



Gabapentin for Treatment of Moderate to Severe Vasomotor Symptoms due to Menopause

Advisory Committee for Reproductive Health Drugs

March 4, 2013

Hylton V. Joffe, M.D., M.M.Sc.

Director

Division of Reproductive and Urologic Products

U.S. Food and Drug Administration

Overview

- Welcome to our newest committee members
- Why bring gabapentin to advisory committee?
- FDA's approach to developing treatments for vasomotor symptoms due to menopause
- Questions for the committee

New Committee Members

- **Toby Chai, M.D.**
 - Vice Chair of Research
 - Co-Director, Female Pelvic Medicine and Reconstructive Surgery Program
 - Department of Urology
 - Yale School of Medicine

New Committee Members

- **Kathryn M. Curtis, Ph.D.**
 - Women's Health and Fertility Branch
 - Division of Reproductive Health
 - Centers for Disease Control and Prevention

Why Discuss Gabapentin?

- Gabapentin is approved for other indications
- Would potentially be the first approved non-hormonal treatment for vasomotor symptoms
- Did not meet all pre-specified co-primary efficacy endpoints

2003 Draft Guidance

- *Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation*
- Consistently applied to hormonal and non-hormonal products

Selected Recommendations in the 2003 Draft Guidance

- Randomized, double-blind, 12-week trial(s)
- ≥ 7 -8 moderate to severe hot flushes per day (or 50-60 per week) at baseline
- Four co-primary efficacy endpoints

Four Co-Primary Efficacy Endpoints

Moderate to severe vasomotor symptoms

- Mean change in:
 - Frequency from baseline to Week 4
 - Frequency from baseline to Week 12
 - Severity from baseline to Week 4
 - Severity from baseline to Week 12

Severity Scoring System

- Mild (1):** Sensation of heat without sweating

- Moderate (2):** Sensation of heat with sweating
Able to continue activity

- Severe (3):** Sensation of heat with sweating
Causes cessation of activity

Severity Scoring System

At Baseline and at Weeks 4 and 12:

$(2 \times \text{No. Moderate}) + (3 \times \text{No. Severe})$

Total Number of Moderate + Severe

Clinical Meaningfulness

- Is the reduction in frequency of moderate to severe hot flushes relative to placebo clinically meaningful?
- Pre-specified, supportive analysis
- Appropriate when there is a small (<2 per day) but statistically significant treatment effect
- Not evaluated by FDA (gabapentin failed to show a statistically significant effect on frequency at Wk 12)

Persistence of Benefit

- One study assessed moderate to severe hot flush frequency at 24 weeks
- Pre-specified, supportive analysis
- Not evaluated by FDA (gabapentin failed to show a statistically significant effect on frequency at Wk 12)

Question 1 for the Committee

VOTE: Based on the pre-specified analyses, is there sufficient evidence to conclude that gabapentin is effective in treating moderate to severe vasomotor symptoms (VMS) due to menopause?

Please provide a rationale for your vote and, if applicable, any additional recommendations.

Question 2 for the Committee

VOTE: Is the overall risk/benefit profile of gabapentin acceptable to support approval of this product for the proposed indication?

Please provide a rationale for your vote and, if applicable, any additional recommendations.



Gabapentin for Treatment of Vasomotor Symptoms due to Menopause

March 4, 2013

**Vaishali Popat, M.D., M.P.H. – Clinical Reviewer
Division of Reproductive and Urologic Products**

Outline of Presentation

- Introduction
- Regulatory History
- Overview of Phase 2 and 3 studies
- Efficacy Results (FDA Statistician, Dr. Fang)
- Safety

Introduction

- Dosing Regimen: titrated to an 1800 mg daily dose, taken orally, 600 mg with the morning meal and 1200 mg with the evening meal.
- Drug Class: Antiepileptic
- Indication Sought: Treatment of moderate to severe vasomotor symptoms (VMS) due to menopause
- One phase 2 dose-finding study (56)
- Three phase 3 studies (58, 59 & 64)
- Not approved in any country for treatment of VMS

History

- First marketed in the US in 1993 as Neurontin
- Approved indications for Neurontin
 - Epilepsy: adjunctive therapy in the treatment of partial seizures
 - Postherpetic neuralgia in adults
- Gralise (current formulation), approved in 2011
 - Postherpetic neuralgia
- Gabapentin enacarbil, was approved in 2011 under the brand name Horizant
 - Restless leg syndrome
 - Postherpetic neuralgia.
- Dosing: 900-1800 mg

