Low-Dose Mesylate Salt of Paroxetine (LDMP)
for Vasomotor Symptoms Associated with Menopause

Reproductive Health Drugs Advisory Committee

March 4, 2013

Introduction

Joel S. Lippman, MD, MPH, FACOG

Chief Medical Officer
Noven Pharmaceuticals, Inc.

Presentation Agenda

Introduction	**Joel S. Lippman, MD, MPH, FACOG** Chief Medical Officer Noven Pharmaceuticals, Inc.
Patient Burden and Treatment	**David Portman, MD** Portman Obstetrics and Gynecology Associates Director, Columbus Center for Women's Health Research Clinical Faculty, Ohio State University College of Medicine
LDMP Efficacy	**Joel Lippman, MD**
Statistical Evaluations	**Brent Blumenstein, PhD** Biostatistician Trial Architecture Consulting
LDMP Safety	**Joel Lippman, MD**
Risk Management	**S. Elizabeth Lucini, PharmD** Sr. Director, Regulatory Affairs & Pharmacovigilance Noven Pharmaceuticals, Inc.
Clinical Perspective	**David Portman, MD**

Low-Dose Mesylate Salt of Paroxetine (LDMP)

- Paroxetine mesylate 7.5 mg capsules
  - For moderate to severe vasomotor symptoms (VMS) associated with menopause
  - Selective serotonin reuptake inhibitor (SSRI)
  - Mechanism of action in VMS thought to be related to potentiation of CNS neurotransmitters which impact regulation of body temperature
- Dosed orally, once daily at bedtime
  - Substantially lower than approved doses for psychiatric use
  - No up or down titration

Patient Burden and Treatment

David Portman, MD

Portman Obstetrics and Gynecology Associates
Director, Columbus Center for Women's Health Research
Clinical Faculty, Ohio State University College of Medicine

Vasomotor Symptoms – Patient Burden

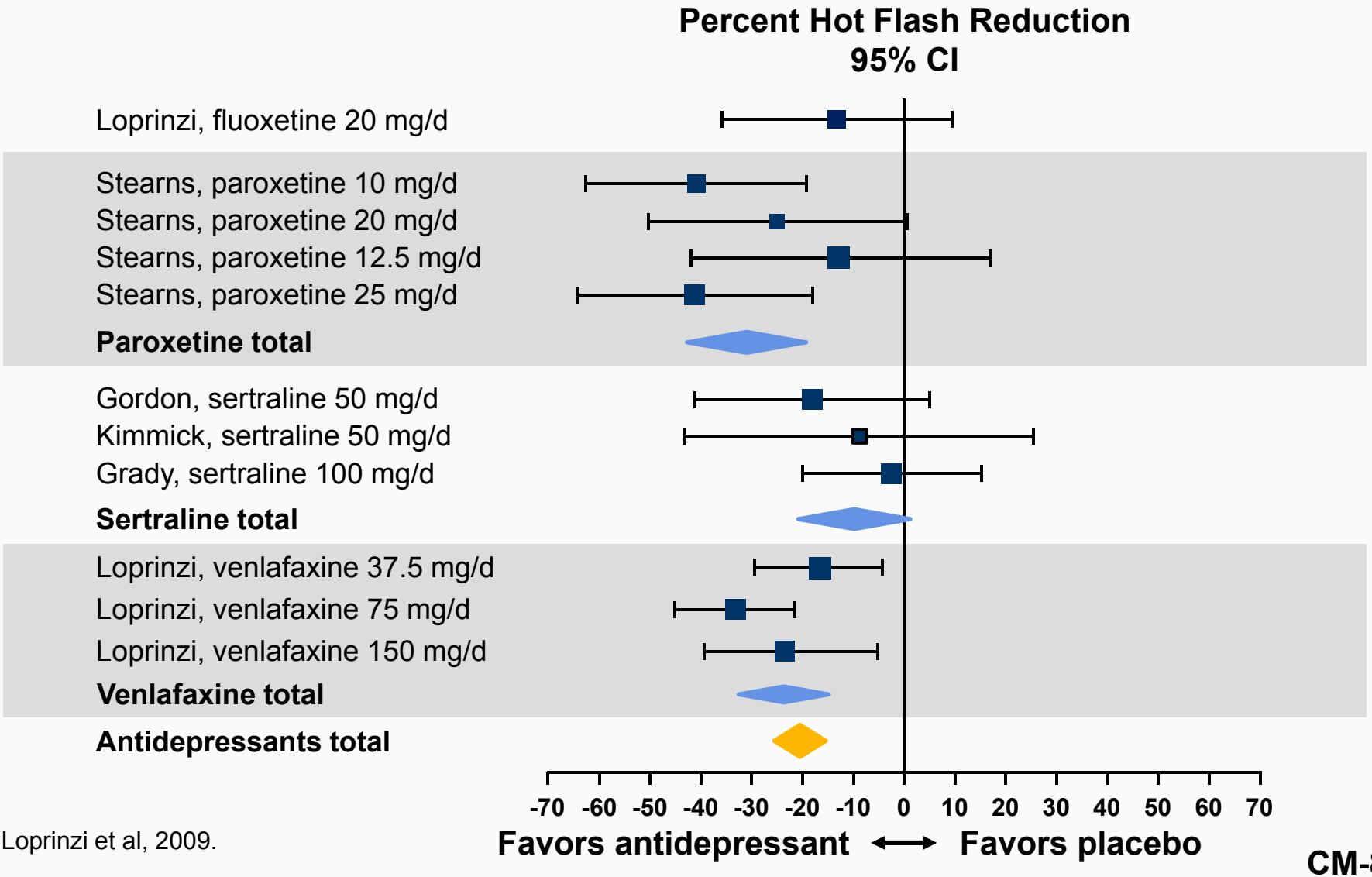
- Frequent and disruptive menopausal symptoms[1]
- Impaired functioning and productivity[1]
- Severe hot flashes interrupt activity[2]
- Sweating accompanies moderate and severe VMS[2, 3]
- Night sweats and night-time awakenings are common[1]

1. Whiteley et al, 2013.
2. FDA Guidance: Estrogen and Estrogen/Progestin drug products to treat VMS, 2003.
3. Ayers B, 2012.

Current Treatment Options

- Hormone therapy
- Over-the-counter and herbal remedies
- Off-label neuropsychiatric drugs

SSRI/SNRI for Vasomotor Symptoms



Loprinzi et al, 2009.

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Off-label Treatments for Vasomotor Symptoms

- Off-label use of prescription antidepressants
  - 3.3 million prescriptions in 2012
  - Of these, 2.4 million were for SSRIs
- Limited data and lack of guidance to support use
- Side effects associated with higher doses
  - Weight gain
  - Sexual dysfunction

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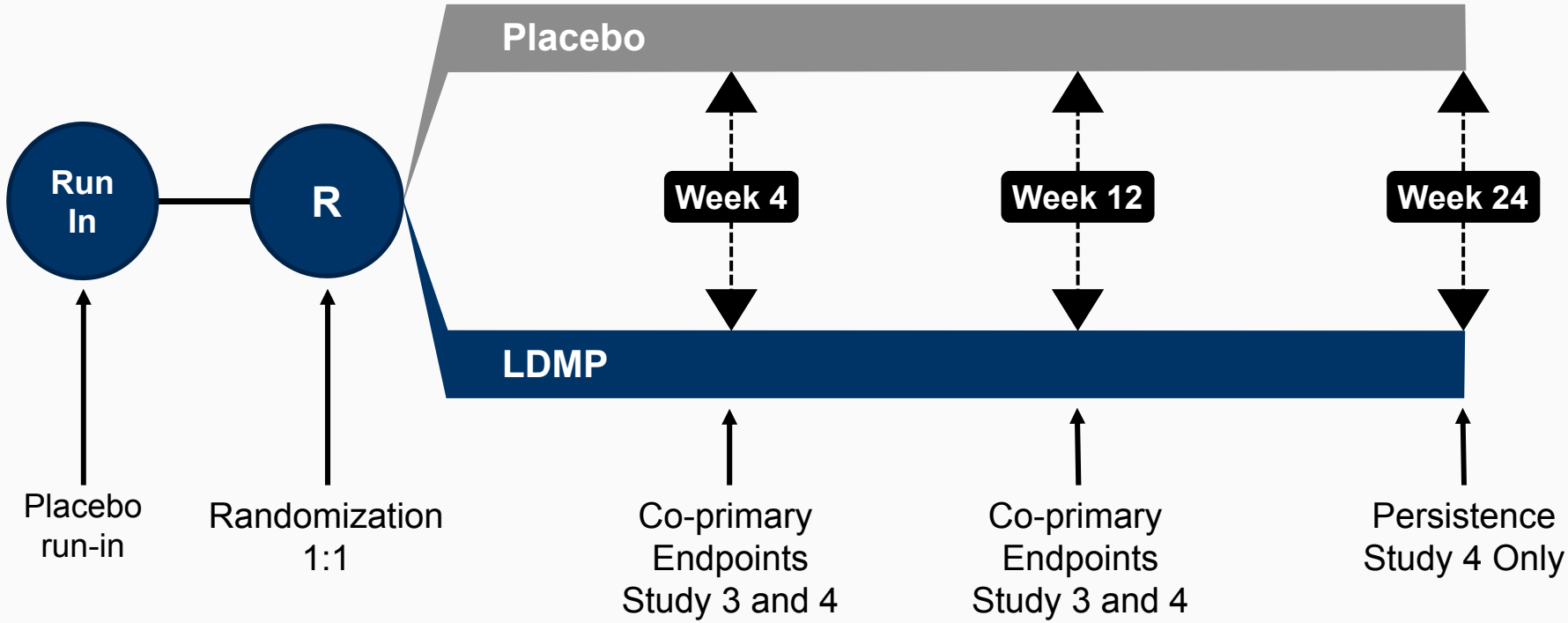
Patient Burden and Treatment Conclusions

- Need nonhormonal treatment options
- Evidenced based
- Labeled

LDMP Efficacy

Joel S. Lippman, MD, MPH, FACOG

Study Design for Both Pivotal Studies



Study Population

- ≥40 years of age
- Postmenopausal
- Moderate to severe hot flashes (HF)
  - ≥7 per day

  OR

  - ≥50 per week

Co-primary Endpoints

- Mean change from Baseline in hot flash frequency
  - Week 4
  - Week 12
- Mean change from Baseline in hot flash severity
  - Week 4
  - Week 12

Pre-specified Supportive Endpoints

- Patient Global Impression (PGI)-anchored receiver operating characteristic analysis
  - Study 3
- Persistence of benefit to 24 weeks
  - Study 4

Pre-specified Secondary Endpoints Related to Clinically Meaningful Change

- Patient Global Impression (Study 3 only)
- Night time awakenings
- Climacteric symptoms
- Daily interference of hot flashes
- Clinical Global Impression

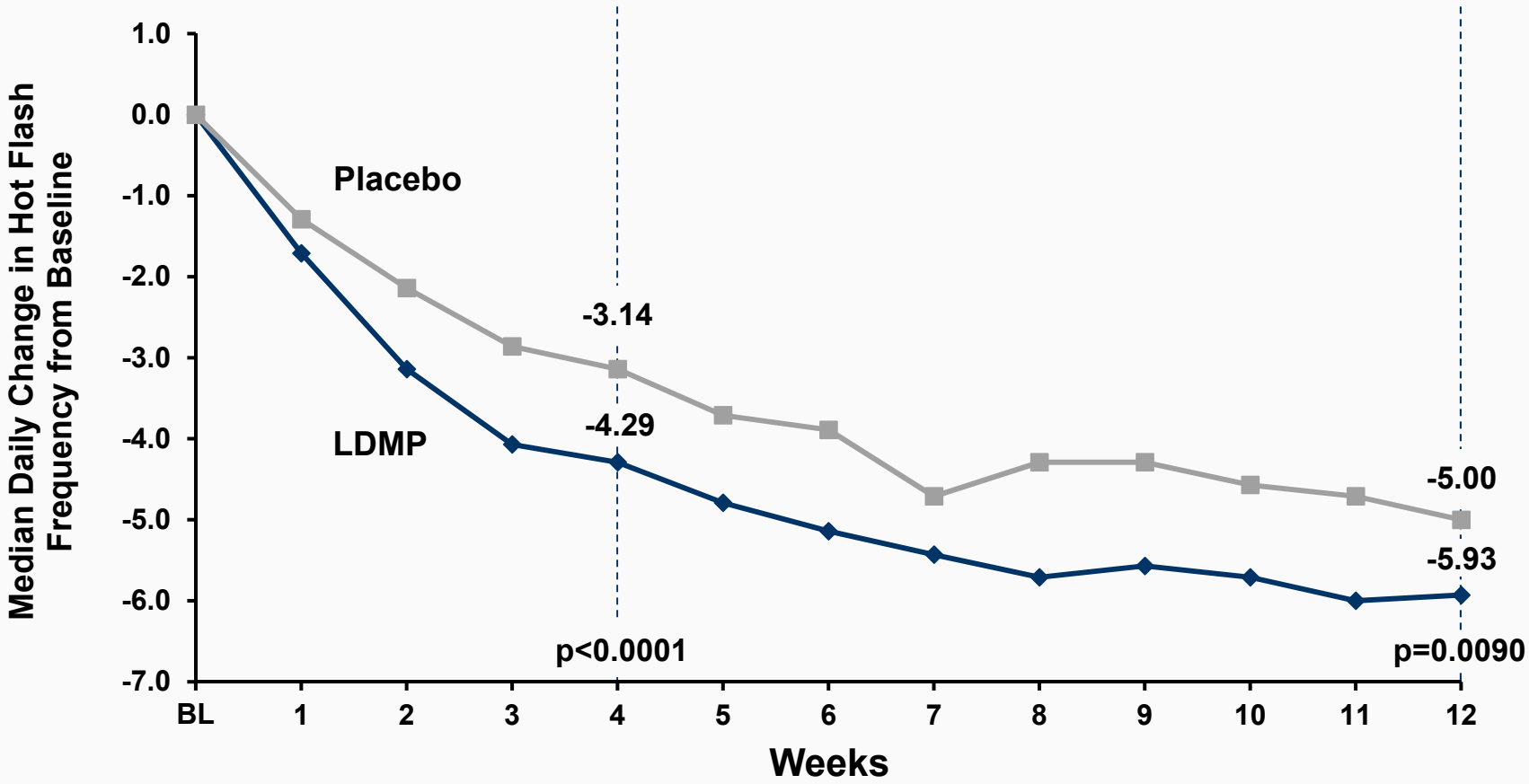
Demographic and Baseline Characteristics

Studies 3 and 4: mITT

	Study 3		Study 4	
	Placebo N=305	LDMP N=301	Placebo N=284	LDMP N=284
Age				
Mean years	54.5	54.9	54.5	54.2
Median	53	54	54	54
White/Caucasian, %	66.2	63.1	78.9	72.2
Black, %	30.5	35.2	18.7	24.3
Hispanic/Latino, %	12.1	9.0	7.4	5.6
Daily hot flash frequency				
Mean	11.65	11.79	10.90	10.83
Median	10.4	10.4	9.6	9.9
Daily hot flash severity score				
Mean	2.53	2.53	2.53	2.53
Median	2.5	2.5	2.5	2.5
Surgical menopause, %	17.0	19.6	19.0	20.1

Median Daily Change in HF Frequency

Study 3: mITT



Placebo	305	293	274
LDMP	301	289	264

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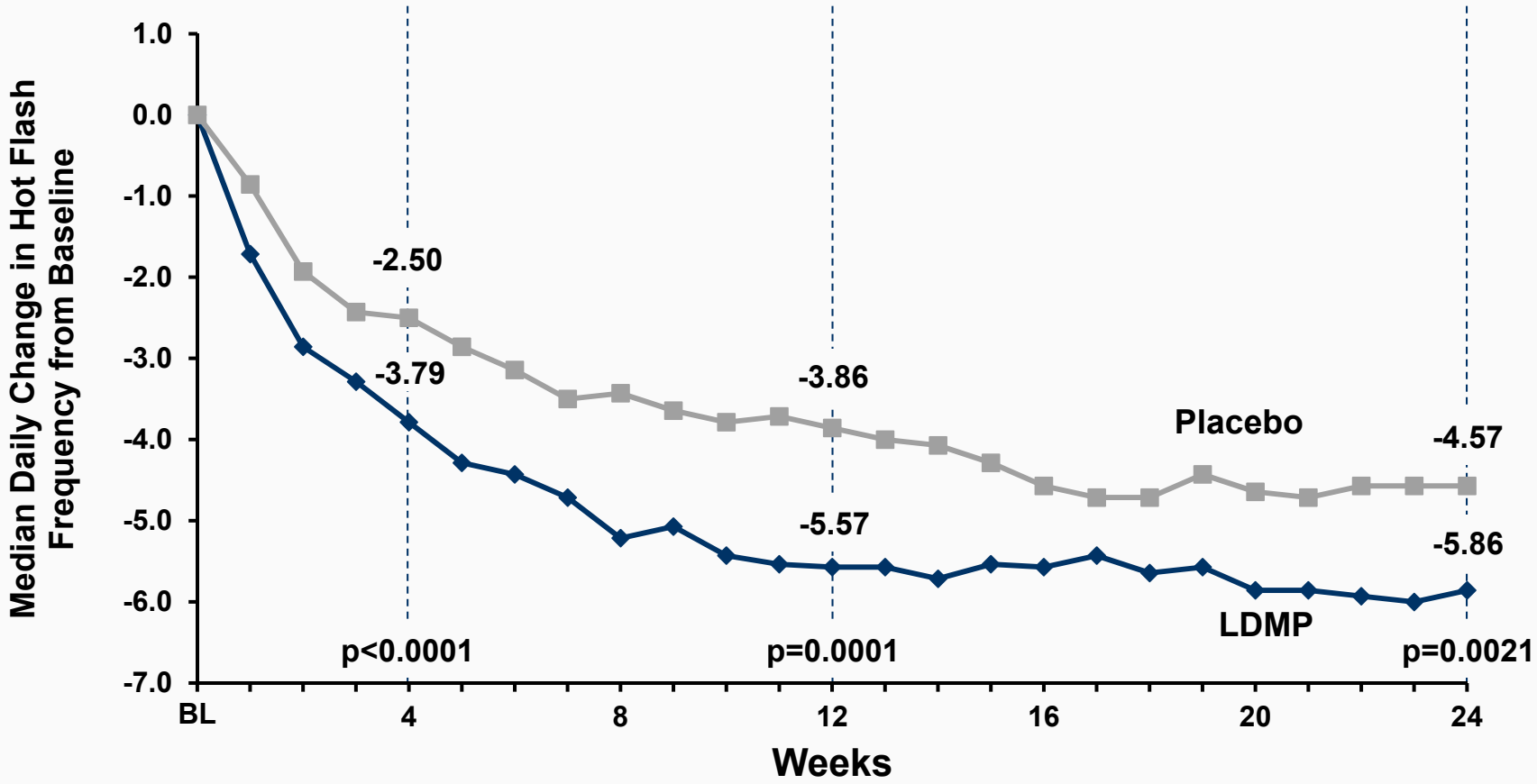
Median Daily Change in HF Frequency

