New Drug Update 2021

Joe Strain, Pharm.D.

SDSU College of Pharmacy and
Allied Health Professions

Monument Health Rapid City Hospital

Disclosure

- I have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in this presentation

Pharmacist Learning Objectives

- Upon successful completion of this activity, pharmacists will be able to:
  - Identify therapeutic indications of drugs recently approved by the FDA.
  - Discuss pharmacological properties of the new medications
  - List side effects, warnings, precautions and significant drug interactions associated with each medication.
  - Identify the normal dose and dosage forms of the drugs presented.
  - Describe limitations to implementing the new medications into clinical practice

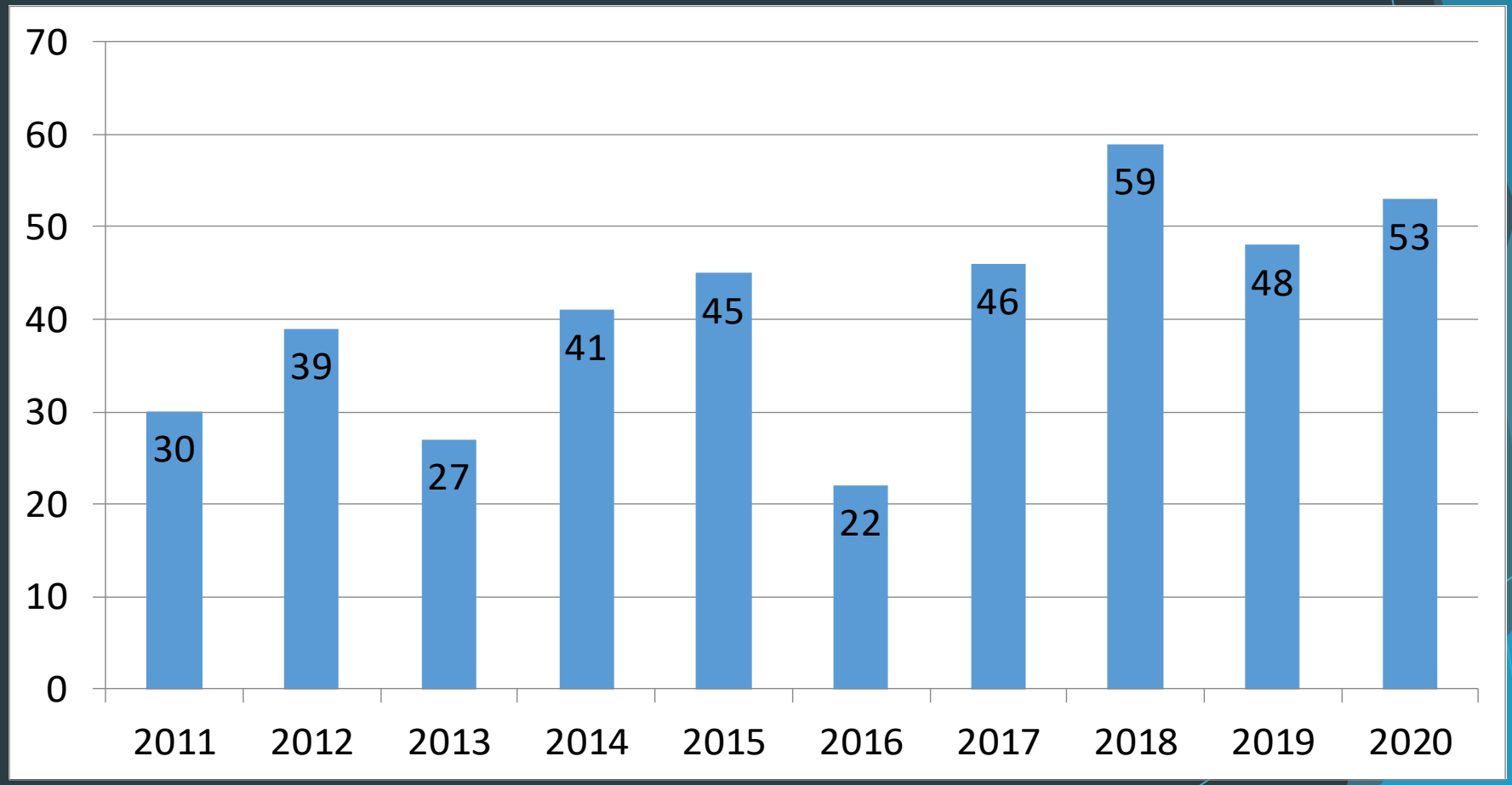
Pharmacy Technician Learning Objectives

- Following this presentation, pharmacy technicians will be able to:
  - Identify new drugs approved by the FDA and their classification.
  - Identify the major uses for the drugs presented.
  - Identify the usual dose and route of administration for each medication.
  - List the cost associated with each of the new drugs approved by the FDA.

Agenda

- Vericiguat (Verquvo™)
- Viloxazine (Qelbree™)
- Olanzapine/samidorphan (Lybalvi™)
- Lemborexant (Dayvigo®)
- Ibrexafungerp (Brexafemme®)
- Aducanumab (Aduhelm™)
- Tirbanibulin (Klisyri®)
- Semaglutide (Wegovy™)
- Setmelanotide (Imcivree™)
- Finerenone (Kerendia®)
- Brincidofovir (Tembexa®)
- Aspirin (Vazalore™)

CDER's Novel Drug Approval Trends



https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020. Accessed January 11th, 2021.

Vericiguat primarily works for heart failure by increasing:

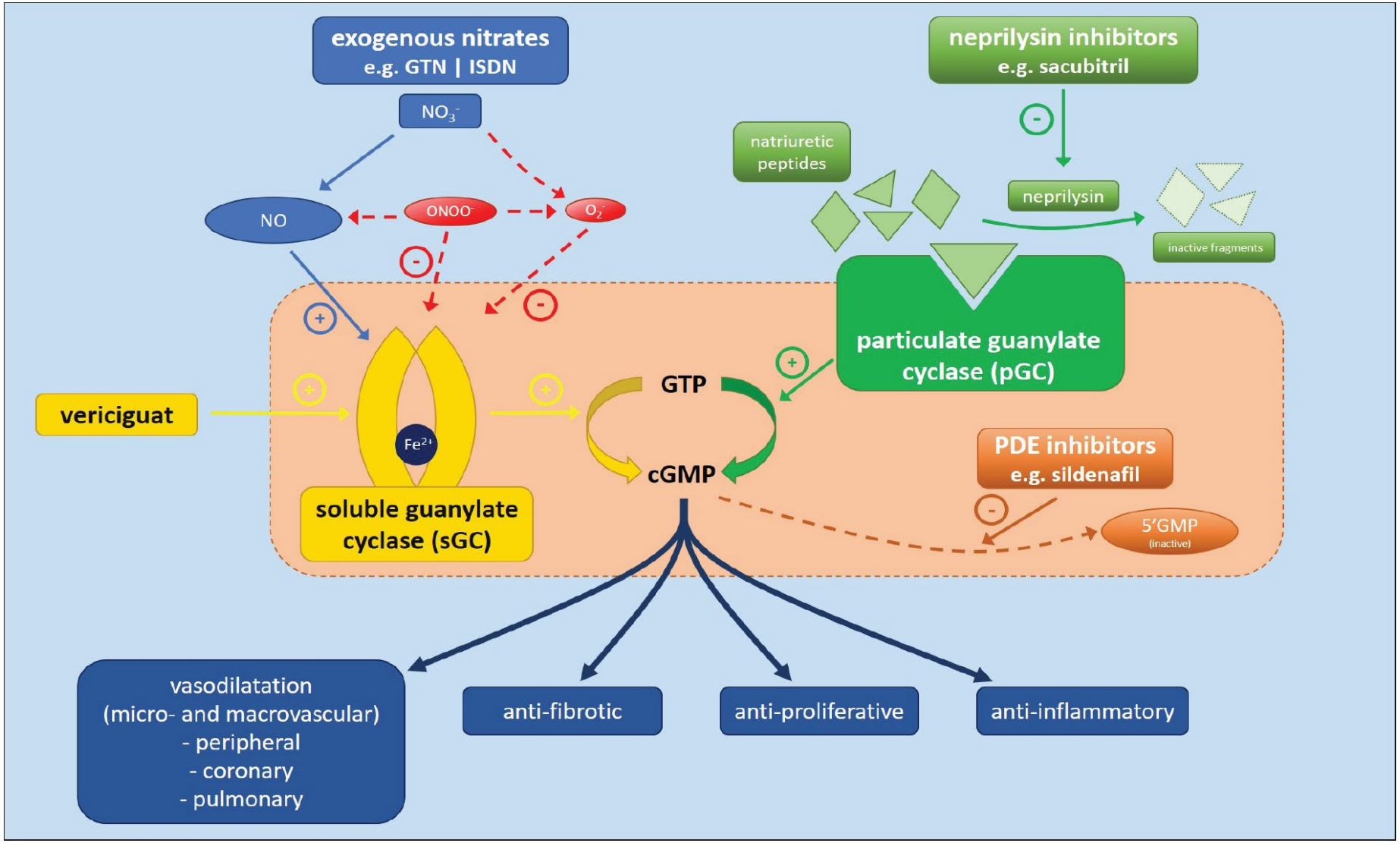
A. Contractility
B. Vasodilation
C. Blood pressure
D. Heart rate

Vericiguat (Verquvo™)

- Indication
  - Adults with symptomatic chronic heart failure (EF < 45%)
  - Reduces risk of CV death and HF hospitalization after a HF hospitalization or need for outpatient IV diuretics
- Pharmacology
  - Soluble guanylate cyclase (sGC) stimulator
  - Enzyme involved in nitric oxide signaling pathway
  - Smooth muscle relaxation & vasodilation

Verquvo PI 2021.