Regulatory History

- Applicant initially planned to submit an NDA based on Studies 58 and 59.
- The studies failed to meet all of the requisite efficacy endpoints.
- Because the completed trials showed a placebo-corrected reduction of VMS frequency that was < 2 hot flushes per day, the Applicant was asked to demonstrate the clinical meaningfulness of the change in VMS frequency in the new trial.
- Asked for evaluation of suicidality in the new trial

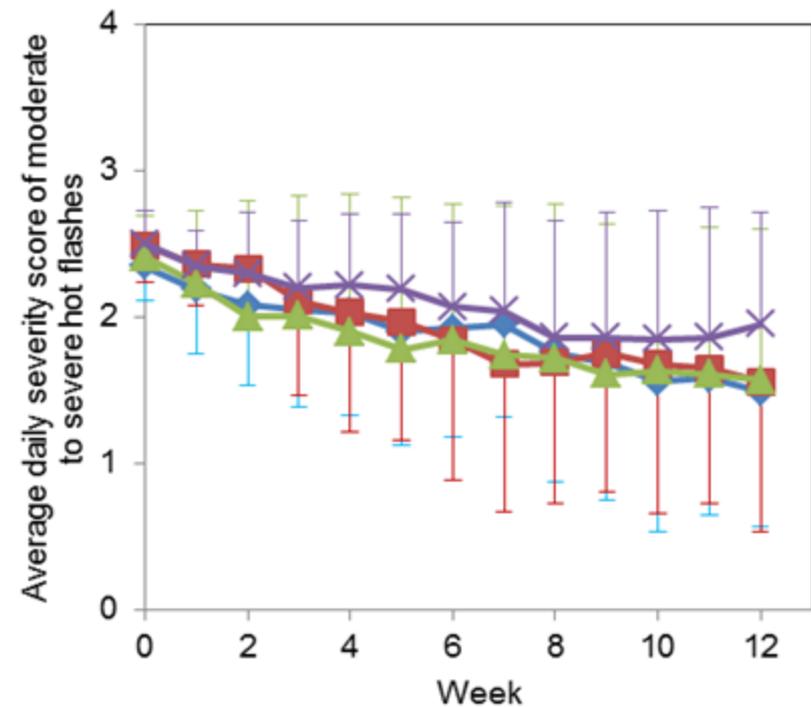
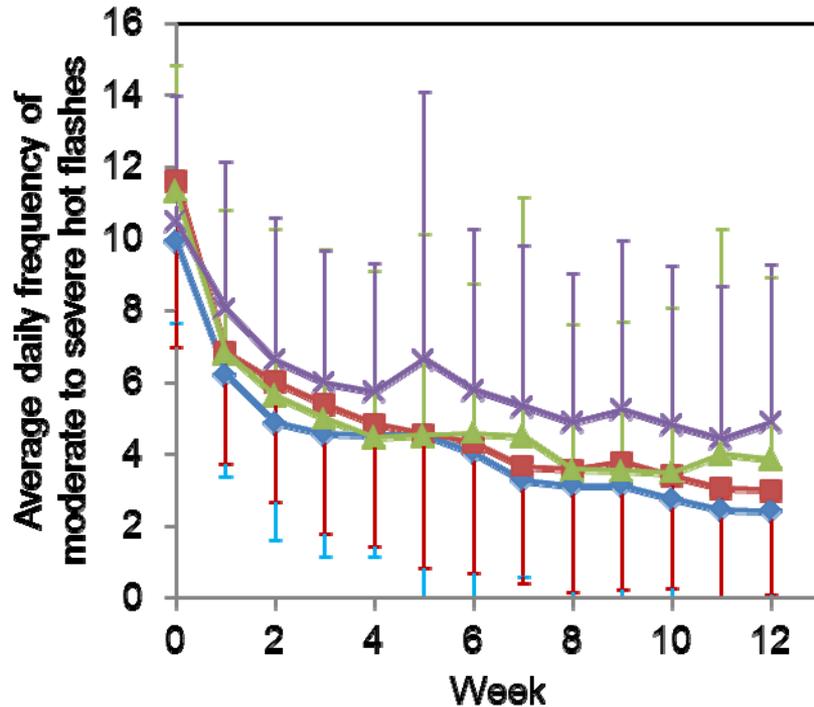
Study 56: Phase 2 design

- N=124
- 2 periods (1 wk titration, 5 wk stable dose)

Group	Period 1 6 weeks with low dose	Period 2 6 weeks with high dose
A	600 mg PM	600 mg AM + 1200 mg PM
B	600 mg AM + 600 mg PM	600 mg AM + 1800 mg PM
C	1200 mg PM	1200 mg AM + 1800 mg PM
	Placebo	Placebo