Study 4: mITT



Placebo	284	274	244	215
LDMP	284	276	257	234

Weighted Average Severity Score

<u>Average severity of an individual hot flash</u>

$$\frac{(2*F_m + 3*F_s)}{(F_m + F_s)}$$

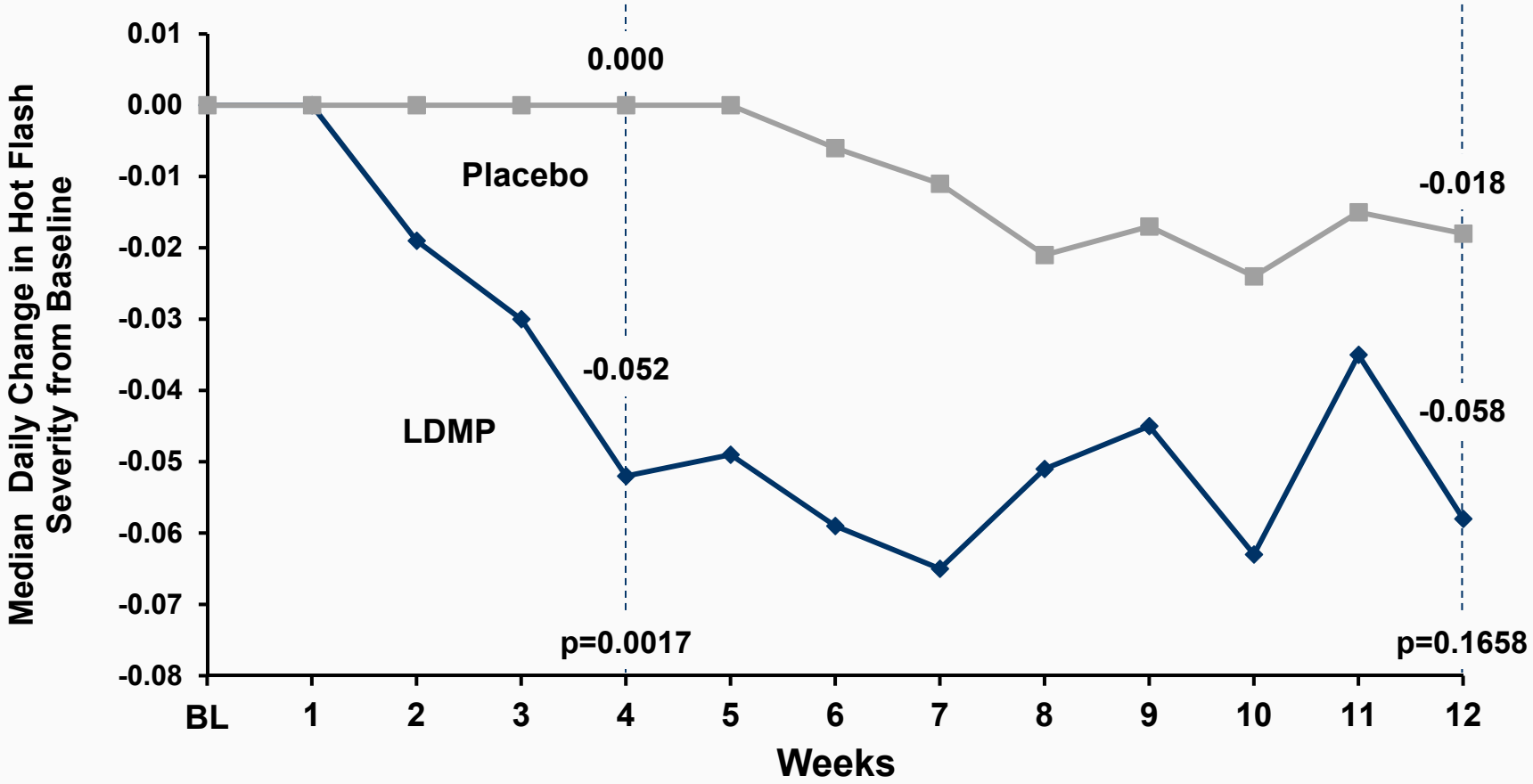
Range: 2 – 3

F_m= frequency of moderate hot flashes

F_s= frequency of severe hot flashes

Median Daily Change in Weighted Average Severity Score

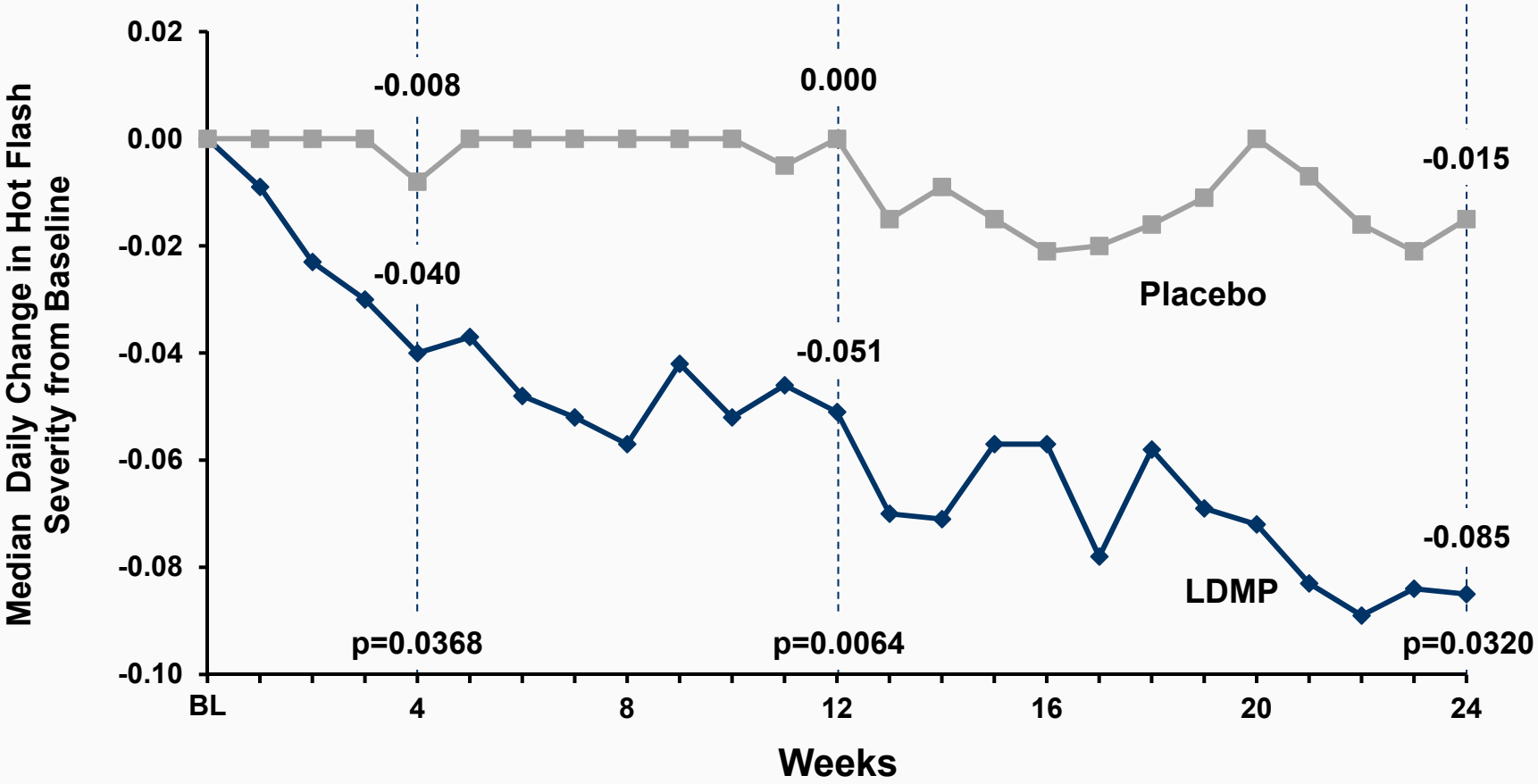
Study 3: mITT



Placebo	305	289	253
LDMP	301	281	236

Median Daily Change in Weighted Average Severity Score

Study 4: mITT



Placebo	284	271	236	201
LDMP	284	268	245	213

Composite Score – Exploratory Analysis

Patient burden of total hot flashes

$2*F_m + 3*F_s$ Range: 0 – 250+

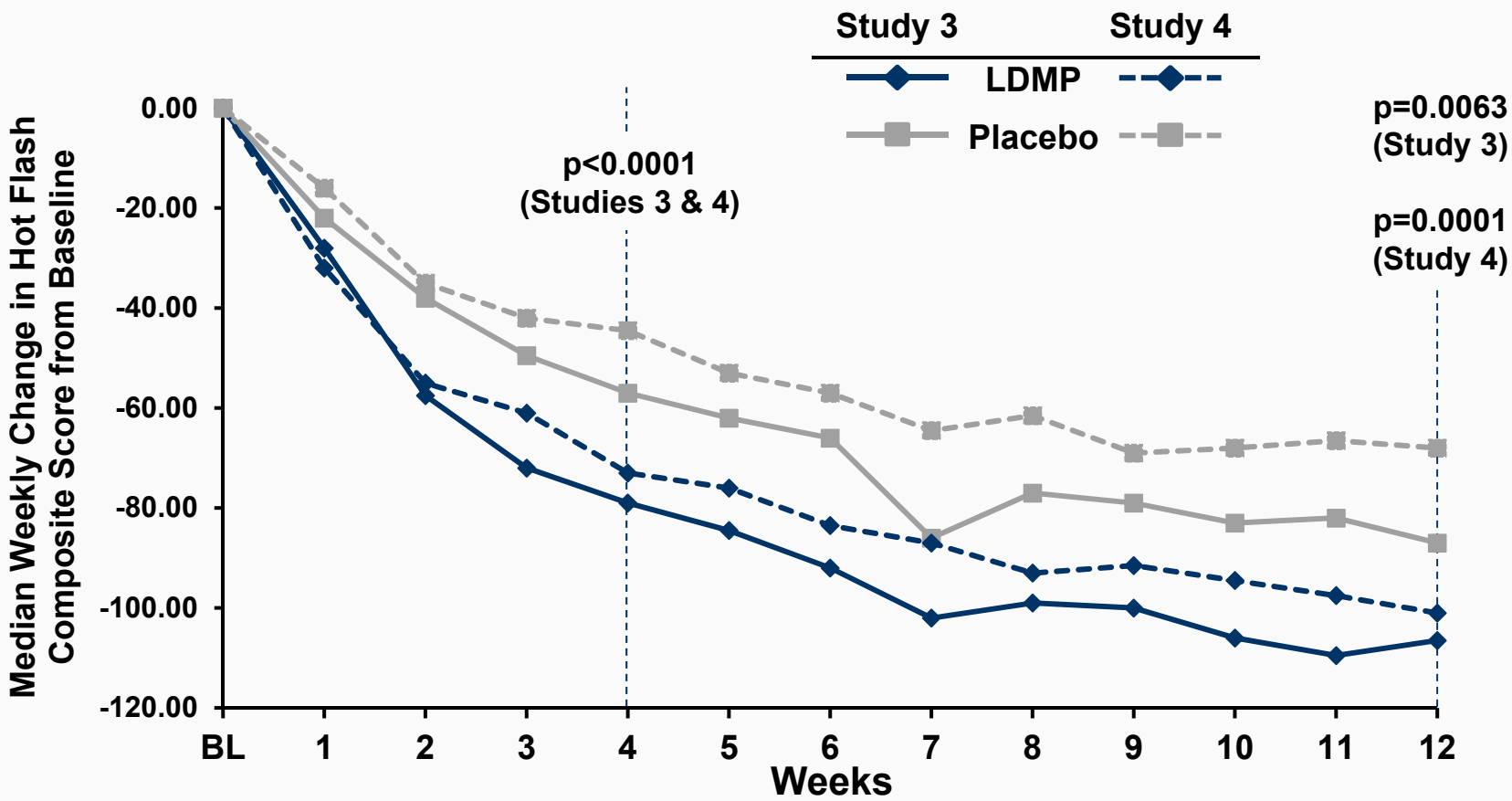
F_m= frequency of moderate hot flashes

F_s= frequency of severe hot flashes

Stearns V et al, 2003.
Notelovitz M et al, 2000.

Median Weekly Change in Composite Score

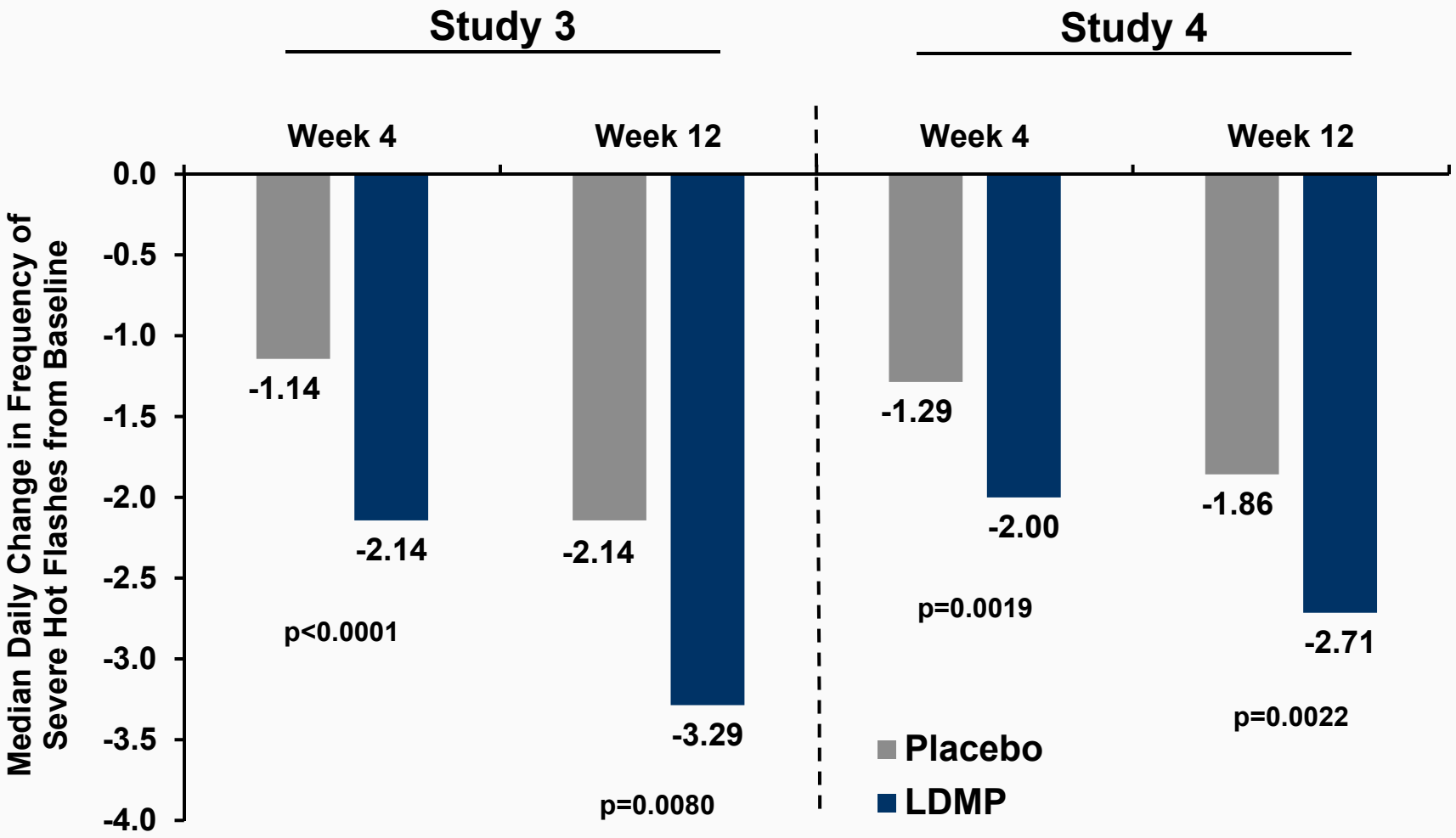
Studies 3 and 4: mITT Population



	BL	1	2	3	4	5	6	7	8	9	10	11	12
Study 3 Placebo	305	305	301	298	293	289	286	285	283	280	278	276	274
Study 3 LDMP	301	301	296	292	289	288	281	277	277	275	273	268	264
Study 4 Placebo	284	284	282	279	274	267	261	256	254	252	252	250	244
Study 4 LDMP	284	284	279	278	276	271	268	265	262	260	258	258	257

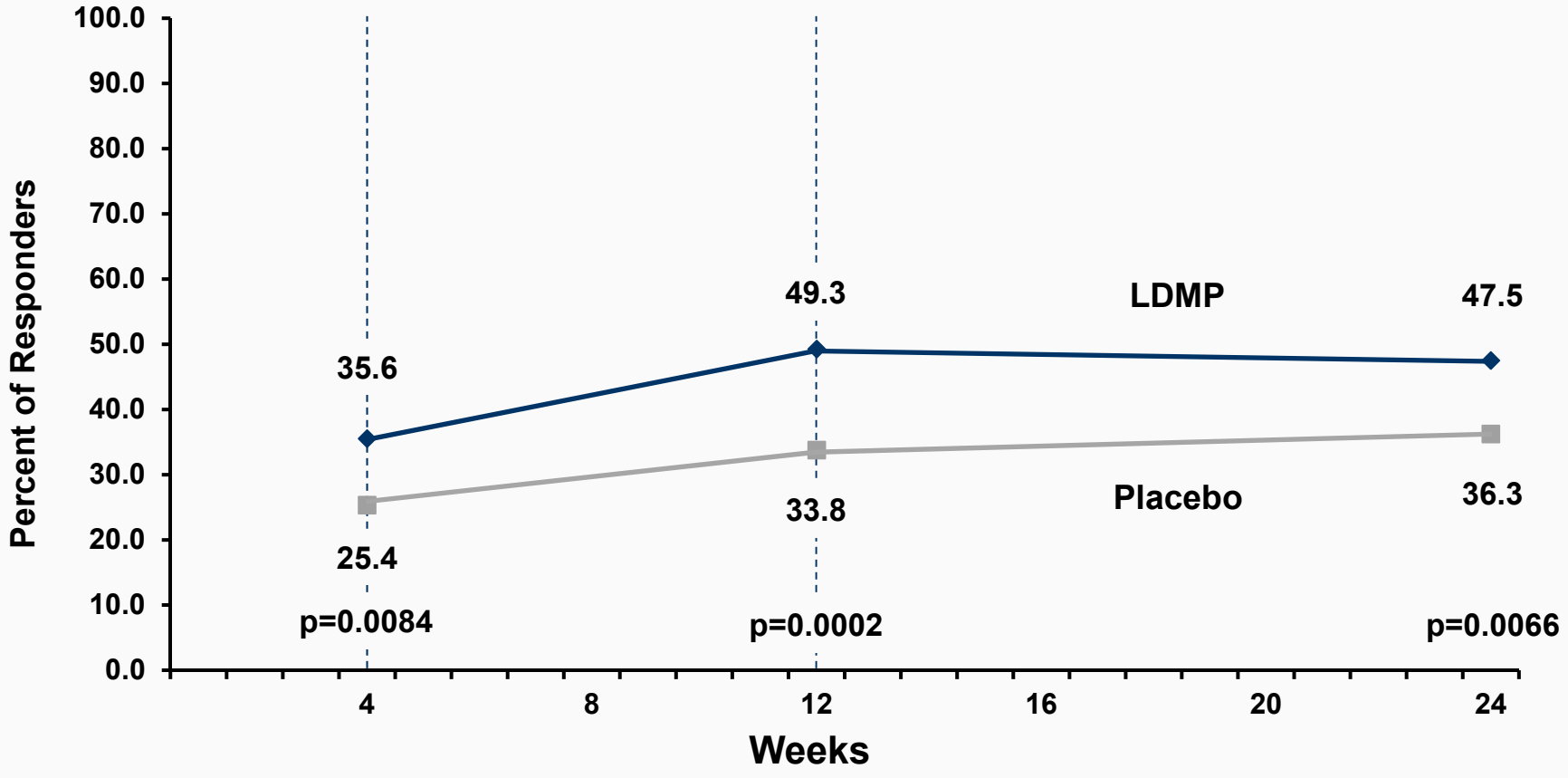
Median Daily Change in Frequency of Severe Hot Flashes – Exploratory Analysis

Studies 3 and 4: mITT Population



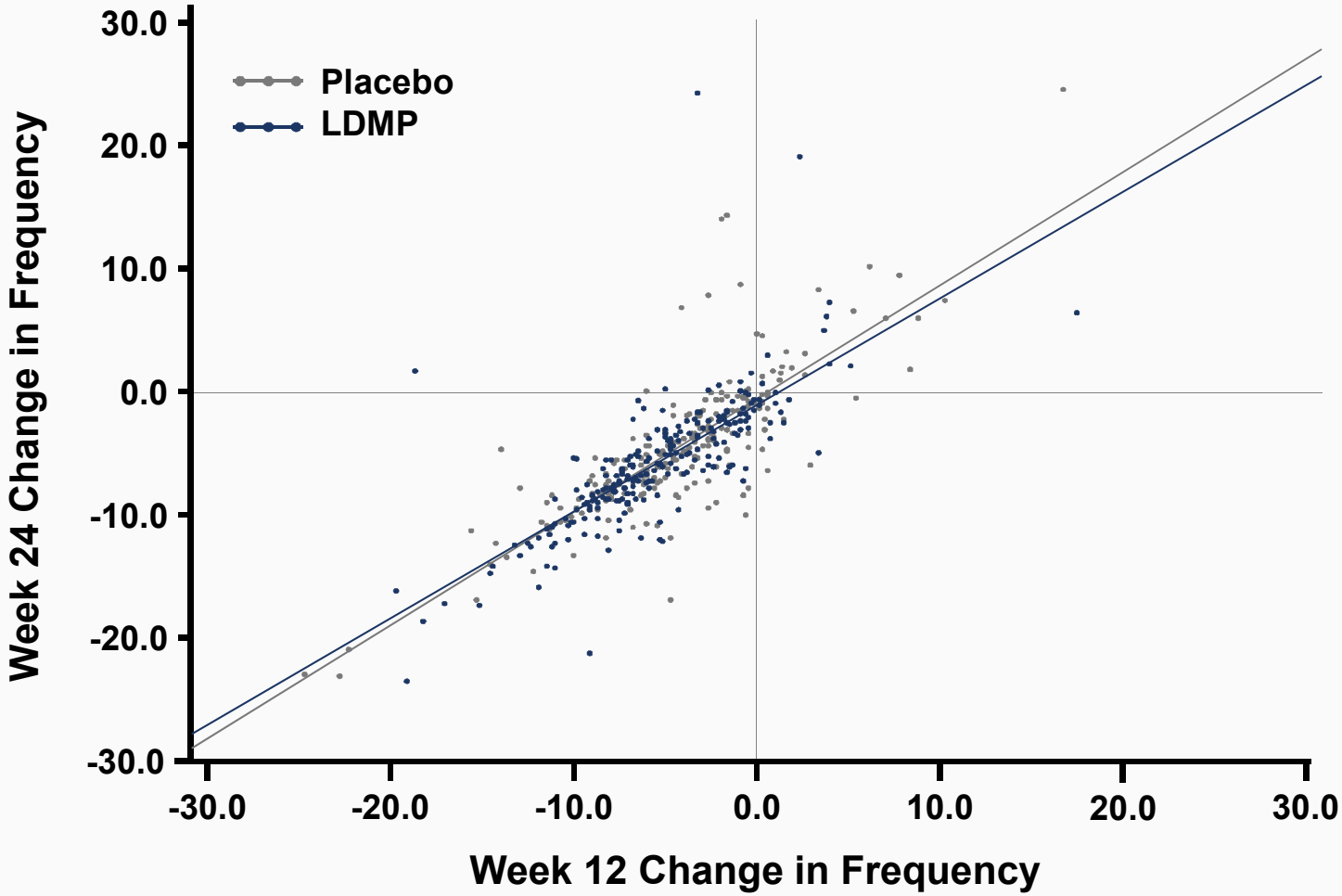
Persistence of Benefit – Baseline to Week 24

