hormones
- Gonadotropin releasing hormone (GHRH) analogues
- Bromocriptine
- Fenfluramine
- Calcium supplementation
- Surgical interventions (eg, oophorectomy)
- Light Therapy

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Published Studies Serotonergic Agents in PMDD/PMS



JE-R-11

Conclusions

- PMDD is a distinct clinical entity that occurs in 3% to 5% of menstruating women
- PMDD has clinical and biological profiles different from those of depression
- PMDD is a severe form of PMS that impacts normal functioning
- PMDD should be better diagnosed and treated

JE-L-12

Clinical Considerations

- There is currently no registered treatment in the United States for PMDD
- There is an unmet clinical need for safe and effective treatment for the psychological as well as the physical symptoms of PMDD
- There is evidence that SSRIs meet this need

JE-R-12

The Efficacy and Safety of Fluoxetine in Premenstrual Dysphoric Disorder (PMDD)

Rajinder Judge, M.D.
Director, Lilly Neuroscience

RJ-EL-1

Outline

Efficacy - mood, physical, social impairment

-PMDD studies

Safety

-PMDD studies

-Fluoxetine safety database

Conclusions and Dosing Recommendations

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Fluoxetine Studies in PMDD

Double-blind

Investigator	Study Design	No. Enrolled	Diagnostic Criteria	Duration of Active Rx (cycles)	Flx Treatment (mg/day)
Steiner	Double-blind, parallel	405	DSM-III-R	6	20 or 60
Su	Double-blind, crossover	19	DSM-III-R	3	20-60
Pearlstein	Double-blind, parallel	42	DSM-III-R	2	20
Stone	Double-blind, parallel	25	DSM-III-R	2	20
Wood	Double-blind, crossover	8	DSM-III-R	3	20
Menkes	Double-blind, crossover	23	DSM-III-R	3	20
Ozeren	Double-blind, parallel	35	DSM-III-R	2	20

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Fluoxetine Studies in PMDD

Open-label

Investigator	Study Design	No. Enrolled	Diagnostic Criteria	Duration of Active Rx (cycles)	Flx Treatment (mg/day)
Rickels	Open-label Matched	20	DSM-III-R	2	20
Brandenburg	Open-label	10	DSM-III-R	2	20
Steiner	Open-label	48	DSM-IV	3	20*
Elks	Open-label	11	DSM-III-R	3-20 months	20
Pearlstein	Open-label	60	DSM-III-R	Mean of 18.6 months	20-40
de la Gandara	Open-label	20	DSM-IV	6-18 months	20

*Either daily or days 14-28 (intermittent dosing)

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PMDD Trials Overview

Study/ No. Centers/ Location	Study Design	Number of Patients	Efficacy Measures
1. B1Y-CA-C019 7 centers Canada	Double-blind, parallel, placebo-controlled	Entered N=405 Randomized N=320	VAS-7 PMTS-P PMTS-C
2. B1Y-MC-X022 1 center United States	Double-blind, crossover, placebo- controlled	Entered N=19 Randomized N=19	VAS-16 DRF PMTS-P PMTS-C STAI BDI
3. B1Y-MC-X037 2 centers United States	Double-blind, parallel, placebo-controlled	Entered N=50 Randomized N=42	CGI-I GAS DAF HAMD

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Efficacy Scales

VAS: Visual Analog Scale
PMTS: Premenstrual Tension Syndrome Scale
DRF: Daily Rating Form
STAI: State Trait Anxiety Inventory
BDI: Beck Depression Inventory
CGI: Clinical Global Impression
GAS: Global Assessment Scale
DAF: Daily Assessment Form
HAMD: Hamilton Depression Rating Scale

Scale Item Comparison to DSM-IV Mood Criteria

DSM-IV Item	VAS 7 Item #	VAS 16 Item #	PMTS-C Item #	PMTS-P Item #	DRF Item #	DAF Item #
Markedly depressed mood, feelings of hopelessness,	2	8	4	18, 35	7	10, 11, 17, 18
Marked anxiety, tension, ...	1	12	2	9, 13, 27, 34	5, 8	5, 20
Marked affective lability	4	1	4	19, 25	6	4, 24
Persistent and marked anger or irritability, ...	7	9	1	4, 7, 17, 29	9	1

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Scale Item Comparison to DSM-IV Physical and Social Impairment Criteria

DSM-IV Item	VAS 7 Item #	VAS 16 Item #	PMTS-C Item #	PMTS-P Item #	DRF Item #	DAF Item #
Physical symptoms (eg. breast tenderness or swelling, headaches, joint or muscle pain, sensation of bloating, weight gain)	3, 5, 6	5, 6, 13	9	2, 11, 15, 24	4, 13, 14, 15, 16	7, 8, 15, 22, 26
Social Impairment		11, 14	10	1, 5, 12, 36	1	23, 31

PMDD Study Population

Inclusion Criteria

- Healthy females ≥ 18 years of age
- Regular menstrual cycles
- DSM-III-R diagnosis of Late Luteal Phase Dysphoric Disorder (LLPDD) as confirmed by prospective ratings during at least 2 menstrual cycles
- Adequate method of birth control (other than hormonal)
- Meet criteria for protocol defined symptom severity

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PMDD Study Population

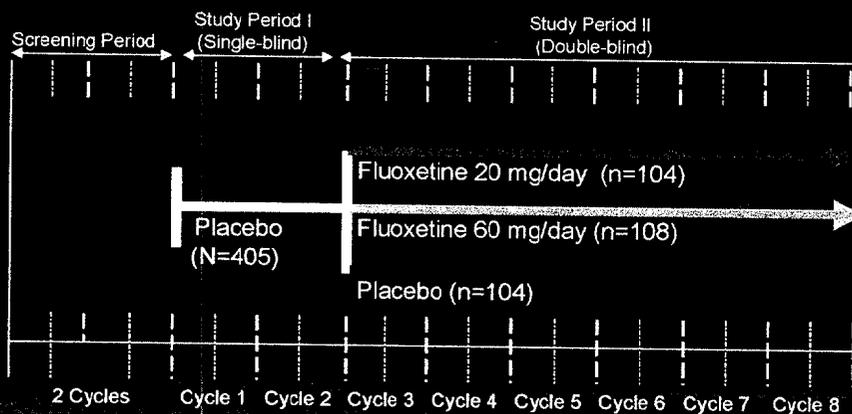
Exclusion Criteria

- Serious health problems, including neurological or gynecological problems
- Concurrent Axis I DSM-III-R diagnosis
- Psychotropics, diuretics, or hormonal medications, including oral contraceptives

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Study 1
B1Y-CA-C019

Study Design



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Study 1
B1Y-CA-C019

Study Objectives

Primary:

- Assess efficacy of fluoxetine in PMDD as measured by the luteal phase VAS Mood-3 Average change from mean baseline to mean treatment score*

Secondary:

Assess efficacy of fluoxetine in PMDD symptom clusters (mood, physical and social impairment) as measured by the:

- 7-item VAS
- PMTS-P
- PMTS-C

Assess safety and tolerability of fluoxetine in PMDD

* not specifically defined in protocol

RJ-ER-6

Study 1
B1Y-CA-C019

Efficacy Analyses

Primary Variable (collected at luteal and follicular phases of each cycle)

-VAS Mood-3 Average=Average score of dysphoria, irritability, tension

Secondary Variables (collected at luteal and follicular phases of each cycle):

-VAS Mood-4 Average=Average of dysphoria, irritability, tension, emotional lability