- Under fed condition with breakfast and/or dinner

Phase 2 Study Results



- ◆ A (600 mg PM at Week 6; 600 mg AM + 1200 mg PM at Week 12)
- B (600 mg AM + 600 mg PM at Week 6; 600 mg AM + 1800 mg PM at Week 12)
- ▲ C (1200 mg PM at Week 6; 1200 mg AM + 1800 mg PM at Week 12)
- ✕ placebo



Phase 3 Studies

Study (Sites)	Phase and Design	# of Subjects per Arm	Treatment Period	Follow-up Period
58 USA (47)	Randomized, Double-blind	Total: 541 1200 mg : 178 1800 mg: 182 Placebo: 181	25 weeks (one week titration, and 24 weeks stable treatment)	1 week
59 USA (44)	Randomized, Double-blind	Total: 565 1200 mg : 192 1800 mg: 190 Placebo: 183	13 weeks (one week titration, and 12 weeks stable treatment)	1 week
64 USA (67)	Randomized, Double-blind	Total: 600 1800 mg: 302 Placebo: 298	24 weeks (one week titration, and 23 weeks stable treatment)	4 weeks 8

Phase 3 Trial Design

- Electronic diary: Mild, moderate and severe hot flushes were defined clearly for subjects
- Trial 58 and 59 sample size:
 - Provided 90% power to detect a difference of 2 episodes in the frequency.
- Trial 64 sample size:
 - Provided 98% power to detect a difference of 1.3 episodes in frequency and at least 94% power to detect a difference of 0.2 in severity score .
- Studies 58 and 59 included three arms: significance testing was based on a two-sided alpha of 0.025
- In Study 64 only a single dose compared to placebo, so the alpha was set at 0.05

Inclusion Criteria

- Postmenopausal women 18-70 years old with ≥ 7 moderate to severe hot flushes per day (≥ 50 per week) during the previous 30 days
- If on antidepressant therapy (including St. John's Wort), no change in dosage during the previous month
- No BMI limit

Exclusion Criteria

- Malignancies within the past 2 years (other than basal cell carcinoma).
- Estimated/calculated GFR < 60 mL/min
- Study 64 only: Women with suicidal ideation at screening per the Columbia-Suicide Severity Rating Scale (C-SSRS)