Therapies targeting the NO/sGC and neprilysin/pGC pathways to increase cGMP generation.



Cardiovasc Res, Volume 116, Issue 12, 1 October 2020, Pages e152–e155, https://doi.org/10.1093/cvr/cvaa247

Vericiguat (Verquvo™)

- Pharmacokinetics
  - Well-absorbed with food (~93%)
  - T ½ ~ 30h
  - Metabolized by glucuronidation to inactive metabolite
    - No adjustment for hepatic impairment (not studied in Child-Pugh C)
  - ~45% renal elimination
    - No dose adjustment for renal impairment

Verquvo PI 2021.

Vericiguat (Verquvo™)

- Contraindications
  - Use with riociguat
  - Pregnancy
    - Must rule out prior to treatment
    - Avoid pregnancy for 1 month after stopping treatment
- Drug interactions
  - Use of PDE-5 inhibitors (e.g. sildenafil) due to hypotension risk

Verquvo PI 2021.

Adverse Reactions from Victoria Trial

	Vericiguat N = 2519	Placebo N = 2525
Hypotension	15.4%	14.1%
Symptomatic Hypotension	9.1%	7.9%
Anemia	7.6%	5.7%
Syncope	4%	3.5%

Armstrong PW, et al. N Engl J Med 2020;382:1883-93.

Efficacy Data from Victoria Trial

Outcome	Vericiguat (N=2526)	Placebo (N=2524)	Hazard Ratio (95% CI)	P Value
Death from cardiovascular causes or first hospitalization for heart failure	35.5%	38.5%	0.90 (0.82-0.98)	0.02
Hospitalization for heart failure	27.4%	29.6%	0.90 (0.81-1.00)	
Death from cardiovascular causes	16.4%	17.5%	0.93 (0.81-1.06)	
Death from any cause or first hospitalization for heart failure	37.9%	40.9%	0.90 (0.83-0.98)	0.02

Armstrong PW, et al. N Engl J Med 2020;382:1883-93.

Vericiguat (Verquvo™)

- Dosing
  - 2.5 mg orally once daily with food
    - May increase every 2 weeks to max dose of 10 mg daily
    - Adjusted primarily based on systolic blood pressure
    - Tablet may be crushed if necessary
- Availability
  - 2.5, 5, and 10 mg tablets
- Cost
  - AWP = $700 per 30 tablets

Verquvo PI 2021.

Vericiguat (Verquvo™)

- Bottom line
  - New mechanism approved for heart failure
  - Reduces risk of CV death and HF hospitalization
  - Approved for EF < 45%
  - Add-on for existing treatments, no comparator trials
  - Well-tolerated
- Additional Review
  - Murphy SP, et al. JAMA. 2020;324;488-504.

Viloxazine is a controlled substance approved for ADHD.

A. True
B. False

Viloxazine (Qelbree™)

- Indication
  - ADHD in ages 6-17 years
- Pharmacology
  - Selective norepinephrine reuptake inhibitor with serotonergic activity
  - Proposed that both mechanisms have a role in ADHD
  - No effect on histamine or cholinergic receptors

Qelbree PI 2021.
Findling RL, et al. CNS Drugs 2021;35:643-53.

Viloxazine (Qelbree™)

- Pharmacokinetics
  - T ½ ~ 7 hours
  - Metabolized by CYP2D6, UGT1A9, UGT2B15
  - Excretion
    - 90% renal
    - No adjustment for mild to moderate renal impairment

Qelbree PI 2021.

Viloxazine (Qelbree™)

- Contraindications
  - Monoamine oxidase inhibitors
  - CYP1A2 substrates with narrow therapeutic range
- Warnings and precautions
  - Suicidal thoughts & behaviors (0.9% vs. 0.4% placebo)
  - Blood pressure and heart rate increases
  - Mania activation
  - Somnolence and fatigue

Qelbree PI 2021.

Viloxazine (Qelbree™)

- Drug interactions
  - MAOI
  - CYP1A2 substrates (e.g. duloxetine, tizanidine, clozapine)
  - CYP2D6 substrates (e.g. dextromethorphan, venlafaxine, risperidone)
  - CYP3A4 Substrates (e.g. buspirone)

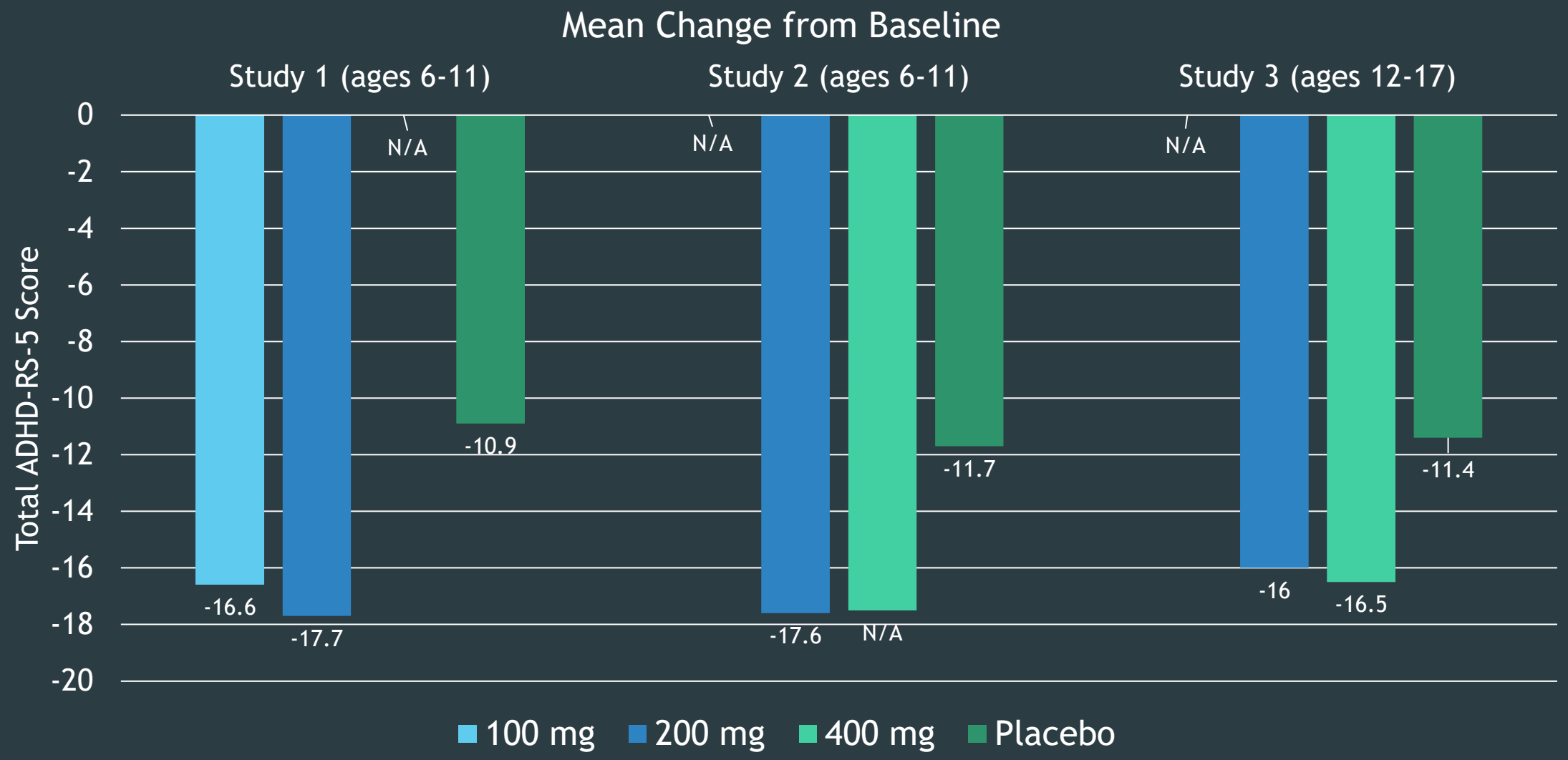
Qelbree PI 2021.