-VAS Physical Average=Average of bloating, breast tenderness, headache

-PMTS-P subtotals for mood, physical, social impairment

-PMTS-C subtotals for mood, physical, social impairment

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Study 1
B1Y-CA-C019

Visual Analogue Scale

How are you feeling today? Please answer by marking a line across the line below

		0 ← Scale → 100		
Item 1	Calm, unruffled			Tense, uptight, uneasy
Item 2	Happy, content, energetic			Extremely depressed, sad, apathetic, lethargic
Item 3	No headache			Severe headache
Item 4	Even tempered			Extreme mood swings
Item 5	No bloating, swelling			Feel bloated, swollen abdomen and/or hands, ankles, feet
Item 6	No breast tenderness or sensitivity			Extreme breast tenderness or sensitivity
Item 7	[Not at all irritable]			[Extremely irritable, short-tempered]

RJ-ER-7

Study 1
B1Y-CA-C019

PMTS Scales

Clinician-Rating Scale		Patient-Rating Scale	
Range 0-36		Yes/No	Range 0-36
1. Irritability	0-4		Anger Irritability Short-fused Hostility
2. Tension	0-4		Tense Unable to relax Noticeable restlessness Upset
3. Efficiency	0-4		Efficiency diminished Difficulty completing tasks Tiredness impairs efficiency Easily fatigued
4. Dysphoria	0-4		Hopelessness Crying Mood swings Sad
5. Motor coordination	0-4		Poor coordination Accident prone Clumsiness Untidy writing

RJ-EL-8

Study 1
B1Y-CA-C019

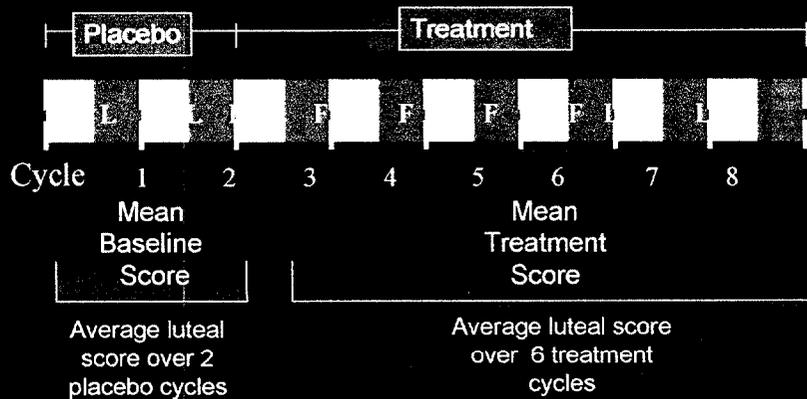
PMTS Scales

Clinician-Rating Scale Range 0-36		Patient-Rating Scale Yes/No Range 0-36	
6. Mental functioning	0-4	Poor judgment Confused Forgetful Easily distracted	
7. Eating habits	0-2	Food cravings Appetite change	
8. Sexual drive/interest	0-2	Changed sexual interest Changed sexual drive	
9. Physical symptoms	0-4	Gain ≥ 5 lbs Physical symptoms impact on function Tender breasts Bloating, swollen breasts	
10. Social impairment	0-4	Avoid social activities Prefer to be alone Cancelled engagements Decreased social activity	

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Study 1
B1Y-CA-C019

Calculation of Efficacy Measures



Follicular  Luteal

RJ-EL-9

Study 1
 B1Y-CA-C019

Calculation of Efficacy Measures =

Mean Treatment

Average
 Luteal
 Score over 6
 treatment
 cycles

minus

Mean Baseline

Average
 Luteal
 Score over 2
 placebo
 cycles

NB: Original Lilly analysis plan defined percent change

RJ-ER-9

Study 1
 B1Y-CA-C019

Baseline Patient Characteristics

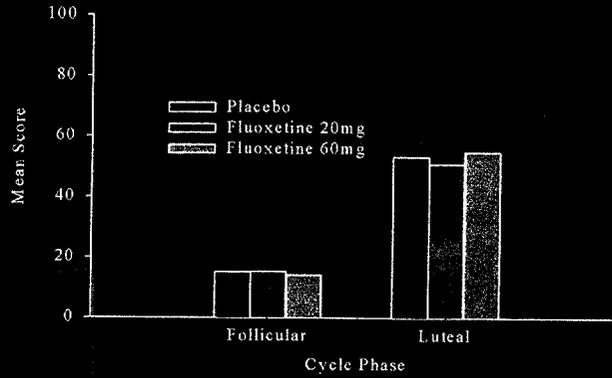
All Randomized Patients

Variable	Placebo (N=108)	Fluox 20 mg (N=104)	Fluox 60 mg (N=108)	p-Value
Age at entry: years				
No. Patients	106	101	107	.16
Mean	37	36	36	
Weight: kg				
No. Patients	108	104	108	.55
Mean	15	15	14	
Height: cm				
No. Patients	108	104	107	.41
Mean	53	51	55	

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Study 1
B1Y-CA-C019

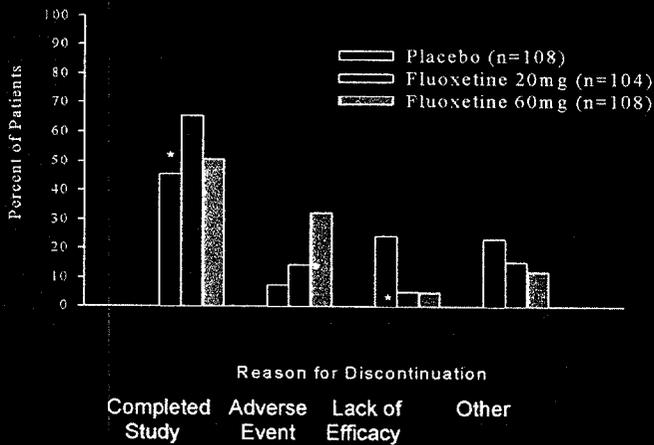
Baseline VAS Mood-3 Scores All Randomized Patients



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Study 1
B1Y-CA-C019

Patient Disposition

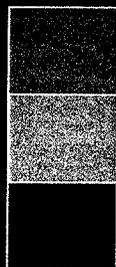


*p < .05

("Other" includes satisfactory response, lost-to-follow-up, patient decision, protocol requirement.)

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Graph Legend



Fluoxetine 20 mg/day

Fluoxetine 60 mg/day

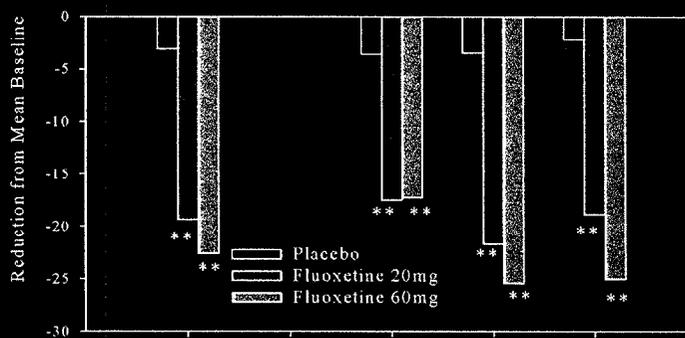
Placebo

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Study 1
B1Y-CA-C019

Mood Symptoms in Luteal Phase

Reduction from Mean Baseline to Mean Treatment



**p<.01 relative to placebo

VAS Mood-3

Dysphoria

Irritability

Tension

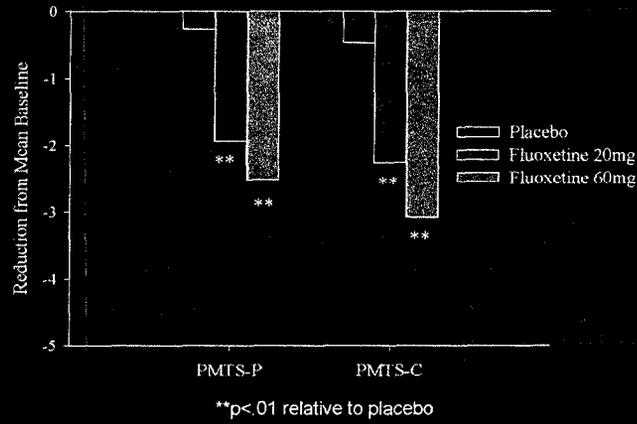
Note: No statistical difference between fluoxetine 20 mg and fluoxetine 60 mg

