New Drug Update 2022

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Disclosure

- I have had no financial relationship over the past 24 months with any commercial sponsor with a vested interest in this presentation

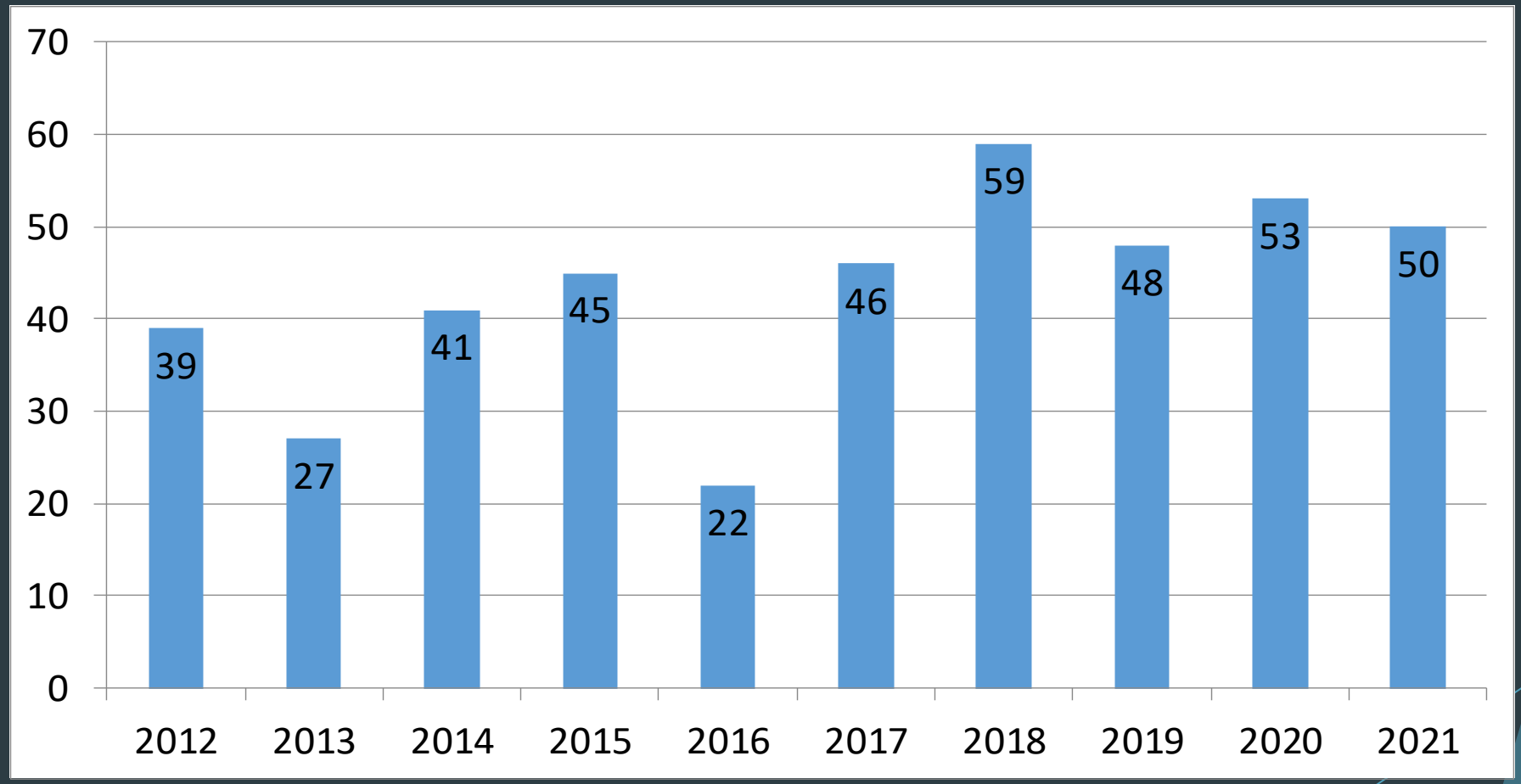
Pharmacist Learning Objectives

- Upon successful completion of this activity, pharmacists will be able to:
  - Summarize therapeutic indications of medications 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 medications recently approved by the FDA
  - List the classification for the new medications
  - Recall major indications for the new medications
  - Identify the usual dose and route of administration for each medication
  - Discuss the cost associated with each of the new medications

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-2021. Accessed January 3rd, 2022.

Agenda

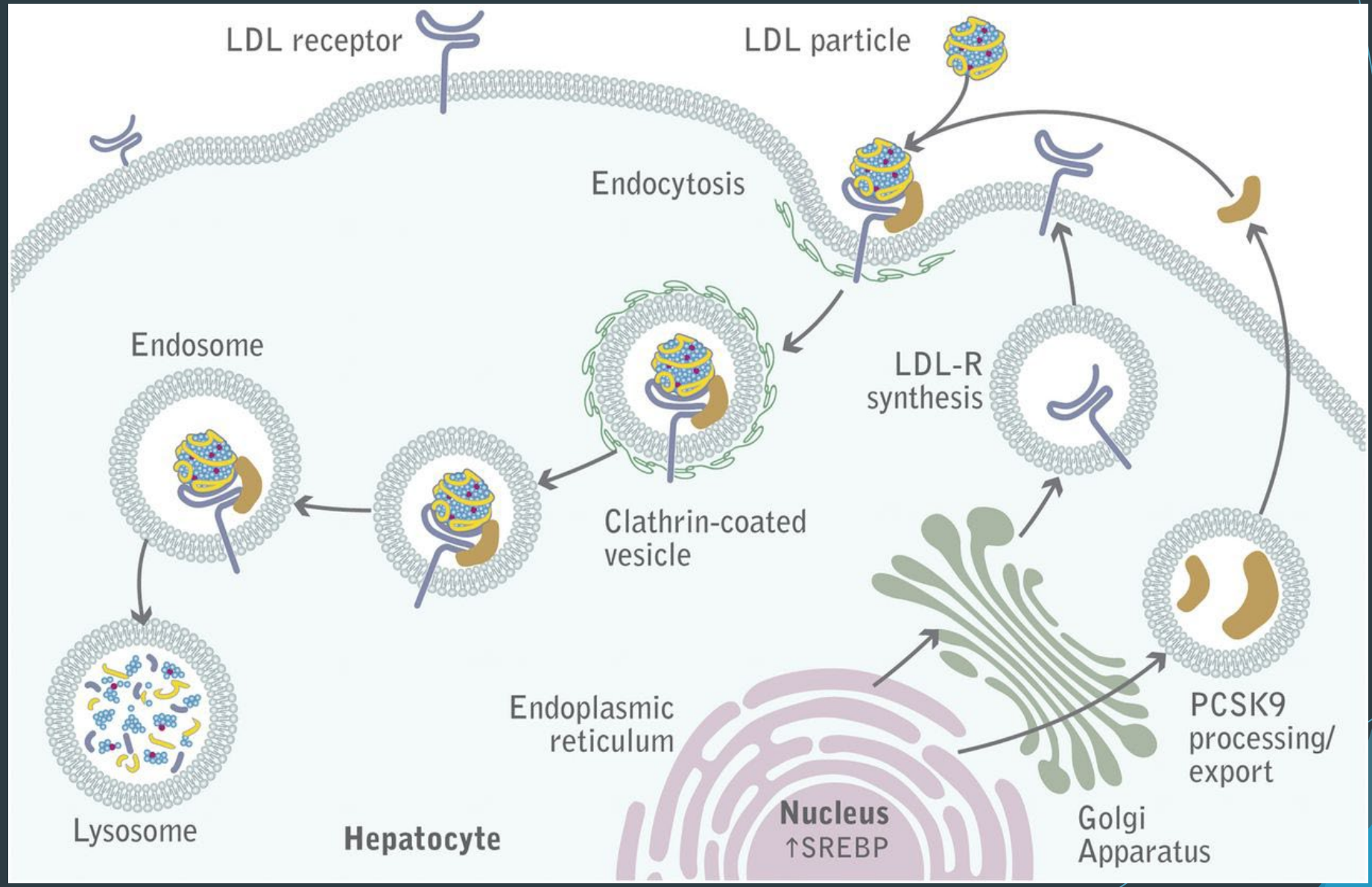
- Inclisiran (Leqvio®)
- Difelikefalin (Korsuva™)
- Dexmedetomidine (Igalmi™)
- Oteseconazole (Vivjoa™)
- Mavacamten (Camzyos™)
- Vonoprazan/Amoxicillin (Voquezna™ Dual Pak™)
- Tirzepatide (Mounjaro™)
- Atogepant (Qulipta™)

