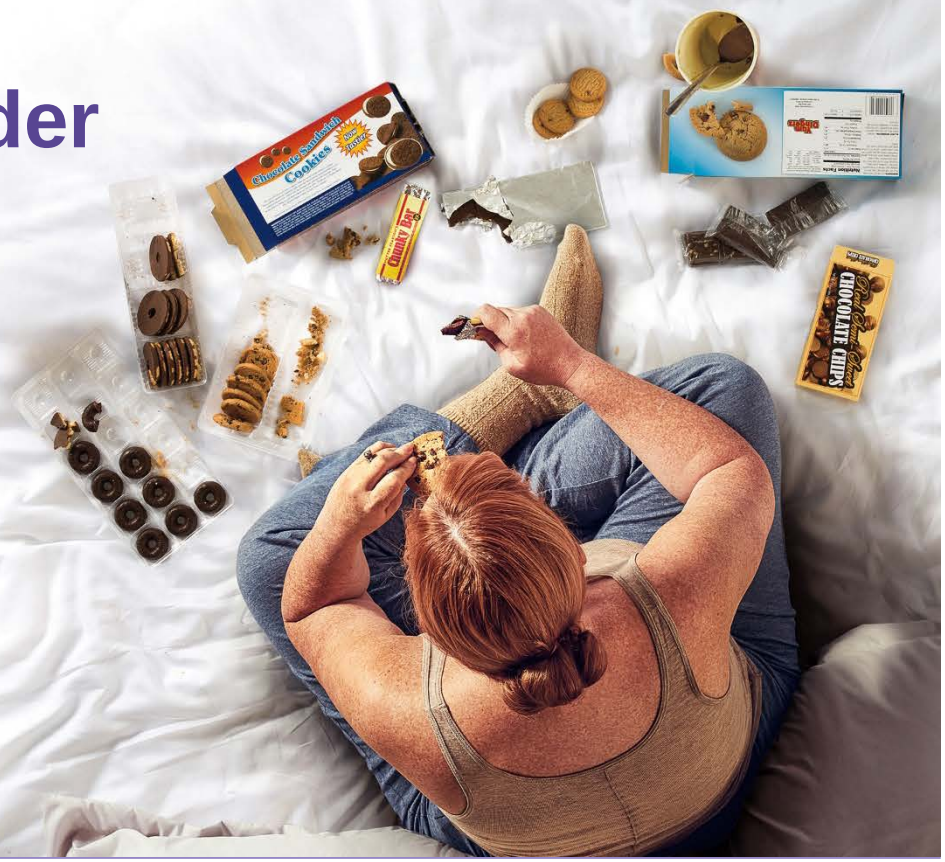
Vyvanse®*
(lisdexamfetamine dimesylate capsules)

for the Treatment of Moderate to Severe Binge Eating Disorder



Limitation of Use for Binge Eating Disorder (BED):

Prescribers should consider that serious cardiovascular (CV) events have been reported with this class of sympathomimetic drugs. The BED clinical trials were not designed to assess CV safety. While there is an accumulation of safety data with VYVANSE use in the ADHD population, this is of limited relevance regarding CV risk in the BED population. Given the higher CV risk associated with obesity, the BED population may be at a higher risk.

The safety and effectiveness of VYVANSE for the treatment of obesity have not been established. VYVANSE is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular adverse events.

Safety and effectiveness in patients less than 18 years of age have not been established. Subjects over 55 years of age were excluded from the BED clinical trials.

Disclosures

- **Faculty**:
  - Brian Stonehocker, MD, FRCPC
    - Divisional Director, Division of Consultation Liaison Psychiatry, University of Alberta
    - Psychiatrist, Edmonton Bariatric Clinic
    - Assistant Clinical Professor, Department of Psychiatry, University of Alberta
- **Relationships with commercial interests**:
  - Speakers' Bureau: Shire, Lundbeck, Lilly

Treatment of Binge Eating Disorder

- Therapy
  - Cognitive Behavioural Therapy
  - IPT
- Medications
  - Approved
    - Lisdexamfetamine
  - Off Label
    - Antidepressants
    - Anticonvulsants - Topiramate

The 1st and Only Medication in Canada Indicated for the Treatment of Moderate to Severe Binge Eating Disorder in Adults†

VYVANSE is indicated for the treatment of: moderate to severe BED in adults

- Recurrent episodes of binge eating are characterized by:
  - consumption of an abnormally large amount of food in a short period of time and sense of lack of control over eating during the episode
  - marked distress about the behavior
  - feeling disgusted or guilty, or eating alone because of embarrassment

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†Moderate binge eating is defined as 4-7 binge-eating episodes per week.
Severe binge eating is defined as 8-13 binge-eating episodes per week.

VYVANSE Product Monograph.