Study 4: mITT



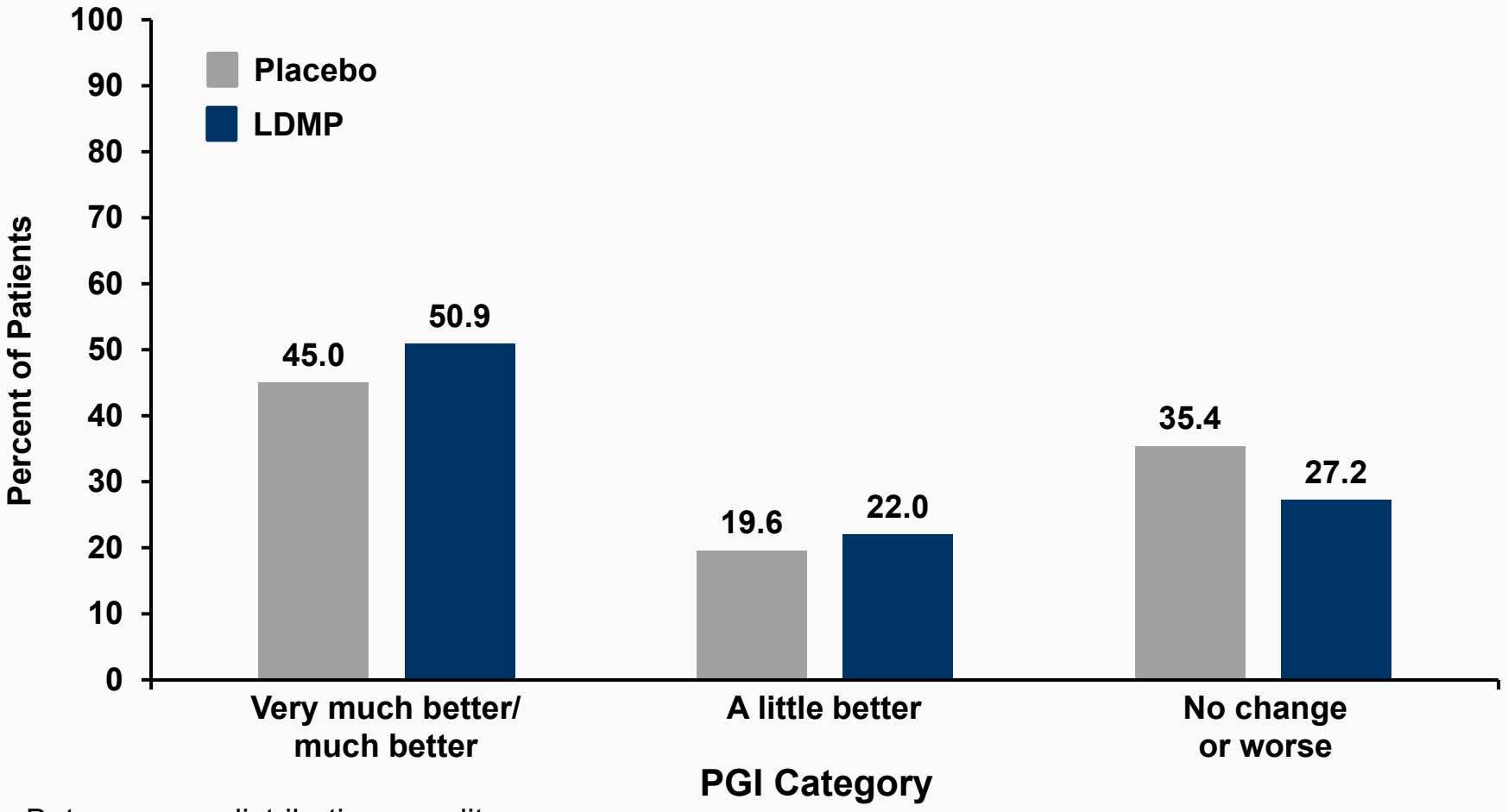
Persistence of Benefit – Week 12 to Week 24

Study 4: mITT



Patient Global Impression (PGI)

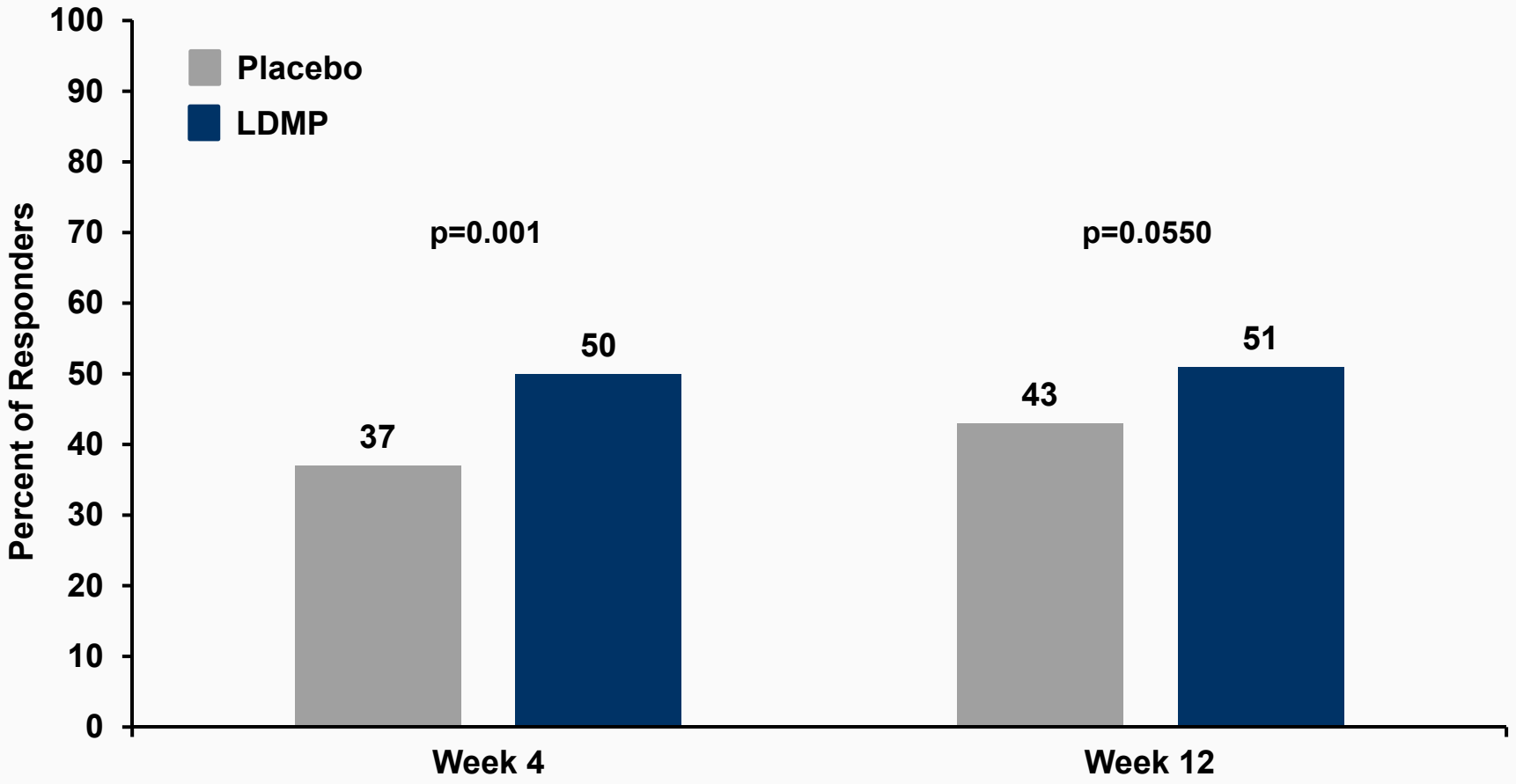
Study 3: Week 12



Between arm distribution equality
p=0.0296 (Exact Wilcoxon)

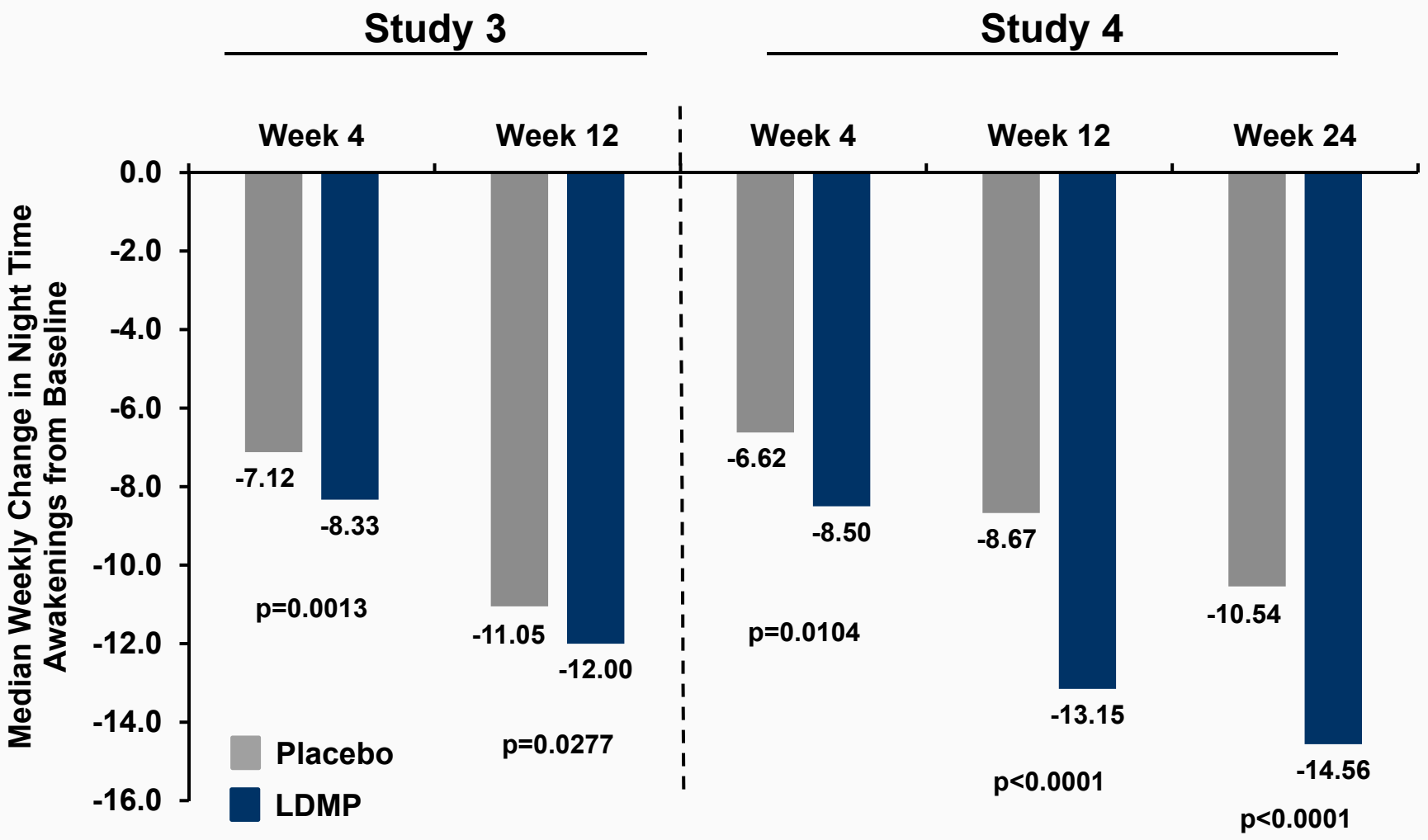
PGI-anchored Receiver Operating Characteristic Analysis (PGI ≤2 for Satisfied Patients)

Study 3: mITT



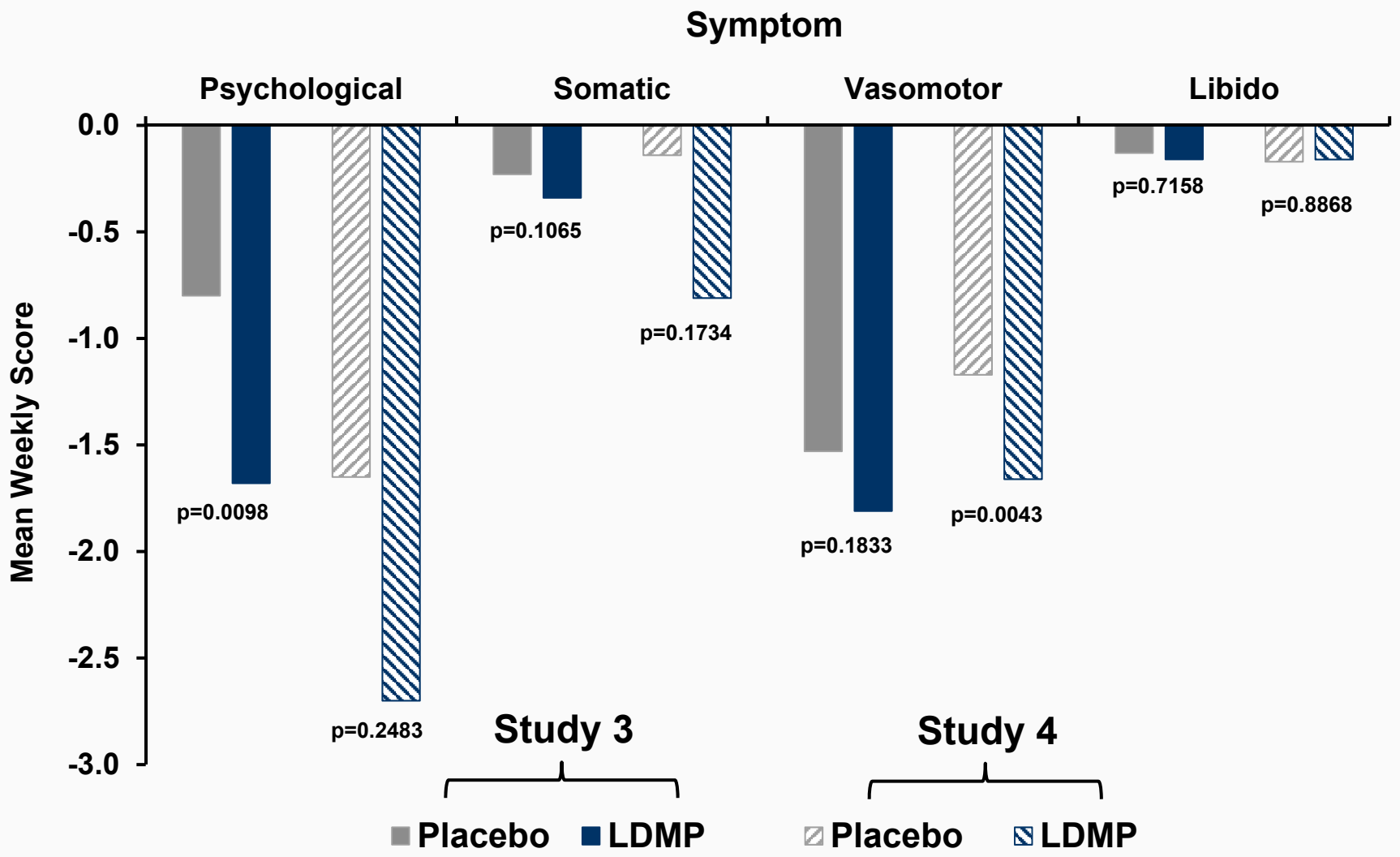
Night Time Awakenings

Studies 3 and 4: mITT Population



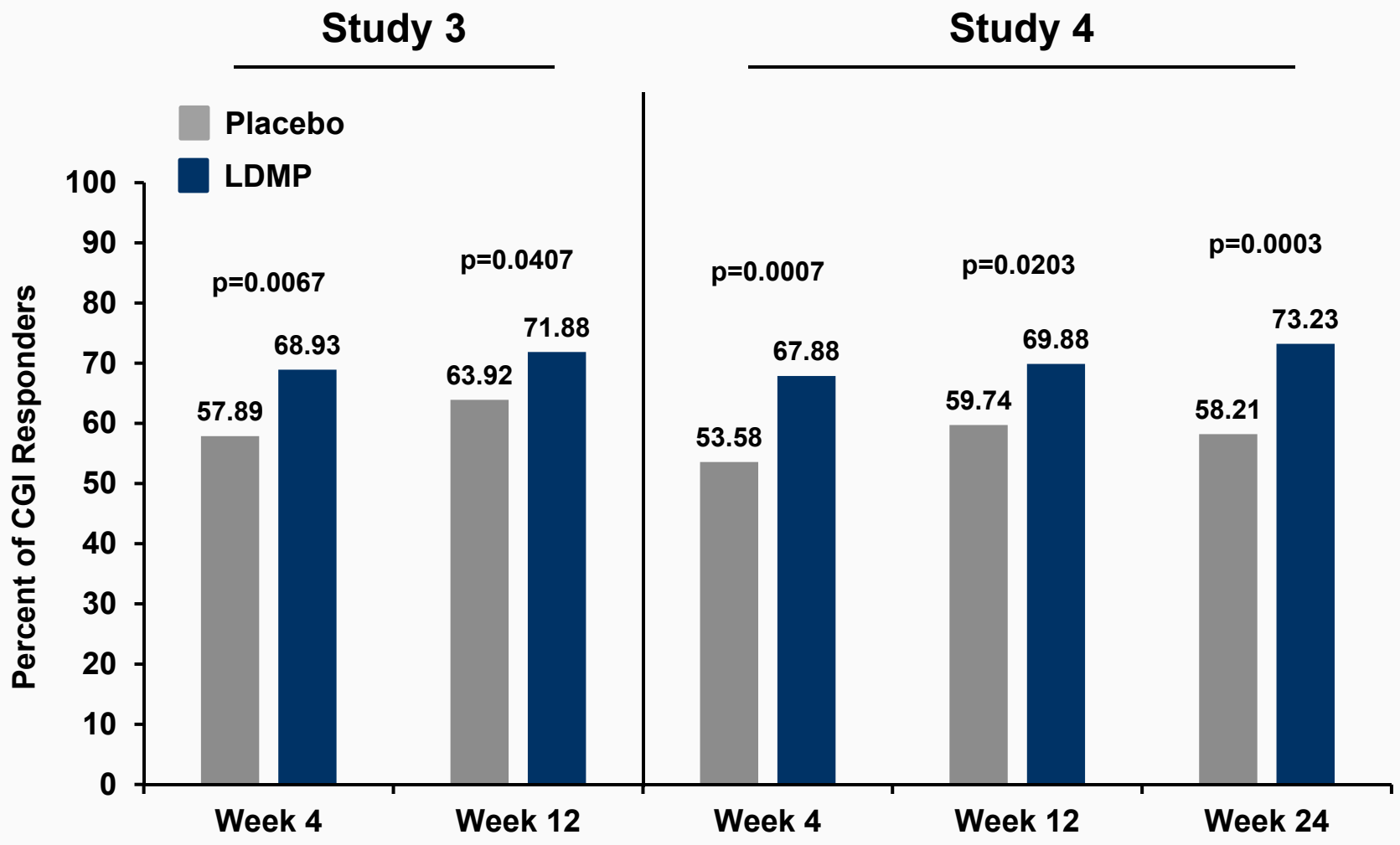
Greene Climacteric Scale (GCS) – Week 12

Studies 3 and 4: mITT Population



Clinical Global Impression (CGI)

Studies 3 and 4: mITT Population



Statistical Evaluations

Brent Blumenstein, PhD

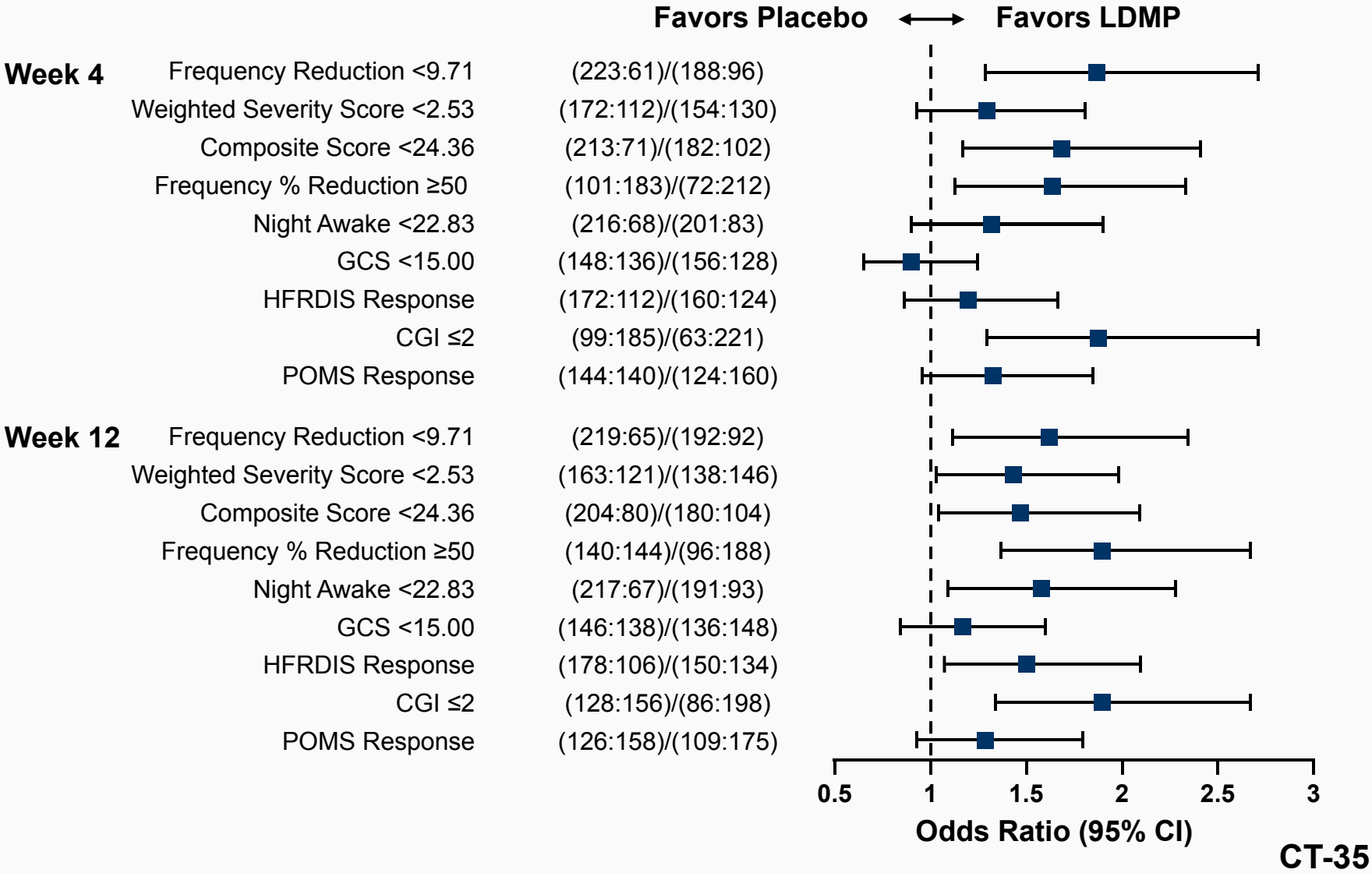
Biostatistician
Trial Architecture Consulting

Dichotomization of Multiple Outcomes

Outcome	Method	Dichotomization of Post-baseline Value
Frequency	Pre-defined criterion	≥50% reduction from baseline
Frequency, severity, composite score, night time awakening, GCS	Baseline data defined	< vs ≥ pooled Baseline median
PGI, CGI	Defined by scale	≤2 vs >2
HFRDIS, POMS	Sign of change	Negative vs positive change from Baseline