Inclisiran (Leqvio®)

- Indication
  - Heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease (ASCVD) requiring additional LDL-C lowering
  - Add on to diet and max tolerated statin
- Pharmacology
  - Double-stranded, small interfering RNA molecule
  - Targets mRNA for PCSK9
  - Inhibiting PCSK9 increases LDL-C receptor recycling to the hepatocyte surface

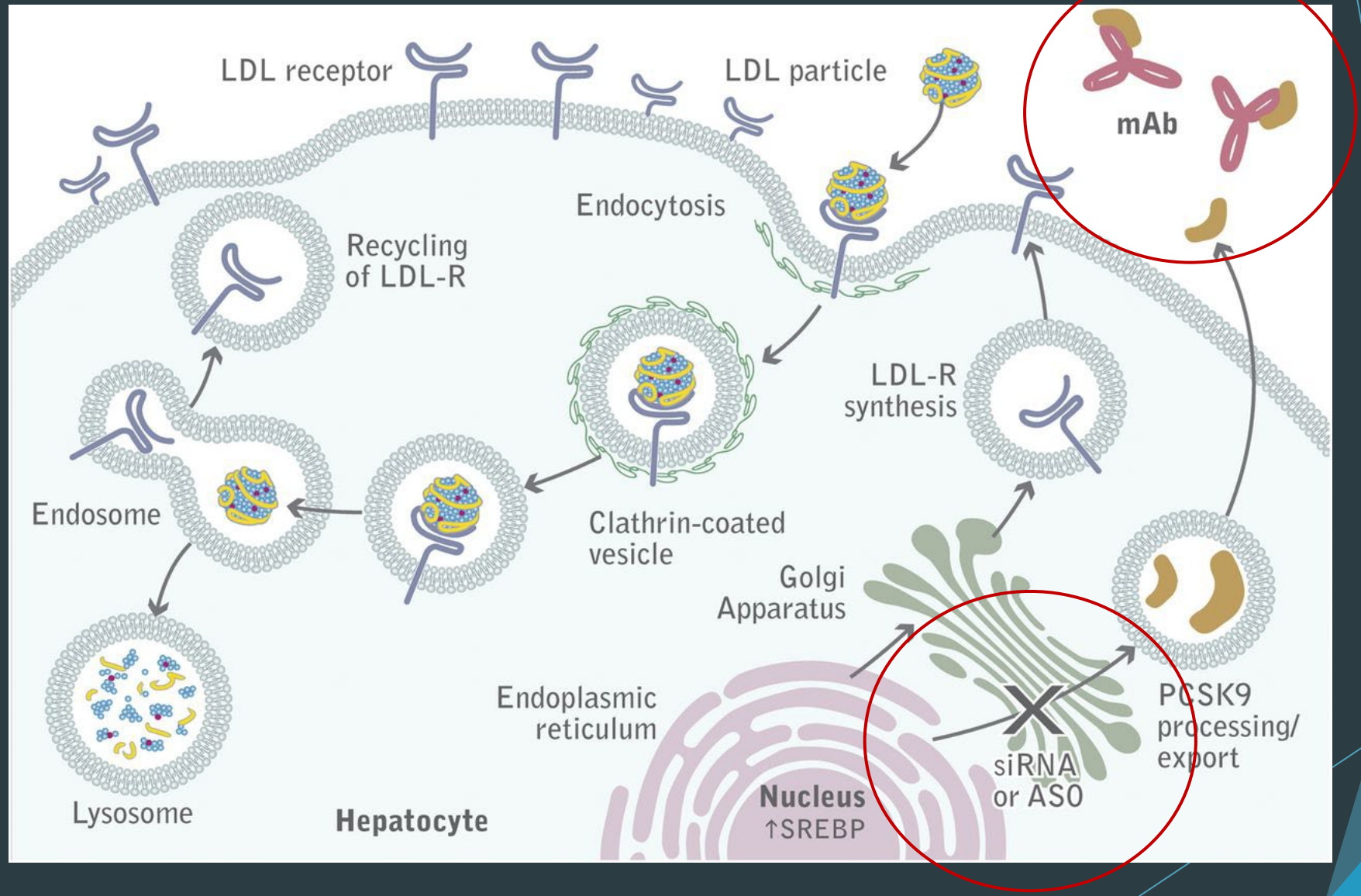
Leqvio (inclisiran) prescribing information. East Hanover NJ: Novartis; December 2021.

PCSK9 and LDL-R Degradation



Used with permission from Gilles Lambert et al. J. Lipid Res. 2012;53:2515-2524

PCSK9 Inhibition



Used with permission from Gilles Lambert et al. J. Lipid Res. 2012;53:2515-2524

Inclisiran (Leqvio®)

- Pharmacokinetics
  - T ½ ~ 9 hours
  - High, selective uptake into hepatocytes
  - Metabolized by nucleases (no CYP450 interactions)
  - 16% renal elimination
  - LDL-C reduction occurs within 14 days of first dose

Leqvio (inclisiran) prescribing information. East Hanover NJ: Novartis; December 2021.

Inclisiran (Leqvio®)

- Contraindications, Warnings, Precautions
  - NONE!.....but do NOT use during pregnancy/lactation
  - No data in severe hepatic or renal disease
- Drug interactions
  - NONE!

Leqvio (inclisiran) prescribing information. East Hanover NJ: Novartis; December 2021.

Adverse Reactions from Phase 3 Trials

Reaction	Inclisiran N = 1,833	Placebo N = 1,822
Injection-site reaction	8.2%	1.8%
Arthralgia	5%	4%
Urinary tract infection	4.4%	3.6%
Bronchitis	4.3%	2.7%
Diarrhea	3.9%	3.5%
Dyspnea	3.2%	2.6%

Leqvio (inclisiran) prescribing information. East Hanover NJ: Novartis; December 2021.

ORION-10 Clinical Results

Outcome	Inclisiran N = 781	Placebo N = 780	Treatment difference
Change from baseline LDL-C at day 510	-51.3%	1.0%	-52.3% (-55.7 to -48.8)*

ORION-11 Clinical Results

Outcome	Inclisiran N = 781	Placebo N = 780	Treatment difference
Change from baseline LDL-C at day 510	-45.8%	4.0%	-49.9% (-53.1 to -46.6)*

Ray K, et al. N Engl J Med 2020;382:1507-19.

*$p < 0.001$

Inclisiran (Leqvio®)

- Dosing
  - 284 mg SubQ injection on day 1, repeat in 3 months then every 6 months
  - Abdomen, upper arm or thigh
  - Recommend administration by health care provider
- Monitoring
  - May check LDL-C as soon as 30 days after initial dose
- Cost
  - ~$3,900 per dose

Leqvio (inclisiran) prescribing information. East Hanover NJ: Novartis; December 2021.