FDA Efficacy Evaluation Gabapentin 1800 mg

March 4, 2013

**Xin Fang, Ph.D., Statistical Reviewer
Division of Biometrics III, Office of Biostatistics**

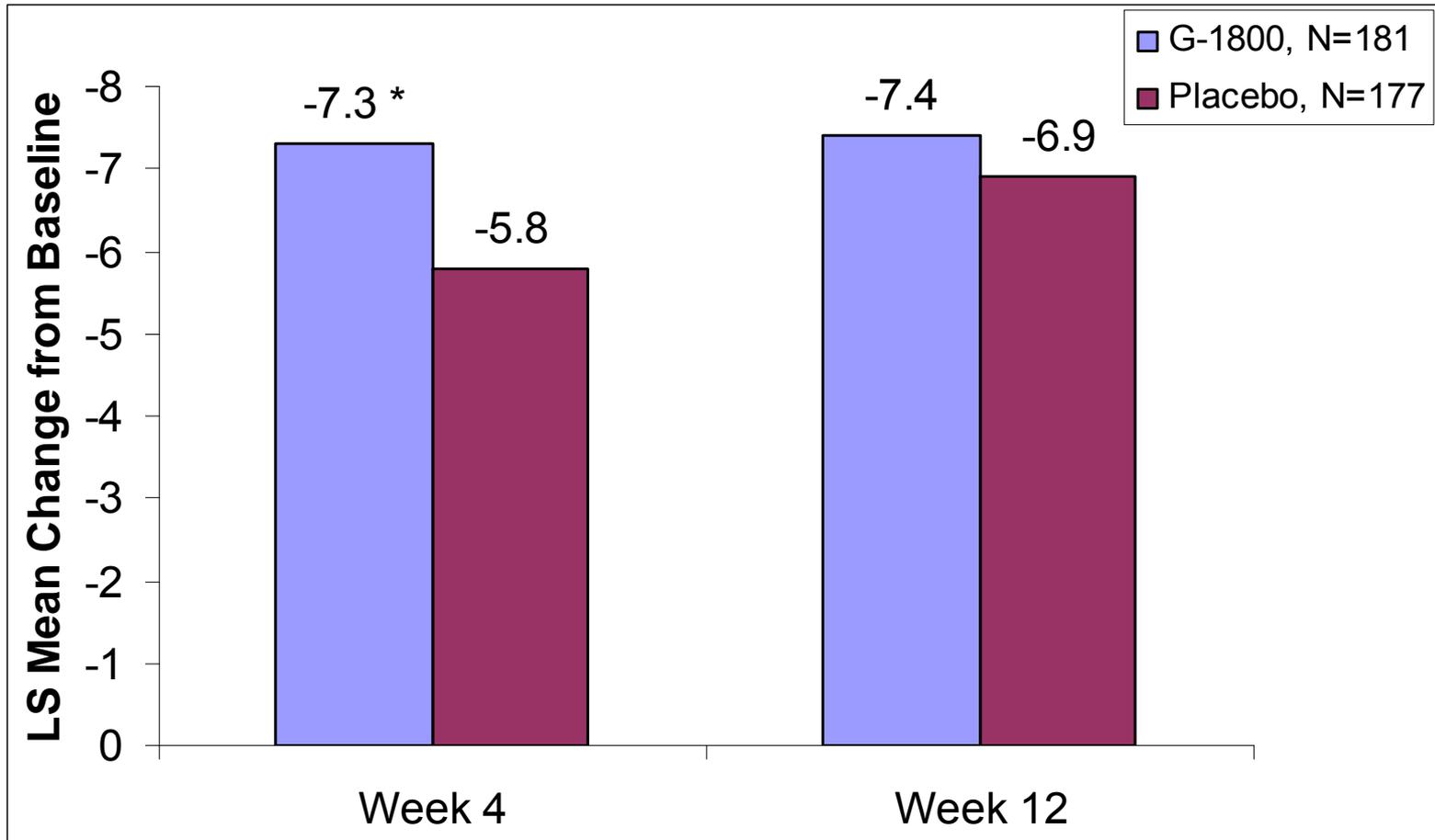
Efficacy Endpoints

- Four Co-Primary Endpoints
 - Change from baseline in daily frequency and severity score at Week 4 and Week 12
- Supportive Endpoints
 - Demonstration that treatment effect is clinically meaningful to women (if placebo-subtracted reduction in frequency is < 2 hot flushes per day)
 - Typically a responder analysis
 - Persistence of treatment difference at Week 24

Pre-Specified Statistical Methods

- Co-primary Endpoints
 - Studies 58 and 59: ANCOVA, $\alpha=0.025$ for each of 2 doses
 - Study 64: van Elteren test (stratified by site), $\alpha=0.05$
- Supportive Analysis
 - Discriminant analysis (Study 64)
 - ANCOVA for persistence in treatment difference at Week 24 (Studies 58, 64)
- We agreed with these pre-specified analyses.