Multiple Outcomes by Treatment Arm

Study 4: mITT



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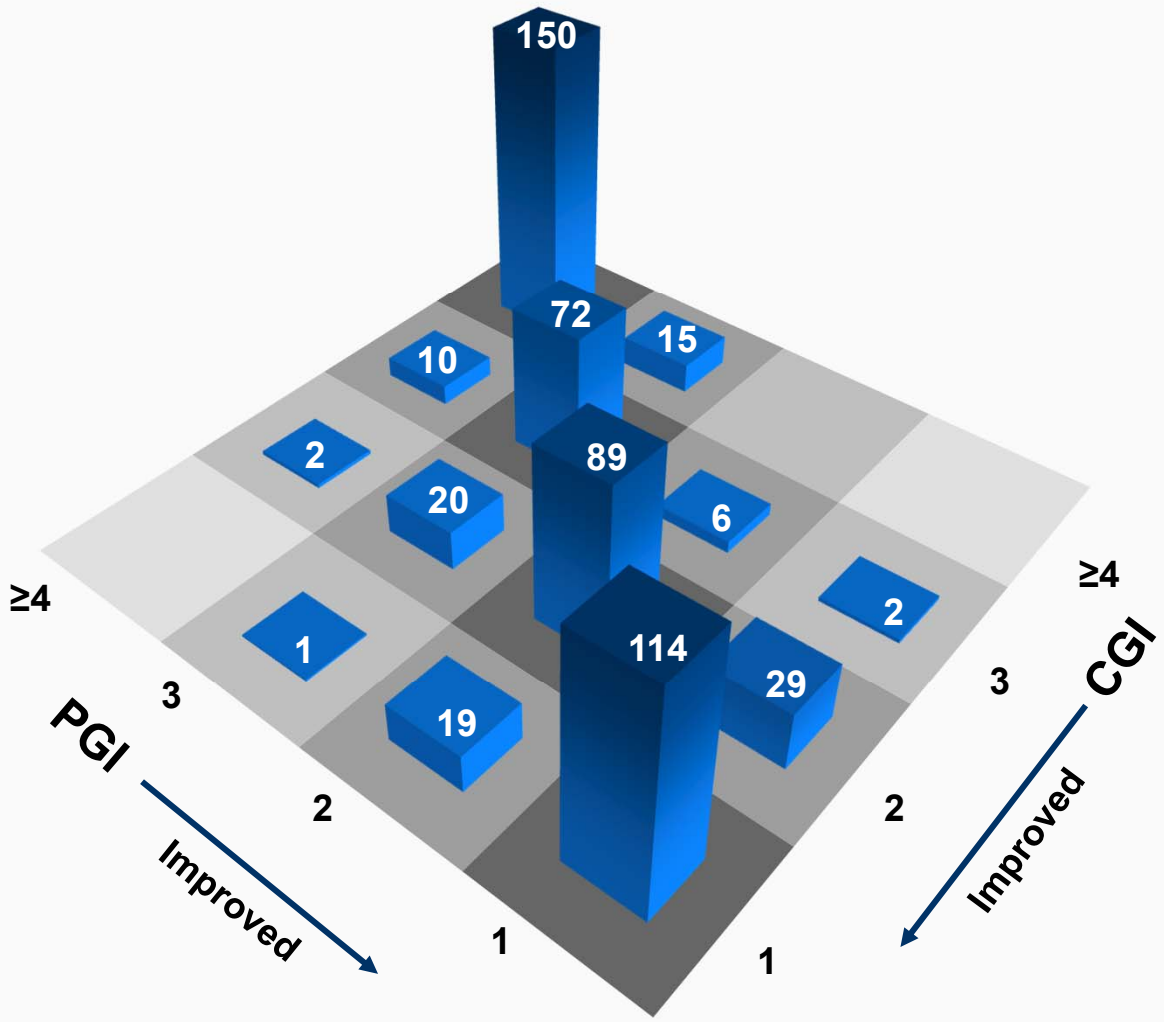
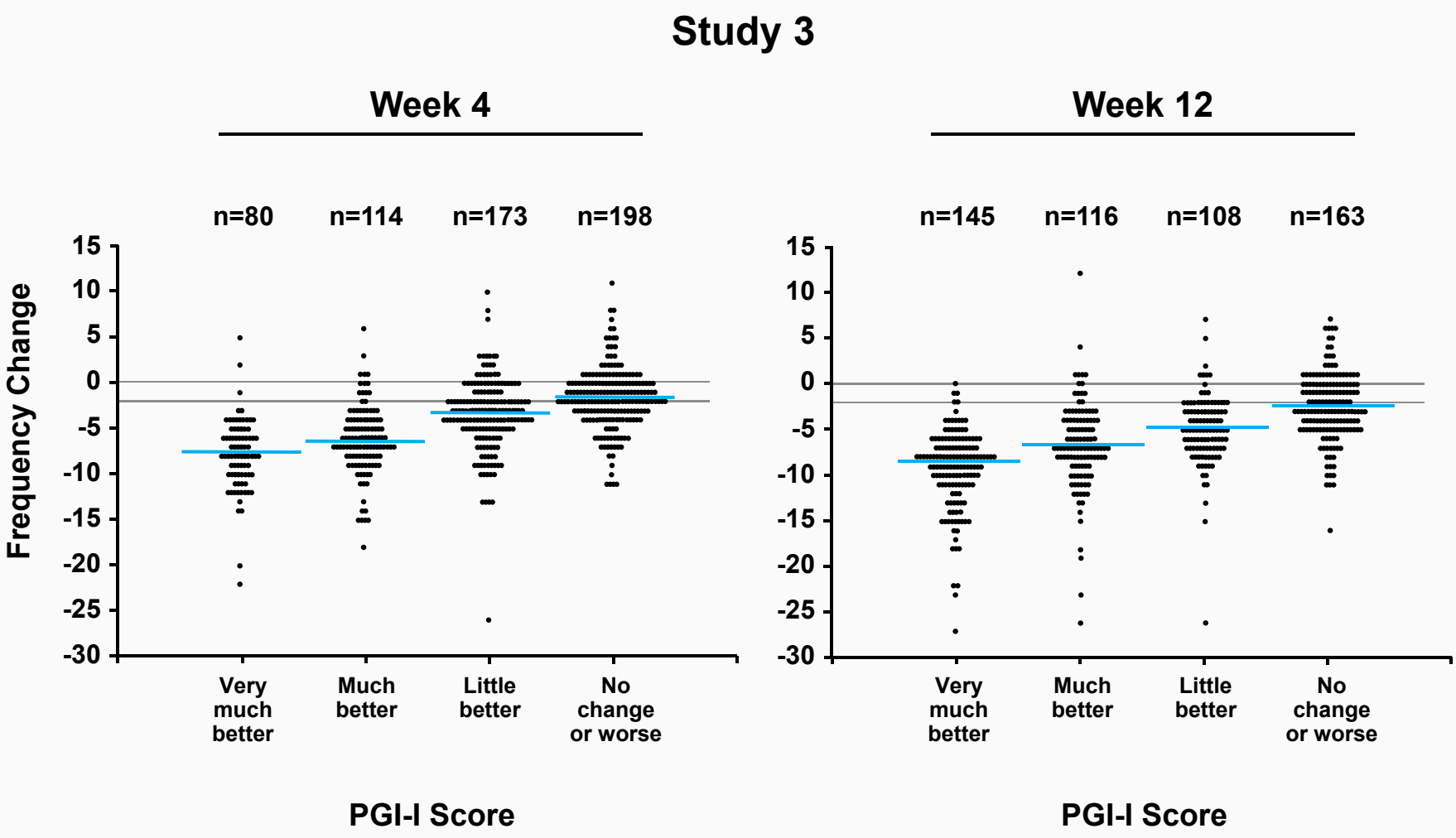
Correlation Between PGI and CGI

Study 3: Week 12



Correlation Between PGI and Hot Flash Reduction



Multivariate Global Test

- Hypothesis:
  - Experimental arm generally favorable shift for multiple outcomes (as compared to control arm)
- Tests below demonstrate experimental arm benefit
- Conclusion applies even when only non-diary outcomes are analyzed

Outcome variables	Meaning	Study	Week	N†	O'Brien p
Freq change, sev change, FAW change, CGI, GCS change, HFRDIS change, POMS change	Primary plus other outcomes	3	12	221:233	0.0026
		4	12	195:186	0.0009
CGI, GCS change, HFRDIS change, POMS change	Other outcomes only	3	12	250:254	0.0022
		4	12	207:194	0.0008

* O'Brien PC. Procedures for comparing multiple endpoints. *Biometric 1985*; 40:1079-1087
† Ns for arms experimental: control

Efficacy Conclusions

- Efficacy demonstrated
  - Frequency
    - Week 4 and Week 12 in both studies; Week 24 in Study 4
  - Severity
    - Week 4 in both studies; Week 12 and Week 24 in Study 4
  - Persistence at Week 24
- Clinically meaningful benefit demonstrated
  - Frequency reduction associated with patient perception of benefit
  - Frequency reduction associated with multiple clinical outcomes
  - Preponderance of clinical outcomes data favors LDMP

LDMP Safety

Joel S. Lippman, MD, MPH, FACOG

Overview of Adverse Events

All Controlled Studies Pooled

Category	Placebo N=641 n (%)	LDMP N=635 n (%)
Any adverse event	301 (47.0)	320 (50.4)
AE leading to D/C	21 (3.3)	28 (4.4)
SAE	9 (1.4)	14 (2.2)

Most Commonly Reported AEs
(>2% and Greater than Placebo)

All Controlled Studies Pooled	Placebo N=641 n (%)	LDMP N=635 n (%)
Any TEAE	301 (47.0)	320 (50.4)
Nasopharyngitis	33 (5.1)	33 (5.2)
Headache	27 (4.2)	29 (4.6)
Fatigue	11 (1.7)	24 (3.8)
Nausea	9 (1.4)	23 (3.6)
Diarrhea	16 (2.5)	17 (2.7)

Phase 3 Studies Pooled	N=589 n (%)	N=586 n (%)
Dizziness	5 (0.8)	12 (2.0)

Events of Special Interest

- Suicidality
- Abnormal bleeding
- Bone fractures
- Discontinuation symptoms
- Weight gain
- Sexual dysfunction

Suicidality: Spontaneously Reported Events

All Controlled Studies Pooled

	Placebo N=641 n (%)	LDMP N=635 n (%)
Completed suicide	0 (0.0)	0 (0.0)
Suicide attempt	0 (0.0)	1 (0.2)
Self-injurious behavior	0 (0.0)	0 (0.0)
Spontaneous suicide ideation/behavior	0 (0.0)	0 (0.0)

Suicidality Assessment Instruments

- Sheehan Suicidality Tracking Scale (STS)
  - Phase 2 and Study 4
- Columbia Suicide Severity Rating Scale (C-SSRS)
  - FDA recommended
  - Study 3

Suicidality Assessment in LDMP Clinical Trials

- Study 4: Numerically increased treatment-emergent adverse events based on STS
- Study 3: No treatment-emergent adverse events based on C-SSRS

Abnormal Bleeding
All Controlled Studies Pooled

Preferred Term	Placebo N=641 n (%)	LDMP N=635 n (%)
Patients with ≥1 TEAE	10 (1.6)	12 (1.9)
Vaginal / Postmenopausal hemorrhage	6 (0.9)	6 (0.9)
Vitreous hemorrhage	0 (0.0)	1 (0.2)
Gingival bleeding	0 (0.0)	1 (0.2)
Rectal hemorrhage	0 (0.0)	1 (0.2)
Periorbital hematoma	0 (0.0)	1 (0.2)
Breast hematoma	0 (0.0)	1 (0.2)
Epistaxis	0 (0.0)	1 (0.2)
Duodenal ulcer	1 (0.2)	0 (0.0)
Gastric ulcer	1 (0.2)	0 (0.0)
Gastrointestinal hemorrhage	1 (0.2)	0 (0.0)
Hematemesis	1 (0.2)	0 (0.0)
Bloody discharge	1 (0.2)	0 (0.0)
Helicobacter infection	1 (0.2)	0 (0.0)

Bone Fractures

All Controlled Studies Pooled

Preferred Term	Placebo N=641 n (%)	LDMP N=635 n (%)
Patients with ≥1 TEAE	3 (0.5)	1 (0.2)
Hand fracture	0 (0.0)	1 (0.2)
Acetabulum fracture[a]	1 (0.2)	0 (0.0)
Femur fracture[a]	1 (0.2)	0 (0.0)
Foot fracture	1 (0.2)	0 (0.0)
Upper limb fracture	1 (0.2)	0 (0.0)

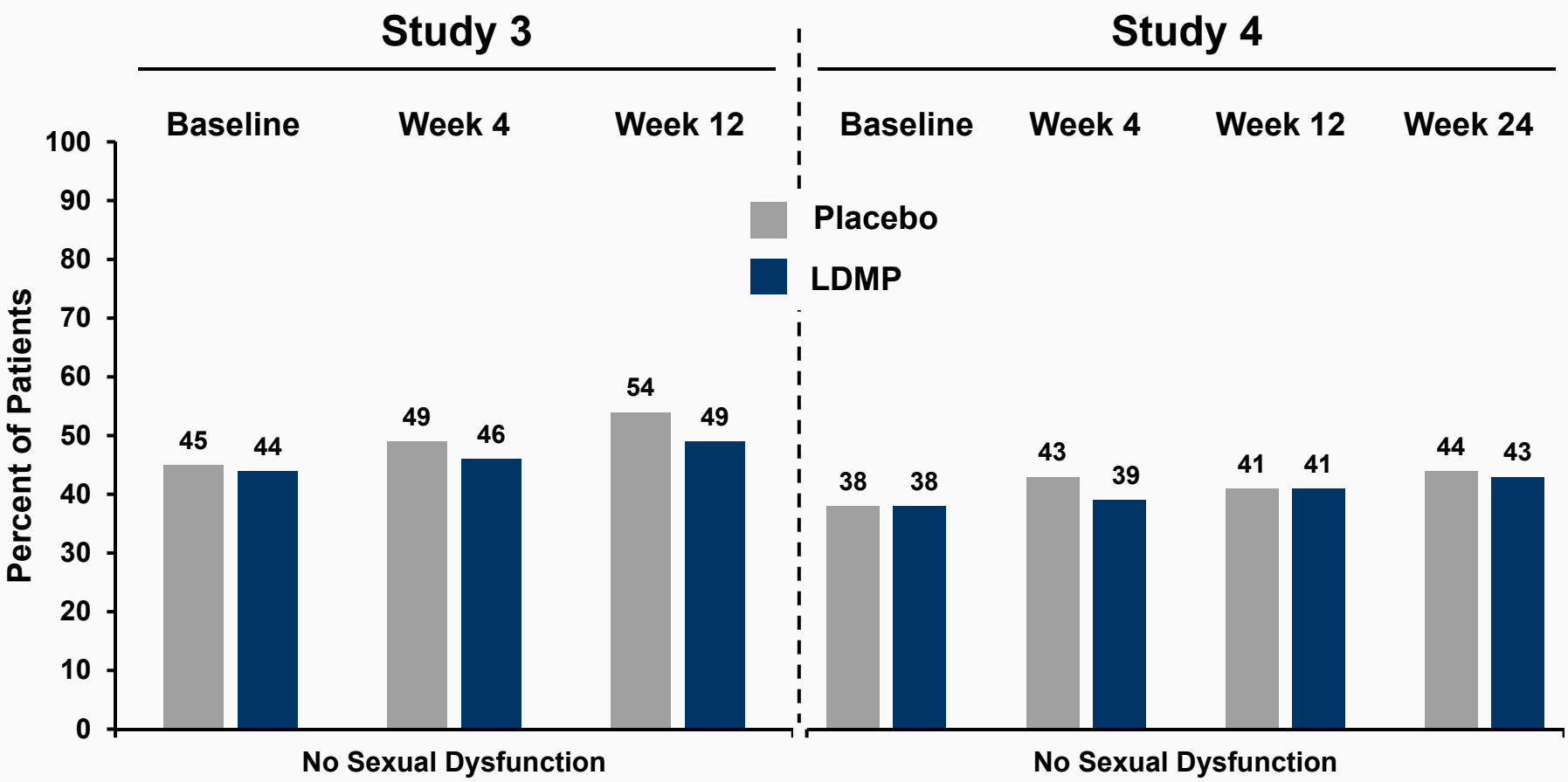
a. Both events occurred in the same patient

Discontinuation Emergent Signs and Symptoms (DESS) Scale
All Controlled Studies Pooled

DESS Category	Placebo N=641 n (%)	LDMP N=635 n (%)
Old symptoms present	414 (100)	405 (100)
Old symptoms worsened	73 (17.6)	102 (25.2)
New symptom: None	429 (66.9)	394 (62.0)
One or more	88 (13.7)	112 (17.6)
Most commonly occurring new symptoms	**%**	**%**
Increased dreaming or nightmares	3.1	4.9
Muscle cramps, spasms or twitching	1.4	3.5
Headache	2.3	3.1
Muscle aches or pains	2.2	2.7
Nervousness or anxiety	1.9	2.7
Fatigue, tiredness	1.4	2.5
Restless feeling in the legs	1.1	2.5
Trouble sleeping, insomnia	1.1	2.4

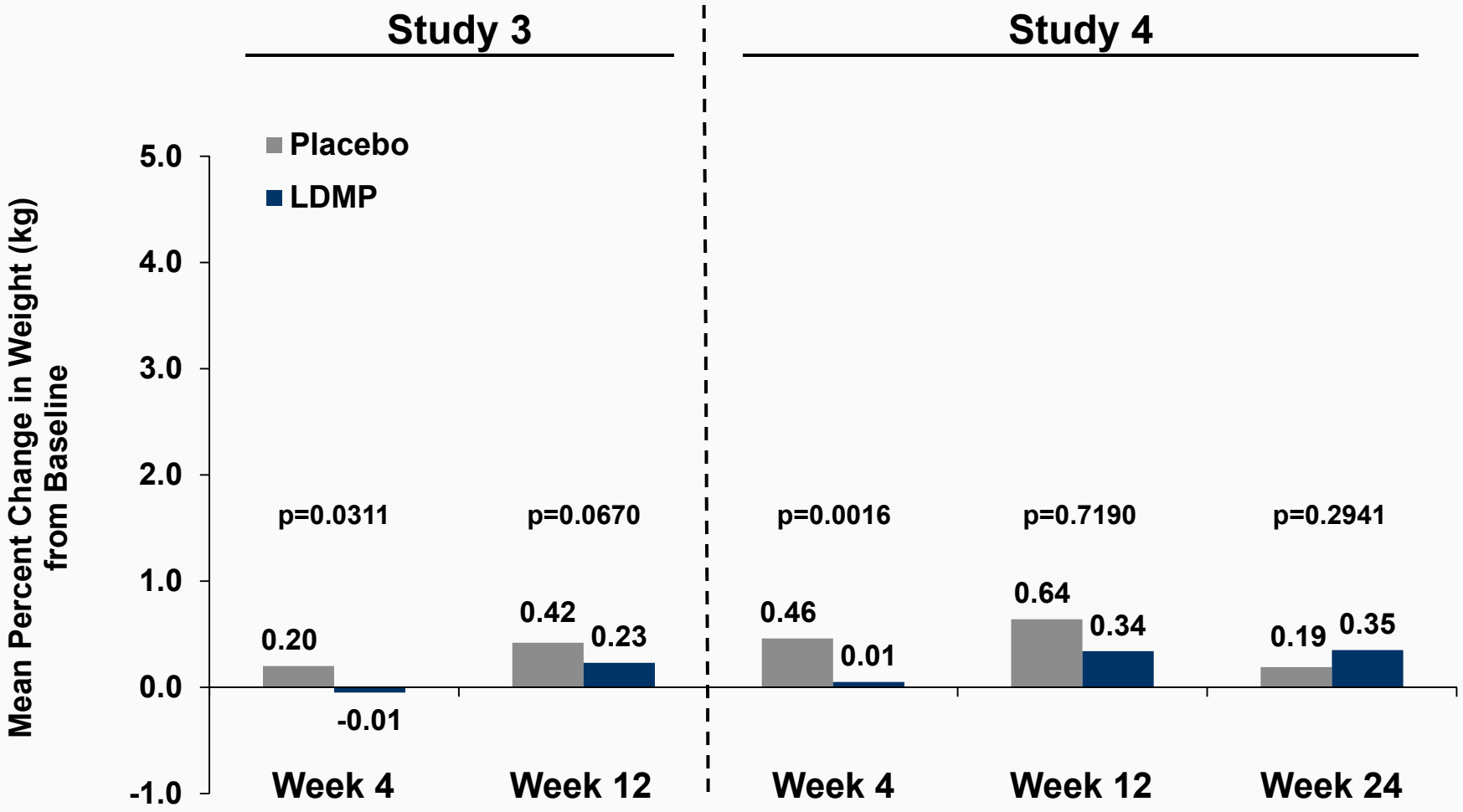
Arizona Sexual Experiences (ASEX) Scale

Studies 3 and 4



Percent Change in Weight (kg)

Studies 3 and 4



Safety Conclusions

- LDMP clinical program
  - Favorable safety and tolerability
  - No new or unexpected safety findings
  - Most common LDMP AEs mild to moderate
    - Nausea, fatigue and dizziness
- Well-established safety profile of paroxetine

Risk Management

S. Elizabeth Lucini, PharmD

Sr. Director, Regulatory Affairs & Pharmacovigilance
Noven Pharmaceuticals, Inc.