Inclisiran (Leqvio®)

- Bottom line
  - LDL-C lowering agent working on PCSK9 pathway
  - Less frequent dosing vs. other PCSK9 inhibitors
  - Recommend administration by health care provider
  - Expensive!
  - Alternative agent after maximizing statins
- Additional review
  - Warden BA, et al. J Cardiovas Pharmcol. 2021;78:157-74.

Difelikefalin (Korsuva™)

- Indication
  - Moderate to severe pruritis associated with chronic kidney disease for patients on hemodialysis
- Pharmacology
  - Peripheral kappa opioid agonist
  - Inhibits the transmission of itch signals

Korsuva (difelikefalin) prescribing information. Stamford CT: Cara Therapeutics; August 2021.

Difelikefalin (Korsuva™)

- Pharmacokinetics
  - T ½ 23-31 hours
  - Steady-state after 2 doses
  - Hemodialysis (4-hour session) removes 70-80%
  - Not detectable after 2 dialysis sessions

Korsuva (difelikefalin) prescribing information. Stamford CT: Cara Therapeutics; August 2021.

Difelikefalin (Korsuva™)

- Contraindications
  - None
- Warnings and precautions
  - Dizziness, somnolence, mental status changes, gait disturbances and falls
  - Driving and operating machinery
- Drug interactions
  - None expected

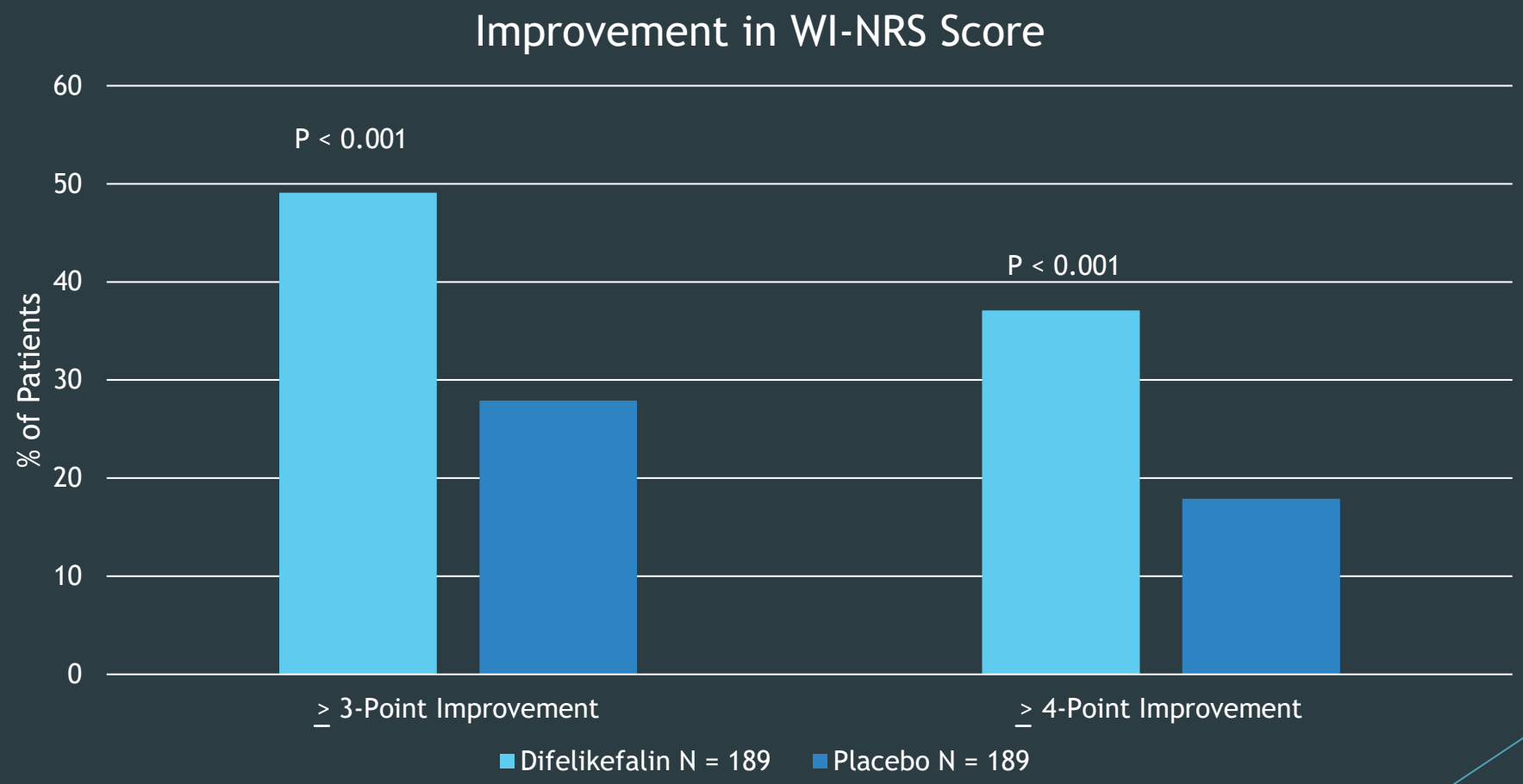
Korsuva (difelikefalin) prescribing information. Stamford CT: Cara Therapeutics; August 2021.

Adverse Reactions Phase 3 Trials (KALM-1 and KALM-2)

Reaction	Difelikefalin N = 424	Placebo N = 424
Diarrhea	9%	5.7%
Dizziness	6.8%	3.8%
Nausea	6.6%	4.5%
Gait disturbances	6.6%	5.4%
Hyperkalemia	4.7%	3.5%
Headache	4.5%	2.6%
Somnolence	4.2%	2.4%
Mental status change	3.3%	1.4%

Korsuva (difelikefalin) prescribing information. Stamford CT: Cara Therapeutics; August 2021.

Difelikefalin (Korsuva™): KALM-1 Trial



WI-NRS = Worst Itching Intensity Numerical Rating Scale

Fishbane S, et al. N Engl J Med. 2020;382:222-32.

Difelikefalin (Korsuva™)

- Dosing and Administration
  - 0.5 mcg/kg based on dry body weight (dosing table in labeling)
  - IV at the END of dialysis
  - Administer within 60 minutes of preparation
- Availability
  - Single vial with 65 mcg per 1.3 ml (50 mcg/ml)
- Cost
  - AWP = $180/vial

Korsuva (difelikefalin) prescribing information. Stamford CT: Cara Therapeutics; August 2021.

Difelikefalin (Korsuva™)

- Bottom line
  - First FDA approved treatment for uremic pruritis associated with chronic kidney disease patients on hemodialysis
  - Given at the end of each dialysis session
  - How does it compare to other non-FDA approved therapies?
- Additional review
  - Trachtenberg AJ, et al. Curr Opin Nephrol Hypertens. 2020;29:465-70.

Dexmedetomidine (Igalmi™)

- Indication
  - Acute treatment of agitation associated with schizophrenia or bipolar I or II in adults
- Pharmacology
  - Centrally acting selective alpha-2 agonist
  - Decreases norepinephrine release
  - Decreases stress-induced hyperarousal

Igalmi (dexmedetomidine) prescribing information. New Haven, CT: BioXcel Therapeutics; April 2022.

Dexmedetomidine (Igalmi™)

- Pharmacokinetics
  - Sublingual (SL) or buccal administration to avoid first-pass metabolism
  - Bioavailability 72% SL, 82% buccal
  - Cmax ~ 2 hours
  - T ½ 2.8 hours
  - Metabolized via glucuronidation and CYP enzymes (primarily 2A6)
  - Inactive metabolites cleared via kidneys

Igalmi (dexmedetomidine) prescribing information. New Haven, CT: BioXcel Therapeutics; April 2022.

