

# Pharmaceutical Pipeline 2018 Update

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# Disclosure:

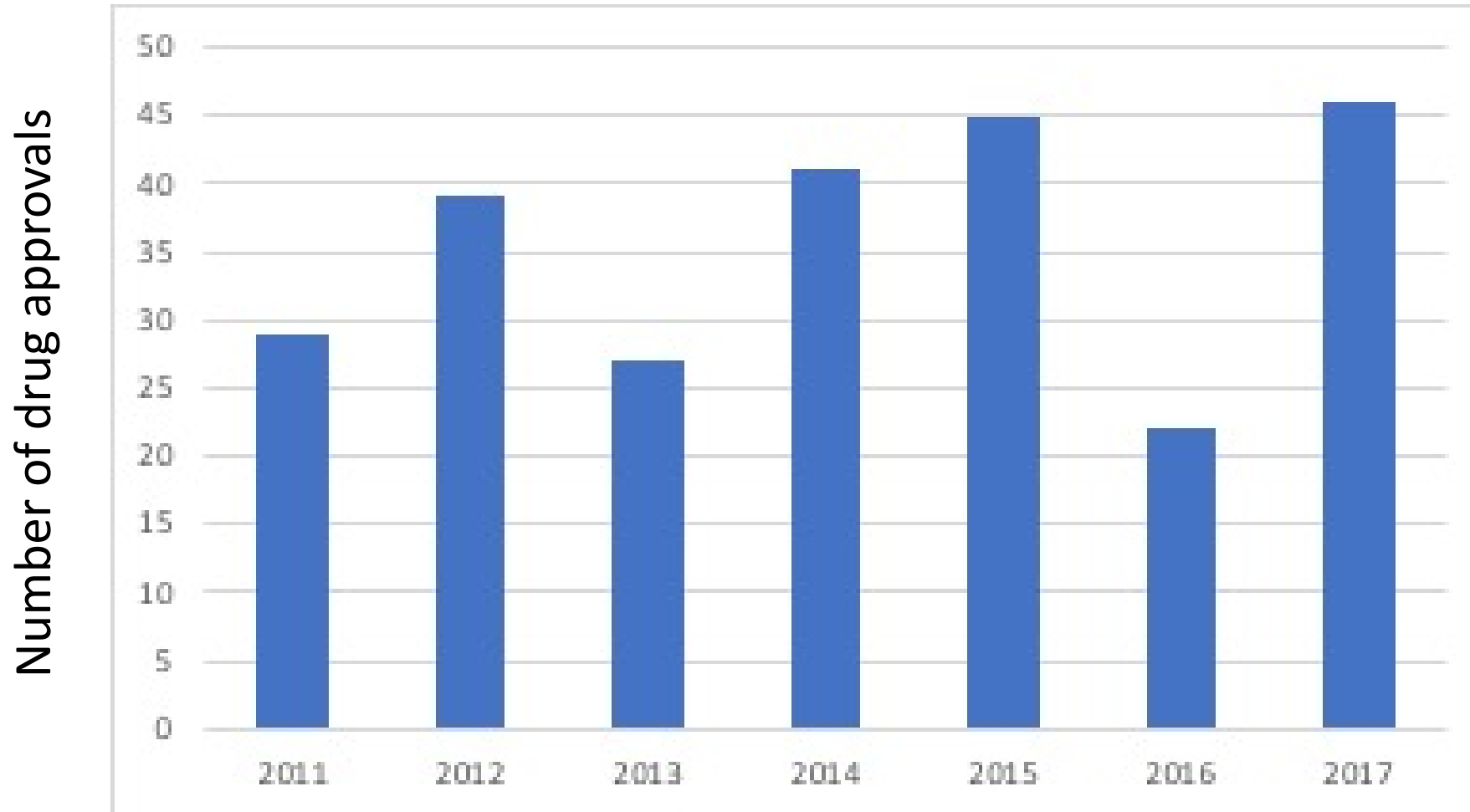
*I have no actual or potential conflict of interest in relation to this presentation.*

# Learning Objectives

At the end of this activity, the participant will be able to...