Foundation for Risk Management Plan

- No new or unexpected safety findings
- Established safety profile of paroxetine
  - 10 to 60 mg for psychiatric indications
- Risk management plan
  - Focused on warnings and precautions from paroxetine label

Elements of Risk Management Plan

- Label
- Medication guide
- Pharmacovigilance with targeted follow-up
- Post-marketing surveillance
- Education and outreach

Proposed LDMP Label and Medication Guide

- SSRI class labeling
- Medication guide
  - Includes list of symptoms that should be monitored and communicated to a healthcare provider

Adverse Events of Special Interest

- Focus on adverse events of special interest, including:
  - Suicidality
  - Abnormal bleeding
  - Bone fracture
- Targeted follow-up on new reports
  - Reporter asked to complete a specialized form
- This information will be reviewed and shared with FDA

Post-marketing Surveillance

- FDA AERS signal detection to identify possible signals
- Active surveillance using medical claims data
  - Assessment of event rates in 2 defined groups:
    - Patients with VMS receiving LDMP
    - Patients with VMS treated with other medications
  - Data collected for adverse events of special interest and all other events

Bone Safety

- Epidemiological studies show an increase in bone fracture risk in depressed patients
  - Further increased by SSRIs
  - Mechanism by which SSRIs increase fracture risk in depressed patients is unknown
- Fracture risk in non-depressed patients taking SSRIs is unknown
- Noven is prepared to conduct a post-marketing study to assess bone safety

Education and Outreach

- Target audience: prescribers, pharmacists, and patients
- Proposed content:
  - Reinforcement of labeled risks
  - Importance of monitoring
  - Potential for drug-drug interactions
- Proposed elements:
  - Dear healthcare provider/pharmacist letter
  - Prescriber branded education slide deck
  - Dissemination at professional societies' scientific meetings
  - Printed patient educational materials
  - Search engine optimized healthcare provider and consumer websites

Clinical Perspective

David Portman, MD

Benefit/Risk Assessment

- LDMP Phase 3 data
  - Demonstrated efficacy for moderate to severe vasomotor symptoms
  - No new or unexpected adverse events
- Paroxetine label and literature
  - Boxed warning for suicidality
- Hormone therapy label and literature
  - VMS, bone, vulvar and vaginal atrophy
  - Boxed warning for DVT, PE, stroke; breast and endometrial cancer risk

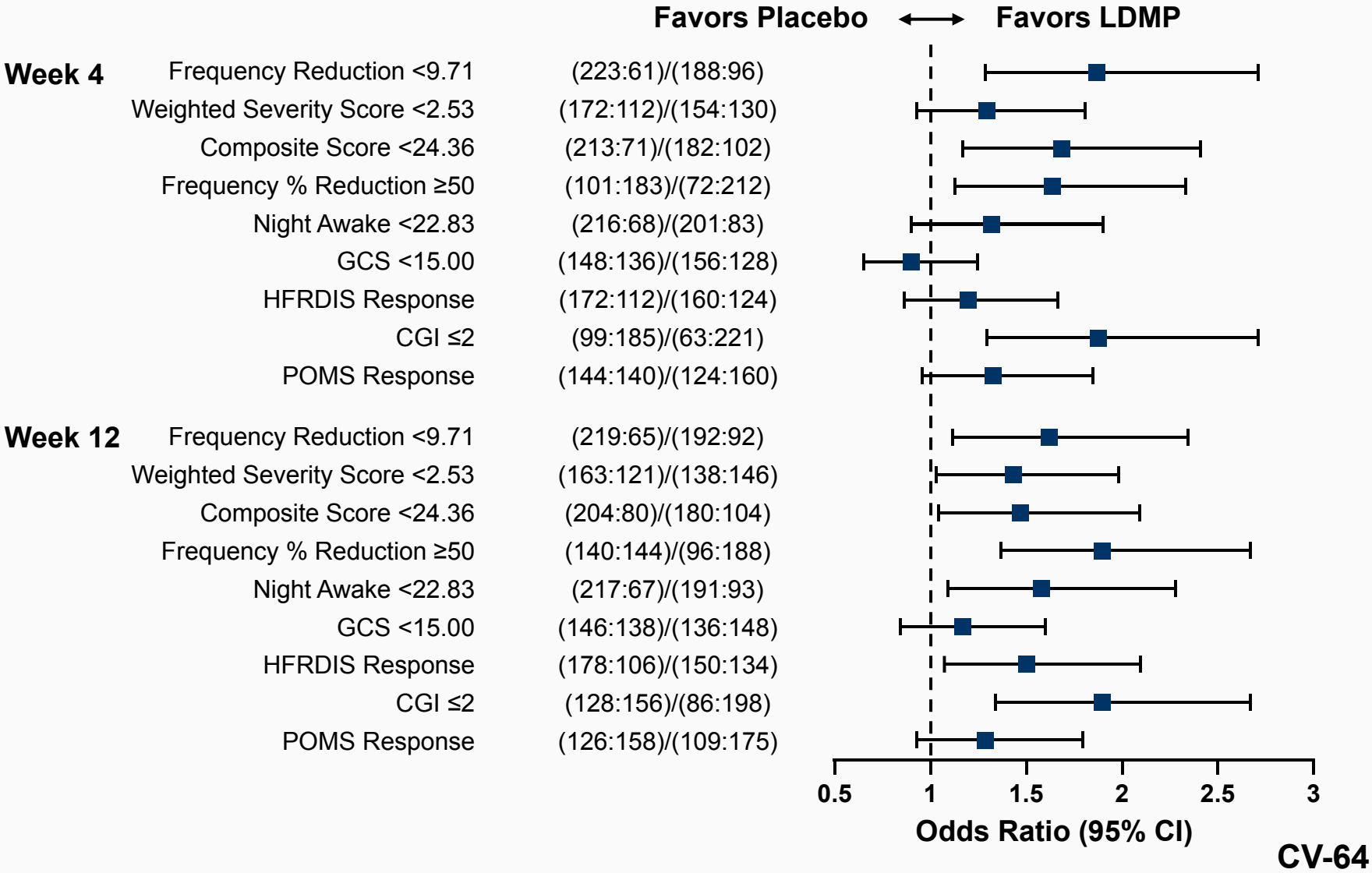
Reduction in Hot Flash Frequency

- 57-59% for LDMP (Phase 3)
  - 40-48% for placebo
- 65-80% for hormone therapy[1, 2]
  - 46-58% for placebo effect

1. Cochrane review, 2009.
2. Ettinger EB, 2005.

Multiple Outcomes by Treatment Arm

Study 4: mITT



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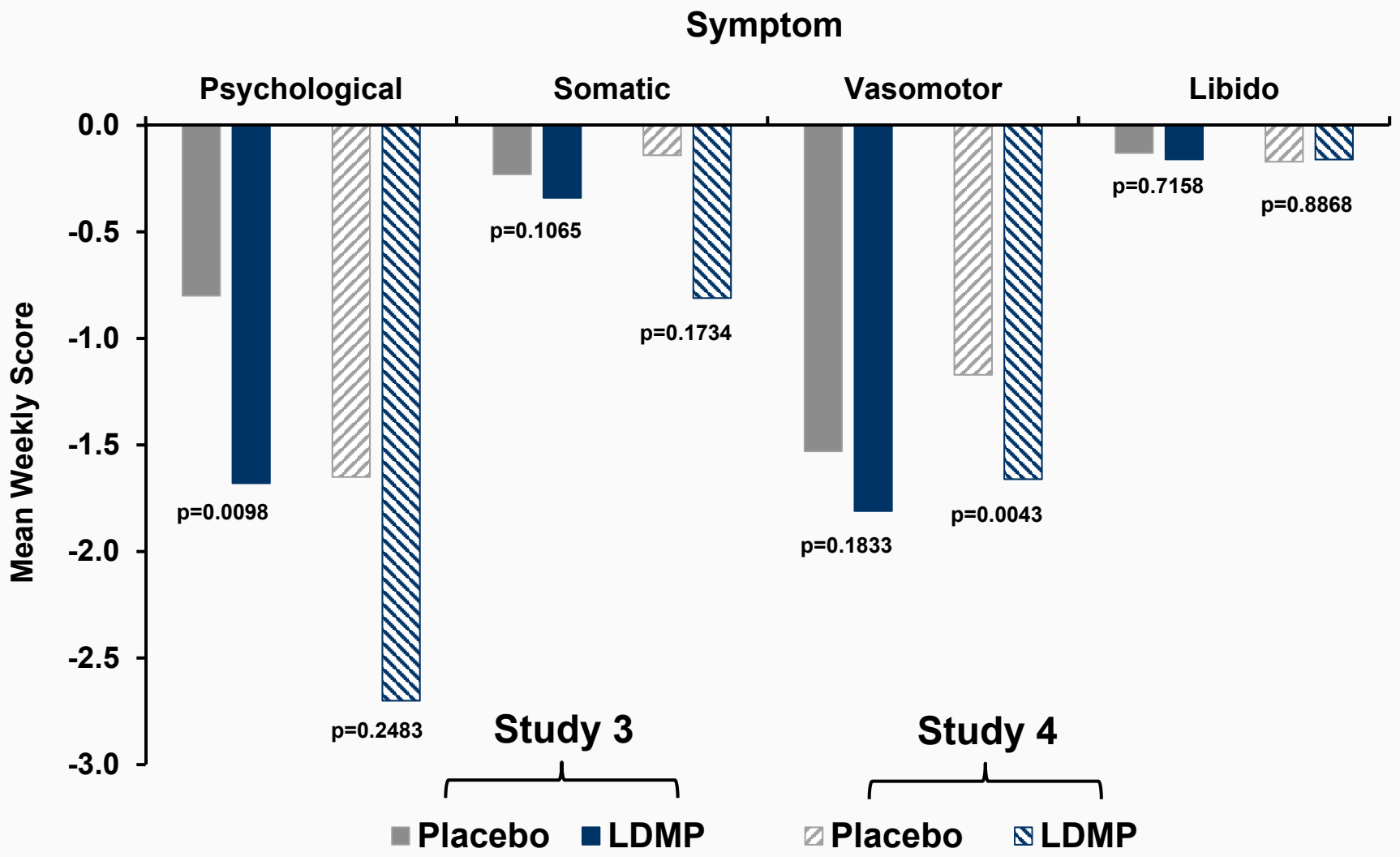
Greene Climacteric Scale (GCS) – Week 12

Studies 3 and 4: mITT Population

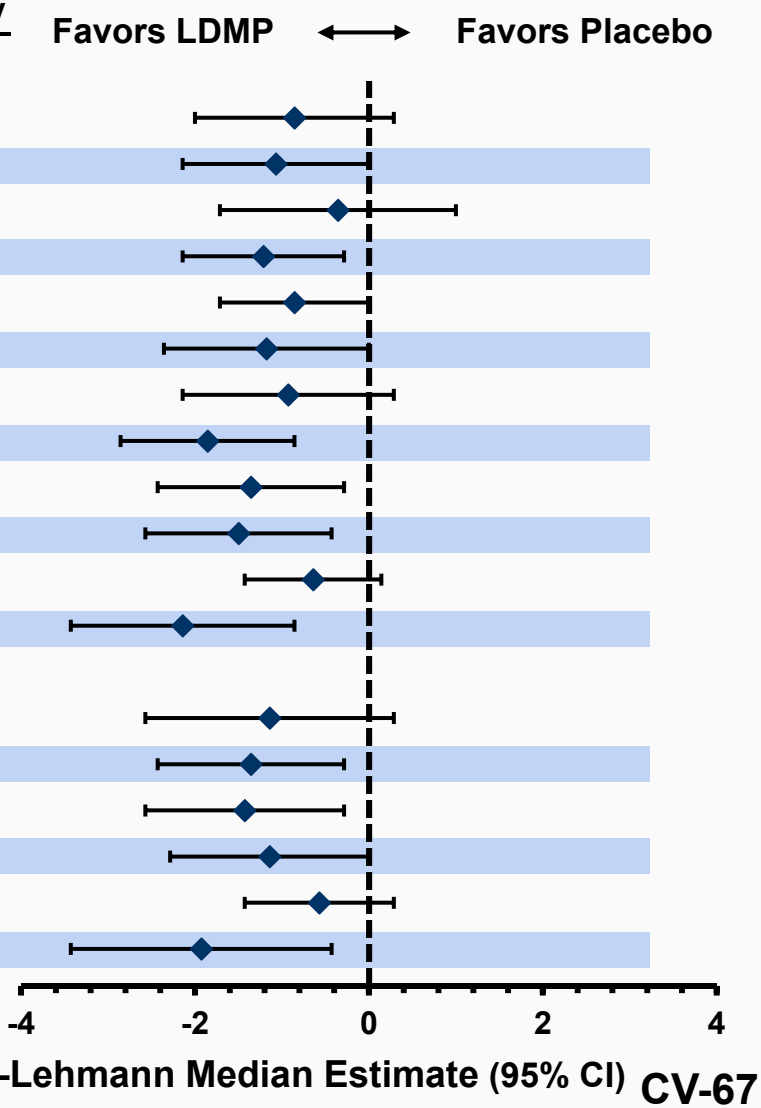


HFRDIS and POMS

- Hot Flash Related Daily Interference Scale (HFRDIS)
  - Less interference in social, leisure, enjoyment domains
  - Less interference with sleep and quality of life
- Profile of Mood States (POMS)
  - Increased vigor and activity
  - Decreased inertia

Hot Flash Frequency Reduction by Baseline Symptom Burden

	Factor	Factor Value	Estimate	Frequency
Week 12				
Study 3	Base GCS >12[1]	No	235	(114:121)
		Yes	294	(148:146)
	Base GCS Q19 >2[1]	No	172	(87:85)
		Yes	349	(170:179)
	Base Freq >10	No	241	(122:119)
		Yes	297	(142:155)
Study 4	Base GCS >12	No	182	(92:90)
		Yes	301	(158:143)
	Base GCS Q19 >2	No	172	(92:80)
		Yes	304	(153:151)
	Base Freq >10	No	272	(136:136)
		Yes	229	(121:108)
Week 24				
Study 4	Base GCS >12	No	161	(82:79)
		Yes	271	(145:126)
	Base GCS Q19 >2	No	153	(82:71)
		Yes	272	(140:132)
	Base Freq >10	No	249	(127:122)
		Yes	200	(107:93)



1. Pinkerton et al, 2013.

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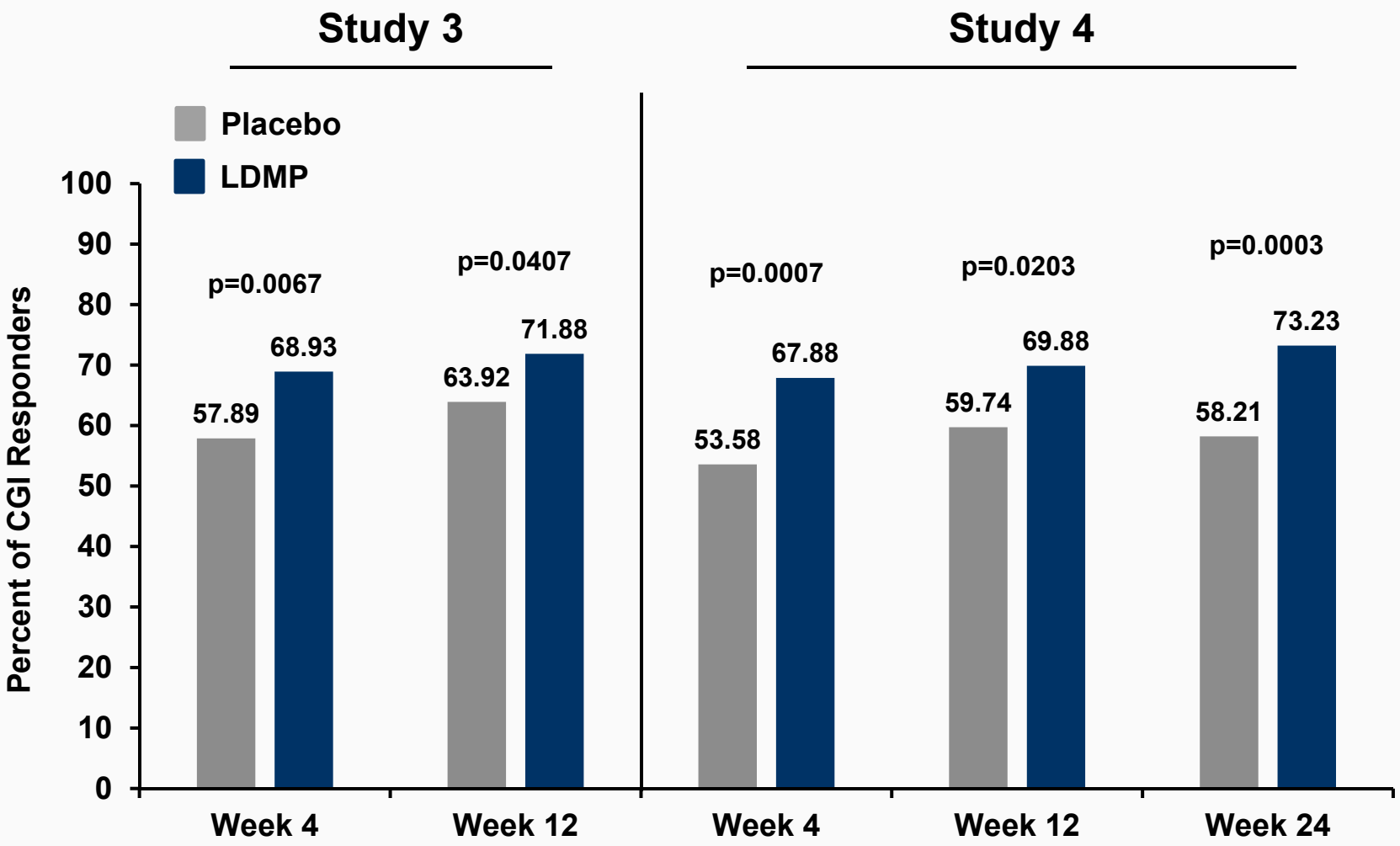
Clinical Global Impression (CGI)

Studies 3 and 4: mITT Population



Benefit/Risk Conclusion

- Need for nonhormonal treatment options
- LDMP demonstrates benefit
  - Reduces frequency and severity
  - Clinically meaningful
  - Persistent
- LDMP well-tolerated
- Favorable benefit/risk profile

Independent Consultants Available to Answer Questions

Gerard Sanacora , MD, PhD

Director of the Yale Depression Research Program
Professor of Psychiatry at Yale School of Medicine

Annette Stemhagen, DrPH, FISPE

Senior Vice President
Safety, Epidemiology, Registries and Risk Management
United BioSource Corporation

Nelson B. Watts, MD

Director, Mercy Health Osteoporosis and Bone Health Services
Cincinnati, OH

Backup Slides Shown

Postmarketing Bone Safety Study

- Prospective, randomized placebo-controlled
- Proposed assessments
  - Spine/hip bone mineral density
  - Bone turnover markers
    - Serum CTX
    - P1NP

Placebo Effect in VMS Clinical Trials

- LDMP phase 3 trials
  - 40-48% for placebo
- Hormone therapy[a]
  - 46-58% for placebo effect
- Literature for paroxetine
  - 42.9% placebo response rate[b]

[a]Cochrane review, 2009
EttingerEB Am J Med (2005) Dec 19; 118 (12 B): 74S-78S
[b]StearnsV et al, Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *JAMA*. 4 Jun 2003; 289: 2827-2834.

Subgroup Analysis by Race for All AEs, Cardiovascular AEs, and Hepatic AEs

Category	Placebo		LDMP	
	White or Caucasian N=462 n (%)	Black or African American N=161 n (%)	White or Caucasian N=430 n (%)	Black or African American N=190 n (%)
All TEAEs	224 (48.5)	69 (42.9)	237 (55.1)	76 (40.0)
CV TEAEs	7 (1.5)	10 (6.2)	15 (3.5)	11 (5.8)
Hepatic TEAEs	5 (1.1)	1 (0.6)	1 (0.2)	2 (1.1)

Single Hot Flash Severity versus Total Patient Burden

Average weighted severity score of a single hot flash

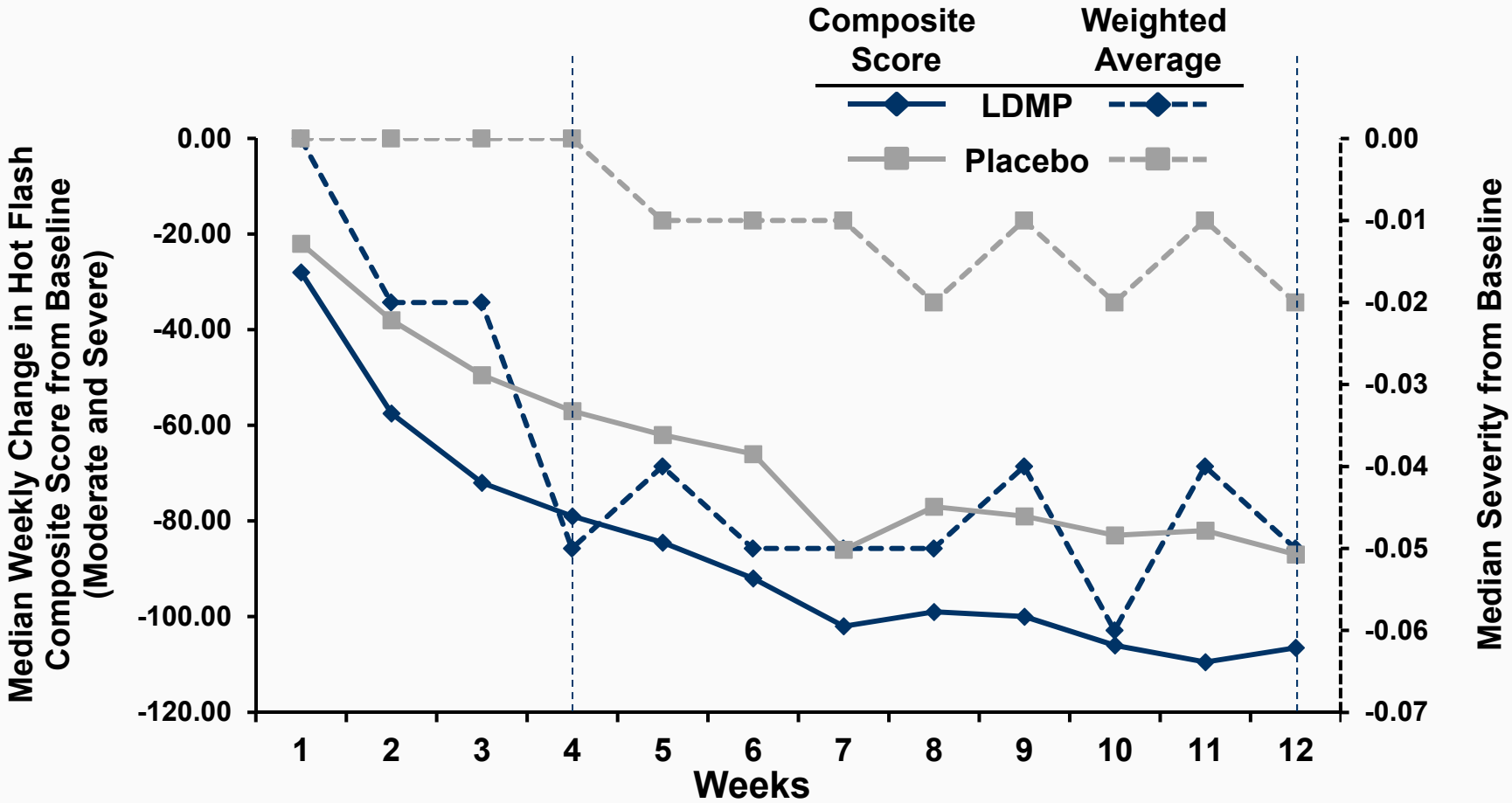
• 50 severe • 50 moderate	$\frac{3 \times 50 + 2 \times 50}{50 + 50} = 2.5$
• 1 severe hot flash	$\frac{3 \times 1 + 2 \times 0}{1 + 0} = 3.0$
• 0 hot flashes	Indeterminate

Composite score (total patient burden)