Dexmedetomidine (Igalmi™)

- Contraindications
  - None
- Warnings and precautions
  - Hypotension and orthostatic hypotension
  - Bradycardia
  - QT prolongation (6-11 msec)
  - Somnolence (avoid driving for at least 8 hours)
  - Risk of withdrawal reactions
  - Tolerance/tachyphylaxis

Igalmi (dexmedetomidine) prescribing information. New Haven, CT: BioXcel Therapeutics; April 2022.

Adverse Reactions from SERENITY I and II Trials

Reaction	Dexmedetomidine 180 mcg N = 252	Dexmedetomidine 120 mcg N = 255	Placebo N = 252
Somnolence	23%	22%	6%
Paresthesia or oral hypoesthesia	7%	6%	1%
Dizziness	6%	4%	1%
Hypotension	5%	5%	0%
Orthostatic hypotension	5%	3%	< 1%
Dry mouth	4%	7%	1%
Bradycardia	2%	2%	0%

Igalmi (dexmedetomidine) prescribing information. New Haven, CT: BioXcel Therapeutics; April 2022.

Dexmedetomidine (Igalmi™)

- Drug interactions
  - No CYP450 interactions
  - QT prolonging medications
  - Anesthetics, sedatives, hypnotics, opioids

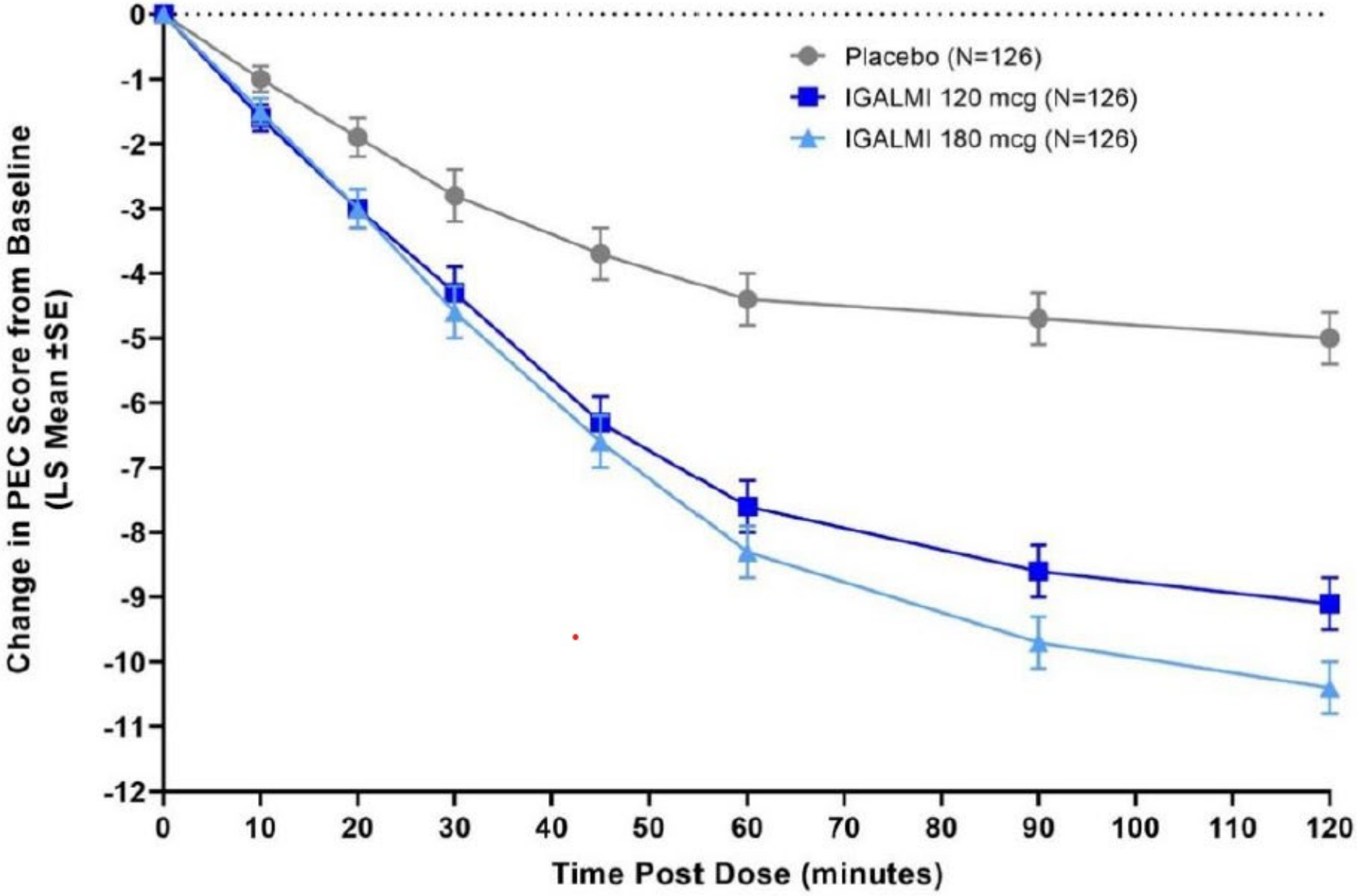
Igalmi (dexmedetomidine) prescribing information. New Haven, CT: BioXcel Therapeutics; April 2022.

SERENITY II Trial Results

	Dexmedetomidine		Placebo N = 126
	120 mcg N = 126	180 mcg N = 126	
Mean Baseline PEC Score	18	18	17.9
Mean Change from Baseline to 2 hours	-9.1	-10.4	-5
Mean Difference (95% CI)	-4.1 (-5.1, -3.0)	-5.4 (-6.5, -4.3)	--

PEC = Positive & Negative Syndrome Scale- Excited Component

Preskorn SH, et al. JAMA. 2022; 327:727-36.



LS = least square; PEC = Positive and Negative Syndrome Scale – Excited Component; SE = standard error
PEC baseline scores were: 17.9, 18.0, and 18.0 in the placebo, IGALMI 120 mcg, and IGALMI 180 mcg groups, respectively

Igalmi (dexmedetomidine) prescribing information. New Haven, CT: BioXcel Therapeutics; April 2022.

Dexmedetomidine SL Dosing

Population	Agitation severity	Initial dose	Optional 2nd/3rd doses	Max daily dose
18-64 years old	Mild/Moderate	120 mcg	60 mcg	240 mcg
	Severe	180 mcg	90 mcg	360 mcg
> 64 years old	Mild/Moderate/ Severe	120 mcg	60 mcg	240 mcg
Child-Pugh A or B hepatic impairment	Mild/Moderate	90 mcg	60 mcg	210 mcg
	Severe	120 mcg	60 mcg	240 mcg
Child-Pugh C hepatic impairment	Mild/Moderate	60 mcg	60 mcg	180 mcg
	Severe	90 mcg	60 mcg	210 mcg

Igalmi (dexmedetomidine) prescribing information. New Haven, CT: BioXcel Therapeutics; April 2022.

Dexmedetomidine (Igalmi™)

- Monitoring
  - Vital signs prior to additional dosing
  - Do not repeat dosing if SBP < 90 mm Hg, DBP < 60 mm Hg, or HR < 60 BPM
- Administration
  - Self-administered under healthcare supervision
  - Avoid eating/drinking for 15 minutes after SL administration; 1 hour after buccal administration
- Availability and cost
  - 120 mcg or 180 mcg individually packaged foil pouches (10 & 30 count)
  - AWP = $120 per dose

Igalmi (dexmedetomidine) prescribing information. New Haven, CT: BioXcel Therapeutics; April 2022.