Two Pivotal Phase 3 RCTs with VYVANSE in BED: Objectives

Primary objective:

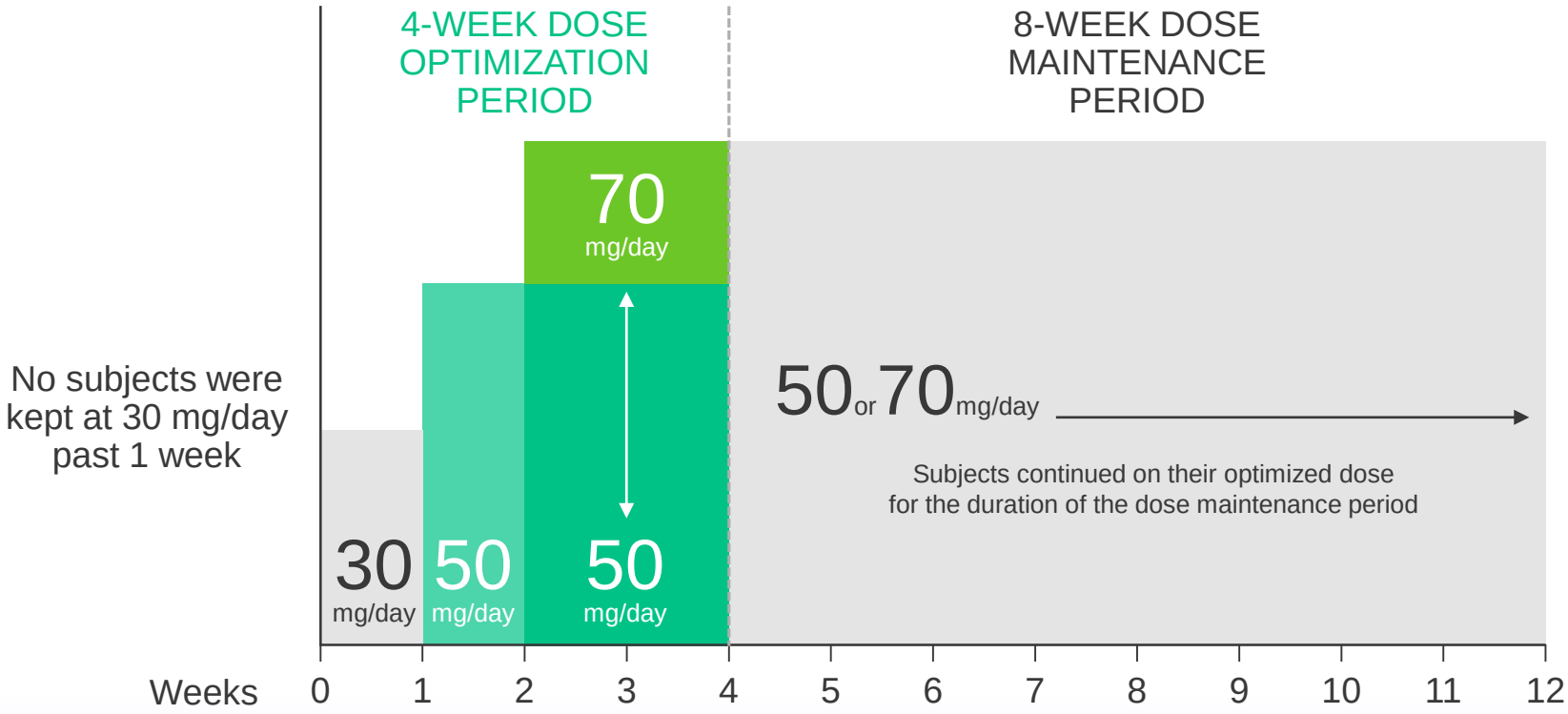
- The primary efficacy outcome for the two studies was defined as the LS mean change from baseline at Week 11/12 in the number of binge days per week. Baseline is defined as the weekly average of the number of binge days per week for the 14 days prior to the baseline visit.

Key secondary objectives:

- To demonstrate the efficacy of VYVANSE compared to placebo from baseline at Visit 8 (Week 12) on:
  - Clinical Global Impression of Improvement (CGI-I) scale
  - 4-week cessation from binge eating behavior for the last 28 days
  - Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE) total score

VYVANSE Product Monograph.
McElroy S, et al. Neuropsychopharmacology 2016; 41(5):1251-60.