• 50 severe • 50 moderate	$3 \times 50 + 2 \times 50 = 250$
• 1 severe hot flash	$3 \times 1 + 2 \times 0 = 3$
• 0 hot flashes	0

Median Weekly Change in Hot Flash Composite Score and Average Weighted Severity Score

Study 3: Week 1 through Week 12, mITT

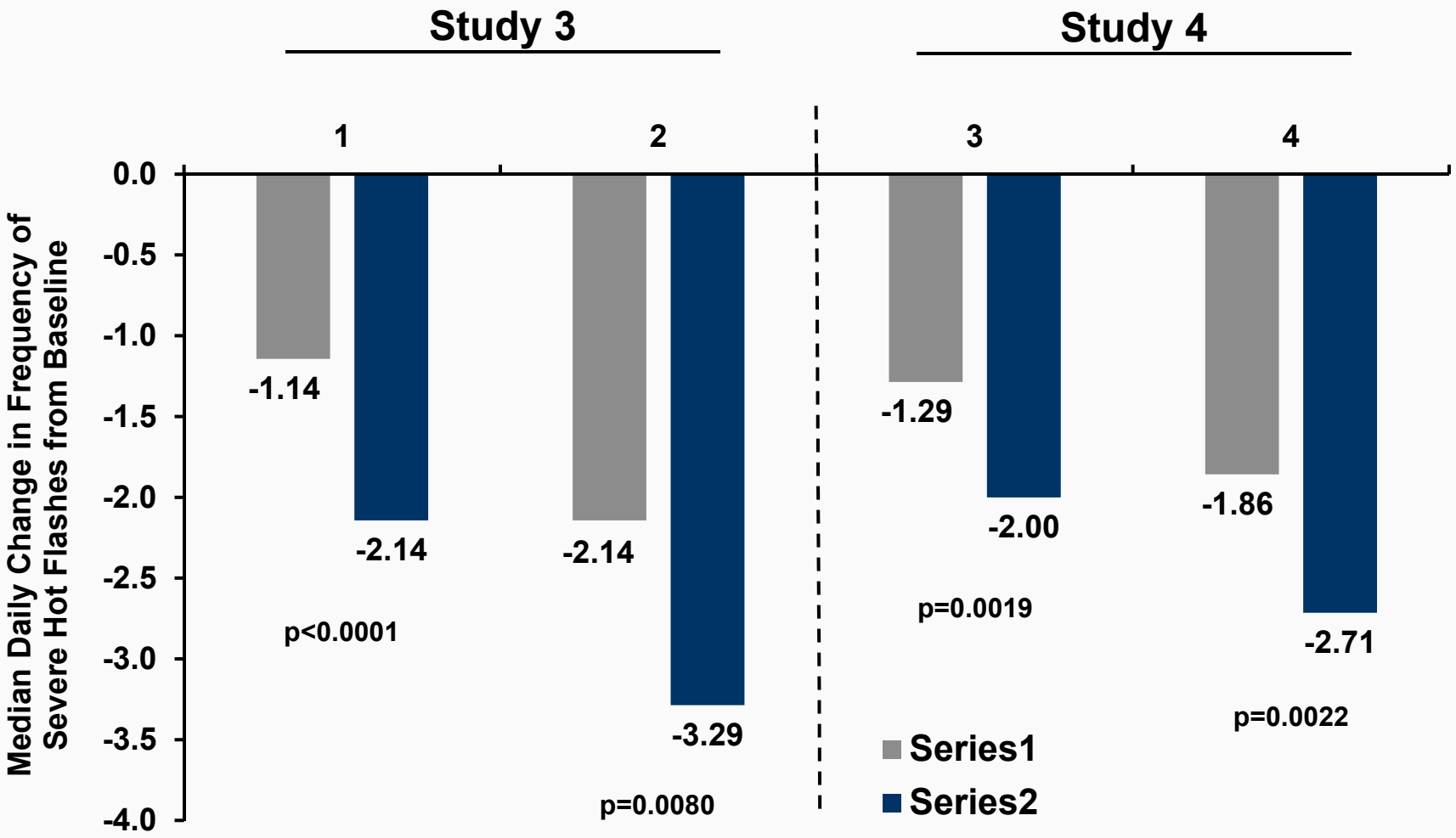


Comp. Scr. PBO (N=305)	305	301	298	293	289	286	285	283	280	278	276	274
Comp. Scr. LDMP (N=301)	301	296	292	289	288	281	277	277	275	273	268	264
Wt. Avg. PBO (N=305)	305	300	295	289	284	278	278	273	265	264	258	253
Wt. Avg. LDMP (N=301)	301	293	287	281	276	267	260	259	254	249	242	236

EF-113

Median Daily Change in Frequency of Severe Hot Flashes – Exploratory Analysis

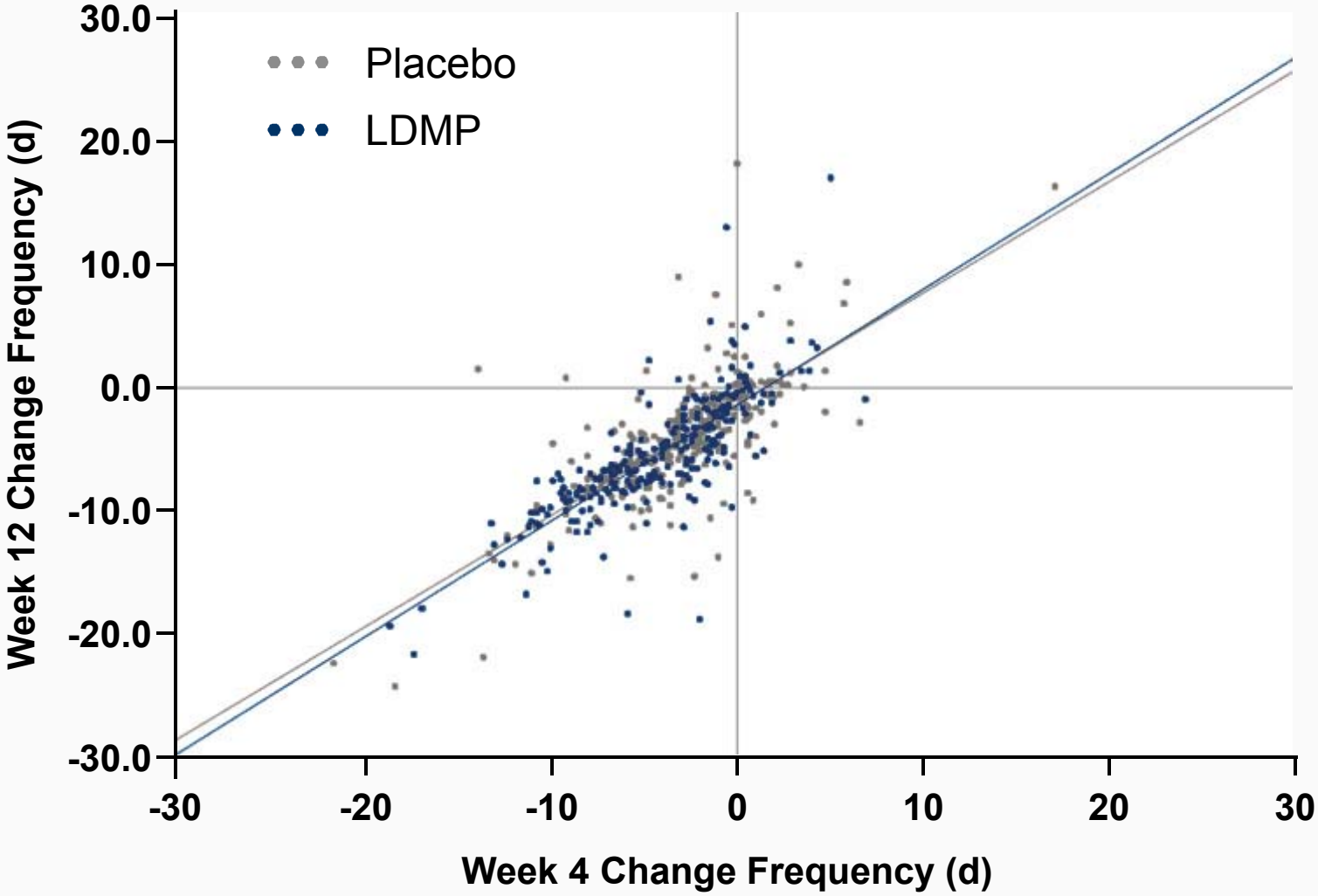
Studies 3 and 4: mITT Population



EF-162

Persistence from 4 Weeks to 12 Weeks

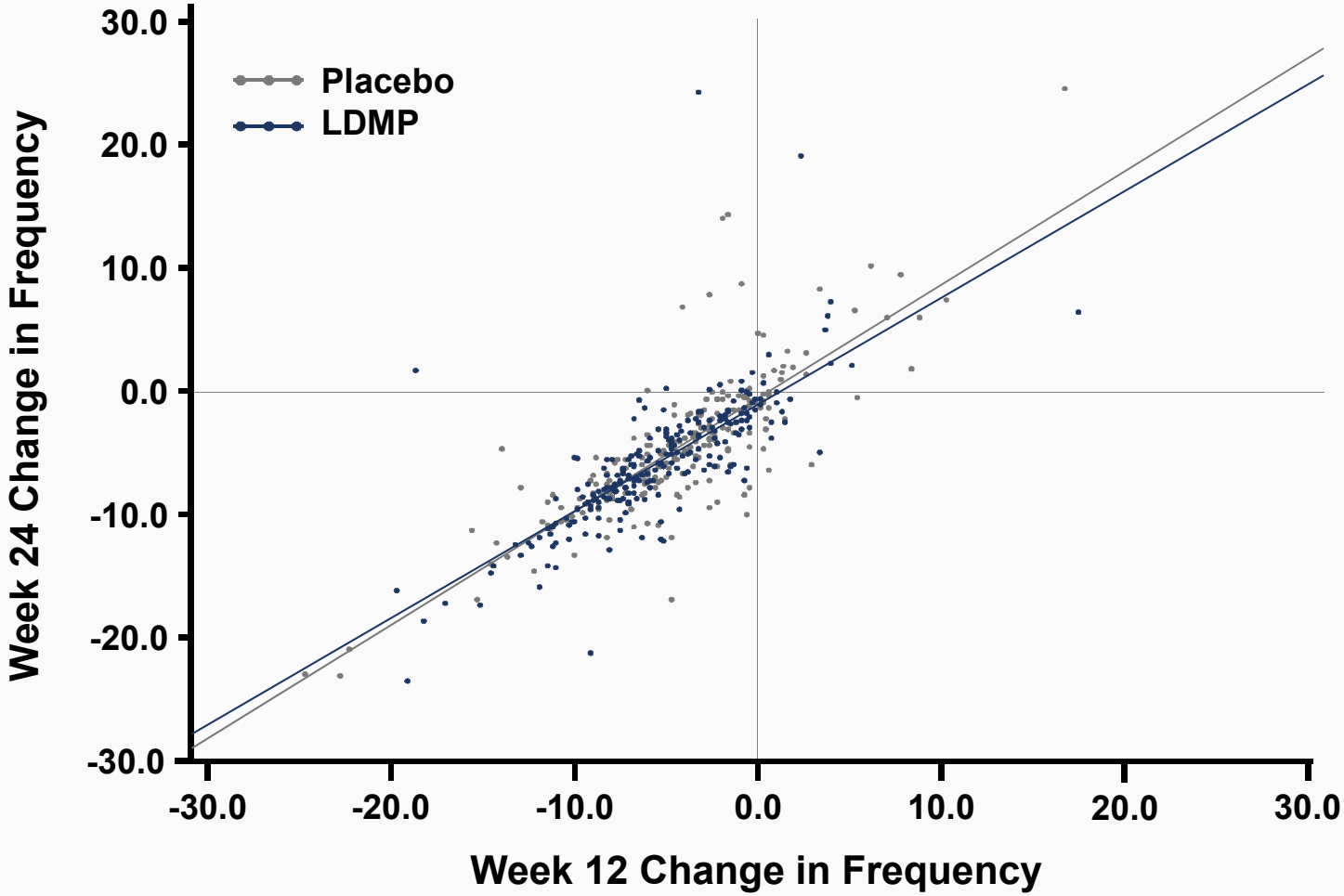
Study 4



EF-207

Persistence of Benefit – Week 12 to Week 24

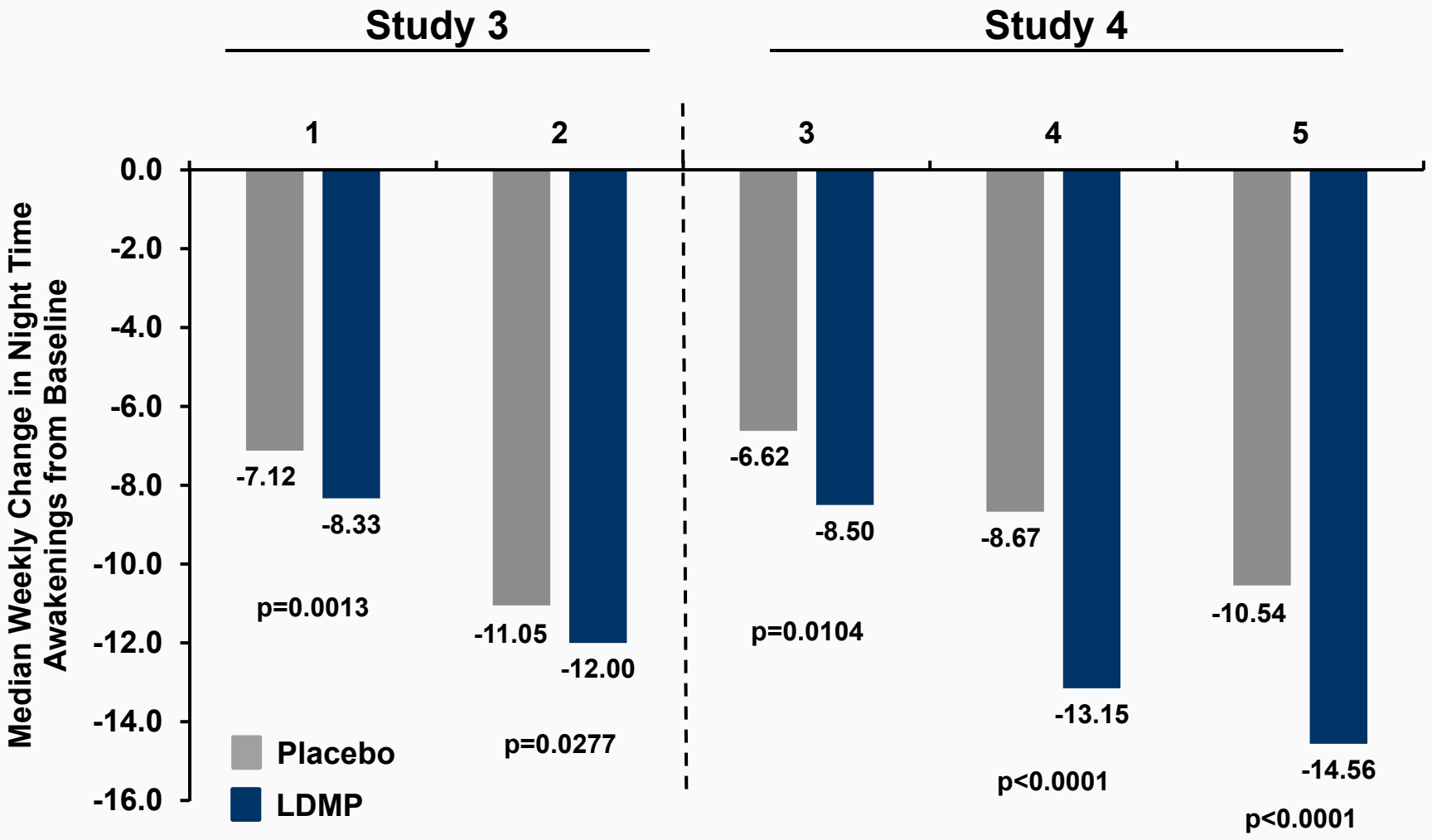
Study 4: mITT



EF-208

Night Time Awakenings

Studies 3 and 4: mITT Population

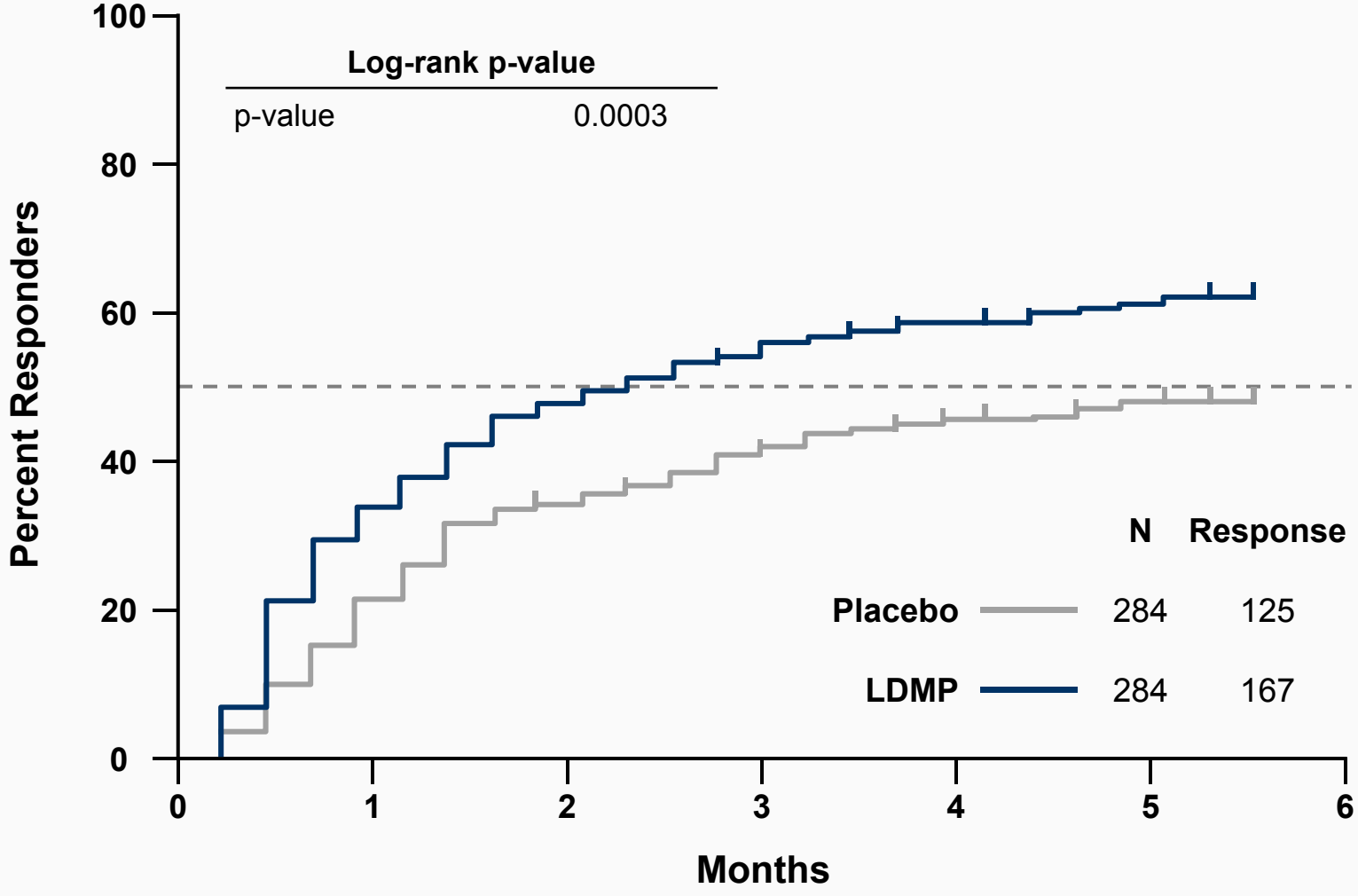


EF-131

Time to Durable Response

Study 4, mITT

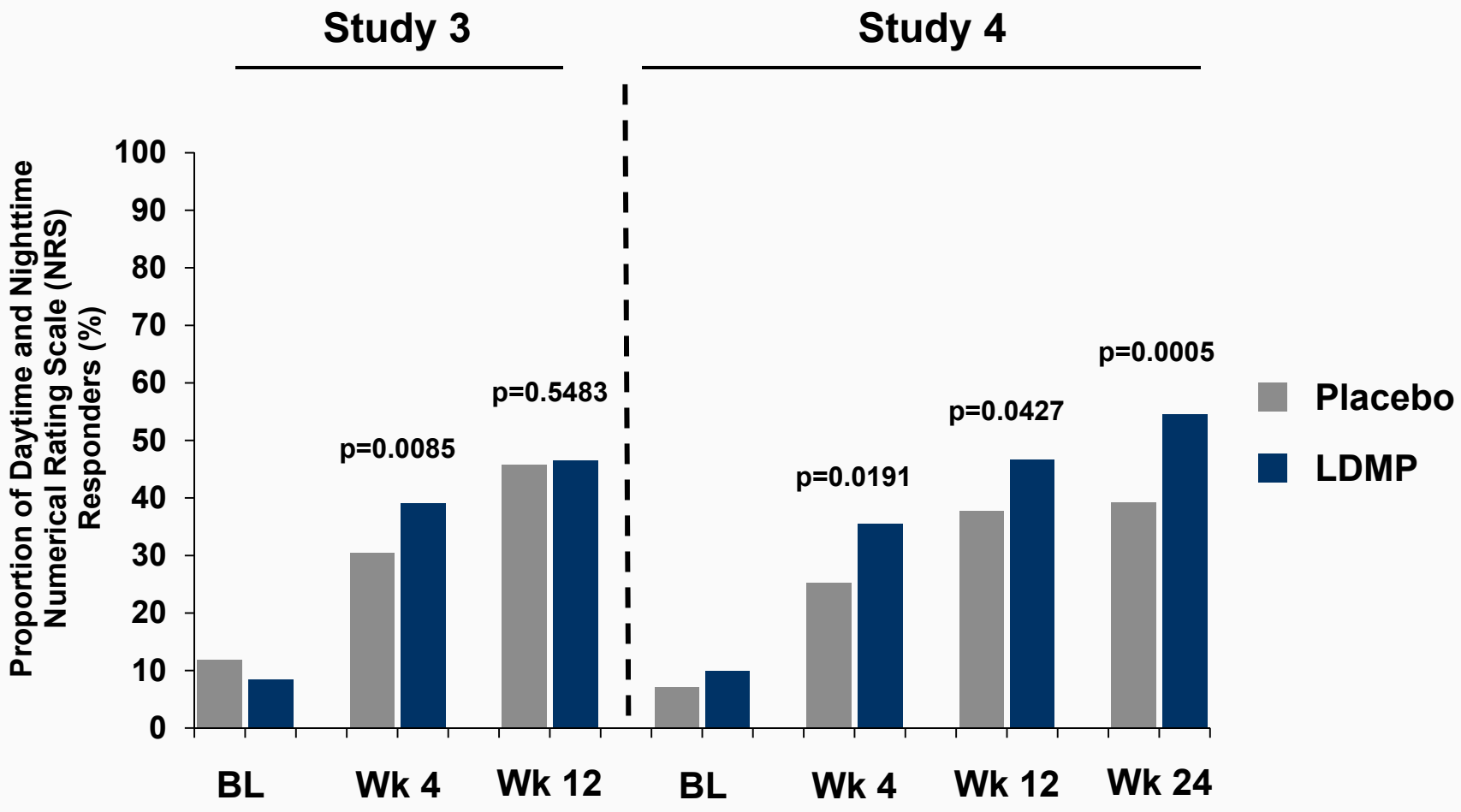
Response: ≥50% decrease in frequency for ≥3 consecutive weeks