Dexmedetomidine (Igalmi™)

- Bottom line
  - First non-antipsychotic approved for agitation associated with bipolar or schizophrenia
  - Significant improvement over placebo as early as 20 minutes
  - No data beyond 24 hours
  - Monitor blood pressure and heart rate
- Additional review
  - Hsiao JK. JAMA 2022;327:723-25.

Oteseconazole (Vivjoa™)

- Indication
  - Reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females who are NOT of reproductive potential
- Pharmacology
  - Azole antifungal, inhibits CYP51
  - Early step in synthesis of ergosterol; key for fungal cell membrane formation
  - Lower affinity for human CYP enzymes

Vivjoa (oteseconazole) prescribing information. Durham, NC: Mycovia Pharmaceuticals; April 2022.

Oteseconazole (Vivjoa™)

- Pharmacokinetics
  - Tmax 5- 10 hours
  - T ½ ~ 138 days
  - No significant metabolism
  - Elimination primarily via biliary system

Vivjoa (oteseconazole) prescribing information. Durham, NC: Mycovia Pharmaceuticals; April 2022.

Oteseconazole (Vivjoa™)

- Contraindications
  - Females of reproductive potential
  - Hypersensitivity
- Warnings and Precautions
  - Ocular toxicities to fetus and infants
- Drug interactions
  - Oteseconazole inhibits BCRP
    - Increases BCRP substrates (rosuvastatin AUC 114%)

Vivjoa (oteseconazole) prescribing information. Durham, NC: Mycovia Pharmaceuticals; April 2022.

Oteseconazole (Vivjoa™)

- Adverse reactions
  - Headache (7.4%), nausea (3.6%)
    - Similar to comparator groups
  - Creatine phosphokinase elevations (10x ULN)
    - 1.9% vs. 0.7% comparator groups
    - Transient
  - 1 out of 580 trial patients dc'd due to allergic dermatitis

ULN = upper limit of normal

Vivjoa (oteseconazole) prescribing information. Durham, NC: Mycovia Pharmaceuticals; April 2022.

Clinical Efficacy of Oteseconazole: VIOLET Trials

	Trial 1		Trial 2	
Outcome	Oteseconazole N = 217	Placebo N = 109	Oteseconazole N = 218	Placebo N = 108
% with ≥ 1 culture verified acute VVC episode (thru week 48)	6.7%*	42.8%	3.9%*	39.4%
% with ≥ 1 culture verified acute VVC episode OR received VVC medication (thru week 48)	27.3%*	50.8%	21.3%*	49.7%

*Treatment difference p-value = < 0.001

Vivjoa (oteseconazole) prescribing information. Durham, NC: Mycovia Pharmaceuticals; April 2022.

Clinical Efficacy of Oteseconazole: ultraVIOLET Trial

Outcome	Oteseconazole N = 147	Fluconazole/Placebo N = 72
% with ≥ 1 culture verified acute VVC episode (thru week 50) or unresolved VVC during induction phase	10.3%*	42.9%
% with ≥ 1 culture verified acute VVC episode OR received VVC medication (thru week 50) or unresolved VVC during induction phase	43.5%**	59%

*Treatment difference p-value = < 0.001
**Treatment difference p-value = < 0.039

Vivjoa (oteseconazole) prescribing information. Durham, NC: Mycovia Pharmaceuticals; April 2022.

Oteseconazole (Vivjoa™)

- Oteseconazole-only dosing (ultraVIOLET Study)
  - 600 mg day 1, 450 mg day 2, then 150 mg weekly starting on day 14 for 11 weeks
- Fluconazole/oteseconazole dosing (VIOLET Studies)
  - Fluconazole 150 mg on day 1, 4, and 7 (for acute episode)
  - Oteseconazole 150 mg daily for 7 days starting on day 14
  - Oteseconazole 150 mg weekly starting on day 28 for 11 weeks
- Availability
  - Capsules, 18-count blister packs
  - ~ $2,800

Vivjoa (oteseconazole) prescribing information. Durham, NC: Mycovia Pharmaceuticals; April 2022.
https://www.drugs.com/price-guide/vivjoa

Oteseconazole (Vivjoa™)

- Bottom line
  - First approved agent for RVVC
  - Appears well-tolerated
  - No direct comparator studies
  - Minimal drug interactions
  - Only approved for post-menopausal or infertile women
- Additional review
  - Sobel JD, Nyirjesy P. Future Microbiol. 2021;16:1453-61.

Mavacamten (Camzyos™)

- Indication
  - New York Heart Association Class II-III obstructive hypertrophic cardiomyopathy (HCM)
  - Improves functional capacity and symptoms
- Pharmacology
  - Cardiac myosin inhibitor
  - Reduces myocardial contractility by decreasing actin-myosin affinity
  - Restores a more typical ratio of myosin heads in the relaxed state

Camzyos (mavacamten) prescribing information. Brisbane, CA: MyoKardia; May 2022.
Zampieri M, et al. Curr Cardiol Rep 2021;23:79.

Mavacamten (Camzyos™)

- Pharmacokinetics
  - T ½ 6-9 days
    - Poor CYP2C19 metabolizers: t ½ 23 days
  - Metabolism via CYP2C19 (74%), CYP3A4 (18%), CYP2C9 (8%)
  - Elimination mostly in urine as metabolites

Camzyos (mavacamten) prescribing information. Brisbane, CA: MyoKardia; May 2022.

Mavacamten (Camzyos™)

- Contraindications
  - Moderate-strong CYP2C19 inhibitors or strong CYP3A4 inhibitors
  - Moderate-strong CYP2C19 inducers or strong CYP3A4 inducers
- Warnings and precautions
  - Heart failure (REMS program)
    - Decreased systolic contraction or complete block of ventricular function
    - Not recommended with EF of < 55%
  - Fetal toxicity

Camzyos (mavacamten) prescribing information. Brisbane, CA: MyoKardia; May 2022.

Mavacamten (Camzyos™)

- Drug interactions
  - Avoid contraindicated CYP2C19 and CYP3A4 inhibitors and inducers
  - Weak CYP2C19 inhibitors or moderate CYP3A4 inhibitors
    - Start usual dose of mavacamten 5mg daily
    - If starting a CYP2C19 or CYP3A4 inhibitor, reduce mavacamten dose by one level (if on lowest dose then do not start)
  - Mavacamten induces CYP3A4, CYP2C9, and CYP2C19
    - Monitor for decreased effectiveness
    - Hormonal contraceptives may be decreased; use alternative method
  - Decreased cardiac contractility
    - Monitor ejection fraction

Camzyos (mavacamten) prescribing information. Brisbane, CA: MyoKardia; May 2022.

Serious Adverse Events from EXPLORER-HCM Trial

Event	Mavacamten N = 123	Placebo N = 128
Atrial fibrillation	2	4
Syncope	2	1
Stress cardiomyopathy	2	0
Sudden death	0	1
EF < 50%	7	2

Olivotto I, et al. Lancet 2020;396:759-69.

Clinical Efficacy from EXPLORER-HCM Study

Endpoint	Mavacamten N = 123	Placebo N = 128	Difference (95% CI)
≥1.5 ml/kg/min increase in pVO2 with > 1 NYHA class improvement **OR** ≥ 3 ml/kg/min increase in pVO2 with no worsening of NYHA class	37%	17%	19.4 (8.7 to 30.1) p value = 0.0005
>1.5 ml/mg per min increase in pVO2 with > 1 NYHA class improvement	33%	14%	19.3 (9 to 29.6)
> 3 ml/kg/min increase in pVO2 with no worsening of NYHA class	24%	11%	12.6 (3.4 to 21.9)
Both > 3 ml/kg/min increase in pVO2 with > 1 NYHA class improvement	20%	8%	12.5 (4 to 21)

Olivotto I, et al. Lancet 2020;396:759-69.

pVO2 = peak oxygen consumption

Clinical Efficacy from Valor Study

Endpoint at 16 weeks	Mavacamten N = 56	Placebo N = 56	Difference (95% CI); p-value
Proceeded with SRT or remained SRT eligible	17.9%	76.8%	58.9 (44.0 to 73.9) < 0.001
At least 1 class of NYHA improvement	62.5%	21.4%	41.1 (24.5 to 57.7) < 0.001

SRT = septal reduction therapy

Desai MY, et al, J Am Coll Cardiol 2022;80:95-108.