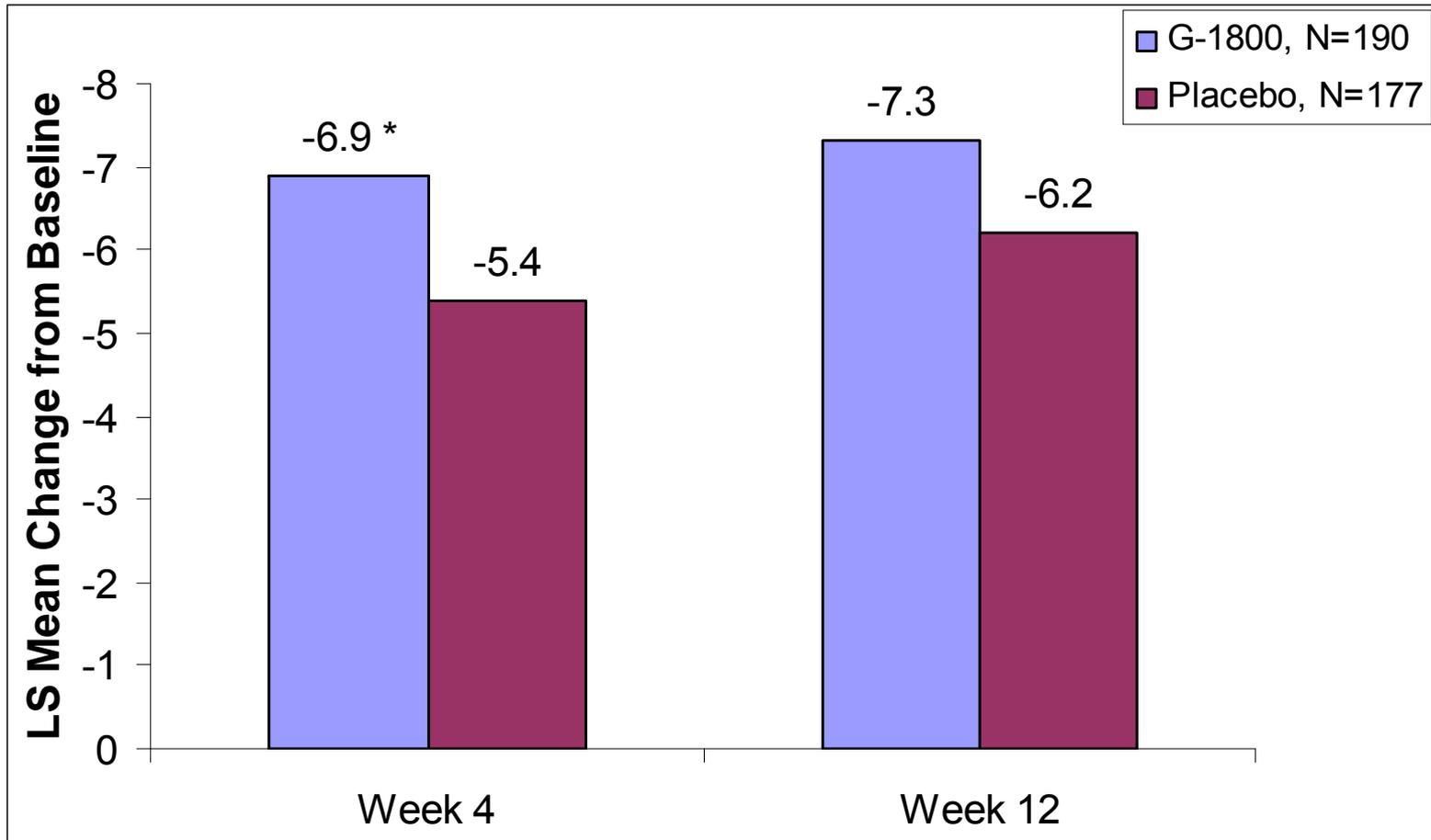
Change in Frequency: Study 58



Baseline Mean: 11.1 (G-1800), 11.3 (Placebo)