1. Discuss new drugs likely to be reviewed by the FDA in the next 12 months.
2. Review new classes of drugs in development.
3. Describe diseases without a current approved treatment that drugs are being developed to treat.

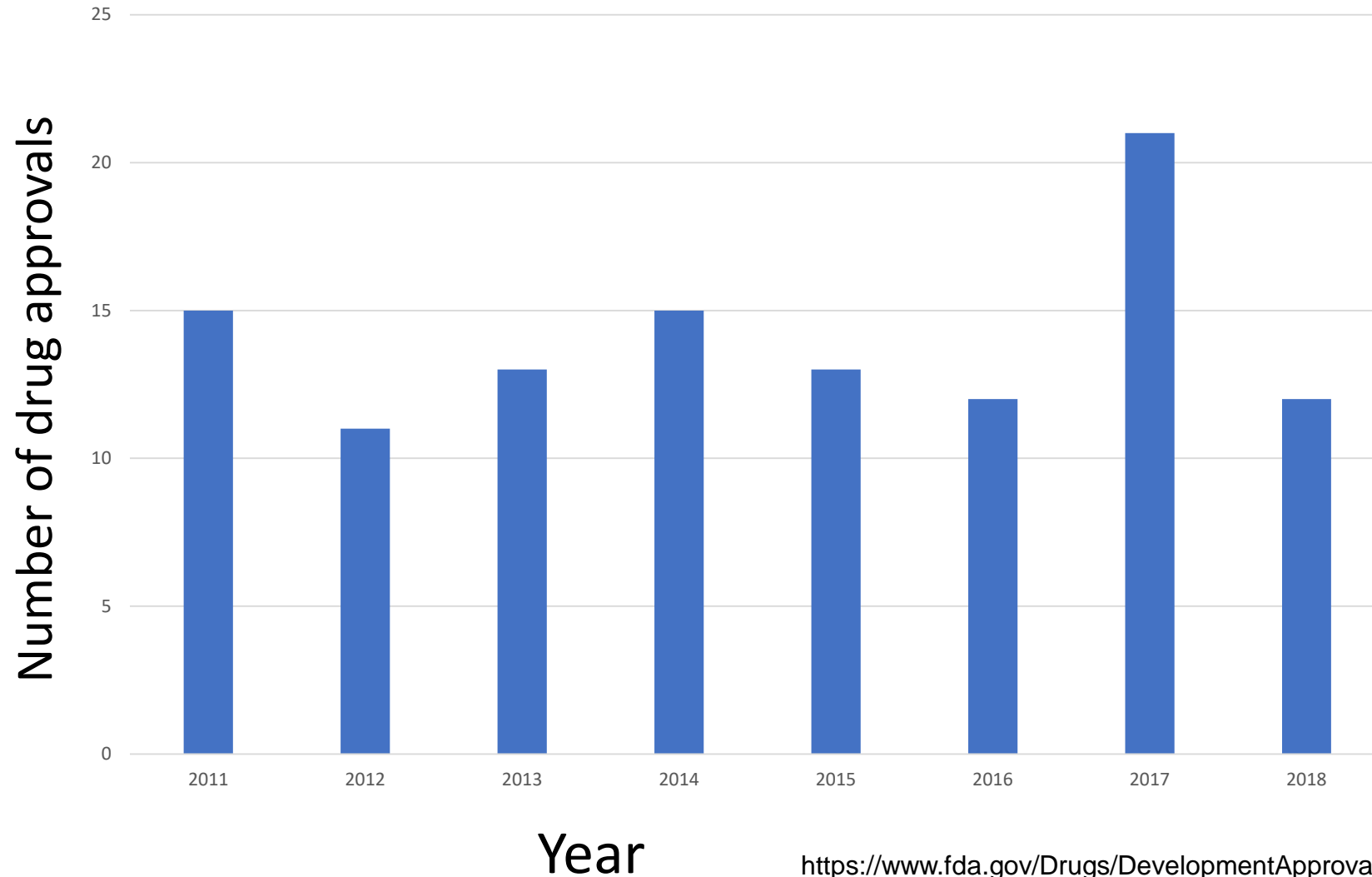
# Unique drug approvals by year



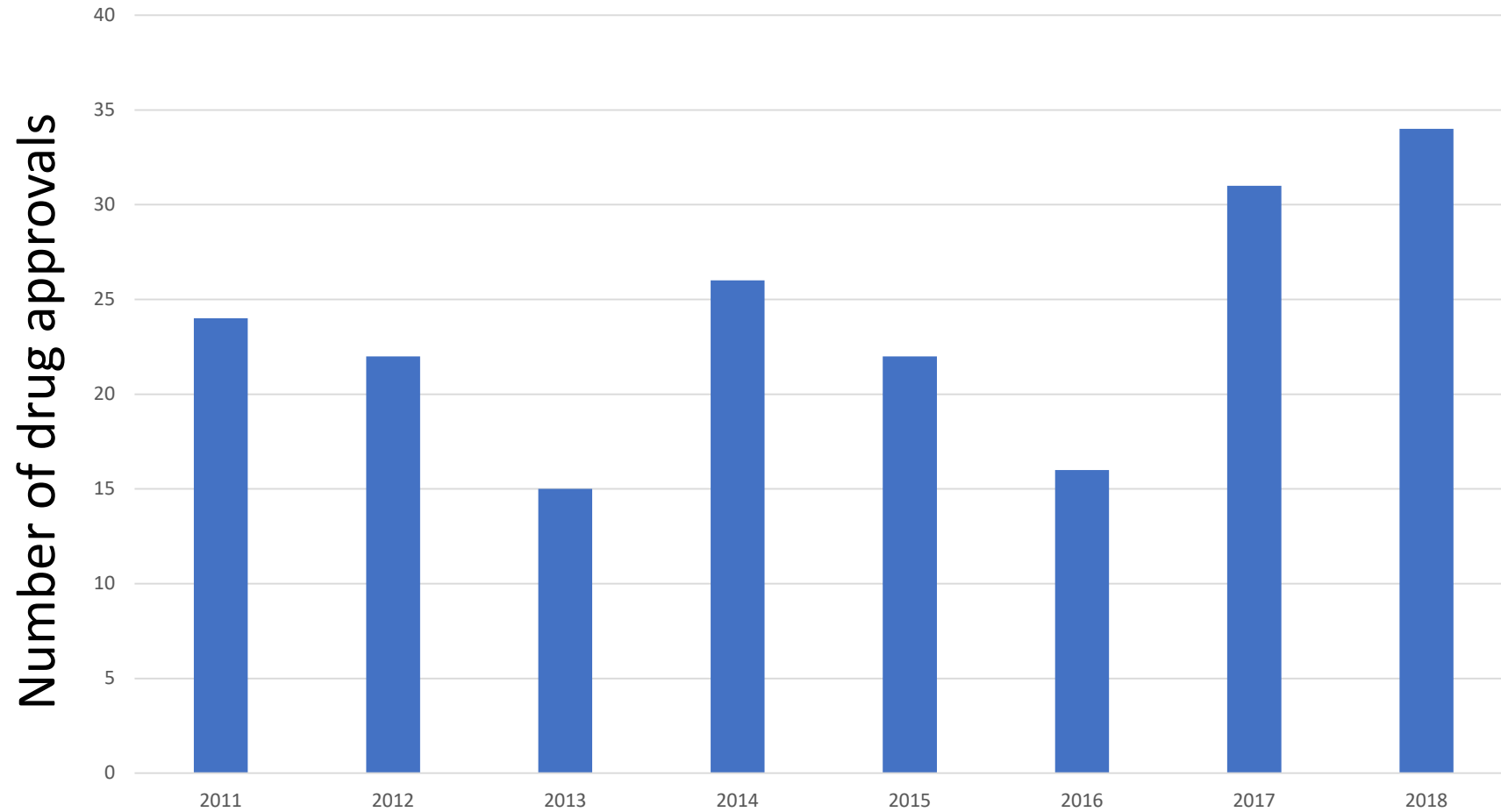
Year

<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm>

# Drug Approvals in First Five Months



# Drug Approvals in First Eight Months



Year

# Migraine Prophylaxis

- Initiate prophylaxis with 6 migraines/month, 4 with some impairment or 3 with severe impairment. (*Neurology*. 2007; 68:343–349)
- Indicated in one-third of patients (*Lancet Neurol*. 2010; 9:285-298)
- Common drugs used include topiramate, propranolol, and amitriptyline. (*N Engl J Med*. 2017; 377:2123-2132)
- A retrospective study estimated that at 6 months adherence is only 26-29% and at 12 months it drops to 17-20%. (*Cephalalgia*. 2015; 35:478-88)
- Half of patients achieve a 50% reduction in monthly headaches. (*Lancet Neurol*. 2010; 9:285-298)

# Calcitonin Gene-Related Peptide (CGRP)

- CGRP is a neuropeptide that has both cerebral arteriolar dilating and pain modulation properties.
- Decreasing CGRP is thought to increase inhibitory mechanisms which decreases the occurrence of migraine headaches.