Viloxazine Adverse Reactions in Ages 6 to 17 Years Old

Reaction	100 mg N = 154	200 mg N = 367	400 mg N = 305	Placebo N = 463
Somnolence	12%	16%	19%	4%
Headache	10%	11%	11%	7%
Decreased appetite	5%	8%	8%	0.4%
Fatigue	4%	5%	9%	2%

Qelbree PI 2021.

Viloxazine Efficacy based on ADHD-RS-5 Scores



Qelbree PI 2021.

Viloxazine (Qelbree™)

- Dosing
  - Ages 6-11
    - 100 mg orally once daily
    - Titrated by 100 mg every week to max dose of 400 mg based on response & tolerability
  - Ages 12-17
    - 200 mg orally once daily
    - Titrate up to max of 400 mg after one week
- Availability & Cost
  - 100, 150, and 200 mg ER capsules
  - AWP = $360 for 30 capsules

Qelbree PI 2021.

Viloxazine (Qelbree™)

- Bottom line
  - Another non-stimulant option for ADHD
  - No direct comparator trials to other agents
  - Well-tolerated
  - Long-term trials on-going
- Additional Review
  - Findling RL, et al. CNS Drugs 2021;35:643-53.

Samidorphan is added to olanzapine to:

A. Enhance efficacy of olanzapine
B. Extend the dosing interval of olanzapine to once weekly
C. Attenuate weight gain associated with olanzapine
D. Decrease drowsiness associated with olanzapine

Olanzapine/samidorphan (Lybalvi™)

- Indication
  - Schizophrenia
  - Bipolar I Disorder
- Pharmacology
  - Olanzapine: atypical antipsychotic
  - Samidorphan: mu opioid antagonist, kappa opioid and delt opioid partial agonist
    - Structurally similar to naltrexone with high affinity for mu-opioid receptors
    - Role for attenuating weight gain from olanzapine

Lybalvi PI 2021.
Potkin SD, et al. J Clin Psychiatry 2020;81:19m12769

Olanzapine/samidorphan (Lybalvi™)

- Pharmacokinetics
  - T ½ 7-11 hours
  - Metabolism
    - CYP3A4 (major)
    - CYP3A5, CYP2C19, CYP2C8 (Minor)
  - Excretion
    - Urine 67%

Lybalvi PI 2021.

Olanzapine/samidorphan (Lybalvi™)

- Contraindications
  - Patients using opioids
  - Patients in opioid withdrawal
- Warnings and precautions
  - Vulnerability to Life-threatening opioid overdose
    - Use of high dose opioids to overcome antagonistic action of samidorphan

Olanzapine/samidorphan (Lybalvi™)

- Drug interactions with samidorphan
  - CYP3A4 inducers (e.g. rifampin)
  - Opioids

Efficacy Results for Change in Weight Over 24 weeks

Treatment group	% Change from Baseline in Body Weight			≥ 10% Body Weight Gain	
	Mean Baseline Weight (kg)	Mean Change from Baseline	Olanzapine-subtracted difference (95% CI)	Patients (%)	Olanzapine-subtracted Risk Difference (95% CI)
Olanzapine/ Samidorphan N = 266	77	4.2	-2.4 (0.39, -0.9)	17.8	-13.7 (-22.8,-4.6)
Olanzapine N = 272	77.5	6.6	NA	29.8	NA

Lybalvi PI 2021.

Olanzapine/samidorphan (Lybalvi™)

- Dosing and availability
  - 10 mg tablets of samidorphan combined with 5, 10, 15, or 20 mg of olanzapine
- Cost
  - TBD, expected availability 4th quarter 2021

Lybalvi PI 2021.

Olanzapine/samidorphan (Lybalvi™)

- Bottom line
  - Added to olanzapine to minimize weight gain
  - Efficacy attributed to olanzapine
  - Watch out for concomitant opioid use
- Additional review
  - Kahn RS, et al. Schizophr Res. 2021;232:45-53.
  - Chaudhary AMD, et al. Cureus. 2019;11:e5139.

Lybalvi PI 2021.

Lemborexant is superior to suvorexant.

A. True
B. False

Lemborexant (Dayvigo®)

- Indication
  - Insomnia, sleep onset and/or sleep maintenance
- Pharmacology
  - Dual orexin receptor antagonist (Ox_1R & Ox_2R)
  - Orexin is a neuropeptide involved with arousal and wakefulness
  - Similar to suvorexant
    - T ½ 17-19 hours vs. 12 hours for suvorexant

Dayvigo PI 2019.

Lemborexant (Dayvigo®)

- Contraindications
  - Narcolepsy
- Warnings/precautions
  - Daytime somnolence
  - Impaired driving ability
  - Alcohol and other CNS depressants
  - Cognitive changes
  - Depression/suicidal ideation
  - No data in severe COPD
  - Sleep paralysis, vivid-disturbing perceptions, cataplexy-like symptoms

Dayvigo PI 2019.

Adverse Effects from Phase 3 Clinical Trial

Event	Zolpidem ER 6.25 mg N = 263	Lemborexant 5 mg N = 266	Lemborexant 10 mg N = 268	Placebo N = 209
Headache	5.3%	6.4%	4.9%	6.2%
Somnolence	1.5%	4.1%	7.1%	1.9%
Dizziness	3%	1.1%	0.7%	1.9%

Rosenberg R, et al. JAMA Netw Open 2019;2:e1918254.

Polysomnographic Time to Sleep Onset (Sunrise 1 Trial)

Time to Sleep Onset	Lem 5 mg N = 266	Lem 10 mg N = 269	Zolp 6.25 mg N = 263	Placebo N= 208
Nights 1 & 2 mean (min)	28.3	25.1	31.9	37.4
Mean change from baseline (min)	-16.6	-19.5	-12.6	-6.5
Time to Sleep Onset	**N = 260**	**N = 260**	**N = 250**	**N = 200**
Nights 29 & 30 mean (min)	25.8	22.8	37.1	36
Mean change from baseline (min)	-19.5	-21.5	-7.5	-7.9

Rosenberg R, et al. JAMA Netw Open 2019;2:e1918254.

Lemborexant (Dayvigo®)

- Dosing
  - 5 mg once nightly immediately before bedtime
  - Must take with at least 7 hours of sleep remaining
  - Increase to max of 10 mg based on response
  - Food may delay time to onset
  - Max of 5 mg if moderate hepatic impairment or on weak CYP3A inhibitors
  - Avoid if on moderate to strong CYP3A inhibitors

Dayvigo PI 2019.

Lemborexant (Dayvigo®)

- Availability
  - 5 and 10 mg tablets
- Cost
  - AWP ~ $350 for 30 tablets
- Controlled substance
  - C-IV

Lemborexant (Dayvigo®)

- Bottom line
  - Another orexin inhibitor
  - No direct comparison to suvorexant
  - Clinical study up to 6 months
  - Lower dose associated with less CNS adverse effects
- Additional review
  - Kishi T, et al. J Psychiatr Res. 2020;128:68-74.

Ibrexafungerp is safe for use in pregnancy.

A. True
B. False

Ibrexafungerp (Brexafemme®)

- Indication
  - Adults with vulvovaginal candidiasis
- Pharmacology
  - Triterpenoid antifungal
  - Inhibits glucan synthase, enzyme involved in cell wall
  - Concentration dependent fungicidal activity

Brexafemme PI 2021.

Ibrexafungerp (Brexafemme®)

Antifungal Spectrum

- Clinical and in vitro
  - C. albicans
- In vitro
  - C. auris
  - C. dubliniensis
  - C. glabrata
  - C. guilleirmondii
  - C. keyfr
  - C. krusei
  - C. lusitaniae
  - C. parapsilosis
  - C. tropicalis

Brexafemme PI 2021.

Ibrexafungerp (Brexafemme®)

- Pharmacokinetics
  - Tmax 4-6 hours
  - T ½ ~ 20 hours
  - Metabolism
    - CYP3A4
  - Excretion
    - 90% feces

Brexafemme PI 2021.

Ibrexafungerp (Brexafemme®)

- Contraindications
  - Pregnancy (toxicities based on animal data)
- Warnings and precautions
  - Verify pregnancy status
  - Contraception for 4 days after last dose

Brexafemme PI 2021.