RJ-EL-12

Study 1
B1Y-CA-C019

Mood Symptoms in Luteal Phase

Reduction from Mean Baseline to Mean Treatment



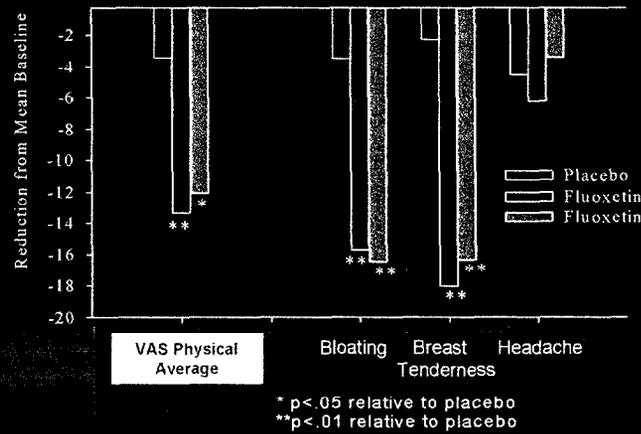
Note: No statistical difference between fluoxetine 20 mg and fluoxetine 60 mg

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Study 1
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Physical Symptoms in Luteal Phase

Reduction from Mean Baseline to Mean Treatment



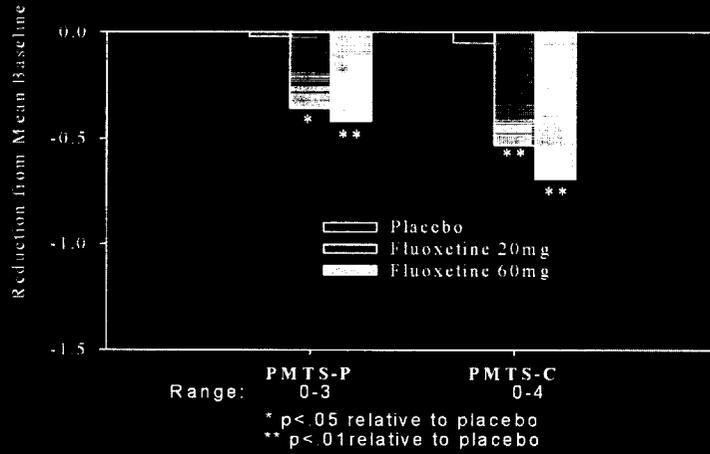
Note: No statistical difference between fluoxetine 20 mg and fluoxetine 60 mg

RJ-EL-13

Study 1
B1Y-CA-C019

Physical Symptoms in Luteal Phase

Reduction from Mean Baseline to Mean Treatment



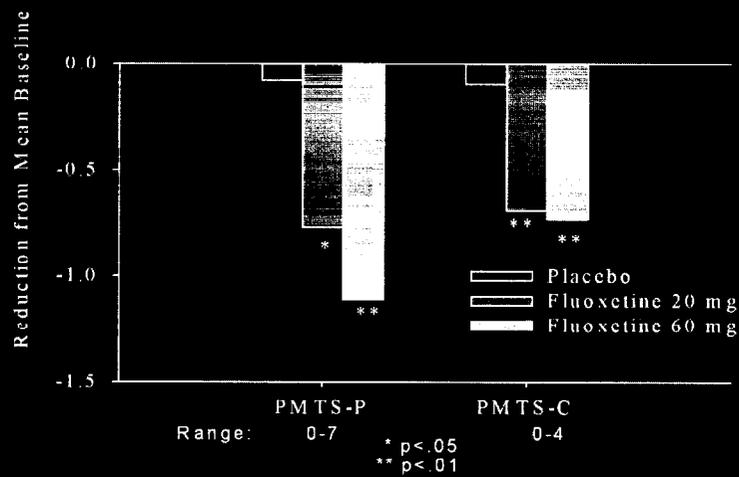
Note: No statistical difference between fluoxetine 20 mg and fluoxetine 60 mg

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Study 1
B1Y-CA-C019

Social Impairment in Luteal Phase

Reduction From Mean Baseline to Mean Treatment



Note: No statistical difference between fluoxetine 20 mg and fluoxetine 60 mg

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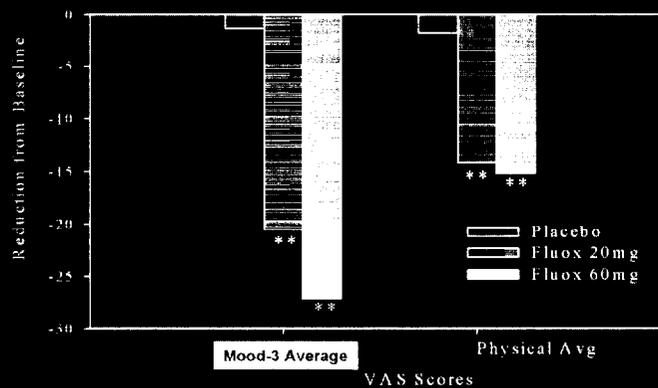
Study 1
B1Y-CA-C019

- Efficacy was seen for both fluoxetine 20 and 60 mg in PMDD for all symptom clusters of PMDD
 - How quickly was the efficacy apparent?
 - What was the course of the treatment effect?

Study 1
B1Y-CA-C019

Efficacy During 1st Treatment Cycle

Change from Mean Baseline to 1st Treatment Cycle



**p < .01 relative to placebo

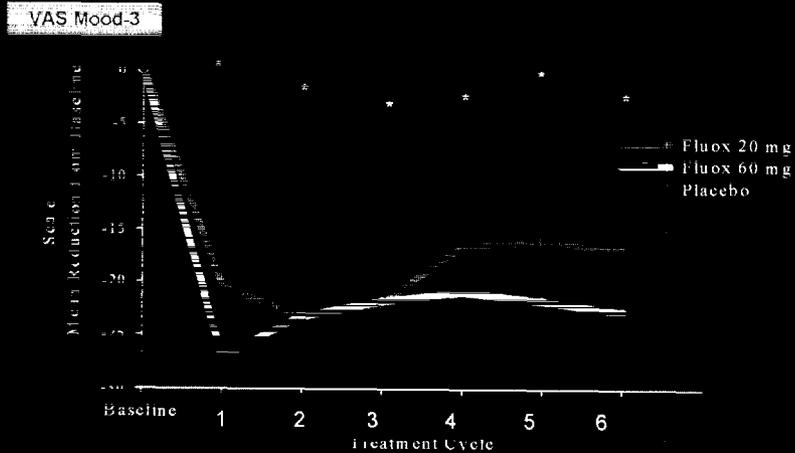
Note: No statistical difference between fluoxetine 20 mg and fluoxetine 60 mg

RJ-EL-15

Study 1
B1Y-CA-C019

Course of Treatment Effect

Change from Baseline to Each Cycle (LOCF)



*p < .05 vs fluoxetine 20mg and 60mg.