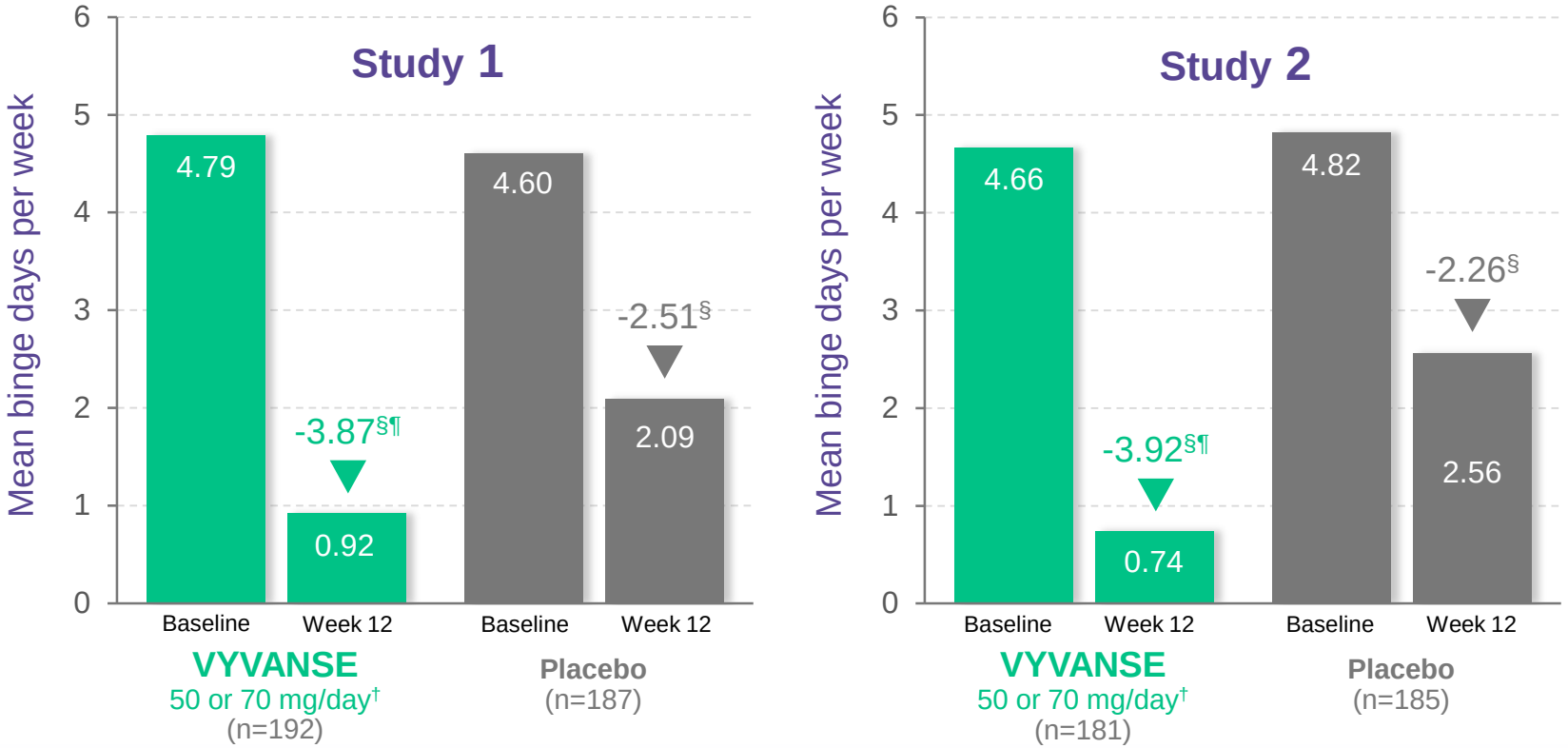
Two Pivotal Phase 3 RCTs with VYVANSE in BED: Design



[†]Both studies were 12 week, randomized, double-blind, multicenter, parallel-group, placebo-controlled dose-optimization studies of adults aged 18-55 years with moderate to severe Binge Eating Disorder. All subjects assigned to VYVANSE treatment were administered a starting titration dose of 30 mg/day up to an optimal dose of either 50 or 70 mg/day, as tolerated and clinically indicated. A “binge day” was defined as a day with at least one binge episode as per the subjects’ daily binge diary.

VYVANSE Product Monograph.
McElroy S, et al. Neuropsychopharmacology 2016; 41(5):1251-60.

Demonstrated Reductions in Mean Number of Binge Days/Week at Week 12 (Primary Endpoint)



Placebo-subtracted difference (95% CI): Study 1: -1.35 (-1.70, -1.01); Study 2: -1.66 (-2.04, -1.28)

†Doses statistically significantly superior to placebo.
§Least-squares mean change from baseline.
¶$p < 0.001$ vs. placebo.

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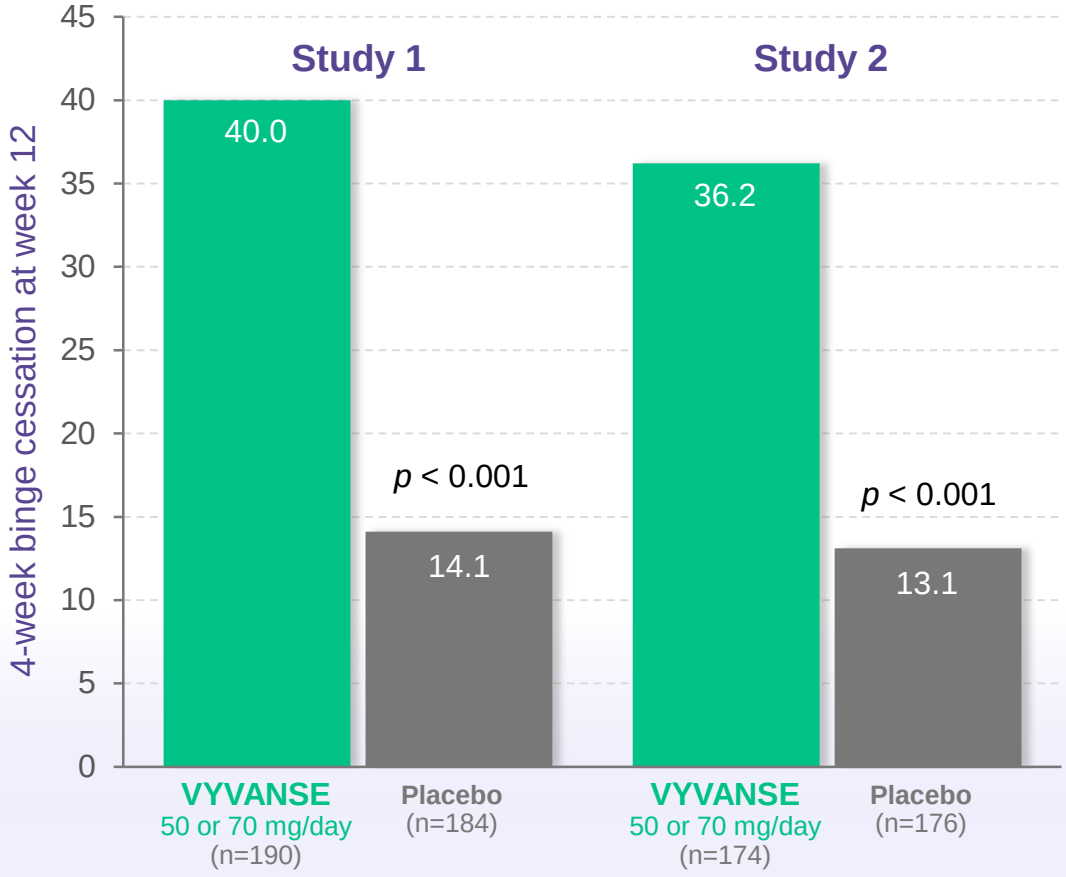
McElroy S, et al. Neuropsychopharmacology 2016; 41(5):1251-60.