Ibrexafungerp (Brexafemme®)

- Drug interactions
  - Strong CYP3A4 inhibitors (e.g. intraconazole, ketoconazole)
    - Dose adjustment required
  - Moderate-strong CYP3A4 inducers (rifampin, phenytoin, St. John's wort, carbamazepine)
    - Avoid use due to significantly decreased ibrexafungerp levels
  - Ibrexafungerp inhibits CYP3A4, P-gp & OATP1B3 transporter
    - Due to short treatment duration effects not clinically significant

Brexafemme PI 2021.

Adverse Reactions from Clinical Trials		
Reaction	Ibrexafungerp N = 545	Placebo N = 275
Diarrhea	16.7%	3.3%
Nausea	11.9%	4%
Abdominal pain	11.4%	5.1%
Dizziness	3.3%	2.5%
Vomiting	2%	0.7%

Brexafemme PI 2021.

Phase 3 Clinical Trial Data

	Study 1		Study 2	
Outcome*	Ibrexafungerp N = 190	Placebo N = 100	Ibrexafungerp N = 189	Placebo N = 89
Clinical Response at TOC	50%	28%	63.5%	44.9%
Negative Culture at TOC	49.5%	19%	58.7%	29.2%
Clinical Response at follow-up†	59.5%	44%	72.5%	49.4%

TOC = test of cure (8-14 days)
†Day 21-29

Brexafemme PI 2021.

*All outcomes met statistical significance

Ibrexafungerp (Brexafemme®)

- Dosing and availability
  - 300 mg every 12 hours x 2 doses
  - 150 mg tablets
  - With or without food
- Cost
  - Anticipated in 2nd half of 2021

Brexafemme PI 2021.

Ibrexafungerp (Brexafemme®)

- Bottom line
  - Novel antifungal agent
  - No comparison data currently to fluconazole
  - Likely limited use for vulvovaginal candidiasis
  - Off-label potential for highly resistant fungal infections
- Additional review
  - Ghannoum M, et al. Antibiotics (Basel). 2020;9:539.

Aducanumab has demonstrated consistent improvement in:

A. Memory
B. Amyloid plaque reduction
C. Brain edema
D. Ability to live independently

Aducanumab (Aduhelm™)

- Indication
  - Alzheimer's disease; mild cognitive impairment/dementia
  - Accelerated approval based on a reduction in amyloid plaques
- Pharmacology
  - Human immunoglobulin gamma 1 monoclonal antibody
  - Reduces amyloid beta plaques

Aduhelm PI 2021.

Aducanumab (Aduhelm™)

- Pharmacokinetics
  - T ½ ~ 25 hours
  - Elimination via catabolic pathways
  - No data with hepatic or renal impairment; not expected to impact clearance
- Contraindications
  - None

Aduhelm PI 2021.

Aducanumab (Aduhelm™)

Warning/Precaution

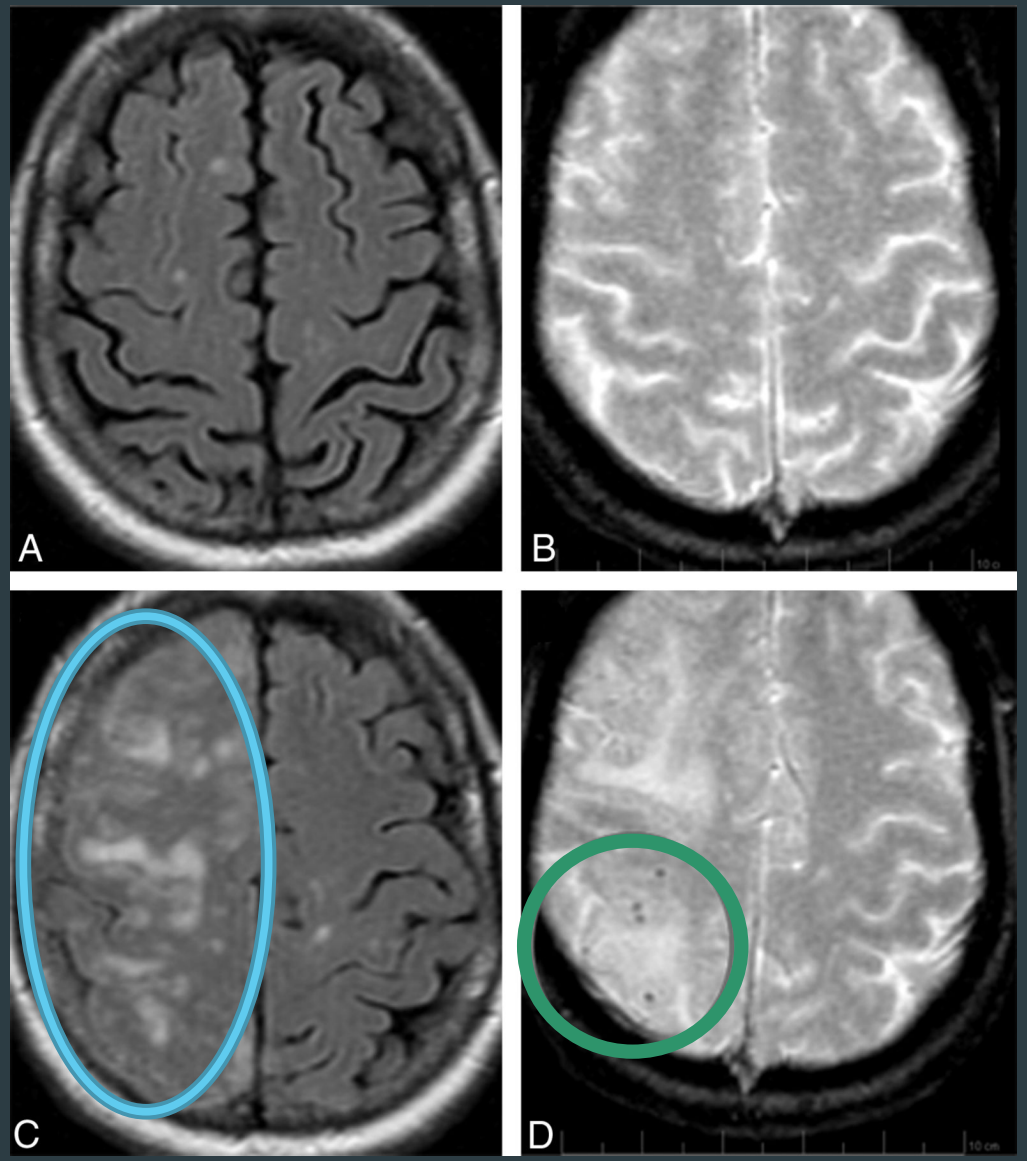
- Amyloid Related Imaging Abnormalities-edema (ARIA-E)
  - 35% vs. 3% placebo
  - Incidence higher in apolipoprotein E ε4 carriers vs. noncarriers (42% vs. 20%)
  - More common within first 8 doses
- Amyloid Related Imaging Abnormalities-hemosiderin (ARIA-H)
  - 21% vs. 1% placebo
  - Microhemorrhage
  - Superficial siderosis

Symptoms resolved in 88% of cases during observation

Aduhelm PI 2021.

BASELINE

BASELINE



ARIA-E

ARIA-H

Barakos J, Sperling R, Salloway S, Jack C, Gass A, Fiebach JB, Tampieri D, Melançon D, Miaux Y, Rippon G, Black R, Lu Y, Brashear HR, Arrighi HM, Morris KA, Grundman M. MR imaging features of amyloid-related imaging abnormalities. AJNR Am J Neuroradiol. 2013 Oct;34(10):1958-65. doi: 10.3174/ajnr.A3500. Epub 2013 Apr 11. PMID: 23578674; PMCID: PMC7965435.

Adverse Reactions from Phase 3 Trials

	Aducanumab 10 mg/kg N = 1105	Placebo N = 1087
ARIA-E	35%	3%
Headache	21%	16%
ARIA-H microhemorrhage	19%	7%
ARIA-H superficial siderosis	15%	2%
Fall	15%	12%
Diarrhea	9%	7%
Altered mental status*	8%	4%

*confusion, delirium, disorientation

Aduhelm PI 2021.

Aducanumab (Aduhelm™)

- Conflicting data from two identical major trials (EMERGE & ENGAGE)
- Both trials stopped early in March 2019; lack of benefit
  - Clinical Dementia Rating Scale-sum of the boxes (CDR-SB) declined in treatment & placebo groups
- Subsequent sub-analysis of EMERGE trial
  - 22% reduction in rate of cognitive decline based on CDR-SB in the high dose aducanumab group after 78 weeks ($p = 0.012$)
- No clinical benefit in ENGAGE trial
- Both trials showed reduction in brain ß-amyloid levels
  - Debatable clinical significance

Aduhelm PI 2021.