Mavacamten (Camzyos™)

- Dosing
  - Start at 5 mg daily
  - Dosing algorithm based on Valsalva left ventricular outflow tract gradient assessment
  - Full dose titration may take up to 36 weeks
  - Follow-up echocardiogram at 4, 8, and 12 weeks; then every 12 weeks
  - Stop treatment if LVEF < 50%; may restart after 4 weeks if LVEF ≥ 50%
- Availability and Cost
  - 2.5, 5, 10, and 15 mg capsules
  - AWP ~ $8,827 per month

Camzyos (mavacamten) prescribing information. Brisbane, CA: MyoKardia; May 2022.

Mavacamten (Camzyos™)

- REMS Program
  - Certified prescribers
  - Patients enroll and must comply with monitoring
  - Only distributed to certified pharmacies

Camzyos (mavacamten) prescribing information. Brisbane, CA: MyoKardia; May 2022.

Mavacamten (Camzyos™)

- Bottom line
  - First approved cardiac myosin inhibitor for obstructive HCM
  - Requires close cardiac monitoring for heart failure
  - Minimal adverse effects in clinical trial
  - Expensive!
- Additional review
  - Zampieri M, et al. Curr Cardiol Rep 2021;23:79.

Vonoprazan/Amoxicillin (Voquezna™ Dual Pak™) + Clarithromycin (Voquezna™ Triple Pak™)

- Indication
  - Adults with *Helicobacter pylori*
- Pharmacology
  - Potassium-competitive acid blocker
  - Suppresses basal and stimulated gastric acid secretion via inhibition of the H^+, K^+- ATPase enzyme
  - Does not require acid for activation, accumulates in parietal cells

Voquezna Dual Pak (vonoprazan; amoxicillin) prescribing information. Buffalo Grove, IL: Phathom Pharmaceuticals; May 2022.

Vonoprazan/Amoxicillin (Voquezna™ Dual Pak™) + Clarithromycin (Voquezna™ Triple Pak™)

- Pharmacokinetics and pharmacodynamics
  - Antisecretory onset 2-3 hours; maintained over 24 hours
  - T ½ ~ 7 hours
  - Steady-state at day 4
  - Metabolized by CYP3A4/5, CYP2B6, CYP2C19, CYP2C9, sulfotranserfases and glucuronosyltransferases
  - Majority (67%) excreted via kidneys as metabolites

Voquezna Dual Pak (vonoprazan; amoxicillin) prescribing information. Buffalo Grove, IL: Phathom Pharmaceuticals; May 2022.

Vonoprazan/Amoxicillin (Voquezna™ Dual Pak™) + Clarithromycin (Voquezna™ Triple Pak™)

- Contraindications
  - Allergy
- Warnings and precautions
  - Related to antimicrobial components (C. diff, clarithromycin QTc prolongation)
- Drug interactions
  - Avoid strong CYP3A4 inducers; may decrease exposure
  - May decrease absorption of drugs dependent on acid environment (e.g. itraconazole, iron, anti-retrovirals)
  - May decrease clopidogrel activation (CYP 2C19 inhibition)

Voquezna Triple Pak (vonoprazan; amoxicillin; clarithromycin) prescribing information. Buffalo Grove, IL: Phathom Pharmaceuticals; May 2022.

Vonoprazan/Amoxicillin (Voquezna™ Dual Pak™) + Clarithromycin (Voquezna™ Triple Pak™)

Adverse Reactions Summary			
Reaction	Dual Pak N = 348	Triple Pak N = 346	LAC N = 345
Diarrhea	5.2%	4%	9.6%
Dysgeusia	0.6%	4.6%	6.1%
Abdominal pain	2.6%	2.3%	2.9%

LAC = lansoprazole, amoxicillin, clarithromycin

Voquezna Triple Pak (vonoprazan; amoxicillin; clarithromycin) prescribing information. Buffalo Grove, IL: Phathom Pharmaceuticals; May 2022.

Eradication Rates of H. pylori

Subgroup	Triple Pak (N)	Dual Pak (N)	LAC (N)
(-) for clarith or amox resistance at baseline*	**84.7% (222)**	**78.5% (208)**	**78.8% (201)**
Treatment difference (95% CI)	5.9 (-0.8, 12.6)	-0.3 (-7.4, 6.8)	--
All H. pylori patients	**80.2% (273)**	**77.2% (250)**	**68.5% (226)**
Treatment difference (95% CI)	12.3 (5.7, 18.8)	8.7 (1.9, 15.4)	--
(+) for clarith or amox resistance at baseline	**65.8% (48)**	**69.6% (39)**	**31.9% (23)**
Treatment difference (95% CI)	33.8 (17.7, 48.1)	37.7 (20.5, 52.6)	--

*primary endpoint

Voquezna Triple Pak (vonoprazan; amoxicillin; clarithromycin) prescribing information. Buffalo Grove, IL: Phathom Pharmaceuticals; May 2022.

Vonoprazan/Amoxicillin (Voquezna™ Dual Pak™) + Clarithromycin (Voquezna™ Triple Pak™)

- Dosing
  - Blister packs labeled with morning and evening doses
  - Take BID x 14 days
- Availability
  - Triple Pak: vonoprazan 20 mg tablets, amoxicillin 500 mg capsules, clarithromycin 500 mg tablets
  - Dual Pak: vonoprazan 20 mg tablets, amoxicillin 500 mg capsules
- Cost
  - Anticipated 3rd quarter 2022

Voquezna Triple Pak (vonoprazan; amoxicillin; clarithromycin) prescribing information. Buffalo Grove, IL: Phathom Pharmaceuticals; May 2022.

Vonoprazan/Amoxicillin (Voquezna™ Dual Pak™) + Clarithromycin (Voquezna™ Triple Pak™)

- Bottom line
  - New acid suppressing therapy for H. pylori
  - Improved efficacy for resistant strains
  - Well-tolerated
  - Potential other indications in the future
- Additional review
  - Kiyotoki S, et al. Intern Med. 2020;59:153-161.

Tirzepatide (Mounjaro™)

- Indication
  - Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- Pharmacology
  - Glucagon-like peptide-1 (GLP-1) receptor agonist
  - Glucose-dependent insulinotropic polypeptide (GIP) receptor agonist
  - "Twincretin"—stimulates two types of incretin receptors
    - Both stimulate insulin after eating
    - GIP impacts lipid homeostasis

Mounjaro (tirzepatide) prescribing information. Indianapolis, IN: Eli Lilly and Company; May 2022.
Karagiannis T, et al. Diabetologia. 2022; 17:1-11.

Tirzepatide (Mounjaro™)

- Pharmacokinetics
  - T ½ ~ 5 days
  - Steady-state in ~ 4 weeks
  - Similar absorption via administration in abdomen, thigh, upper arm
  - Metabolism via protein breakdown
  - Renal or hepatic impairment does not impact clearance

Mounjaro (tirzepatide) prescribing information. Indianapolis, IN: Eli Lilly and Company; May 2022.