03-17-16

Study 1
B1Y-CA-C019

Efficacy Conclusions

- Fluoxetine 20 mg and 60 mg/day were effective in the treatment of PMDD:
 - statistically significantly superior to placebo with respect to both the primary objective and the secondary objectives
 - efficacy was seen in all symptom clusters of PMDD
 - mood symptoms
 - physical symptoms
 - social impairment

RJ-EL-16

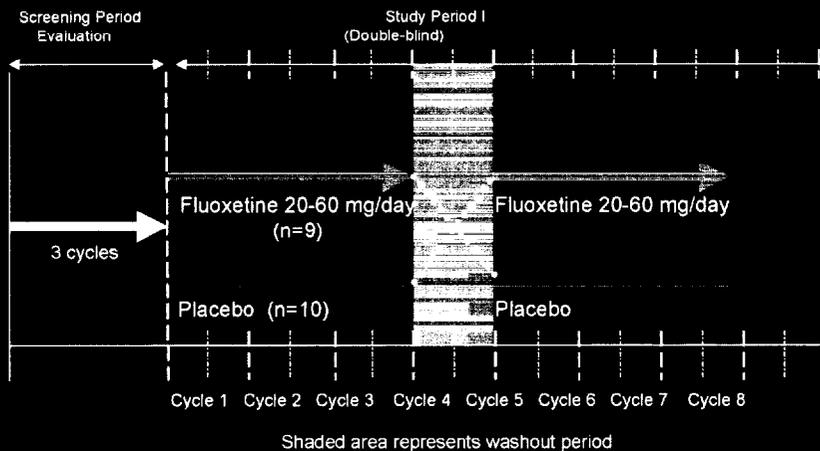
Study 1
B1Y-CA-C019

Efficacy Conclusions

- Improvement was demonstrated in first treatment cycle
- Effect was maintained for up to 6 months
- Improvement with fluoxetine 60 mg was in general numerically greater than fluoxetine 20 mg but the differences were not usually statistically significant

Study 2
B1Y-MC-X022

Study Design



RJ-EL-17

Study 2
B1Y-MC-X022

Study Objectives

Primary objective:

- Assess the efficacy of fluoxetine (20-60 mg/day) in the treatment of PMDD as measured by average within-cycle change from follicular to luteal phase ratings in the VAS Mood-4 subtotal (mood swings, depression, irritability, and anxiety).

Secondary objectives:

- Assess the efficacy of fluoxetine (20-60 mg/day) in the treatment of PMDD symptom clusters (mood, physical, and social impairment) as measured by the:
 - 16-item VAS
 - PMTS-P
 - PMTS-C
- Assess the safety of fluoxetine (20-60 mg/day)

RJ-ER-17

Study 2
B1Y-MC-X022

Efficacy Analyses

Primary Variable (collected daily):

-VAS Mood-4 subtotal=sum of mood swings, depression, irritability, anxiety

Secondary Variables (collected daily):

-VAS Mood-3 subtotal=sum of depression, irritability, anxiety

-VAS Physical subtotal=sum of breast pain, bloating, physical discomfort

-VAS Social Impairment subtotal=sum of work efficiency, social activity

-DRF subtotals for mood, physical, social impairment

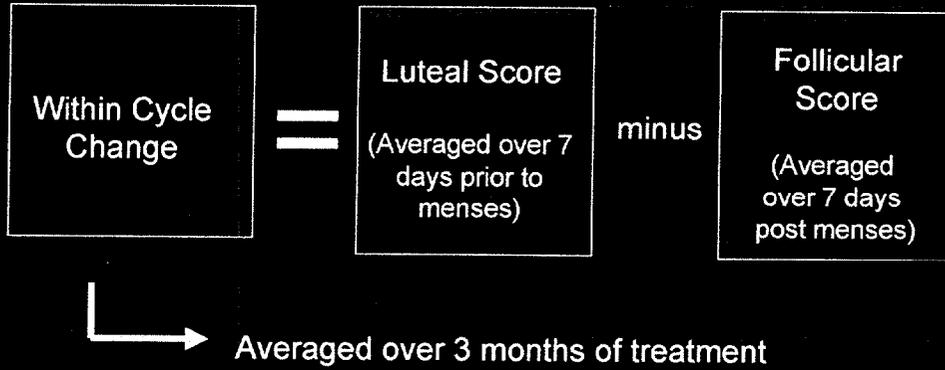
Secondary Variables (collected at each visit):

-PMTS-P and PMTS-C subtotals for mood, physical, social impairment

RJ-EL-18

Study 2
B1Y-MC-X022

Patient Primary Treatment:



RJ-ER-18

Study 2
B1Y-MC-X022

Visual Analogue Scale

Please rate the way you feel right now on the following scales. Place a line through the scale line at a point that best describes how you are feeling on that particular item.

Item #	0	Scale	100
1 Rapidly changing mood		—————>	Mood very stable
2 No appetite at all		—————>	Ravenously hungry, food cravings
3 Lonely, feel rejected		—————>	Secure, cared for
4 Impulse to hurt others		—————>	No impulse to hurt others
5 Extreme breast pain or discomfort		—————>	Breast discomfort absent
6 Extreme bloating or swelling		—————>	No bloating or swelling
7 Impulse to hurt self		—————>	No impulse to hurt self
8 Most sad ever		—————>	Most happy ever
9 Extremely irritable		—————>	Most tranquil ever

RJ-EL-19

Study 2

B1Y-MC-X022

Visual Analogue Scale

Please rate the way you feel right now on the following scales. Place a line through the scale line at a point that best describes how you are feeling on that particular item.

Item #	0 ←	Scale	→	100
10	Most tired ever	-----		Most energetic ever
11	Work very impaired,	-----		Work very efficiently, highly inefficient productive
12	Most anxious ever	-----		Most calm ever
13	Extreme physical discomfort	-----		Very comfortable physically
14	Avoid social activity	-----		Very socially active
15	Feel worst ever	-----		Feel best ever
16	No self esteem	-----		High self esteem

RJ-ER-19

Study 2

B1Y-MC-X022

Daily Rating Form (DRF)

- Patient rates the severity of each item on a scale from 1 (none) to 6 (extreme). Total score ranges from 18 to 108.

Mood

Mood swings

Depressed, sad

Anxious, nervous

Irritable, angry

Physical

Bloating, swelling

Joint, muscle pain

Cramps

Breast pain

Social Impairment

Avoid social activity

Impaired function

RJ-EL-20

Study 2
B1Y-MC-X022

Daily Rating Form (DRF)

- Other symptoms rated were:

Loss of interest	Sexual interest
Appetite up	Headaches
More sleep	Active, efficient
Loneliness, rejection	Alcohol habits
Disturbed sleep	Caffeine habits
Low energy	
Impulse to hurt someone	
Act on impulse to hurt	
- Menstruation dates and other "life events" are also recorded

RJ-ER-20

Study 2
B1Y-MC-X022

Baseline Patient Characteristics

All Randomized Patients

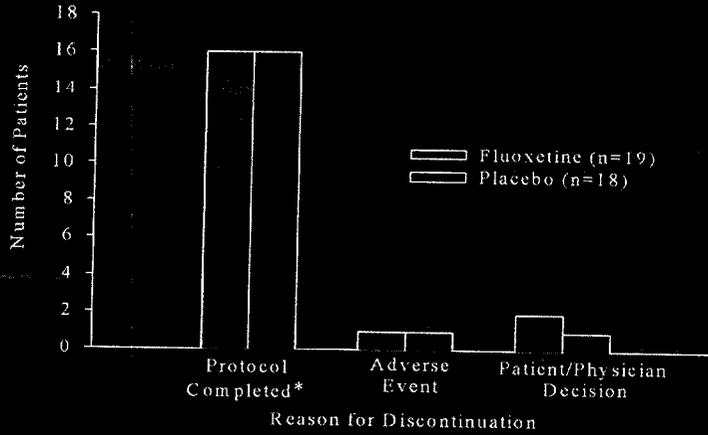
Variable	Flx/Plac (n=9)	Plac/Flx (n=10)	p-Value
Origin No. (%)			
Caucasian	8 (89%)	7 (70%)	0.58
African Descent	1 (11%)	3 (30%)	
Age (years)			
Mean	39	35	0.12
Follicular PMTS-Patient Total			
Mean	2.6*	3.6	0.53
Range	0-12	0-10	
Follicular PMTS-Clinician Total			
Mean	4.11	4.0	0.71
Range	0-14	0-10	
Follicular BDI Total			
Mean	4.6	3.6**	0.53
Range	0-13	0-11	