Demonstrated 4-week Cessation of Binge Eating at Week 12 (Secondary Endpoint)

Percentage of patients who experienced 4-week cessation of binge eating
in the last 28 days of the study ($p < 0.001$ vs. placebo)



Approximately 6 binge episodes/week at baseline for each of the 4 study arms from the 2 studies
(range 5.96-6.65)

4-week cessation of binge eating was defined as no binge episode for 28 consecutive days before the last study visit.

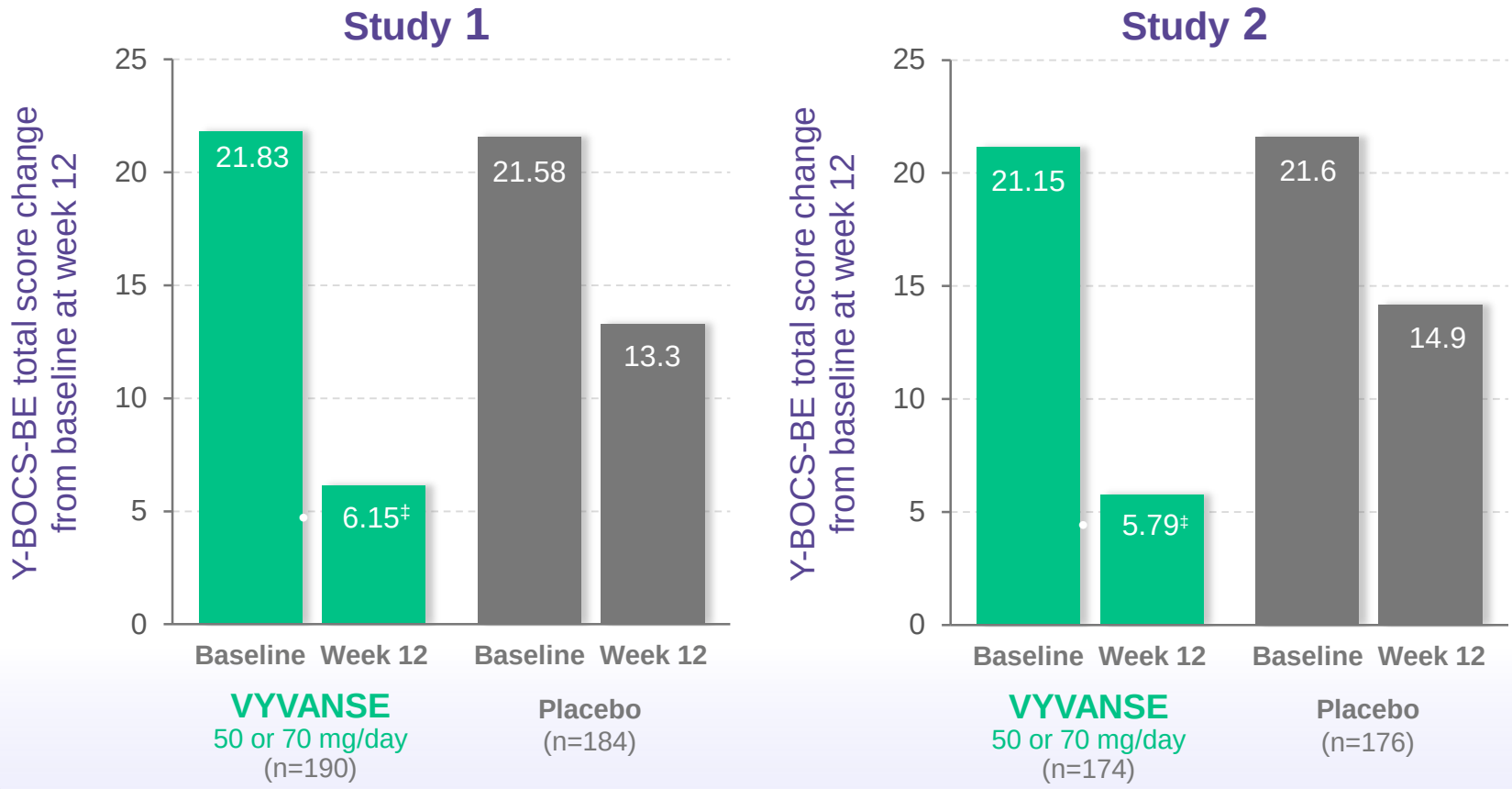
VYVANSE Product Monograph.
McElroy S, et al. Neuropsychopharmacology 2016; 41(5):1251-60.