Primary Efficacy Endpoint-Engage Study

CDR- SB at Week 78	High dose Aducanumab (N=547)	Placebo (N = 548)
Mean baseline	2.51	2.47
Change from baseline	1.35	1.74
Difference from placebo	-0.39 (-22%) P= 0.0120	--

Aduhelm. Package Insert. Biogen Pharmaceuticals Inc; 2021

Clinical Application

- Clinical significance is not compelling for primary endpoint
- Placebo: 2.47 to 4.21 (+1.74)
- Aducanumab: 2.51 to 3.86 (+1.35)

CDR Sum of Boxes	Staging Category
0	Normal
0.5 - 4	Questionable cognitive impairment
0.5-2.5	Questionable impairment
3 - 4	Very mild dementia
4.5 - 9	Mild dementia
9.5 – 15.5	Moderate dementia
16 – 18	Severe dementia

Aduhelm. Package Insert. Biogen Pharmaceuticals Inc; 2021

Aducanumab (Aduhelm™)

Aducanumab Dosing Schedule	
IV Infusion given every 4 weeks	Dose based on actual body weight
Infusion 1 & 2	1 mg/kg
Infusion 3 & 4	3 mg/kg
Infusion 5 & 6	6 mg/kg
Infusion 7 +	10 mg/kg

- MRI monitoring schedule
  - Baseline and prior to 7th and 12th infusion
  - If ≥ 10 new microhemorrhages or > 2 focal areas of superficial siderosis then must see stabilization before treatment is continued

Aduhelm PI 2021.

Aducanumab (Aduhelm™)

- Dosage forms
  - 170 mg/1.7ml single dose vial
  - 300 mg/3 ml single dose vial
- Administration
  - Added to 100 ml of normal saline and preferably use immediately
    - May be refrigerated for up to 3 days or stored at room temperature for up to 12 hours
    - Warm to room temperature before administration
  - Use 0.2 or 0.22 micron in-line filter
  - Infuse over 1 hour

Aduhelm PI 2021.

Cost-Effectiveness

- Preliminary reports by the Institute for Clinical and Economic Review determined aducanumab is cost-effective at $3,000 to $8,400 per year[1]
  - Annual WAC ~$56,000 based on 67 kg patient
  - Annual WAC ~$65,500 based on a 90 kg patient
- Medicare Coverage[2]
  - Using a conservative analysis by Altarum including only drug cost
    - 1.2% of all costs; adds 73 billion in expenditures by 2028

1. The Institute for Clinical and Economic Review https://icer.org/news-insights/press-releases/in-revised-evidence-report-icer-confirms- judgment-that-evidence-is-insufficient-to-demonstrate-net-health-benefit-of-aducanumab-for-patients-with-alzheimers-disease/

2. Miller, G., Turner, A., & Rhyan, C. (C. (2021, June 16). *New Alzheimer's Drug Projected to Increase National Health Expenditures by More Than One Percent*. Altarum. https://altarum.org/news/new-alzheimer-s-drug-projected-increase-national-health-expenditures-more-one-percent#:~:text=New%20Alzheimer%27s%20Drug%20is%20Projected,Altarum.

Aducanumab (Aduhelm™)

- Bottom line
  - Highly controversial approval
  - Based on a biomarker vs. mixed clinical improvement
  - On-going data collection will determine future use
    - Company projects it may take until 2030 to complete
- Additional Review
  - Tolar M, et al. Alzheimers Res Ther. 2020;12:95.

Tirbanibulin is administered topically once daily for:

A. 5 days
B. 30 days
C. 6 months
D. Indefinitely

Tirbanibulin (Klisyri®)

- Indication
  - Topical treatment of actinic keratosis on face or scalp
- Pharmacology
  - Microtubule inhibitor
  - Exact mechanism unknown for actinic keratosis

Klisyri PI. 2021.

Tirbanibulin (Klisyri®)

- Pharmacokinetics
  - Systemic absorption is minimal
- Contraindications
  - None
- Warnings and precautions
  - Avoid eye contact (irritating)
  - Local skin reactions
- Drug interactions
  - No studies, none expected

Klisyri PI. 2021.

Local Skin Reactions from Phase 3 Trials

Reaction	Tirbanibulin N = 353			Placebo N = 349		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Erythema	22%	63%	6%	28%	6%	0
Flaking/scaling	26%	47%	9%	25%	9%	< 1%
Crusting	30%	14%	2%	9%	2%	0
Swelling	29%	9%	< 1%	4%	< 1%	0
Vesicles/pustules	7%	< 1%	< 1%	< 1%	0	0
Erosion/Ulcers	9%	3%	0	3%	0	0

Blauvelt A, et al. N Engl J Med 2021;384:512-20.

Phase 3 Clinical Trial Data

	Study 1			Study 2		
Variable	Tirbanibulin N = 175	Placebo N = 176	Difference (95% CI)	Tirbanibulin N = 178	Placebo N = 173	Difference (95% CI)
100% clearance*	44%	5%	40 (32-47)	54%	13%	42 (33-51)
≥ 75% clearance	68%	16%	52 (43-60)	76%	20%	57 (48-65)

*Primary outcome

Blauvelt A, et al. N Engl J Med 2021;384:512-20.

Tirbanibulin (Klisyri®)

- Dosing
  - Apply once daily for 5 days
  - Avoid areas near mouth and lips
  - Avoid washing/touching area for 8 hours after treatment
  - Wash hands after applying
- Availability and Cost
  - Single dose packets with 250 mg of 1% ointment
  - AWP = $1,188 for 5-day course

Klisyri PI. 2021.

Tirbanibulin (Klisyri®)

- Bottom line
  - Well-tolerated, effective agent for actinic keratosis
  - No direct comparator trials to other agents
  - Convenient once daily dosing x 5 days
  - Expensive; patient assistance card available
- Additional Review
  - Blauvelt A, et al. N Engl J Med 2021;384:512-20.

Reaching the target dose of semaglutide for weight loss takes at least:

A. 1 week
B. 4 weeks
C. 16 weeks
D. 32 weeks

Semaglutide (Wegovy™)

- Indication
  - Adjunct to diet and exercise for weight management
    - BMI ≥ 30 kg/m2
    - BMI ≥ 27 kg/m2 with at least one weight-related condition (e.g. hypertension, T2DM, dyslipidemia)
- Pharmacology
  - Glucagon-like peptide-1 agonist
  - GLP-1 receptor involved in regulation of food intake

Wegovy PI 2021.

Semaglutide (Wegovy™)

- Pharmacokinetics
  - Max levels in 1-3 days post dose
  - Similar absorption from abdomen, thigh or upper arm
  - T ½ ~ 7 days
  - Metabolism through protein breakdown

Wegovy PI 2021.

Adverse Reactions		
Reaction	Semaglutide N = 1261	Placebo N = 1261
Nausea	44%	16%
Diarrhea	30%	16%
Vomiting	24%	6%
Constipation	24%	11%
Abdominal pain	20%	10%
Headache	14%	10%
Hypoglycemia in T2DM	6%	2%