* Significant Treatment Difference at week 4, alpha of 0.025

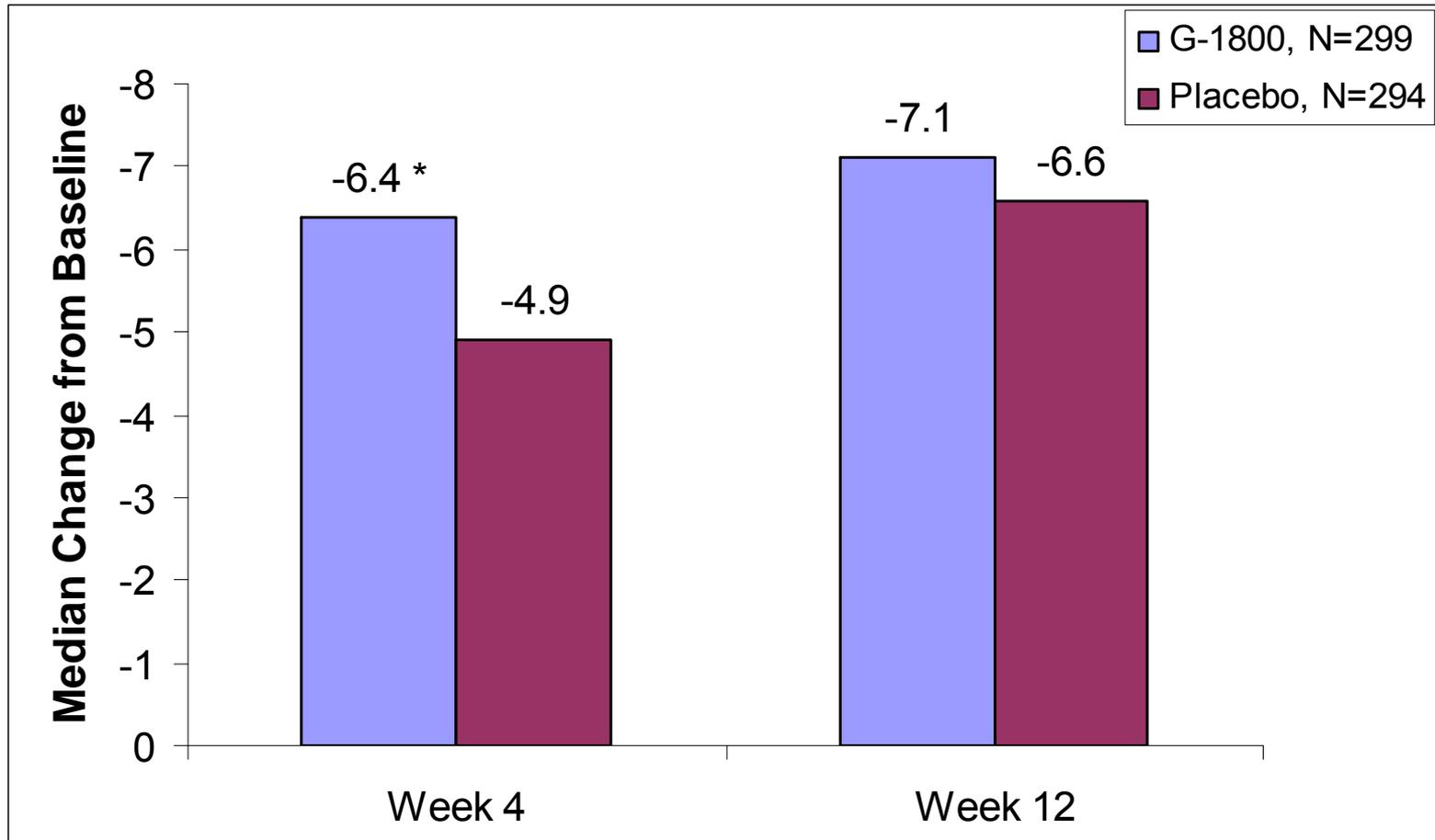
Change in Frequency: Study 59



Baseline Mean: 11.2 (G-1800), 11.2 (Placebo)

* Significant at week 4, alpha of 0.025

Change in Frequency: Study 64



Baseline Median: 10.5 (G-1800), 10.4 (Placebo)

* Significant at week 4, alpha of 0.05

Primary Efficacy Results

Parameter	Week	Treatment Difference in Change from Baseline (p-Value)		
		Study 58	Study 59	Study 64
Frequency	4	-1.5 (<.001)	-1.5 (0.004)	-1.6 (<.001)
	12	-0.5 (0.198)	-1.1 (0.028) ^{\$}	-0.6 (0.100)
Severity	4	-0.3 (<.001)	-0.3 (<.001)	-0.1 (<.001)
	12	-0.2 (0.047) ^{\$}	-0.3 (0.003)	-0.2 (<.001)

^{\$} Not significant at Alpha of 0.025

Summary of Efficacy

Study	Efficacy Analyses	Results
58 59 64	Change from Baseline in Frequency	<ul style="list-style-type: none"> ▪ Statistically significant at Weeks 4 ▪ NOT statistically significant at Week 12 in all 3 studies
	Change from Baseline in Severity	<ul style="list-style-type: none"> ▪ Statistically significant at Week 4 ▪ Statistically significant at Week 12 in Studies 59 and 64
64	Clinical Meaningfulness	<ul style="list-style-type: none"> ▪ Not Applicable due to failure to meet the primary efficacy endpoints
58 64	Persistence of Efficacy at Week 24	



FDA Safety Evaluation Gabapentin 1800 mg

March 4, 2013

**Vaishali Popat, M.D., M.P.H. – Clinical Reviewer
Division of Reproductive and Urological Products**

Safety: Labeled Safety Issues

- Gralise (same formulation): Warnings
 - Risk of suicidality (class labeling for antiepileptic drugs)
 - Need for gradual withdrawal over a week or longer
 - Tumorigenic potential as demonstrated in nonclinical studies; lack of human data on the incidence of new tumors or the worsening/recurrence of existing tumors
 - Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and multiorgan hypersensitivity
- Horizant (prodrug): Warnings
 - Driving impairment: Warn patients not to drive until they have gained sufficient experience to assess whether it will impair their ability to drive.
 - Somnolence/sedation and dizziness: May impair the patient's ability to operate complex machinery.