The Yale-Brown Obsessive Compulsive Scale Modified for Binge Eating (Y-BOCS-BE)

- Y-BOCS-BE assesses **obsessiveness** of binge eating thoughts and **compulsiveness** of binge eating behaviors using a 10-item clinician-rated scale from 0 (no symptoms) to 4 (extreme symptoms)

McElroy S, et al. Neuropsychopharmacology 2016; 41(5):1251-60

Reduced Obsessive Compulsive Binge Eating Symptoms on Y-BOCS-BE at Week 12 (Secondary Endpoint)



‡$p < 0.001$ vs. placebo.

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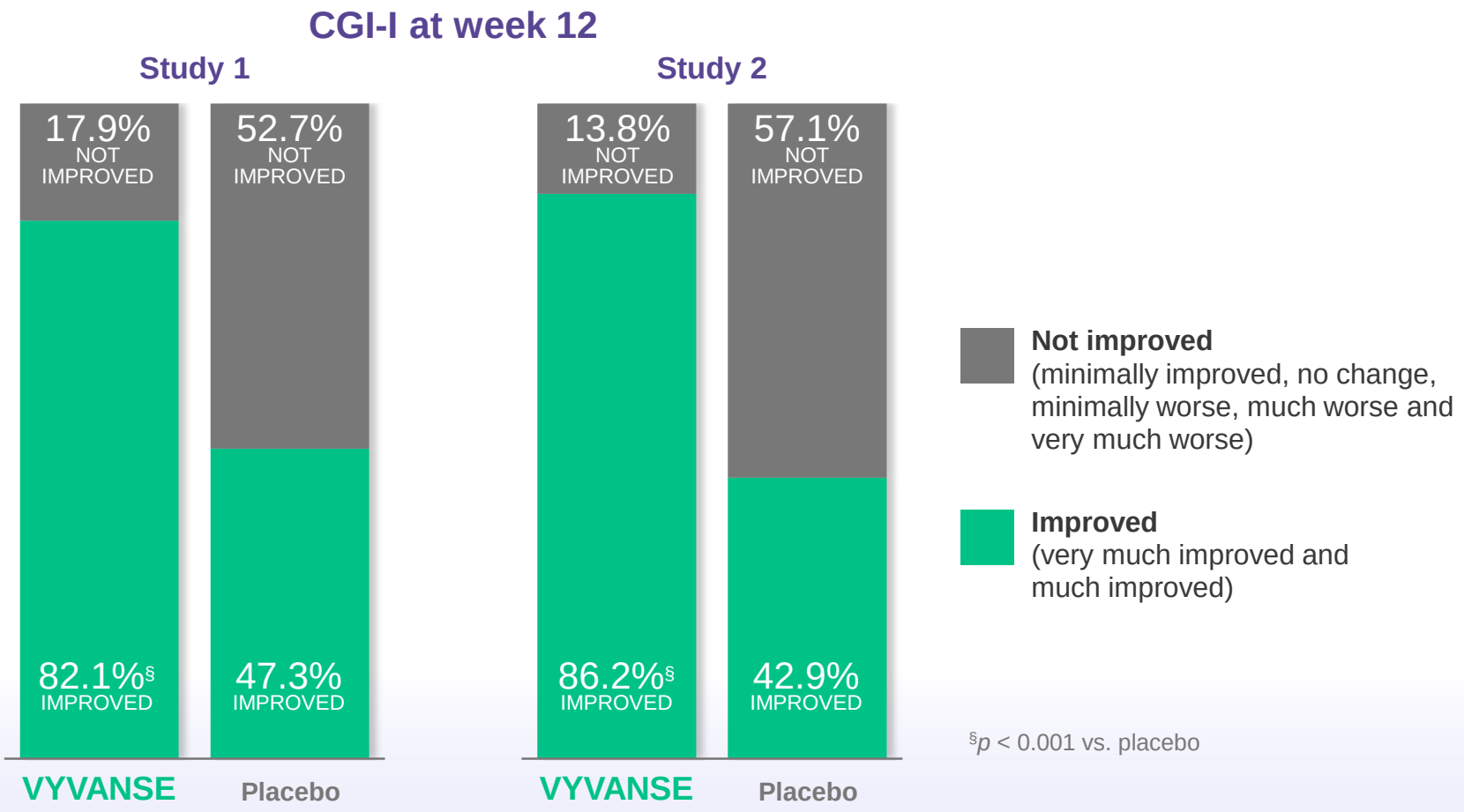
The Clinical Global Impression-Improvement (CGI-I) Scale

- The CGI-I scale was used to assess the overall clinical state of each patient relative to their personal baseline.
- Responses were dichotomized into two categories: Improved or Not Improved

McElroy S, et al. Neuropsychopharmacology 2016; 41(5):1251-60.
Busner J, Targum SD. Psychiatry 2007; 4:28-37.