*n=8 **n=9

RJ-EL-21

Study 2
B1Y-MC-X022

Patient Disposition



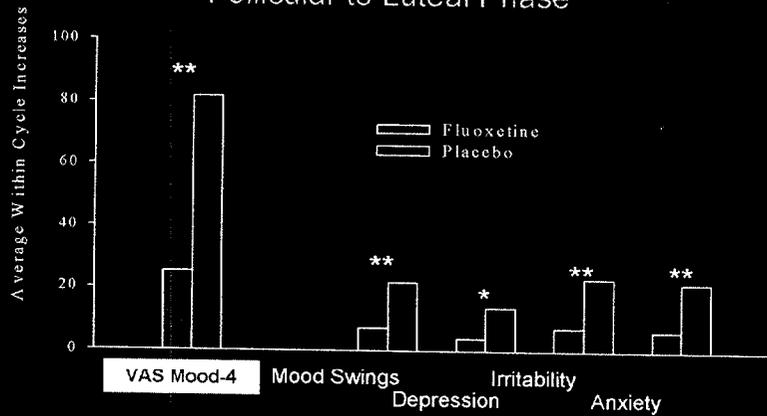
*Completed specified treatment period

RJ-ER-21

Study 2
B1Y-MC-X022

Mood Symptoms

Average of Within-Cycle Increases from Follicular to Luteal Phase



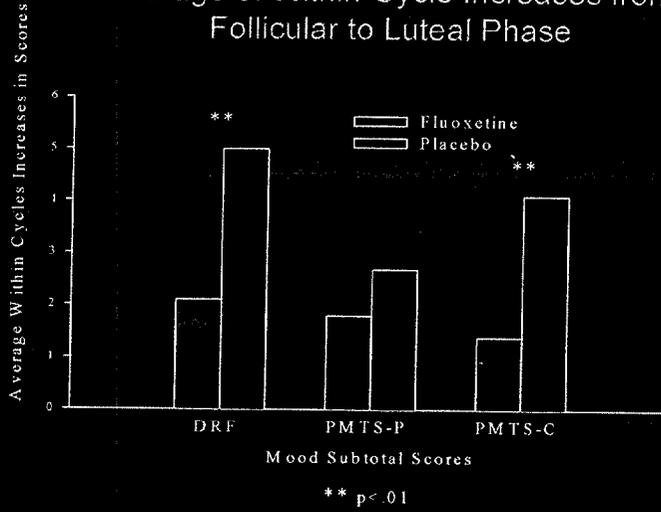
*p<.05
**p<.01

RJ-EL-22

Study 2
B1Y-MC-X022

Mood Symptoms

Average of Within-Cycle Increases from Follicular to Luteal Phase

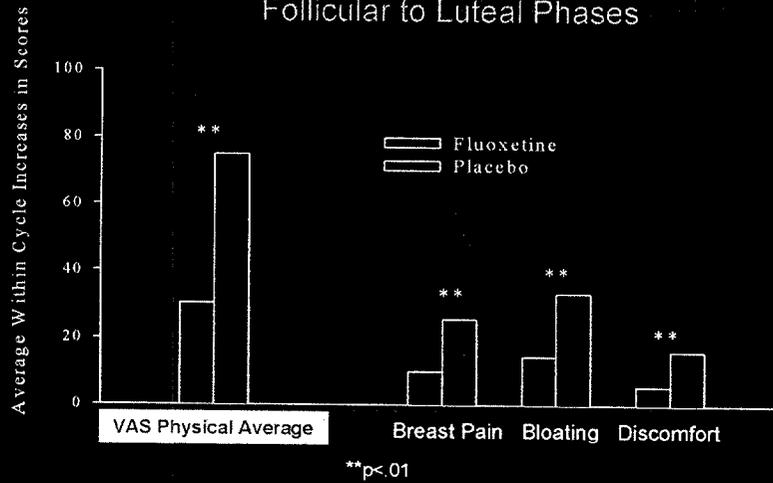


RJ-ER-22

Study 2
B1Y-MC-X022

Physical Symptoms

Average of Within-Cycle Increases from Follicular to Luteal Phases

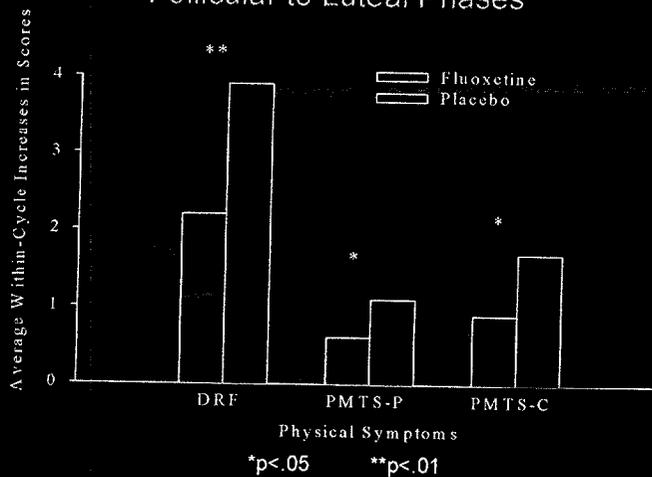


RJ-EL-23

Study 2
B1Y-MC-X022

Physical Symptoms

Average of Within-Cycle Increases from
Follicular to Luteal Phases

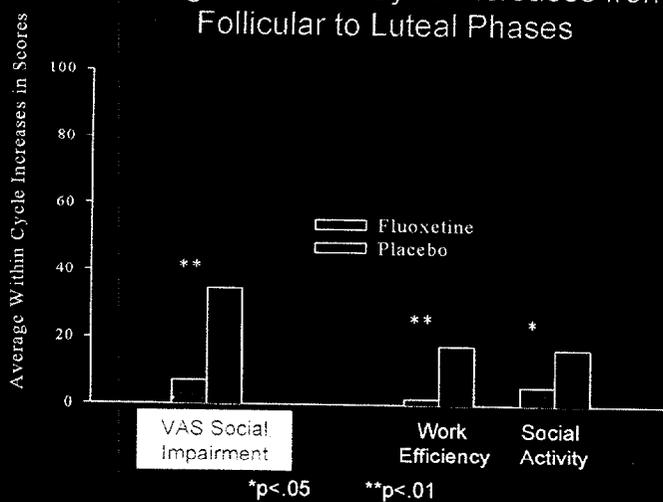


RJ-ER-23

Study 2
B1Y-MC-X022

Social Impairment

Average of Within-Cycle Increases from
Follicular to Luteal Phases

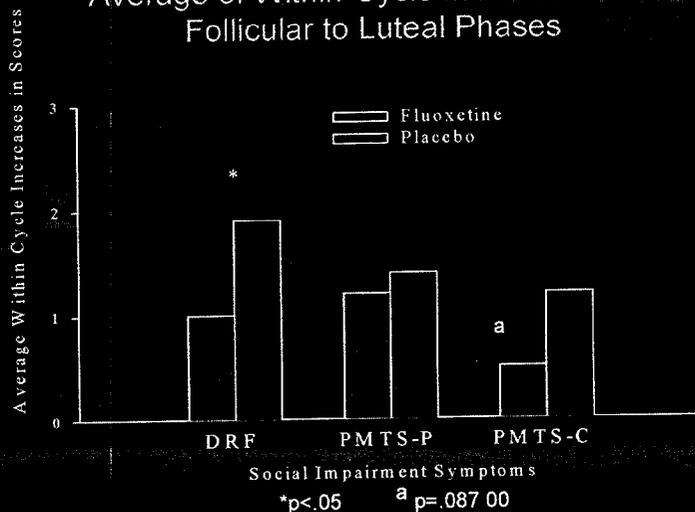


RJ-EL-24

Study 2
B1Y-MC-X022

Social Impairment

Average of Within-Cycle Increases from
Follicular to Luteal Phases

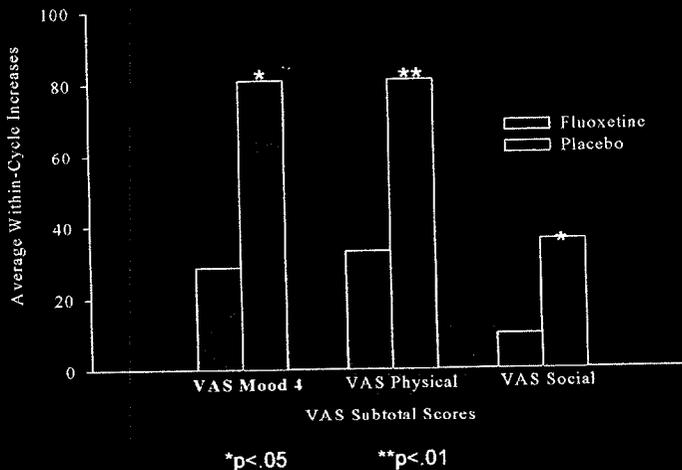


RJ-ER-24

Study 2
B1Y-MC-X022

Efficacy During 1st Treatment Cycle

Within-Cycle Increase

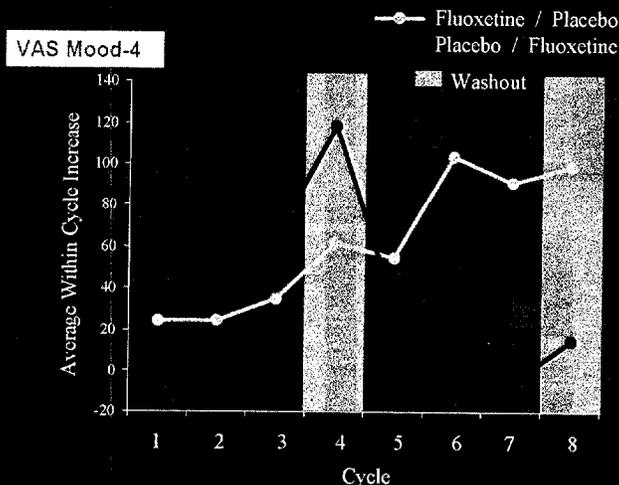


RJ-EL-25

Study 2
B1Y-MC-X022

Course of Treatment Effect

Average of Within-Cycle Increases from Follicular to Luteal Phase



RJ-ER-25

Study 2
B1Y-MC-X022

Mood Symptoms Across Treatment Cycles

Average of Within-Cycle Increases from Follicular to Luteal Phase
B1Y-MC-X022

	Mean Follicular Phase		Within-Cycle Increase from Follicular to Luteal Phase		F v P p-Value	Sequence (Carry-over) p-Value	Trt-by-Seq (Period) p-Value
	N	Mean	SD	Mean			
VAS Mood-4 Subtotal							
Placebo	18	128.5	76.4	81.8	51.5		
Fluoxetine	19	100.7	45.5	25.1	35.0	.002	.989
DRF Mood Subtotal							
Placebo	18	7.4	3.5	5.0	2.8		
Fluoxetine	19	5.8	2.3	2.1	2.3	.002	.263

Note: n = Total number of patients in each treatment group having both the follicular and luteal score for the particular cycle.

Note: p-Values from type III Sums of Squares repeated measures analysis of variance (ANOVA) : PROC MIXED model = treatment, sequence, and interaction.

RJ-EL-26

Study 2

B1Y-MC-X022

Mood Symptoms: First Treatment Cycle

Average Within-Cycle Increases from Follicular to Luteal Phase
B1Y-MC-X022

	N	Mean Follicular Phase		Within-Cycle Increase from Follicular to Luteal Phase		F v P p-Value	Sequence (Carry-over) p-Value	Trt-by-Seq (Period) p-Value