Tirzepatide (Mounjaro™)

- Contraindications
  - Medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2
  - Hypersensitivity
- Warnings and precautions
  - Pancreatitis
  - GI adverse effects
    - Acute kidney injury due to dehydration
  - Diabetic retinopathy
  - Acute gallbladder disease (0.6% vs. 0%)

Mounjaro (tirzepatide) prescribing information. Indianapolis, IN: Eli Lilly and Company; May 2022.

Tirzepatide (Mounjaro™)

- Drug interactions
  - Delays gastric emptying
  - Weight loss medications
  - Insulin secretagogues (insulin, sulfonylureas)
    - May increase hypoglycemia when used in combination
  - Warfarin
    - Monitor INR closely
  - Oral hormonal contraceptives
    - Change to a non-oral contraceptive method or add barrier method for 4 weeks after initiation and for 4 weeks after dose escalations

Mounjaro (tirzepatide) prescribing information. Indianapolis, IN: Eli Lilly and Company; May 2022.

Adverse Reactions from SURPASS-2 trial

Reaction	Tirzepatide 5 mg N = 470	Tirzepatide 10 mg N = 469	Tirzepatide 15 mg N = 470	Semaglutide 1 mg N = 469
Any GI adverse event	40%	46.1%	44.9%	41.2%
Nausea	17.4%	19.2%	22.1%	17.9%
Diarrhea	13.2%	16.4%	13.8%	11.5%
Vomiting	5.7%	8.5%	9.8%	8.3%
Dyspepsia	7.2%	6.2%	9.1%	6.6%
Decreased appetite	7.4%	7.2%	8.9%	5.3%
Constipation	6.8%	4.5%	4.5%	5.8%
Abdominal pain	3%	4.5%	5.1%	5.1%

Frias JP, et al. N Engl J Med. 2021;385:503-15.

Adverse Reactions from SURPASS-3 trial

Reaction	Tirzepatide 5 mg N = 358	Tirzepatide 10 mg N = 360	Tirzepatide 15 mg N = 359	Insulin degludec N = 360
Nausea	12%	23%	24%	2%
Diarrhea	15%	17%	16%	4%
Vomiting	6%	9%	10%	1%
Dyspepsia	4%	9%	5%	0%
Decreased appetite	6%	10%	12%	1%
Hypoglycemia (< 70 mg/dl)	8%	14%	14%	48%
Hypoglycemia (< 54 mg/ml)	1%	1%	2%	7%

Ludvik B, et al. Lancet. 2021;398:583-98.

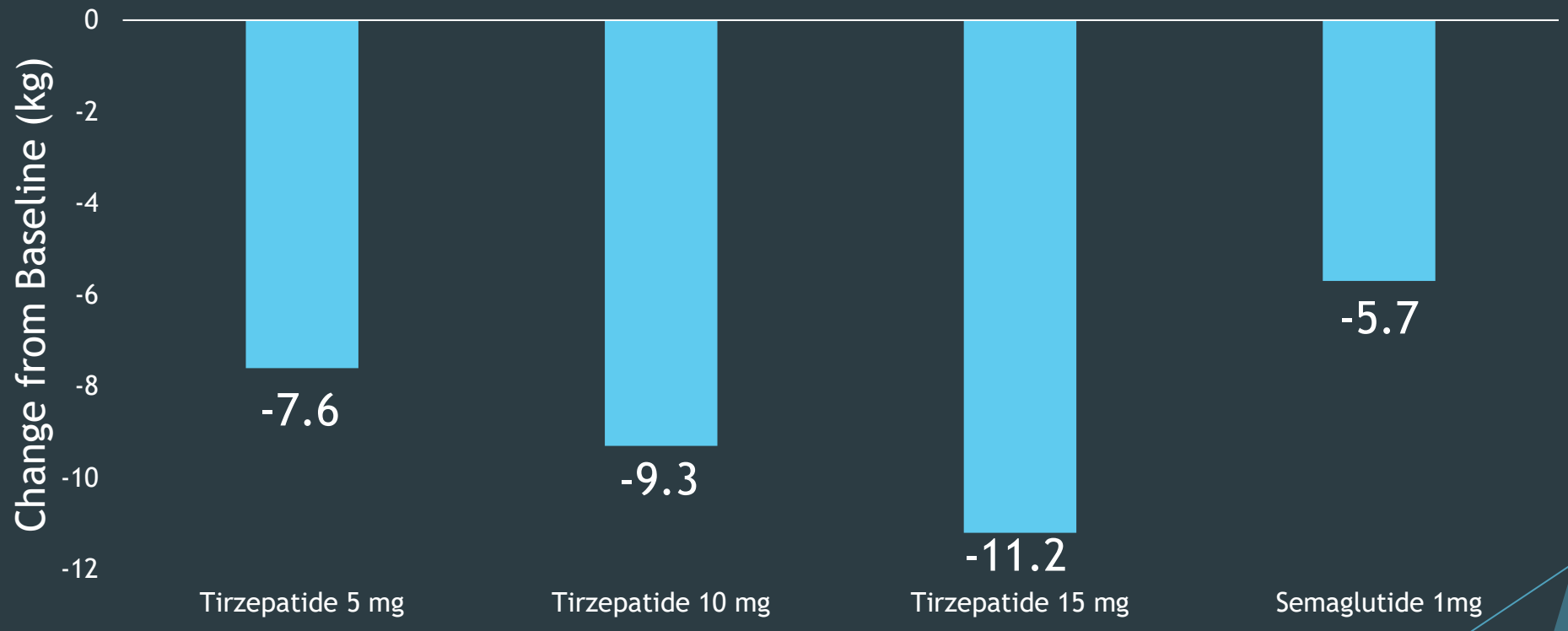
SURPASS-2 Clinical Trial Results

	Tirzepatide 5 mg N = 470	Tirzepatide 10 mg N = 469	Tirzepatide 15 mg N = 470	Semaglutide 1 mg N = 469
Change in A1C % at week 40*	-2.01	-2.24	-2.3	-1.86
Treatment Difference (95% CI)	-0.15 (-0.28, -0.03)	-0.39 (-0.51, -0.26)	-0.45 (-0.57, -0.32)	--

*primary endpoint

Frias JP, et al. N Engl J Med. 2021;385:503-15.

SURPASS-2 Weight Loss Data



*P < 0.001 for all tirzepatide groups vs. semaglutide

Frias JP, et al. N Engl J Med. 2021;385:503-15.

SURPASS-3 Clinical Results

Outcome	Tirzepatide 5 mg N = 358	Tirzepatide 10 mg N = 360	Tirzepatide 15 mg N = 358	Insulin degludec N = 359
Change in A1C % at week 52*	-1.93	-2.2	-2.37	-1.34
A1C < 7%	82%	90%	93%	61%
A1C < 6.5%	71%	80%	85%	44%
A1C < 5.7%	26%	39%	48%	5%

P < 0.001 for above tirzepatide endpoints vs. degludec

*primary endpoint

Ludvik B, et al. Lancet. 2021;398:583-98.

Tirzepatide (Mounjaro™)

- Dosing & Administration
  - 2.5 mg subQ once weekly x 4 weeks then increase to 5 mg
  - Increase by 2.5 mg every 4 weeks if additional glycemic control needed
  - Max dose of 15 mg weekly
  - Administer without regards to meals
  - Rotate injection sites
- Pre-filled 0.5 ml pens
  - 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg
- Cost
  - Retail ~ $975 for 4 weeks

Mounjaro (tirzepatide) prescribing information. Indianapolis, IN: Eli Lilly and Company; May 2022.

Tirzepatide (Mounjaro™)

- Bottom line
  - First “twincretin” agent on the market
  - Comparative data available
  - Warn for GI side effects, similar to other GLP-1 agonists
  - Cardiovascular data pending
- Additional review
  - Karagiannis T, et al. Diabetologia. 2022; 17:1-11.