Demonstrated Improvement on CGI-I Scale at Week 12 (Secondary Endpoint)



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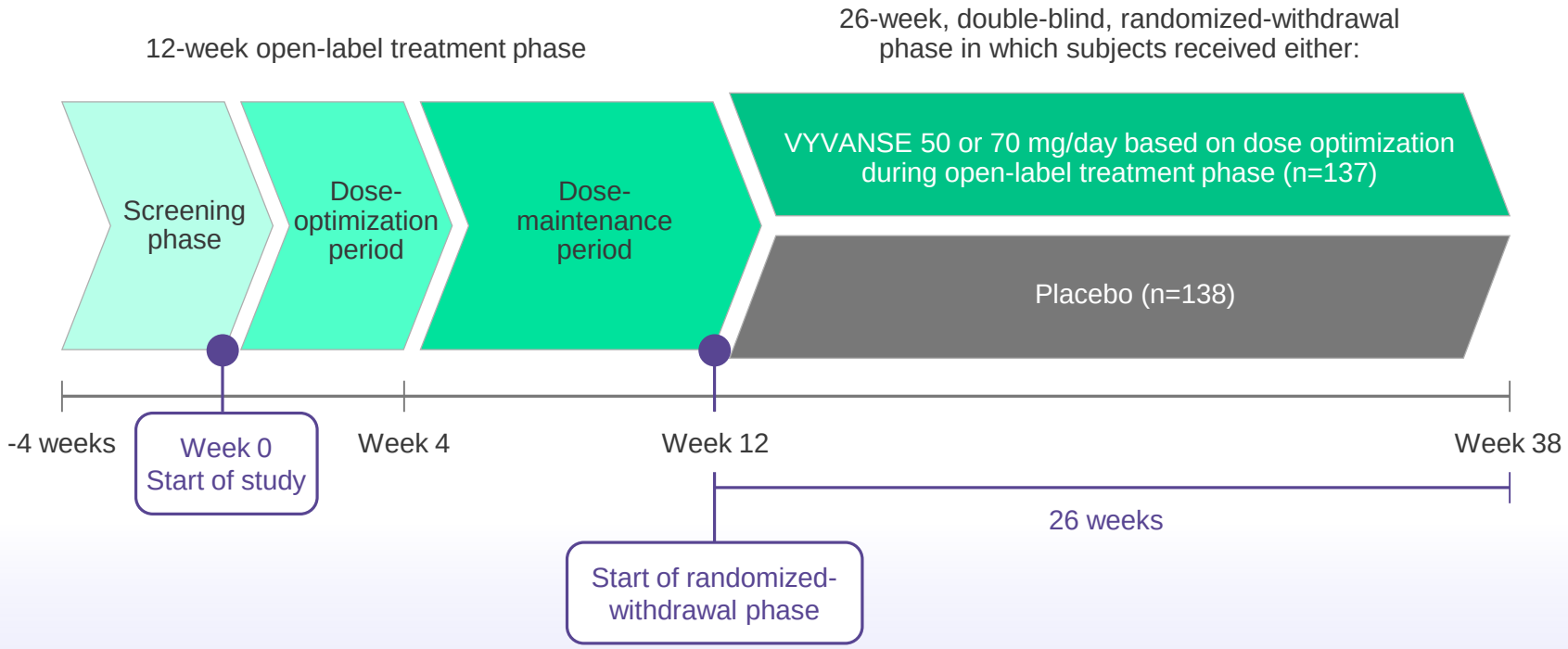
6-Month Randomized Withdrawal Phase: Design

In the 6-month randomized withdrawal phase of the study, VYVANSE responders from the pivotal 12-week trial were randomized to either placebo or continued on VYVANSE



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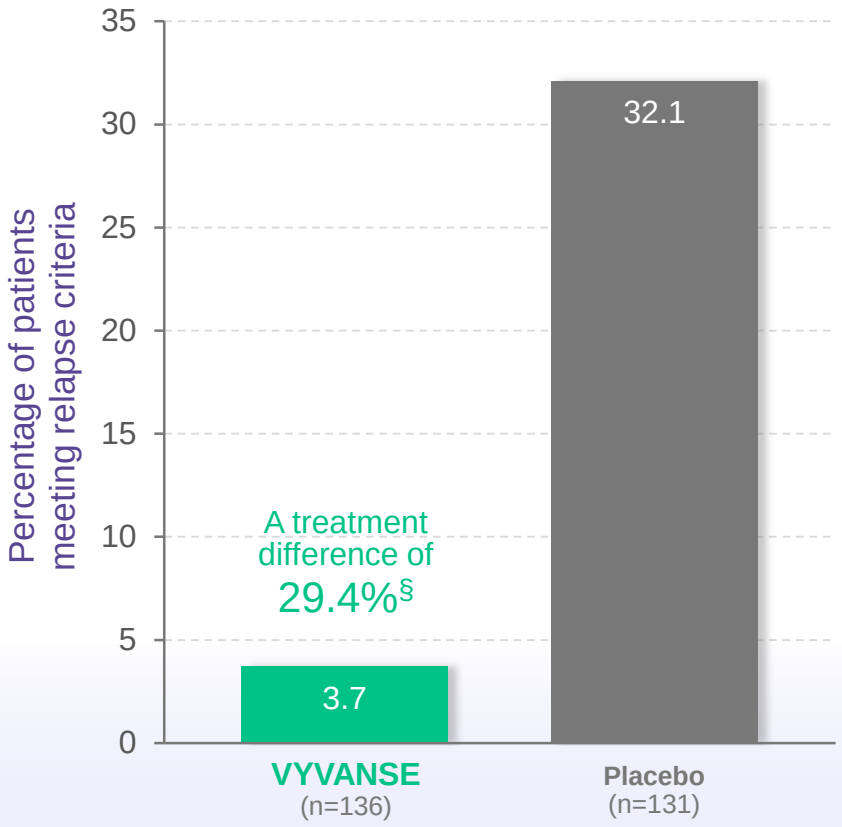
Relapse Rates at End of Randomized Withdrawal Phase (26 Weeks) (Primary Endpoint)