		Mean	SD	Mean	SD			
VAS Mood-4 Subtotal								
Placebo	18	118.5	72.4	80.9	63.77			
Fluoxetine	18	99.7	42.4	28.5	49.48	.034	.096	.391
DRF Mood Subtotal								
Placebo	18	6.9	2.7	4.9	3.27			
Fluoxetine	18	5.4	1.8	2.3	3.12	.039	.012	.303

Note: n = Total number of patients in each treatment group having both the follicular and luteal score for the particular cycle.

Note: p-Values from type III Sums of Squares repeated measures analysis of variance (ANOVA) : PROC MIXED model = treatment, sequence, and interaction.

^a The p-Value for fluoxetine versus placebo was statistically significant when Cycle 1 from Period 1 only was analyzed (6.5 vs 1.6, p<.001)

RJ-ER-26

Study 2

B1Y-MC-X022

Mood Symptoms: First Period Analysis

Average of Within-Cycle Increases Across Treatment Cycles from Follicular to Luteal Phase
B1Y-MC-X022

	N	Follicular Phase		Within-Cycle Increase from Follicular to Luteal Phase		p-Value
		Mean	SD	Mean	SD	
VAS Mood-4 Subtotal						
Placebo	10	131.5	74.2	84.9	54.0	
Fluoxetine	9	104.8	50.4	28.5	29.2	.013
DRF Mood Subtotal						
Placebo	10	7.6	3.4	5.5	2.9	
Fluoxetine	9	6.4	2.3	1.6	1.6	.002
PMTS-P Subtotal						
Placebo	10	1.5	1.4	3.0	2.5	
Fluoxetine	9	0.4	0.6	1.1	1.3	.051
PMTS-C Subtotal						
Placebo	10	1.9	1.5	4.0	2.0	
Fluoxetine	9	1.4	2.0	0.7	1.5	.001

RJ-EL-27

Study 2

B1Y-MC-X022

Physical Symptoms: First Period Analysis

Average of Within-Cycle Increases Across Treatment Cycles from Follicular to Luteal Phase
B1Y-MC-X022

	N	Follicular Phase		Within-Cycle Increase from Follicular to Luteal Phase		p-Value
		Mean	SD	Mean	SD	
VAS Physical Subtotal						
Placebo	10	54.7	31.4	75.3	49.1	.033
Fluoxetine	9	42.7	42.6	32.1	27.6	
DRF Physical Subtotal						
Placebo	10	5.1	1.3	4.3	2.6	.026
Fluoxetine	9	4.8	2.0	2.0	1.3	
PMTS-P Physical Subtotal						
Placebo	10	0.2	0.3	0.9	0.6	.047
Fluoxetine	9	0.1	0.2	0.4	0.6	
PMTS-C Physical Subtotal						
Placebo	10	0.8	0.9	1.6	0.8	.021
Fluoxetine	9	0.6	0.8	0.7	0.7	

RJ-ER-27

Study 2

B1Y-MC-X022

Efficacy Conclusions

- Flexible dosing of fluoxetine 20 - 60 mg/day (mean dose =27 mg) was effective in the treatment of PMDD.
 - statistically significantly superior to placebo with respect to primary objective and to most secondary objectives
 - efficacy was seen in symptom clusters of PMDD for most variables
 - mood
 - physical symptoms
 - social impairment
- Improvement was demonstrated in first treatment cycle.
- Efficacy was maintained for up to 3 months.