Exposure

- Safety population: All subjects who took at least one dose of study drug
- A total of 1,686 subjects received at least one dose of study drug in the phase 3 trials,
 - 360 received gabapentin 1200 mg/day,
 - 671 received gabapentin 1800 mg/day,
 - 655 received placebo.
- Longest trial duration was 6 months

Overview of Safety

Category	Gabapentin 1800 N=671 n, (%)	Placebo N=655 n, (%)
Any Treatment Emergent Adverse Event (AE)	449 (66.9)	348 (53.1)
Deaths	1 (0.15)	1 (0.15)
Serious Adverse Events (SAE)	12 (1.8)	13 (2.0)
Discontinuations due to AEs	92 (13.7)	49 (7.5)
Malignancy SAE	3 (0.4)	0
Suicidality (Study 64 only)	6 (2.0)	2 (0.7)
Withdrawal-emergent AE		
Study 58 and 59	49 (13.2)	22 (6.1)
Study 64	35 (11.7)	23 (7.8)

Common Adverse Events

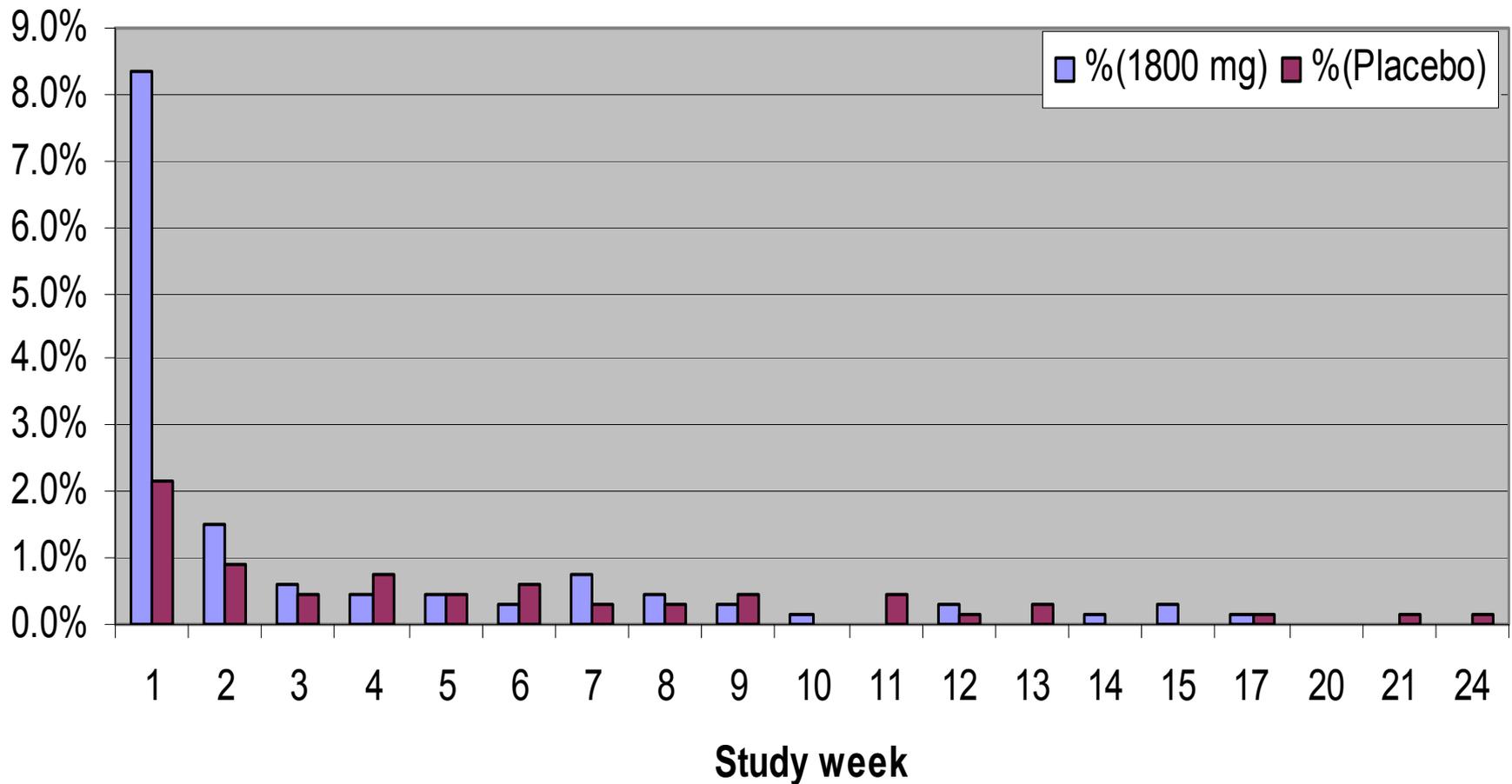
Combined terms	Gabapentin 1800 (N = 671)		Placebo (N = 655)	
	n	%	n	%
Any AE	449	66.9	348	53.1
Dizziness/ vertigo	118	17.5	22	3.4
Somnolence/sedation	78	11.6	19	2.9
Nausea/vomiting	58	8.7	28	4.3
Dry mouth	20	3	10	1.5
Disorientation	17	2.5	0	0
Edema peripheral	9	1.3	3	0.5
Contusion	8	1.2	3	0.5
Balance disorder	7	1	1	0.2
Disturbance in attention	7	1	2	0.3
Fall	6	0.9	1	0.2
Amnesia	5	0.8	0	0