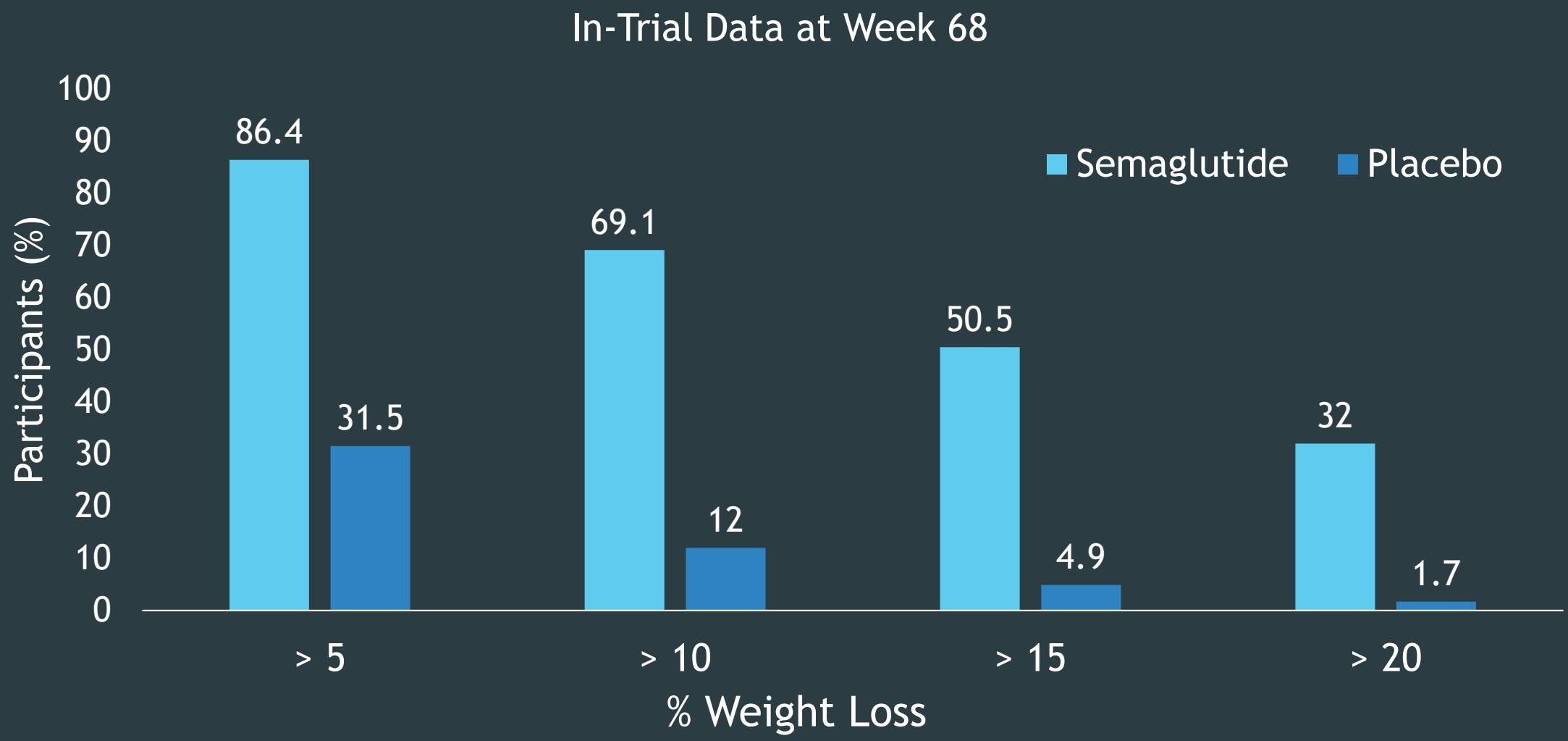
Wegovy PI 2021.

Summary of Phase 3 Clinical Trials Change in Weight at week 68

	Study 1		Study 2		Study 3	
	Semaglutide N = 1306	Placebo N = 655	Semaglutide N = 404	Placebo N = 403	Semaglutide N = 407	Placebo N = 204
Baseline	105.4 kg	105.2 kg	99.9 kg	100.5 kg	106.9 kg	103.7 kg
% Change from baseline	-14.85	-2.41	-9.6	-3.4	-16	-5.7
% difference from placebo (95% CI)	-12.44 (-13.37, -11.51)		-6.2 (-7.3, -5.2)		-10.3 (-12, -8.6)	

Wilding JPH, et al. N Engl J Med 2021; 384:989-1002.
Wegovy PI 2021.
Wadden TA, et al. JAMA 2021;325;1403-13.

Weight loss vs. placebo



Wilding JPH, et al. N Engl J Med 2021; 384:989-1002.

Semaglutide (Wegovy™)

Dose Escalation Schedule	
Weeks	Weekly Dose
1-4	0.25 mg
5-8	0.5 mg
9-12	1 mg
13-16	1.7 mg
17 +	2.4 mg

- If a dose is not tolerated may delay escalation for 4 weeks
- May use the 1.7 mg dose for additional 4 weeks
- If 2.4 mg dose is not tolerated then discontinue

Wegovy PI 2021.

Semaglutide (Wegovy™)

- AWP ~ $400 per week
- Storage
  - Refrigerator (do NOT freeze)
  - Room temperature up to 28 days
- Dosage forms
  - 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2.4 mg auto-injector
  - Discard after use

Wegovy PI 2021.

Semaglutide (Wegovy™)

- Bottom line
  - Effective as an adjunct to diet & exercise for weight loss
  - Patients lost 6-12% more weight vs. placebo at 1 year (~ 15-30 pounds)
  - Slow titration due to GI side effects (e.g. nausea)
  - May be used in patients without diabetes
- Additional review
  - Christou GA, et al. Obes Rev 2019;20:805-815.

The most common side effect of setmelanotide is:

A. Abdominal pain
B. Hypertension
C. Hyperpigmentation
D. Hyperbilirubinemia

Setmelanotide (Imcivree™)

- Indication
  - Chronic weight management in patients ≥ 6 years old with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency
- Pharmacology
  - Melanocortin 4 (MCR4) receptor agonist
  - MCR4 regulates hunger, satiety, and energy expenditure
  - POMC, PCSK1 & Leptin receptor deficiency associated with reduced MCR4 activation
  - Stimulation of MCR4 decreases hunger and increases energy expenditure
  - 20x less activity at MCR1 vs. MCR4

Imcivree PI 2020.

Setmelanotide (Imcivree™)

- Pharmacokinetics
  - Tmax 8 hours
  - T ½ ~ 11 hours
  - Metabolized by catabolic pathways
  - ~ 39% excreted unchanged in urine within 24 hours

Imcivree PI 2020.

Setmelanotide (Imcivree™)

- Contraindications
  - None
- Warnings and precautions
  - Disturbance in sexual arousal
  - Depression (26%) & suicidal ideation (11%)
  - Skin hyperpigmentation
- Drug interactions
  - None expected

Imcivree PI 2020.

Adverse Reactions in Open-Label Studies	
Reaction	Setmelanotide N = 27
Injection site reaction	26 (96%)
Skin hyperpigmentation	21 (78%)
Nausea	15 (56%)
Headache	11 (41%)
Diarrhea	10 (37%)
Abdominal pain	9 (33%)
Back pain	9 (33%)
Fatigue	8 (30%)
Vomiting	8 (30%)

Imcivree PI 2020.

Clinical Effects on Body Weight

	POMC or PCSK1 deficiency (N = 10)	LEPR deficiency (N = 11)
≥ 10% Weight loss at 1 year*	8 (80%)	5 (45.5%)
95% CI (P-value)	44.4%, 97.5% (0.0001)	16.8%, 76.6% (0.0002)
Mean Baseline Weight	118.7 kg	133.3 kg
Mean % change in Body Weight at 1 year (range)	-23.1% (-35, -1.2)	-9.7% (-23.3, 0.1)

*primary endpoint

Imcivree PI 2020.
Clement K, et al. Lancet Diabetes Endocrinol 2020;8:960-70.

Setmelanotide (Imcivree™)

- Dosing
  - Once daily SubQ injection
  - ≥ 12 years old
    - Start at 2mg (0.2ml) x 2 weeks
    - Titrate up (3 mg) or down (1 mg) based on tolerability and weight loss
  - 6-11 years old
    - Start at 1 mg (0.1 ml) x 2 weeks
    - Titrate up (2 mg) or down (0.5 mg) based on tolerability and weight loss
- Monitoring
  - D/C if patient has not lost ≥ 5% of baseline weight or BMI at 12-16 weeks

Imcivree PI 2020.

Setmelanotide (Imcivree™)

- Bottom line
  - Unique mechanism for weight loss
  - Currently only for specific genetic mutations causing obesity
  - Hyperpigmentation
- Additional review
  - Ayers KL, et al. J Clin Endocrinol Metab. 2018;103:2601-2612.

Imcivree PI 2020.

When adjusting the dose of finerenone, providers must evaluate:

A. Heart rate
B. Potassium levels
C. Liver function tests (AST/ALT)
D. Urine output

Finerenone (Kerendia®)

- Indication
  - Adult patients with chronic kidney disease associated with Type 2 diabetes mellitus
  - Reduces risk of renal disease and cardiovascular death, non-fatal myocardial infarction and heart failure hospitalization
- Pharmacology
  - Non-steroidal mineralocorticoid receptor antagonist
  - Blocks sodium reabsorption and overaction of mineralocorticoid receptors in kidney, heart and blood vessels
    - Reduces fibrosis and inflammation

Kerendia PI 2021.

Finerenone (Kerendia®)

- Pharmacokinetics
  - T ½ 2-3 hours
  - Metabolized by CYP3A4 (~ 90%), CYP2C8 (~ 10%)
    - Inactive metabolites
    - Moderate hepatic impairment (Child Pugh B) = 38% increase in AUC
    - Not studied in severe hepatic impairment (Child Pugh C)
  - Metabolites excreted via kidneys

Kerendia PI 2021.

Finerenone (Kerendia®)

- Contraindications
  - Strong CYP3A4 inhibitors
  - Adrenal insufficiency
- Warnings and precautions
  - Hyperkalemia
    - Do not use if serum potassium is > 5 mEq/L

Kerendia PI 2021.

Finerenone (Kerendia®)

- Drug interactions
  - Avoid strong CYP3A4 inhibitors (> 400% AUC increase)
    - Itraconazole, Grapefruit juice
  - Moderate-weak CYP3A4 inhibitors
    - May increase risk of adverse reactions
  - Avoid strong CYP3A4 inducers (90% AUC decrease)
  - Potassium supplements
    - Monitor levels more frequently

Kerendia PI 2021.