EF-203

Proportion of Daytime and Nighttime Numerical Rating Scale (NRS) Responders

Studies 3 and 4: mITT Population

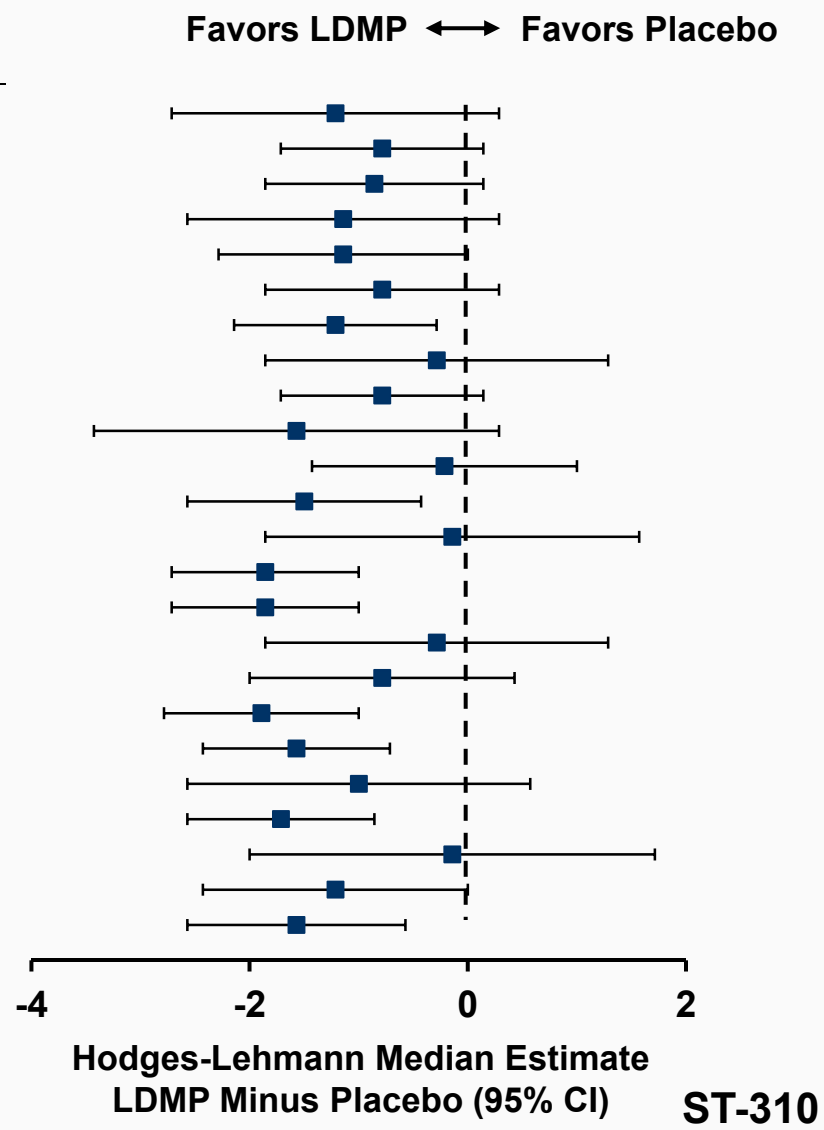


EF-157

Effect Modification Analysis: Change Frequency Difference

Week 12

	Factor	Factor Value	N	Frequency (d)
Study 3	Race	AfAm	164	(84:80)
		Non-AfAm	374	(180:194)
		Cauc	361	(176:185)
		Non-Cauc	177	(88:89)
	Age	<54.0	261	(126:135)
		≥54.0	277	(138:139)
	BMI Class	BMI <32	389	(193:196)
		BMI ≥32	148	(70:78)
	Menopause Type	Natural	437	(212:225)
		Surgical	101	(52:49)
	Menopause Dur. (y)	<5.0	241	(120:121)
		≥5.0	295	(143:152)
Study 4	Race	AfAm	108	(60:48)
		Non-AfAm	393	(197:196)
		Cauc	378	(188:190)
		Non-Cauc	123	(69:54)
	Age	<54.0	226	(115:111)
		≥54.0	275	(142:133)
	BMI Class	BMI <32	376	(197:179)
		BMI ≥32	125	(60:65)
	Menopause Type	Natural	402	(206:196)
		Surgical	99	(51:48)
	Menopause Dur. (y)	<5.0	210	(113:97)
		≥5.0	285	(143:142)

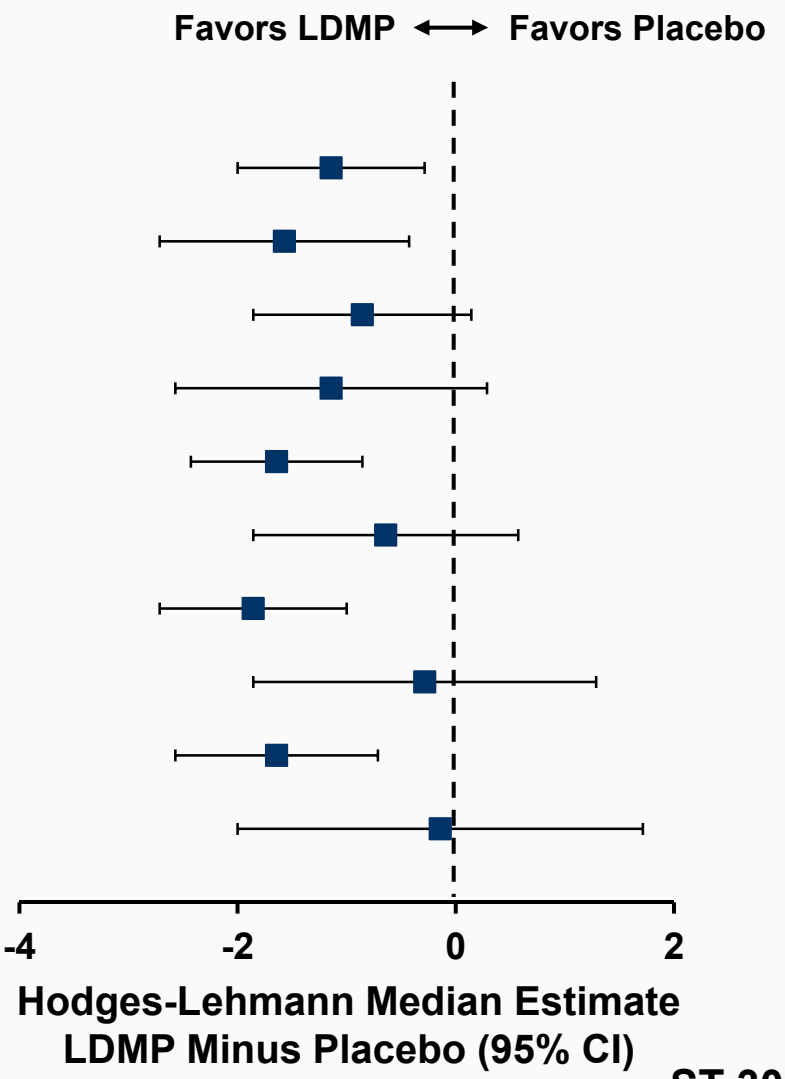


ST-310

Effect Modification Analysis: Change Frequency Difference

Factor: Race

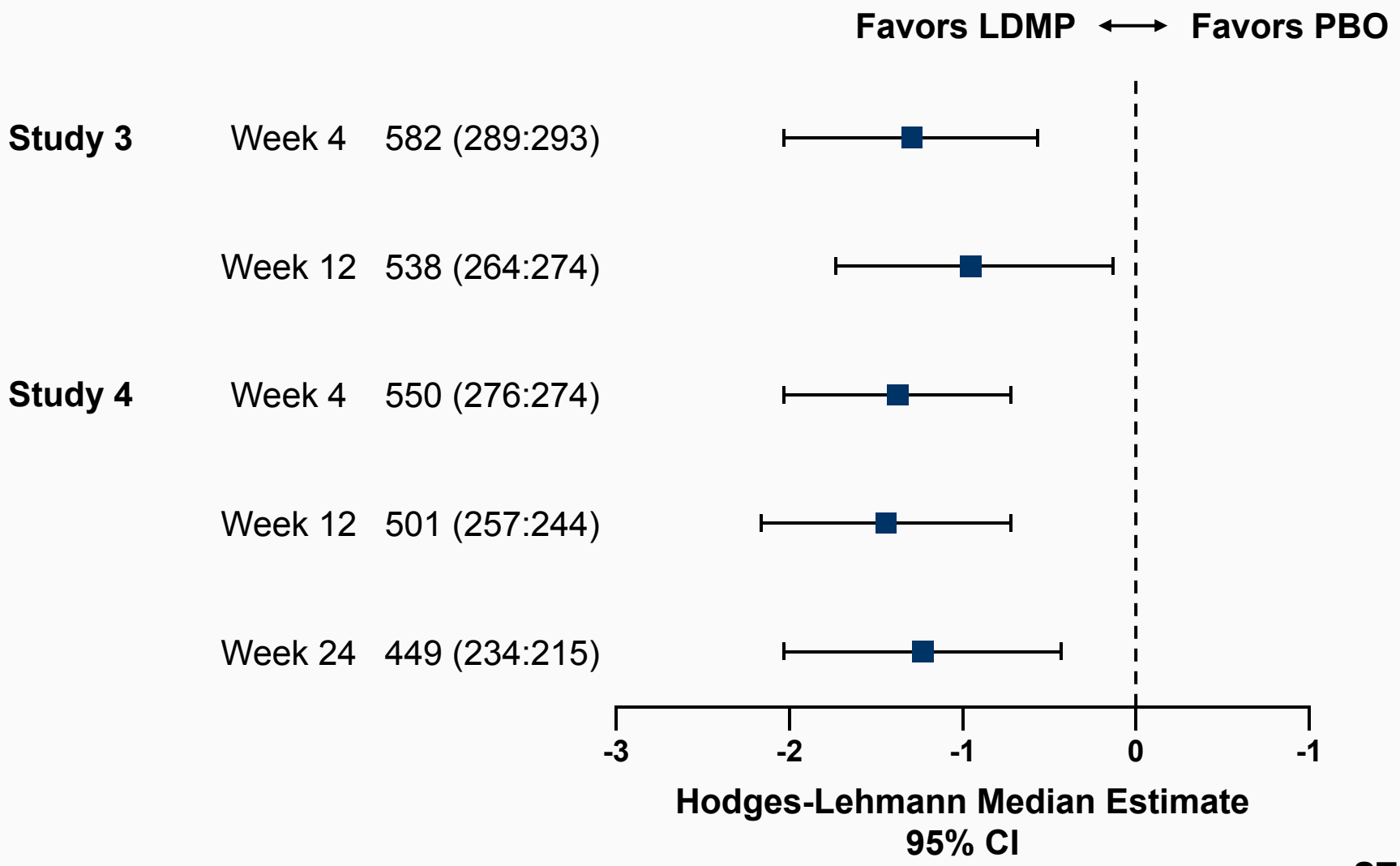
	Week	Race	N	Frequency (d)
Study 3	4	Cauc	380	(185:195)
		Non-Cauc	202	(104:98)
	12	Cauc	361	(176:185)
		Non-Cauc	177	(88:89)
Study 4	4	Cauc	416	(200:216)
		Non-Cauc	134	(76:58)
	12	Cauc	378	(188:190)
		Non-Cauc	123	(69:54)
	24	Cauc	346	(177:169)
		Non-Cauc	103	(57:46)



Cauc= Caucasian

ST-304

Change Frequency
Studies 3 and 4 by Arm



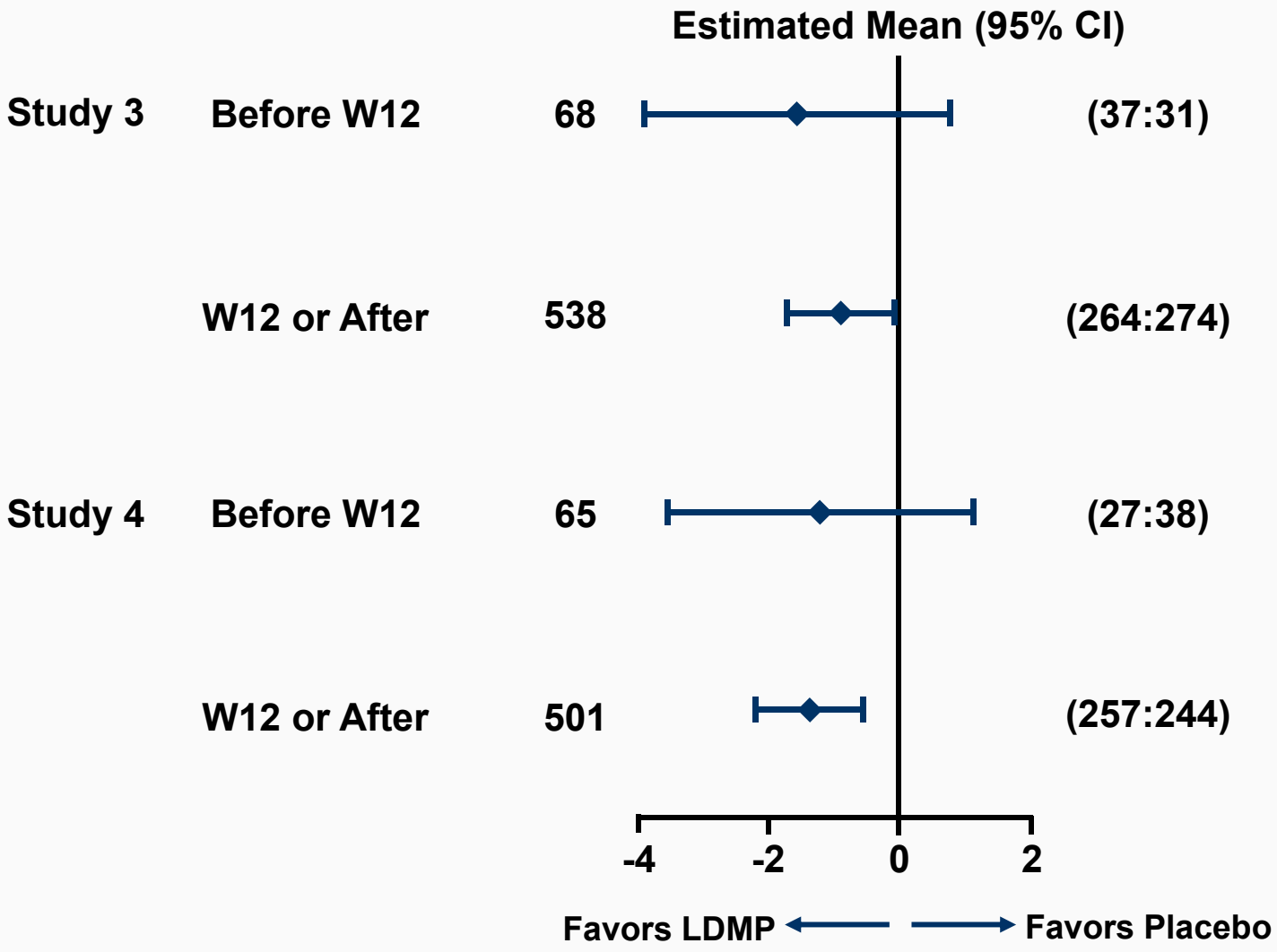
ST-276

Missing Data

- Primary analysis done on observed data (completers analysis)
- High percentage of completers at Weeks 4 and 12 for example at Week 12:
- No evidence of imbalance between arms

	Study3	Study 4
Control arm	90%	87%
Experimental arm	88%	91%

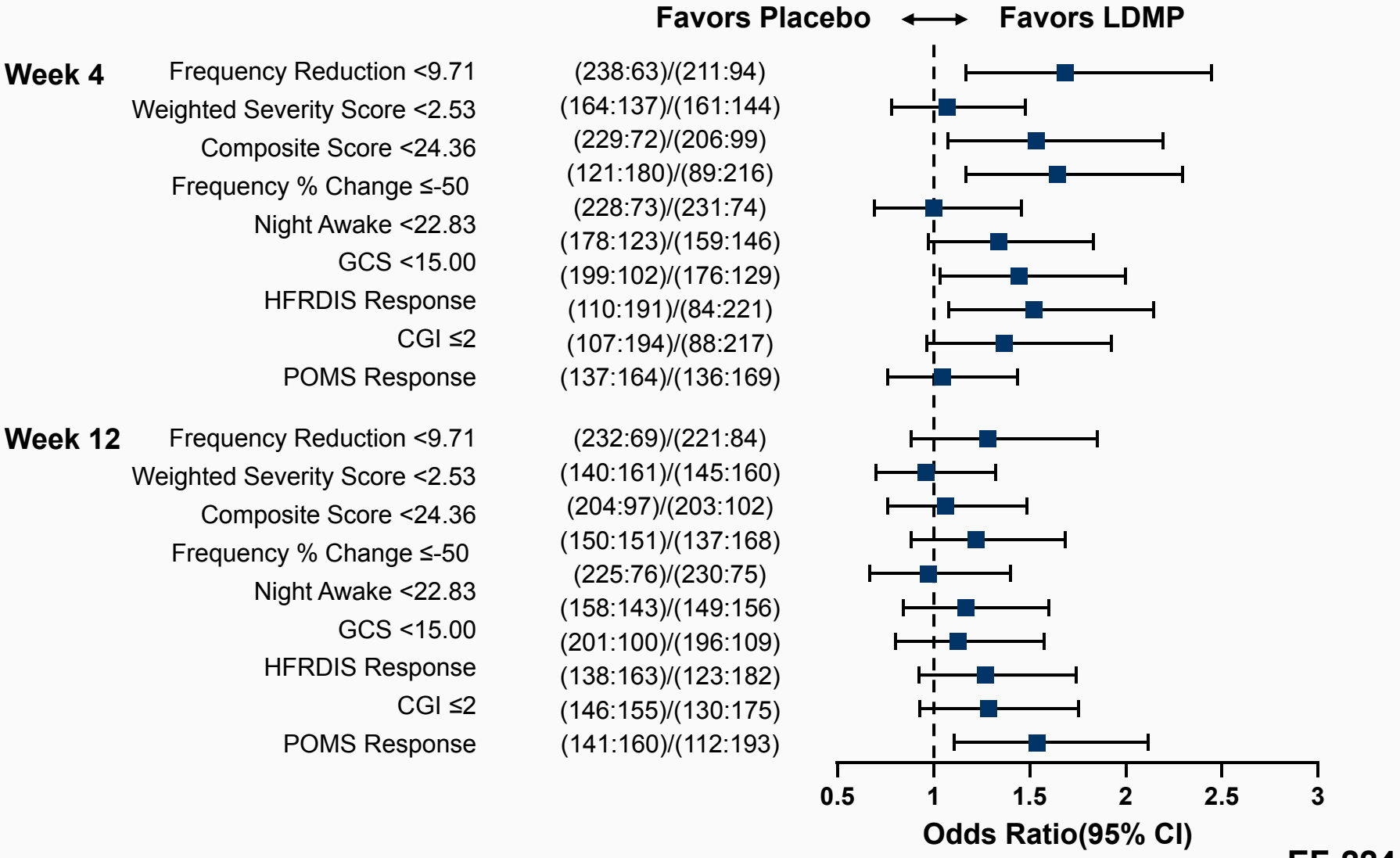
Study Exit Before Week 12 vs After Week 12 Between-arm Difference of Daily Frequency Change At Week 12 or Last Measured before Week 12