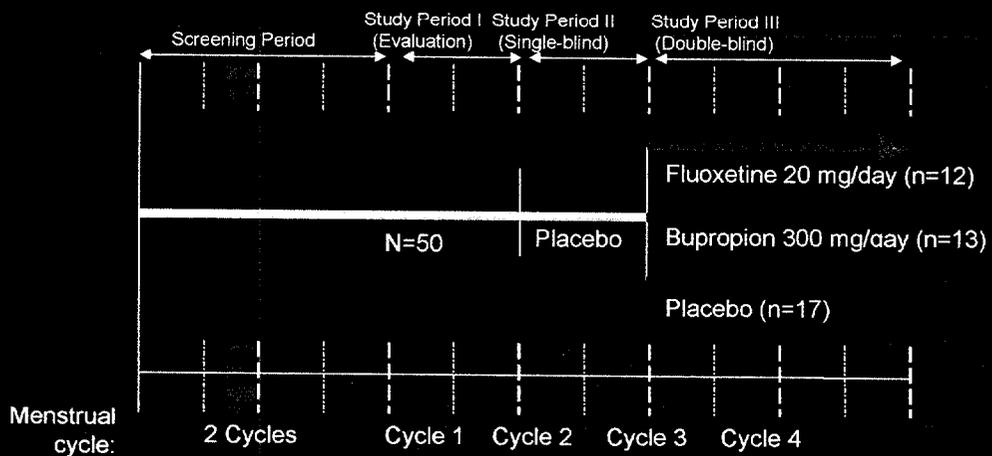
RJ-EL-28

Two well designed, randomized, placebo controlled studies have shown fluoxetine is statistically significantly superior to placebo in the treatment of PMDD.

RJ-ER-28

Study 3
B1Y-MC-X037

Study Design

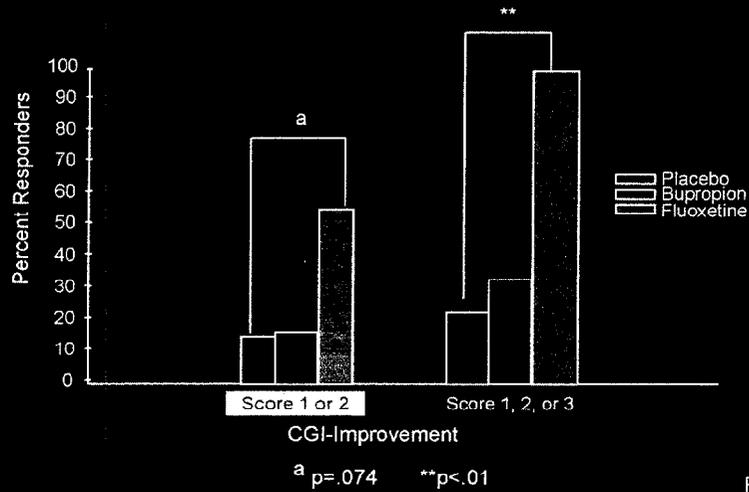


RJ-EL-29

Study 3
B1Y-MC-X037

CGI Responders

Percentage of Responders at Endpoint



RJ-ER-29

Two studies confirmed the efficacy of fluoxetine in PMDD. A third study provided supportive data with respect to the efficacy of fluoxetine in PMDD.

RJ-EL-30

Efficacy of fluoxetine is entirely consistent with other double-blind studies reported in the literature.

RJ-ER-30

Comparison of Efficacy Across Different Studies

- Effect size is a unitless measure that can be compared across different studies and scales. The larger the effect size, the larger the effect of the treatment

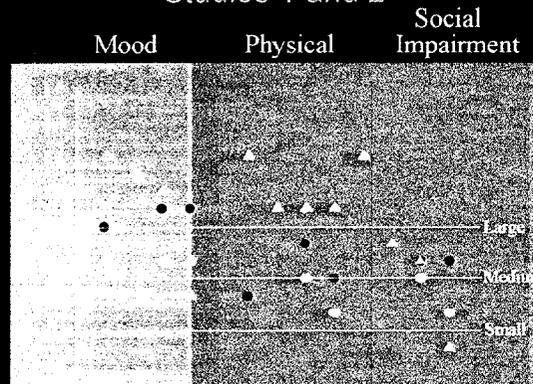
Effect size = $\frac{\text{Mean difference between treatment and placebo}}{\text{Standard Deviation}}$

0.2 = small effect of treatment
0.5 = medium effect of treatment
0.8 = large effect of treatment

RJ-EL-31

Effect Sizes - Mood, Physical and Social Impairment Symptoms

Studies 1 and 2



- Study 1 (20 mg fluoxetine)
- Study 1 (60 mg fluoxetine)
- ▲ Study 2 (20 and 60 mg fluoxetine)

RJ-ER-31

Overall Efficacy Conclusions

- PMDD studies were randomized, double-blind, placebo controlled.
- Study populations were appropriate and consistent.
- Outcome measures were appropriate to assess change in PMDD symptoms.

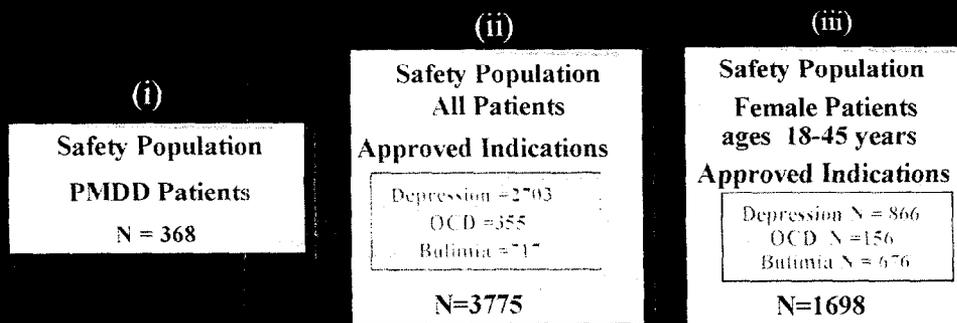
RJ-EL-32

Overall Efficacy Conclusions

- PMDD studies demonstrated the efficacy of fluoxetine 20-60 mg daily in treating the symptoms of PMDD.
- Fluoxetine 20 mg and 60 mg are similarly effective in treating the symptoms of PMDD for up to six months. There was evidence for numerical superiority with 60 mg.
- The efficacy of fluoxetine was evident during the first treatment cycle and was maintained for up to 6 months.

RJ-ER-32

The Safety Databases



RJ-SL-33

Adverse Event Assessments PMDD Safety Population

- Study 1
The largest dataset with assessable treatment-emergent adverse events
 - severity
 - dose-related adverse events
- Studies 2 and 3
These adverse event datasets were collected differently than in Study 1 and were not assessable as treatment emergent

RJ-SR-33

Duration of Study Drug Exposure PMDD Safety Population

Duration (Days)	Fluoxetine			Fluoxetine All Doses N=241	Placebo N=143
	20-60mg* N=19	20mg N=116	60mg N=106		
Up to 60	1 (5.3)	29 (24.9)	36 (34.0)	66 (27.4)	38 (26.6)
61-150	18 (94.7)	22 (19.0)	20 (18.9)	60 (24.9)	58 (40.6)
151-220	0 (0)	65 (56.1)	50 (47.2)	115 (47.8)	47 (32.9)
Total days of exposure	1539	14,247	11,431	27,217	14,866

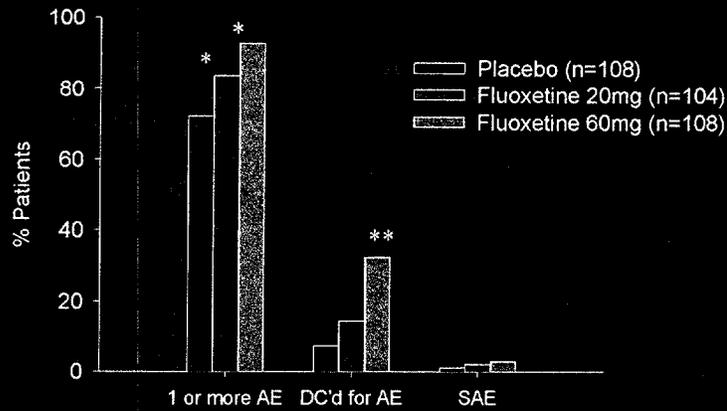
Note: Exposure data for Study B1Y-MC-X022 are included in the titration column, the all fluoxetine doses column, and the placebo column.