Atogepant (Qulipta™)

- Indication
  - Prevention of episodic migraines in adults
- Pharmacology
  - Calcitonin gene-related peptide receptor antagonist
  - Rimegepant (Nurtec® ODT) approved for migraine prevention (every other day dosing) and acute migraine treatment
  - Ubrogepant (Ubrelvy™) approved for acute treatment

Qulipta (atogepant) prescribing information. North Chicago, IL: AbbVie Inc; October 2021
Nurtec ODT (rimegepant) prescribing information. New Haven, CT: Biohaven Pharmaceuticals Inc; May 2021
Ubrelvy (ubrogepant) prescribing information. Madison, NJ: Allergan USA; March 2021

Preventative CGRP Pharmacokinetic Comparison

	Atogepant	Rimegepant
Tmax	1-2 hours	1.5 hours
Effect of food	Not significant	Tmax delayed ~ 1 hour Cmax reduced 42-53% (high fat meal); 36% (low fat meal)
Metabolism/ elimination	CYP3A4 (major) CYP2D6 (minor) Biliary excretion	Primarily eliminated unchanged; Metabolized CYP3A4, CYP2C9
T ½	~ 11 hours	~ 11 hours

Qulipta (atogepant) prescribing information. North Chicago, IL: AbbVie Inc; October 2021
Nurtec ODT (rimegepant) prescribing information. New Haven, CT: Biohaven Pharmaceuticals Inc; May 2021

Atogepant (Qulipta™)

- Contraindications
  - None
- Warnings and precautions
  - No data in pregnancy, breast-feeding or pediatrics
- Drug interactions
  - Moderate to strong CYP3A4 inducers and inhibitors
  - OATP inhibitors

Qulipta (atogepant) prescribing information. North Chicago, IL: AbbVie Inc; October 2021.

Adverse Reactions ADVANCE Trial

Outcome	Atogepant 10 mg N = 221	Atogepant 30 mg N = 228	Atogepant 60 mg N = 231	Placebo N = 222
Constipation	7.7%	7%	6.9%	0.5%
Nausea	5%	4.4%	6.1%	1.8%
Fatigue	1.4%	3.1%	3.9%	1.8%
Somnolence	3.2%	1.8%	1.7%	0.9%

Ailani J, et al. N Engl J Med. 2021;385:695-706.

ADVANCE Trial Results

Outcome	Atogepant 10 mg N = 214	Atogepant 30 mg N = 223	Atogepant 60 mg N = 222	Placebo N = 214
Reduction in Monthly Migraine Days (MMD) from baseline across 12 weeks	-3.7	-3.9	-4.2	-2.5
≥ 50% reduction in MMD	55.6%	58.7%	60.8%	29%

P < 0.001 for all endpoints vs placebo

Ailani J, et al. N Engl J Med. 2021;385:695-706.

Preventative CGRP Dosing Comparison

	Atogepant	Rimegepant
Usual Dose	10 mg, 30 mg or 60 mg PO daily	75 mg PO every other day
Renal impairment	10 mg daily if CrCl < 30 ml/min	Avoid if CrCl < 15 ml/min
Strong CYP3A4 inhibitor	10 mg daily	Avoid use
Strong CYP3A4 inducers	30 mg or 60 mg PO daily	Avoid use
OATP inhibitors	10 or 30 mg PO daily	No adjustment
P-gp or BCRP inhibitors	No adjustment	Avoid use

Qulipta (atogepant) prescribing information. North Chicago, IL: AbbVie Inc; October 2021
Nurtec ODT (rimegepant) prescribing information. New Haven, CT: Biohaven Pharmaceuticals Inc; May 2021

Preventative CGRP Price Comparison		
	Atogepant 10 mg, 30 mg or 60 mg	Rimegepant 75 mg ODT
Average wholesale price per tablet	$39.64	$137.89
Monthly AWP	$1,189.20	$2,068.35

Atogepant (Qulipta™)

- Bottom line
  - CGRP receptor antagonist
  - Daily dosing for episodic migraine prevention
  - Well-tolerated
  - No direct comparison with other preventative agents
- Additional review
  - De Vries T, et al. Pharmacol Ther. 2020;211:107528.

Rivaroxaban (Xarelto®)

- New pediatric indication
  - Treatment of VTE from birth to 18 years old who were treated with a parenteral agent for at least 5 days
- Similar efficacy compared to warfarin, enoxaparin, or fondaparinux

Xarelto (Rivaroxaban) package insert. Titusville, NJ: Janssen; Dec 2021.

Rivaroxaban Dosing for Pediatric VTE Treatment

Dosage Form	Body Weight	Dosage			Total Daily Dose
		Once daily	Twice daily	Three times daily	
Oral Suspension	2.6 kg to 2.9 kg			0.8 mg	2.4 mg
	3 kg to 3.9 kg			0.9 mg	2.7 mg
	4 kg to 4.9 kg			1.4 mg	4.2 mg
	5 kg to 6.9 kg			1.6 mg	4.8 mg
	7 kg to 7.9 kg			1.8 mg	5.4 mg
	8 kg to 8.9 kg			2.4 mg	7.2 mg
	9 kg to 9.9 kg			2.8 mg	8.4 mg
	10 kg to 11.9 kg			3 mg	9 mg
	12 kg to 29.9 kg		5 mg		10 mg
Oral Suspension or Tablets	30 kg to 49.9 kg	15 mg			15 mg
	≥ 50 kg	20 mg			20 mg

Xarelto (Rivaroxaban) package insert. Titusville, NJ: Janssen; Dec 2021.

Rivaroxaban (Xarelto®)

- Pediatric dosing
  - Tablets (15 or 20 mg)
    - 2.5 mg tablets not recommended
  - Suspension 155 mg bottle (1mg/ml)
  - Take all doses with food!

Xarelto (Rivaroxaban) package insert. Titusville, NJ: Janssen; Dec 2021.

Others Approvals

- Daridorexant (Quviviq™)
  - 3rd Orexin receptor antagonist for insomnia
- Donepezil (Adlarity®)
  - Transdermal patch for Alzheimer's Disease
- Omeprazole delayed-release "Mini Capsules"
  - 70% smaller than current version
- Cabotegravir/Rilpivirine (Cabenuva)
  - Extended-release injectable suspension for HIV treatment in adolescents; given every 1-2 months
- Cabotegravir (Apretude)
  - Extended-release injectable suspension for HIV prevention; given every 8 weeks

Questions?

Inclisiran lowers LDL-C via a pathway most similar to:

A. Statins
B. Fish oil
C. Ezetimibe
D. PCSK9 inhibitors

Difelikefalin is the first FDA approved agent to treat pruritis associated with:

A. Dermatitis
B. End Stage Renal disease (on hemodialysis)
C. Cirrhosis
D. Insect bites

Dexmedetomidine sublingual has NOT been studied beyond:

A. One dose
B. 24 hours
C. 6 weeks
D. 12 weeks

Oteseconazole should NOT be used in patients:

A. Of reproductive potential
B. Taking CYP3A4 inhibitors
C. Taking medications that prolong QTc
D. Over 65 years old

Monitoring patients on mavacamten includes regularly scheduled:

A. Brain MRIs
B. Chest CTs
C. Echocardiograms
D. Liver function tests

Vonoprazan is currently indicated for:

A. Esophageal varices
B. Helicobacter pylori
C. Inflammatory bowel disease
D. Irritable bowel syndrome

What is the most common side effect associated with tirzepatide?

A. Hypoglycemia
B. Nausea
C. Constipation
D. Hyperkalemia

Atogepant is dose adjusted for:

A. Severe renal impairment
B. CYP2D6 inhibitors
C. P-glycoprotein inhibitors
D. All of the above