ST-125

Multiple Outcomes by Treatment Arm

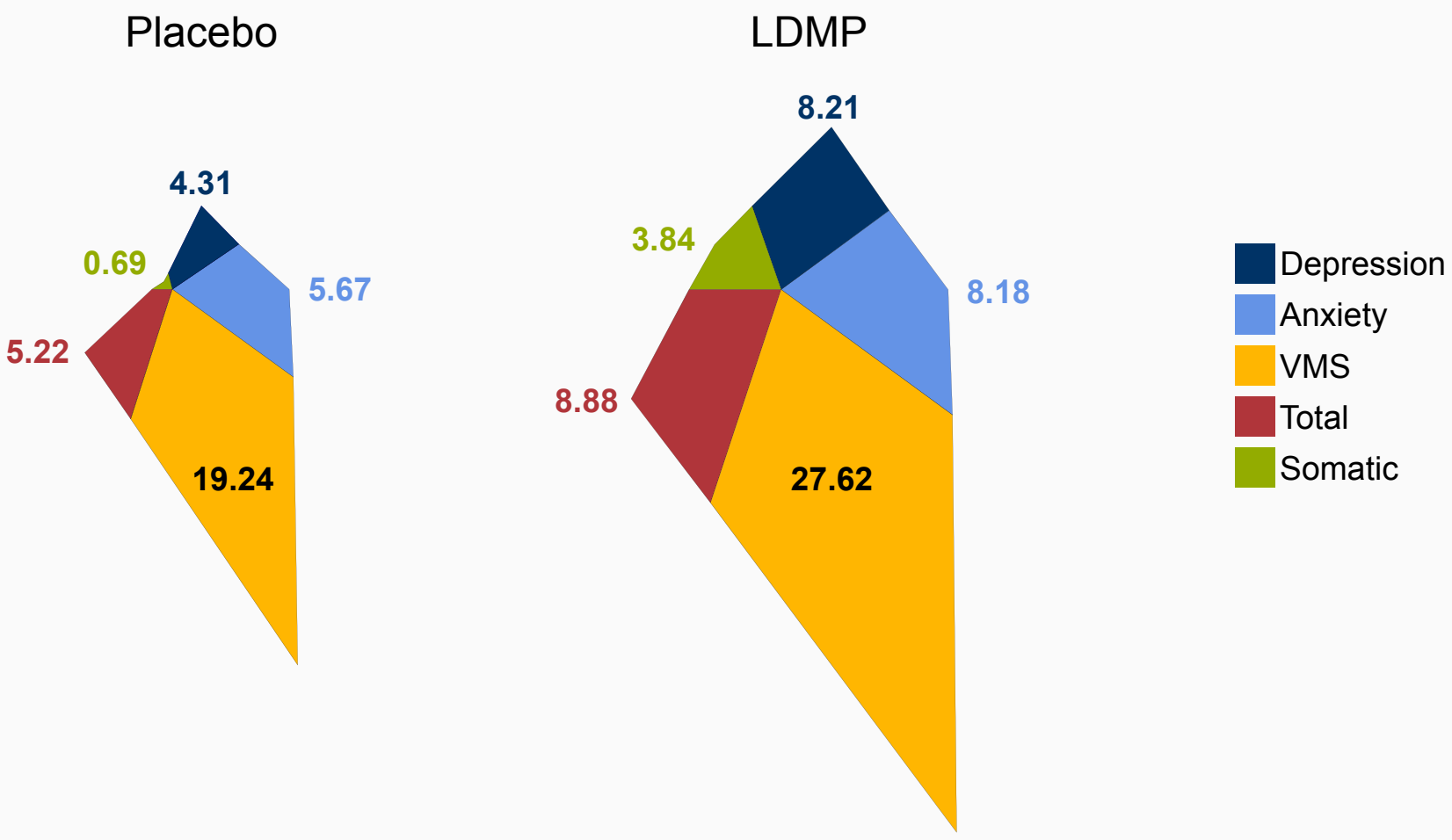
Study 3: mITT



EF-224

GCS Changes: Percent of Maximum Possible Reduction

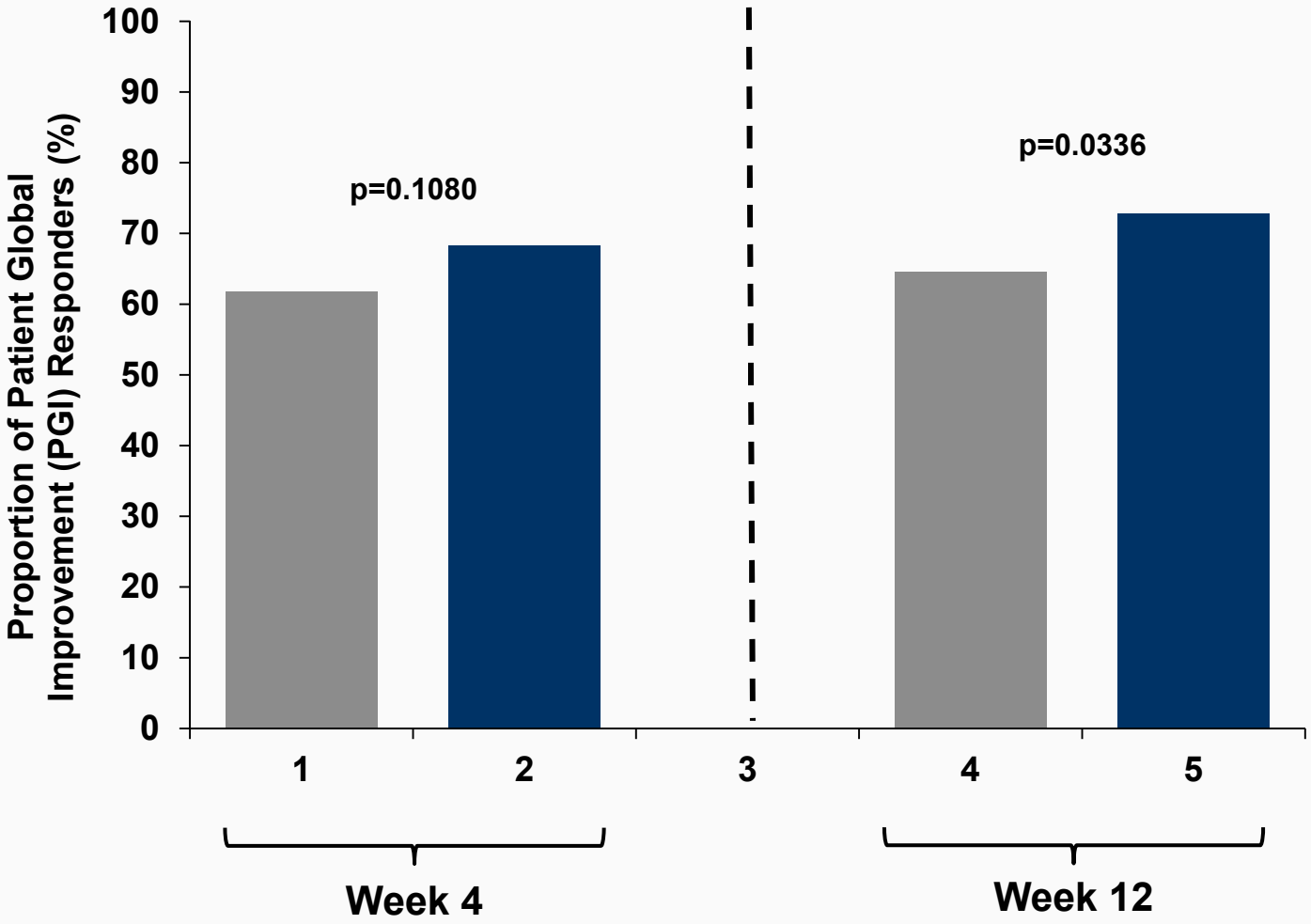
Study 4: Week 12



EF-240

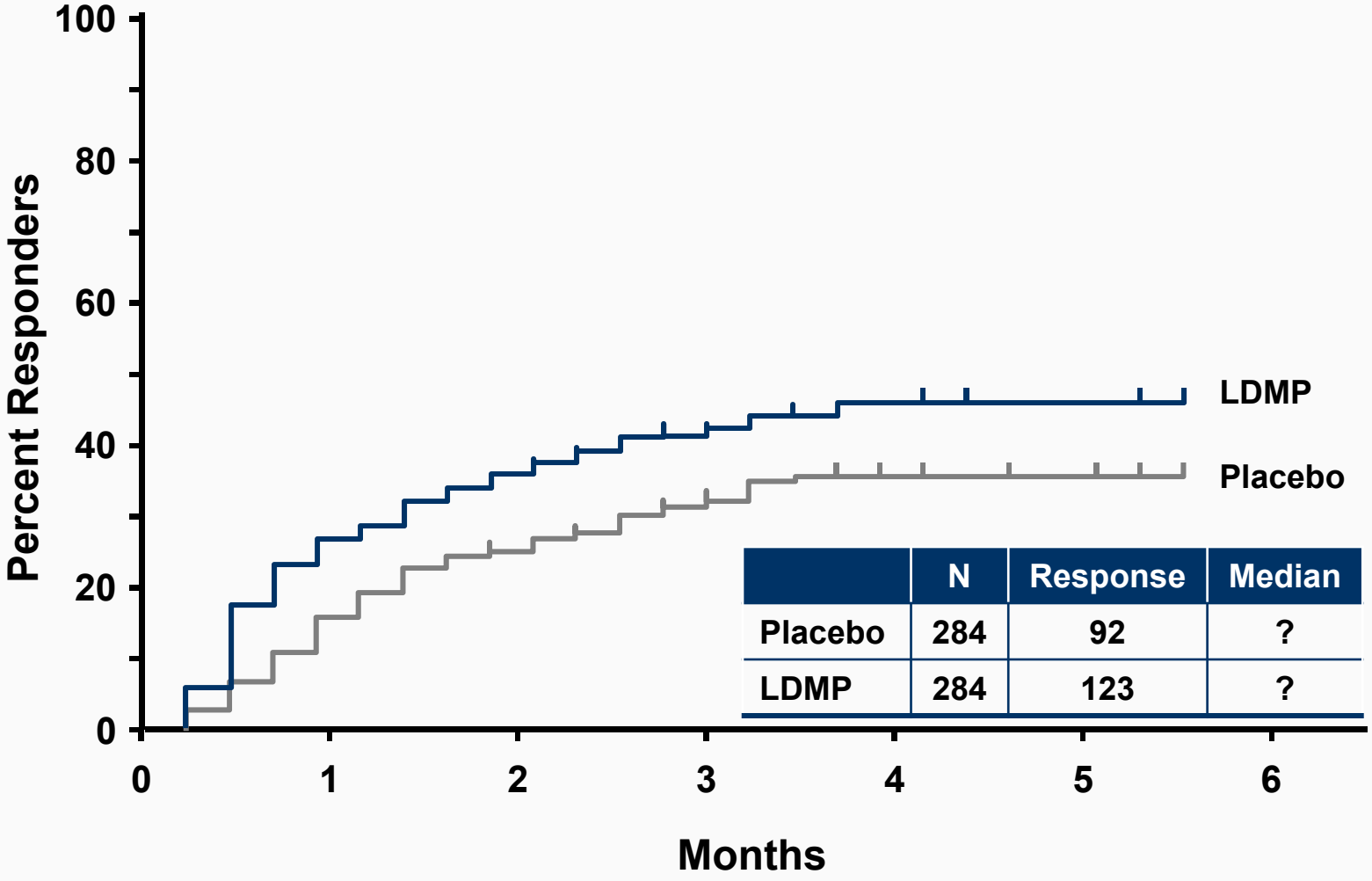
Patient Global Improvement

Study 3: mITT Population



Missing values equals non-responders

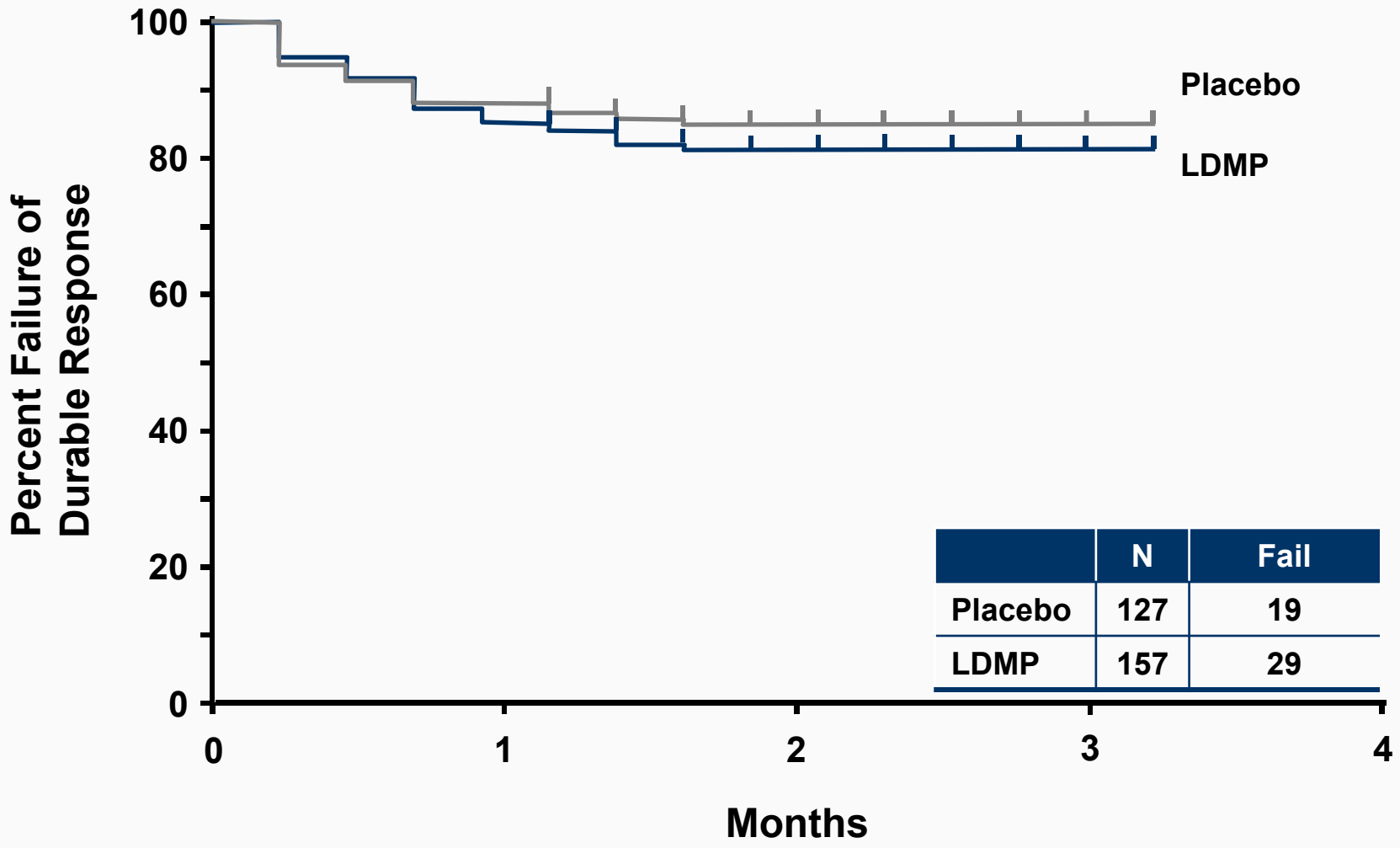
Time to Durable Response
Durable Response: ≥50% Decrease for ≥8 Weeks
Study 4



	N	Response	Median
Placebo	284	92	?
LDMP	284	123	?

ST-293

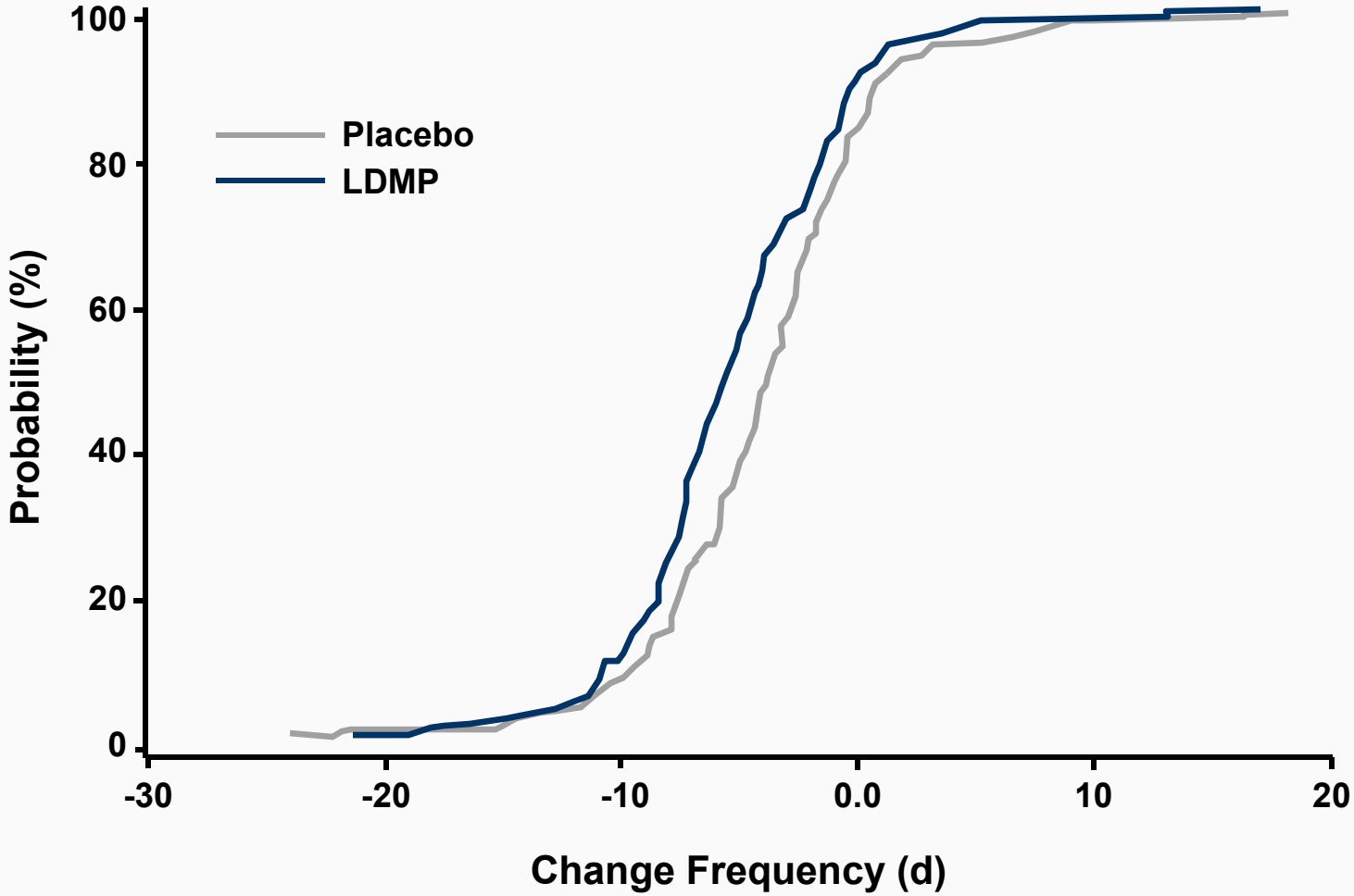
Time to Failure of Durable Response
Durable Response: ≥50% Decrease for ≥3 Weeks
Study 3



	N	Fail
Placebo	127	19
LDMP	157	29

ST-289

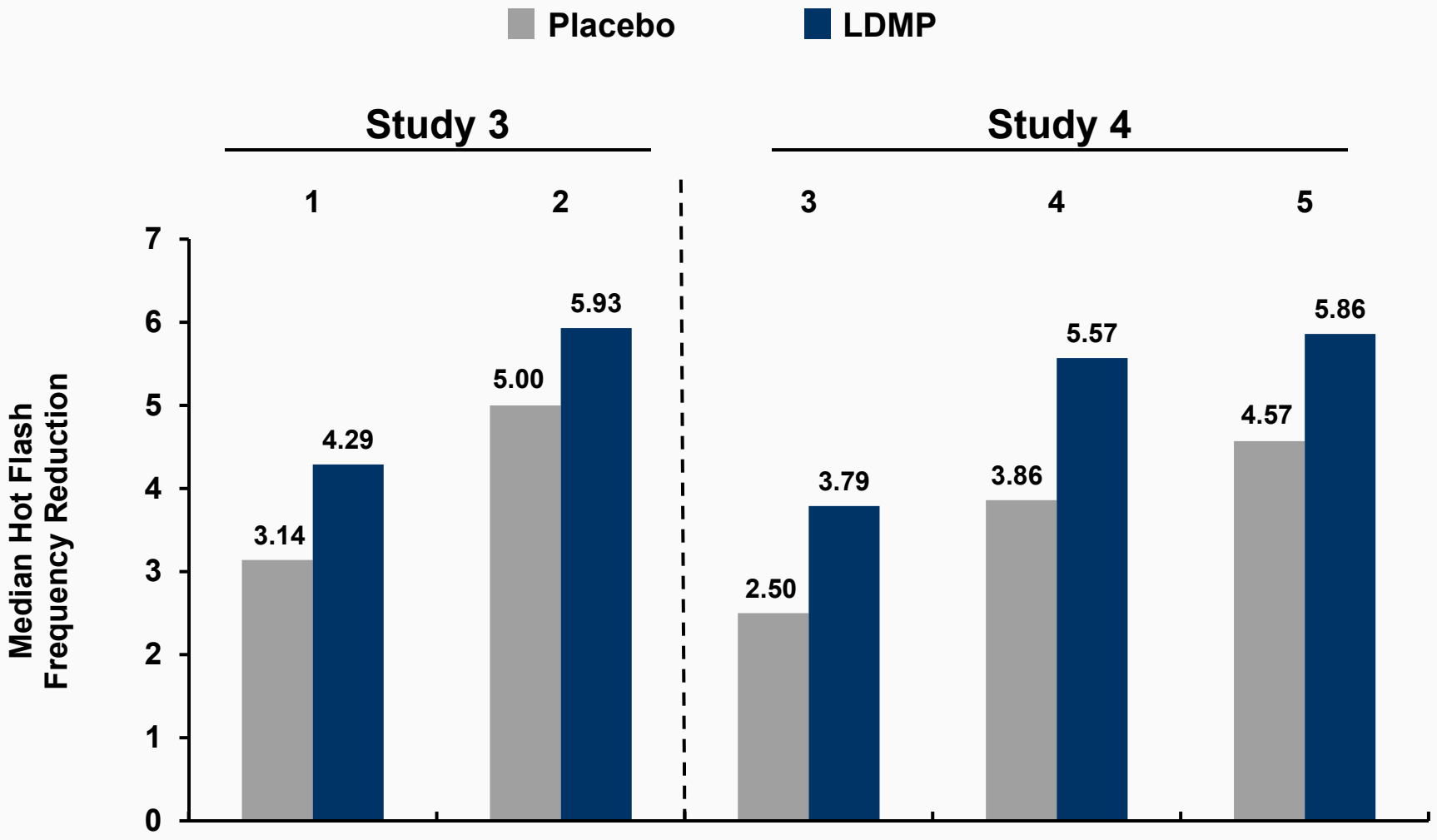
Change Frequency Cumulative Distributions by Arm
Study 4: Week 12



ST-189

Absolute Daily Reduction in Frequency

Studies 3 and 4



EF-205

Paroxetine by Strengths

	Dose						
Diagnosis	**10 mg**	**12.5 mg**	**20 mg**	**25 mg**	**30 mg**	**37.5 mg**	**40 mg**
GYN + Other	1.30%	0.15%	3.93%	0.41%	0.96%	0.17%	1.91%
NEUR	5.55%	0.63%	17.08%	1.86%	4.58%	0.83%	8.91%
PAIN + Other	4.72%	0.52%	14.53%	1.52%	3.71%	0.68%	7.27%
SKIN + URI + Other	1.06%	0.12%	3.26%	0.34%	0.85%	0.15%	1.65%
VMS + Other	0.86%	0.10%	2.59%	0.27%	0.64%	0.12%	1.25%
VMS Only	0.82%	0.10%	2.46%	0.27%	0.61%	0.10%	1.16%