Percentage of patients with relapse at the end of the randomized withdrawal phase



VYVANSE Product Monograph.
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At the end of the randomized withdrawal phase (26 weeks) VYVANSE had a lower proportion of relapse vs. placebo (as measured by time to relapse; primary endpoint; $p < 0.001$)

For patients continuing on VYVANSE during the 6-month randomized withdrawal phase:

- 9 out of 10 adult patients did not relapse
- 3.7% relapsed vs. 32.1% on placebo
- 96.3% did not experience a relapse

Relapse was defined as having 2 or more binge days/week for 2 consecutive weeks prior to any visit and having an increase in CGI-S score of ≥ 2 points compared with baseline

Tolerability in the Pivotal Phase 3 RCTs

TEAEs reported by ≥ 5% of adult patients with BED taking VYVANSE, and at incidence rates greater than for placebo

Adverse event	VYVANSE (%, n=373)	Placebo (%, n=372)
Dry mouth	36	7
Insomnia[†]	20	7
Headache	16	9
Decreased appetite[‡]	8	2
Nausea	9	6
Constipation	6	1
Irritability	7	5
Anxiety	5	1
Feeling jittery	6	1
Fatigue	6	5
Increased heart rate[§]	7	1

Other common adverse events reported across five pooled studies included upper respiratory tract infection, nasopharyngitis and diarrhea

[†]Insomnia includes preferred terms of Insomnia, Initial Insomnia and Middle Insomnia.
[‡]Decreased appetite includes preferred terms Anorexia and Decreased Appetite.
[§]Increased heart rate includes preferred terms Heart Rate Increased and Tachycardia.

VYVANSE Product Monograph.

Important Safety Information

Indications and Clinical Use:

VYVANSE (lisdexamfetamine dimesylate capsules) is indicated for the treatment of Moderate to Severe Binge Eating Disorder (BED) in adults.

Recurrent episodes of binge-eating are characterised by:

- consuming an abnormally large amount of food in a short period of time and sense of lack of control over eating during the episode
- marked distress about the behavior
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Limitation of Use for BED:

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Contraindications:

- Moderate to severe hypertension
- Advanced arteriosclerosis
- Symptomatic cardiovascular disease
- Hyperthyroidism
- Known hypersensitivity or idiosyncrasy to the sympathomimetic amines
- Allergy to amphetamines or to components of VYVANSE or its container
- Glaucoma
- Agitated states
- History of drug abuse
- During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result)

Most Serious Warnings and Precautions:

- **Abuse and Dependence:** Amphetamines have a potential for abuse, misuse, dependence or diversion for non-therapeutic uses.
- **Cardiovascular:** The misuse of amphetamines may cause serious cardiovascular adverse events and sudden death.

Other Relevant Warnings and Precautions:

- Cardiovascular:
  - Hypertension or other cardiovascular conditions, including pre-treatment evaluation and continuous monitoring
  - Sudden death and pre-existing structural cardiac abnormalities or other serious heart problems
- Pre-existing psychosis, aggression, suicidal behavior and ideation
- Seizures, tics in Tourette's syndrome
- Visual disturbance
- Peripheral vasculopathy, including Raynaud's phenomenon
- Patients who use other sympathomimetic medications
- Pregnant and nursing women
- Dosing considerations in patients with severe renal insufficiency
- Effects on ability to operate machinery or vehicles

The most commonly observed adverse events reported with exposure to VYVANSE in BED across the five studies (> 5%) were: dry mouth, insomnia, headache, decreased appetite, nausea, upper respiratory tract infection, nasopharyngitis, tachycardia, constipation, irritability, anxiety, feeling jittery, fatigue and diarrhea.

For More Information:

Please consult the product monograph at www.shirecanada.com/vyvpm/en for important information relating to adverse reactions, drug interactions and dosing information which have not been discussed in this piece.

The product monograph is also available by calling Shire Pharma Canada ULC at 1-800-268-2772.

Shire

PAAB

MEMBER OF INNOVATIVE MEDICINES CANADA

Vyvanse®* (lisdexamfetamine dimesylate capsules)

Managing Safety Considerations

- Cardiovascular events have been reported with sympathomimetic agents
- Managing patients with Cardiovascular Risks and Stimulants
  - Family history of sudden cardiac death or known structural abnormality – cardiology referral
  - Consider 12 lead ECG
  - Monitor for new onset syncope, dizziness, or exercise intolerance