Finerenone Adverse Reactions

	Finerenone N = 2827	Placebo N = 2831
Hyperkalemia	18.3%	9%
Hospitalization due to hyperkalemia	1.4%	0.3%
Hypotension	4.8%	3.4%
Hyponatremia	1.4%	0.7%

Kerendia PI 2021.
Bakris GL, et al. N Engl J Med 383; 2219-29.

FIDELIO-DKD Clinical Trial Results

	Finerenone N = 2833	Placebo N = 2841	HR (95% CI)
Primary composite outcome	17.8%	21.1%	0.82 (0.73-0.93)
Kidney failure*	7.3%	8.3%	0.087 (0.72-1.05)
Sustained eGFR declined of ≥ 40%*	16.9%	20.3%	0.81 (0.72-0.92)
Renal death*	<0.1%	<0.1%	NR
Secondary CV composite outcome	13%	14.8%	0.86 (0.75-0.99)

*Component of composite outcome

Kerendia PI 2021.
Bakris GL, et al. N Engl J Med 383; 2219-29.

Finerenone (Kerendia®)

Starting Dose based on Renal Function	
eGFR (ml/min/1.73m^2)	Starting Dose
≥ 60	20 mg once daily
25-60	10 mg once daily
< 25	Not recommended

Dose Titration Schedule based on Potassium Level			
Potassium level checked every 4 weeks		Current Dose	
		10 mg daily	20 mg daily
Potassium Level (mEq/L)	≤ 4.8	20 mg daily	20 mg daily
	4.9-5.5	10 mg daily	20 mg daily
	> 5.5	Hold & may restart at 10 mg when K ≤ 5	Hold & restart at 10 mg when K ≤ 5

Kerendia PI 2021.

Finerenone (Kerendia®)

- Bottom line
  - Non-steroidal mineralocorticoid receptor antagonist
  - Slows renal decline in T2DM patients
  - Trial data for CV outcomes—published August 2021
  - Monitor potassium
- Additional Review
  - Rico-Mesa, et al. Curr Cardiol Rep. 2020;22:140.

Brincidofovir (Tembexa®)

- Indication
  - Smallpox
  - Concerns of potential bioterrorism
- Pharmacology
  - Prodrug converted to cidofovir intracellularly
  - Inhibits orthopoxvirus DNA polymerase thus blocking viral DNA synthesis

Tembexa PI 2021.

Brincidofovir (Tembexa®)

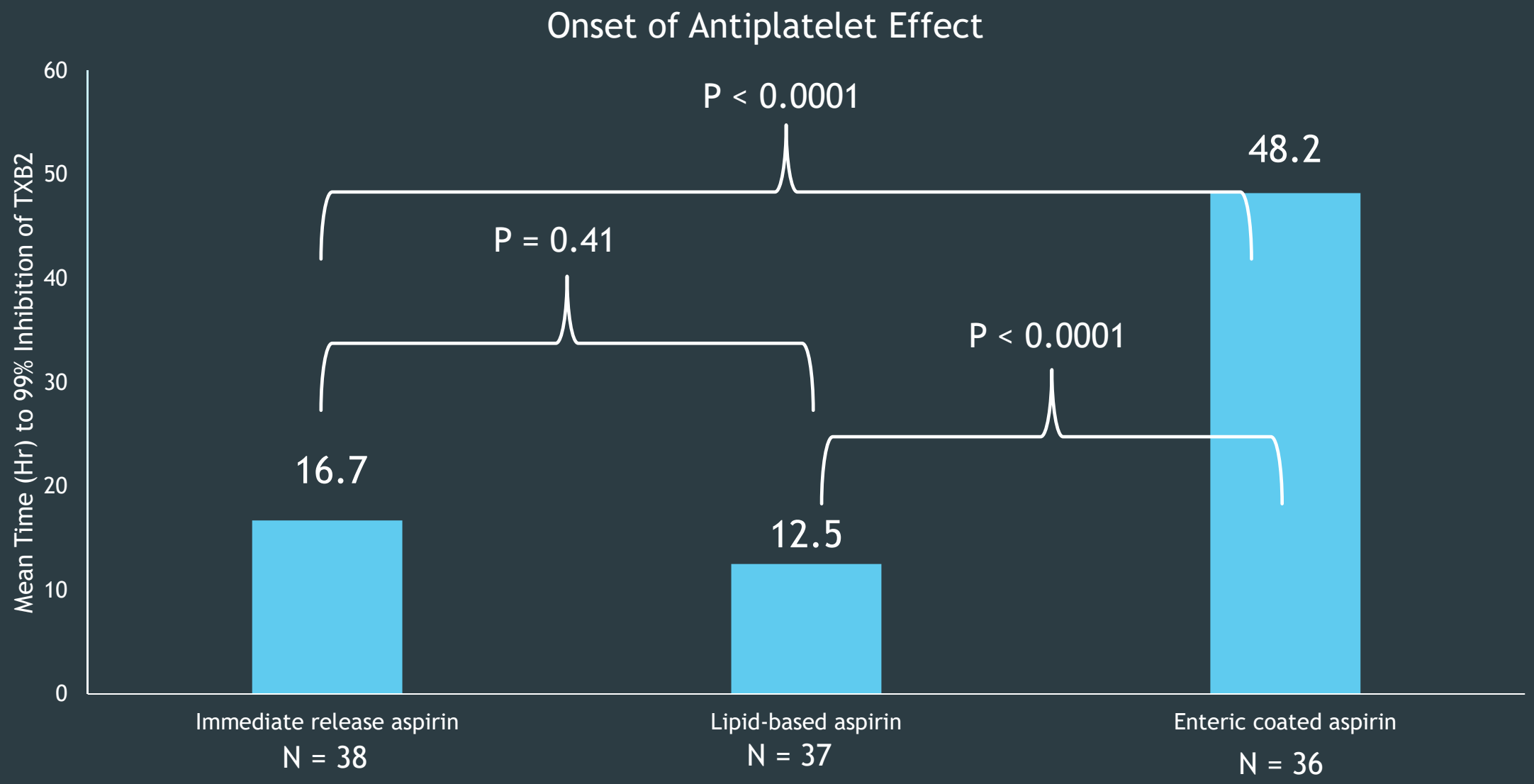
- Clinical efficacy
  - Based on mouse and rabbit data
  - 80-90% survival if started on day 4 after inoculation
  - 34-69% survival if started on day 6 after inoculation
- Bottom line
  - We have a treatment for smallpox
  - Hope we NEVER need it!

Tembexa PI 2021.

Aspirin (Vazalore™)

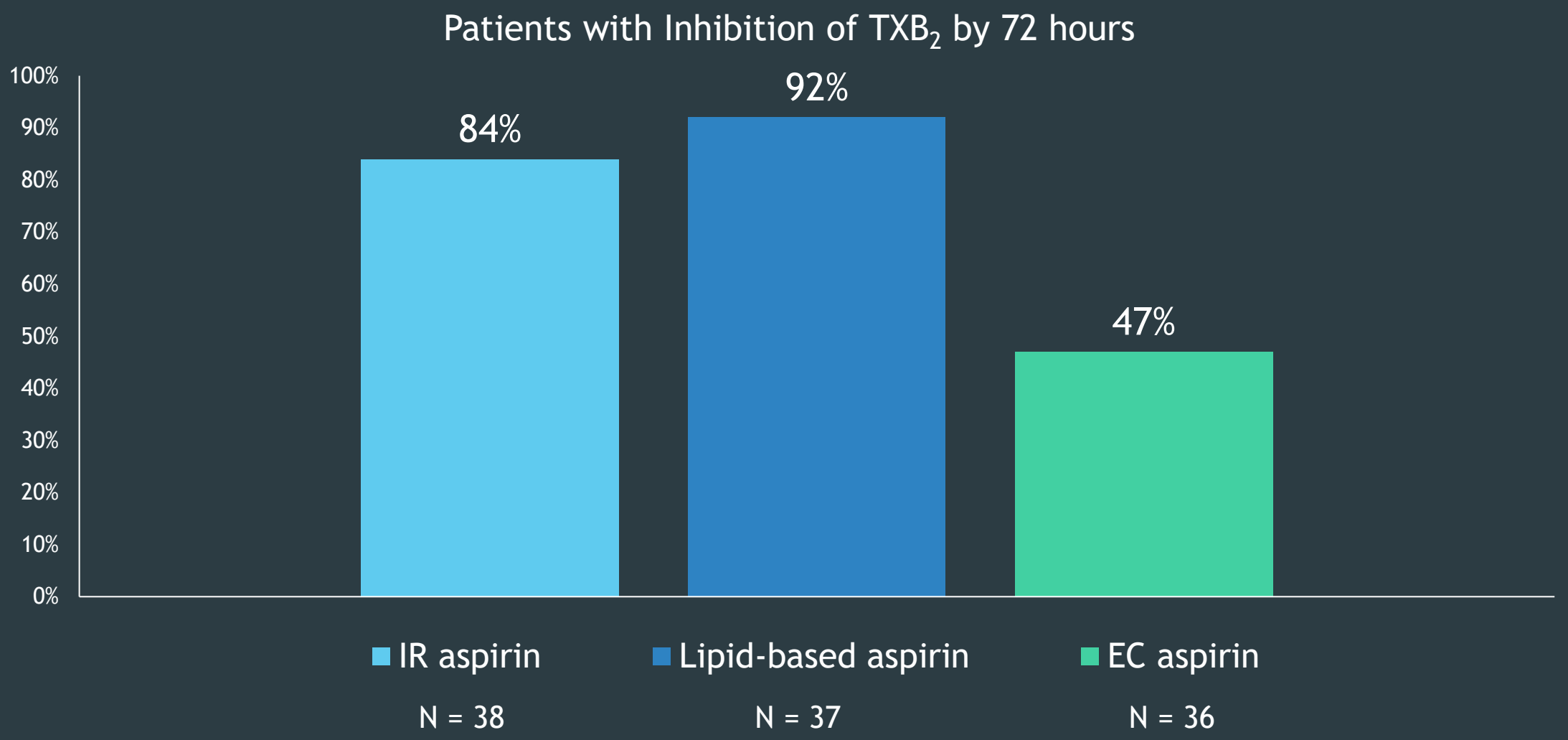
- New liquid-filled aspirin 81 mg and 325 mg capsule
- Lipid-based formulation
- Designed for fast-onset and improved gastrointestinal tolerability