†

Adverse Events Leading to Study Drug Discontinuation

AE	Gabapentin 1800 mg N=671		Placebo N=655	
	n	%	n	%
Any	89	13.3	51	7.8
Dizziness/vertigo	21	3.1	2	0.3
Somnolence/sedation	16	2.3	4	0.6
Headache	6	0.9	3	0.5
Nausea	6	0.9	1	0.2
Lethargy	3	0.4	0	0
Disorientation	3	0.4	0	0
Myalgia	3	0.4	0	0

Adverse Event Leading to Discontinuation by Treatment Group over Time



Deaths

- Two subjects died during the phase 3 program, one on gabapentin 1800 mg in Study 59 and one on placebo in Study 64
 - A 49 year-old female randomized to the gabapentin 1800 mg treatment group in Study 59 died due to a fentanyl overdose on Study Day 43.
 - The toxicology screen showed detectable levels of methadone, hydrocodone, bupropion, and citalopram in addition to fentanyl.
 - While the investigator determined this to be not related, the possibility of suicide cannot be ruled out based on the information provided.

Malignancy

Treatment	Serious Adverse Event	Details
Gabapentin 1800 mg	Chronic lymphocytic leukemia	59 year old woman took gabapentin for about one month before she reported a diagnosis of chronic lymphocytic leukemia.
Gabapentin 1800 mg	Malignant Lung neoplasm	50 year old woman hospitalized for lung cancer 3.5 months after starting gabapentin. The Applicant reports that no further information can be obtained for this event.
Gabapentin 1800 mg	Breast cancer	58 year old woman was diagnosed with breast cancer two months after starting gabapentin. The pathology report revealed invasive ductal carcinoma, Black's Modified Nuclear Grade 1.
Gabapentin 1200 mg	Breast cancer	46 year old woman was diagnosed with right breast cancer after 5 months on gabapentin. A breast core biopsy showed an invasive, 2.3 cm ductal carcinoma, no regional lymph node metastasis.
Gabapentin 1200 mg	Ovarian cancer	63 year old woman received gabapentin for two weeks before she underwent a CT of the abdomen and pelvis which revealed ovarian cancer stage 3.

Suicidality (Study 64)

TX Grp	Visit	Items Endorsed (see the key)		C-SSRS Item Key:
Gabapentin	Week 4	SI-1		SI-1 = wish to be dead.
Gabapentin	Week 12	SI-2, SI-3		SI-2= non-specific active suicidal thoughts.
Gabapentin	Week 12	SI-1		SI-3 = active suicidal thoughts by any method, no specific plan or intent.
Gabapentin	Week 24/ET	SI-1		SI-4 = active suicidal thoughts with some intent to act but no specific plan.
Gabapentin	Week 28	SI-1, SI-2, SI-3, SI-4		SB5 = preparatory acts or behavior.
Gabapentin	Week 28	SB-6		SB6 = suicidal behavior present during the rating period.
Placebo	Week 24/ET	SI-1, SI-4, SB5		
Placebo	Week 24/ET	SI-1		

Suicidality

- An additional subject on gabapentin 1200 mg (Study 59) hospitalized as an apparent attempted suicide after being found unresponsive on Study Day 53
- Medical history included depression; concomitant meds included Lyrica (pregabalin) and Cymbalta.
- Subject took an overdose of multiple drugs including benzodiazepines, a tricyclic antidepressant, Seroquel and Percocet
- Division of Psychiatry Products was consulted
 - Recommended continued use of class labeling for suicidality

Summary

- Efficacy:
 - None of the 3 Phase 3 studies met the frequency endpoint of at Week 12
 - Clinical meaningfulness was not considered
- Safety:
 - Higher number of subjects with common adverse events as well as AE leading to discontinuation in the gabapentin group (dizziness, somnolence and disorientation)
 - Higher number of subjects with withdrawal-emergent AEs in the gabapentin group
 - Higher number of subjects with suicidal ideation/behavior in the gabapentin group