*Titrated dosing

RJ-SL-34

Study 1
B1Y-MC-C019

Safety Overview



*p<.05 vs. placebo

**p<.01 vs. placebo and fluoxetine 20mg

RJ-SR-34

Study 1
B1Y-MC-C019

Most Common Treatment-Emergent Adverse Events

Adverse Event ^a	Placebo (N=108)	Fluoxetine 20 mg (N=104)	Fluoxetine 60 mg (N=108)
	%	%	%
Rhinitis	17	23	18
Nausea	7	13	29**
Headache	9	13	18
Asthenia	3	12*	12*
Pharyngitis	6	10	9
Insomnia	7	9	26**
Pain	7	9	10

^aIncluded are events reported by at least 10% of patients taking fluoxetine except flu syndrome which had an incidence on placebo \geq fluoxetine 20 mg and 60 mg

* p<.05 compared with placebo

**p<.05 compared with fluoxetine 20 mg and with placebo

RJ-SL-35

Study 1
B1Y-MC-C019

Most Common Treatment-Emergent Adverse Events

Adverse Event ^a	Placebo	Fluoxetine 20 mg	Fluoxetine 60 mg
	(N=108) %	(N=104) %	(N=108) %
Dizziness	4	7	14*
Diarrhea	7	6	12
Somnolence	4	5	12*
Anorexia	3	4	13**
Dyspepsia	6	3	10
Tremor	1	2	13**

^aIncluded are events reported by at least 10% of patients taking fluoxetine except flu syndrome which had an incidence on placebo \geq fluoxetine 20 mg and 60 mg

* $p < .05$ compared with placebo

** $p < .05$ compared with fluoxetine 20 mg and with placebo

RJ-SR-35

Most Common Treatment-Emergent Adverse Events in 3 Placebo Controlled Clinical Trial Databases

Adverse Event ^a	% of Fluoxetine Patients Reporting Event		
	Study 1 20mg & 60mg (N=212)	Approved Indications Database (N=2444)	Approved Indications Females 18-45 (N=1145)
Nausea	21	23	27
Rhinitis	20	13	16
Insomnia	17	20	24
Headache	15	21	24
Asthenia	12	12	14
Dizziness	10	10	11

^aIncluded are events reported by at least 10% of patients taking fluoxetine in any of the 3 databases except flu syndrome which had an incidence on placebo \geq fluoxetine in the Study 1 database.

RJ-SL-36

Most Common Treatment-Emergent Adverse Events in 3 Placebo Controlled Clinical Trial Databases

Adverse Event ^a	% of Fluoxetine Patients Reporting Event		
	Study 1 20mg & 60mg (N=212)	Approved Indications Database (N=2444)	Approved Indications Females 18-45 (N=1145)
Diarrhea	9	12	10
Anorexia	8	11	11
Nervousness	8	13	14
Somnolence	8	13	13
Anxiety	7	13	13
Tremor	8	10	12
Dry mouth	5	10	11

^aIncluded are events reported by at least 10% of patients taking fluoxetine in any of the 3 databases except flu syndrome which had an incidence on placebo \geq fluoxetine in the Study 1 database.

RJ-SR-36

Study 1
B1Y-MC-C019

Most Common Adverse Events Leading to Discontinuation

Event ^a	Placebo (N=108)	Fluoxetine 20 mg (N=104)	Fluoxetine 60 mg (N=108)
	%	%	%
Nausea	0.9	2.9	5.6
Unintended Pregnancy	0.9	1.9	1.9
Headache	0	1.9	1.9
Somnolence	0	1.9	1.9
Nervousness	0.9	1.9	0
Insomnia	0.9	1.0	3.7
Anxiety	1.9	0	5.6*
Confusion	0	0	2.8
Dyspepsia	0	0	2.8

^aIncluded are events that occurred in more than 2 fluoxetine-treated patients.

*p < .05 compared with fluoxetine 20 mg

RJ-SL-37

Study 2&3
B1Y-MC-X022
B1Y-MC-X037

Adverse Events Leading to Discontinuation

Study 2	Placebo	Fluoxetine
	N=18 n (%)	N=19 n (%)
Headache	0 (0)	1 (5)
Depression	1 (6)	0 (0)

Study 3	Placebo	Fluoxetine
	N=17 n (%)	N=12 n (%)
Anxiety	0 (0)	1 (8)
Headache	0 (0)	1 (8)
Other*	1 (6)	0 (0)

* One placebo treated patient discontinued for all of the following reasons: asthenia, breast enlargement, breast pain, depersonalization, hallucinations, hostility, increased appetite, mucous membrane disorder, tremor

RJ-SR-37

Safety Conclusions

- Fluoxetine has been used in more than 39 million patients worldwide
- A very large safety database exists for fluoxetine
 - PMDD patients
 - Approved indications database
 - Post marketing surveillance

RJ-SL-38

Safety Conclusions

- Fluoxetine in patients with PMDD is safe and well tolerated, and clinically comparable to the known profile of fluoxetine
- Fluoxetine 20 mg appears to be better tolerated than fluoxetine 60 mg
- Fluoxetine 20 mg daily is safe and well tolerated

RJ-SR-38

Dosing Recommendations

- Fluoxetine 20 and 60 mg daily are similarly effective for patients with PMDD
- While fluoxetine 20-60 mg daily is safe for patients with PMDD, 20 mg daily is better tolerated than 60 mg daily

RJ-SL-39

Dosing Recommendations

- The risk-benefit ratio supports the dose of 20 mg daily for patients with PMDD
- Some patients may benefit by increasing the dose to 60 mg daily

RJ-SR-39

Other Considerations Use with Oral Contraceptives

RJ-SL-40

Potential for Interactions Between Oral Contraceptives and Fluoxetine

- Fluoxetine, like TCAs and other SSRIs, is primarily metabolized by the cytochrome P450 2D6 enzyme system
- OCs are primarily metabolized by the cytochrome P450 3A4 enzyme system; interactions with OCs are most commonly ascribed to drugs that induce the drug-metabolizing enzyme P450 CYP3A¹

¹C. Fattore et al, 1999

RJ-SL-41

Oral Contraceptives and Fluoxetine Efficacy

- Many of the women in the approved indications database were also taking OCs.
- In the approved indications database, females 18-45 (depression studies only), there is no clinical evidence that concomitant use of OCs augments or lessens the efficacy of fluoxetine.

RJ-SL-42

Oral Contraceptives and Fluoxetine Safety

- During clinical trials for fluoxetine, no drug interactions were noted for patients who were taking oral contraceptives.
- Extensive postmarketing surveillance has not shown any evidence for interactions between fluoxetine and oral contraceptives.
- A search of the literature yielded no case reports of such an interaction.

Overall Conclusions

Premenstrual dysphoric disorder (PMDD):

- is a distinct clinical entity, and can be differentiated from depression and anxiety disorders
- is a severe form of premenstrual syndrome (PMS) that causes impairment of functioning
- is inadequately recognized and treated

RJ-L-1

Overall Conclusions

Fluoxetine in PMDD:

- The three randomized double-blind, controlled studies presented support the efficacy of fluoxetine in PMDD
- Results presented are consistent with other published literature on fluoxetine in the treatment of PMDD
- Fluoxetine was safe and well tolerated at the recommended dose
- The dosing recommendation is appropriately supported by the data