Onset of Antiplatelet Effect in Type 2 DM



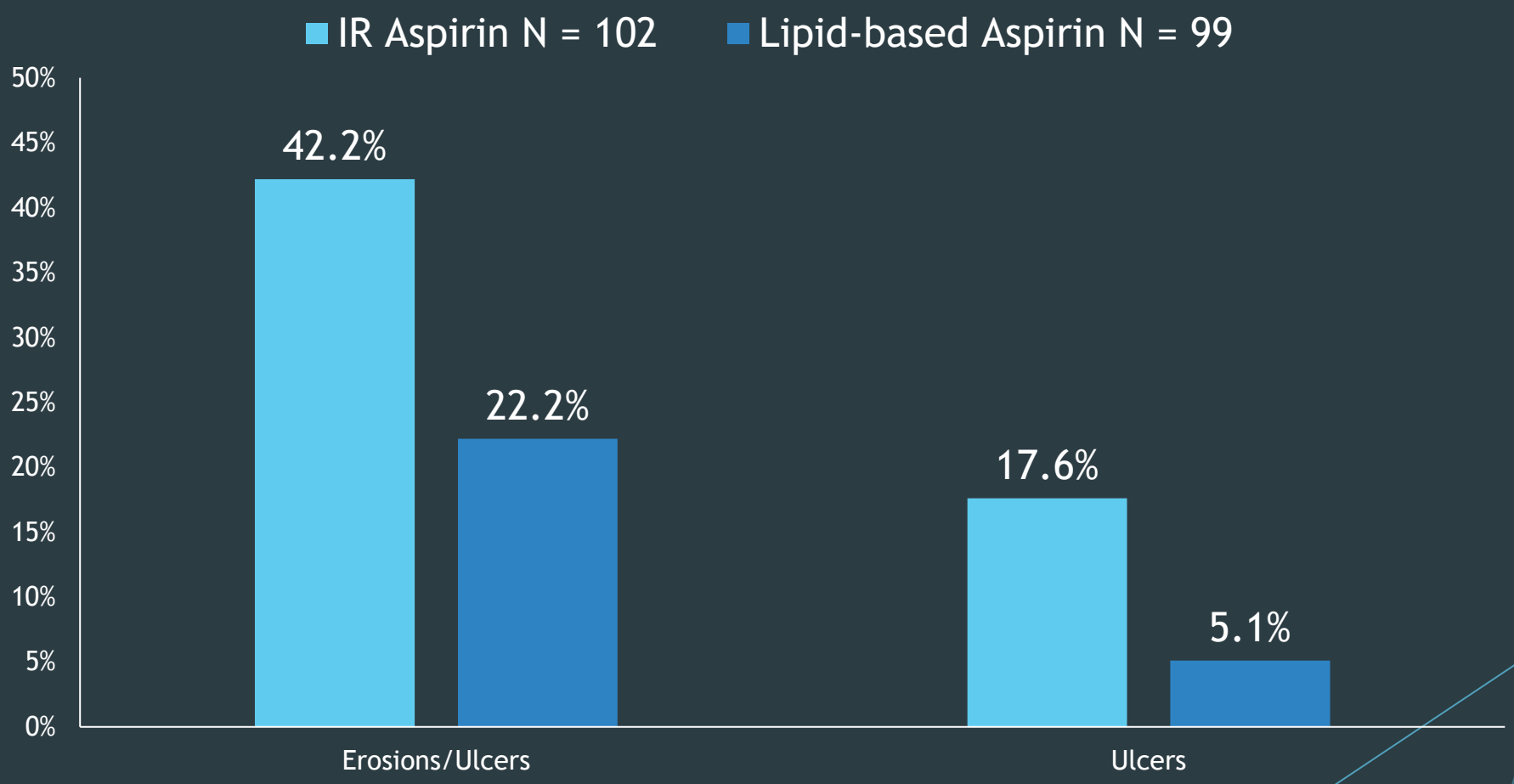
Bhatt DL, et al. J Am Coll Cardiol 2017;69:603-12.

Platelet Inhibition at 72 hours



Bhatt DL, et al. J Am Coll Cardiol 2017;69:603-12.

Gastroduodenal Injury



Cryer B, et al. Am J Gastroenterol 2011;106:272-7.

Aspirin (Vazalore™)

- Bottom line
  - Quick onset of platelet inhibition
  - GI side effects favorable based on small trial
  - No clinical data based on cardiovascular outcomes
  - Cost????
- Additional review
  - Bhatt DL, et al. J Am Coll Cardiol 2017;69:603-12.
  - Cryer B, et al. Am J Gastroenterol 2011;106:272-7.

Sodium sulfate, magnesium sulfate & potassium chloride (Sutab®)

- Indication
  - Colonoscopy preparation
- Pharmacology
  - Osmotic laxative
  - Similar to Suprep® (contains potassium sulfate)

Sutab PI 2020.

Sodium sulfate, magnesium sulfate & potassium chloride (Sutab®)

- Dose 1 (evening prior to colonoscopy)
  - 12 tablets with 16 oz of water over 15-20 min
  - 1 hour later drink 16 oz of water over 30 minutes
  - 30 minutes later drink 16 oz of water over 30 minutes
- Dose 2 (morning of colonoscopy)
  - Repeat above regimen
- Complete dose 2 at least 2 hours before colonoscopy
- Total volume = ~ 2840 ml
- Cost ~ $150 for 24 tablets

Sutab PI 2020.

Outcome	Sutab® N = 281	PEG 3350 ELS N = 271
Clinical Success	92%*	89%
≥ 1 GI adverse effect	71%	34%
Nausea	52%	18%
Abdominal distention	34%	15%
Vomiting	16%	2%
Upper abdominal pain	23%	13%

*Non-inferior

Sutab PI 2020.

Dabigatran

- New pediatric indication
  - Treatment of VTE in ages 3 months to 18 years old who were treated with a parenteral agent for at least 5 days
    - Capsule formulation approved in ages 8 and older
    - New oral pellet formulation for ages 3 months to 12 years
- Similar efficacy compared to warfarin, enoxaparin or fondaparinux

Pradaxa PI 2021.

Dabigatran Pediatric Capsule Dosing Ages 8-17 Years

Weight	Dose
11 to ≤ 26 kg	75 mg BID
16 to ≤ 26 kg	110 mg BID
26 to ≤ 41 kg	150 mg BID
41 to ≤ 61 kg	185 mg BID
61 kg to ≤ 81 kg	220 mg BID
≥ 81 kg	260 mg BID

Pradaxa PI 2021.

Dabigatran

- Pellet formulation for ages 3 months to 12 years old
  - 20, 30, 40, 50, 110, 150 mg packets
- Dose based on age and weight
  - See labeling
  - Max dose of 260mg BID for ages 2-12 years ≥ 41 kg
- Administration
  - Mix with soft foods (e.g. applesauce)
  - May add to 1-2 ounces of apple juice

Pradaxa PI 2021.

Questions?