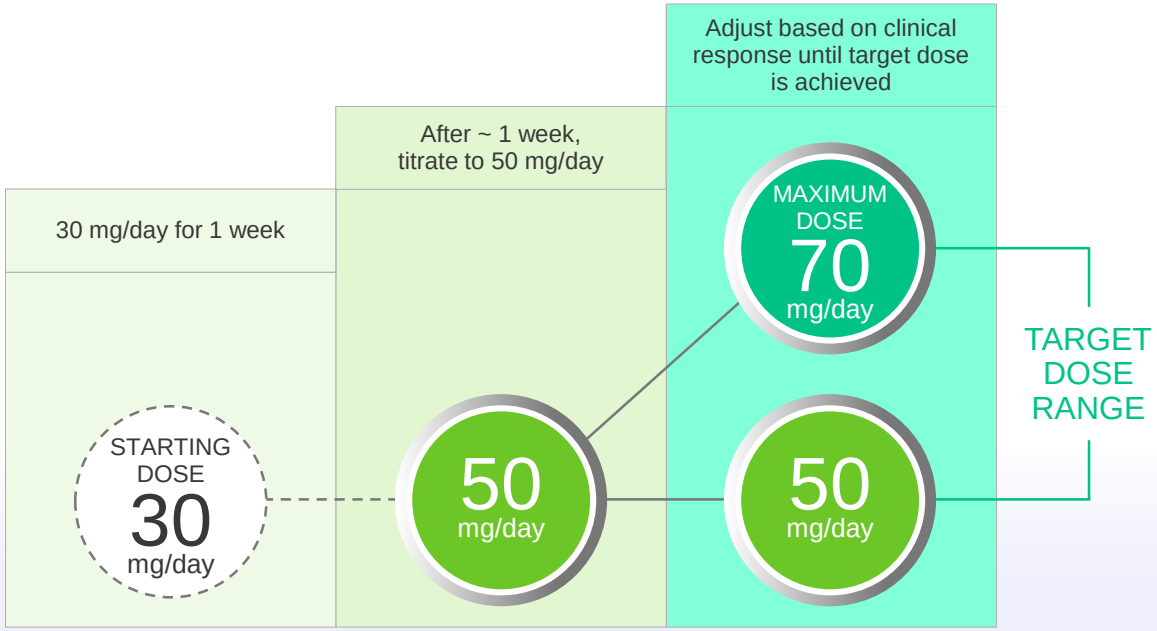
- https://caddra.ca/pdfs/caddraGuidelines2011Chapter07.pdf

Recommended VYVANSE Dosing for Adults with Moderate to Severe BED

Take once daily in the morning, with or without food

- Afternoon doses should be avoided because of the potential for insomnia

Titrate to the target dose of 50 to 70 mg/day



- Recommended starting dose is 30 mg/day
- Titrate in increments of 20 mg at approximately weekly intervals to achieve target dose
  - Recommended target dose of 50 to 70 mg/day
- Maximum dose is 70 mg/day

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VYVANSE Dosing Considerations

- **Patients with severe renal insufficiency:** In patients whose glomerular filtration rate is 15 to < 30 mL/min/1.73 m^2, the maximum dose should not exceed 50 mg/day. Further dosage reduction should be considered in patients undergoing dialysis.
- **Administer the lowest effective dosage:** Dosage should be individualized according to the therapeutic needs and response of the patient.
- **VYVANSE should be prescribed for the shortest duration that is clinically indicated** in order to minimize exposure to the cardiovascular risk in this population; the risk-benefit profile of the drug for the individual patient should be periodically re-evaluated.

VYVANSE should not be used in patients with symptomatic cardiovascular disease including coronary artery disease nor in patients with moderate to severe hypertension. Blood pressure and pulse should be monitored in all patients taking VYVANSE.

VYVANSE should generally not be used in patients with known serious structural cardiac abnormalities or other serious heart problems (*e.g.,* cardiomyopathy, serious heart rhythm abnormalities) that may place them at increased vulnerability to the sympathomimetic effects of Attention Deficit Hyperactivity (ADHD) or Binge Eating Disorder (BED) drugs.

VYVANSE Product Monograph.

Dealing with Comorbidities

- Psychiatric Comorbidities are common including Affective, Anxiety, Substance Use Disorders
- Treatment sequencing
  - Generally treat the most severe disorder first
  - Consider diagnostic certainty, patient preference, disorder causing most impairment, disorder most likely to respond to treatment, and potential impact of treatment on comorbid conditions.

A Call to Action: The 7-item BED Screener

Help identify your patients with BED using the 7-item BED Screener (BEDS-7)

This tool is intended *for screening use only*. It should not be used as a diagnostic tool.

1. During the last 3 months, did you have any episodes of excessive overeating (*i.e.,* eating significantly more than what most people would eat in a similar period of time)? YES NO

NOTE: if you answered "no" to question 1, you may stop. The remaining questions do not apply to you.

2. Do you feel distressed about your episodes of excessive overeating? YES NO

WITHIN THE PAST 3 MONTHS…	NEVER OR RARELY	SOMETIMES	OFTEN	ALWAYS
3. During your episodes of excessive overeating, how often did you feel like you had no control over your eating (*e.g.,* not being able to stop eating, feel compelled to eat, or going back and forth for more food)?	●	●	●	●
4. During your episodes of excessive overeating, how often did you continue eating even though you were not hungry?	●	●	●	●
5. During your episodes of excessive overeating, how often were you embarrassed by how much you ate?	●	●	●	●
6. During your episodes of excessive overeating, how often did you feel disgusted with yourself or guilty afterward?	●	●	●	●
7. During the last 3 months, how often did you make yourself vomit as a means to control your weight or shape?	●	●	●	●

Scoring the BEDS-7: if the response to Q1 is "YES," Q2 through Q7 are answered. If the response to Q1 is "NO," the remaining questions do not apply as the screening result is negative. If the response to Q2 is "YES" and a shaded box is checked for each of the items Q3 through Q7, the screening result is positive.

Herman BK, et al. Prim Care Companion CNS Disord 2016; 18(2).