# CGRP Antagonists

- Monoclonal antibody that binds the calcitonin gene-related peptide (CGRP) or its receptor
- Indications: Episodic migraine prophylaxis
- Reduction in monthly migraine days has been 1-3 days
- ADR: Injection site reactions, upper respiratory symptoms
- High cost
- Lack of long-term safety data
- Limited comparative data

# CGRP Antagonists

- Erenumab decreased monthly migraine days by 2.5 days/month
- Fremanezumab decreased monthly migraine days by 2 days/month
- Galcanezumab decreased monthly migraine days by 2 days/month
- Eptinezumab decreased monthly migraine days by 2.1 to 2.6 days/month
- Sub-group analysis has shown improved efficacy in patients that have failed previous prophylactic treatment
- Fremanezumab and galcanezumab did not reduce weekly headaches in patients with chronic cluster headache

# CGRP Antagonists

The CGRP antagonists differ by: Route, Duration & Dosage form

Drug	Company	Route	Dose form	Status
Erenumab	Amgen, Novartis	Monthly SubQ	Auto-injector	Approved
Fremanezumab	Teva	Quarterly SubQ	Pre-filled syringe	Sept review
Galcanezumab	Lilly	Monthly SubQ	Auto-injector	Sept review
Eptinezumab	Alder Biopharmaceuticals	Quarterly IV infusion	Vial?	2019 review

# CGRP Antagonists

- ICER only found evidence to evaluate erenumab or fremanezumab
- In sufficient to recommend as 1<sup>st</sup> line treatment in untreated patients
- Evidence did support use in patients that failed preventative therapy for chronic migraine
- Data was supportive but inconclusive for prevention of episodic migraine.
- CGRP inhibitors were estimated to improve quality of life years (QALY) for episodic and chronic migraine patients
- Erenumab or fremanezumab were found to be cost effective in QALY gained in patients that had failed at least one preventative therapy
- ICER felt that insurers would be justified in setting limits or restrictions on CGRP inhibitors due to insufficient long-term safety data and high cost

# FDA Migraine Guidance

- For acute treatment
- Formerly, trials were required to address pain, nausea, and sensitivity to light and sound individually
- Now trials will need to address pain and the symptoms an individual patient finds most bothersome.
  - Identify most bothersome symptoms for each patients
  - Efficacy is relief of pain and bothersome symptoms within two hours
  - 48 hours follow-up for rescue meds
  - Separate studies are required for safety and use in children

# Gepants

- Small molecule CGRP antagonist
- Oral administration
- Development of the early gepant, telcagepant, was terminated for transaminase elevation
- NDAs may be filed in 2019

Drug	Company	Route
Atogepant	Allergan	Migraine prophylaxis
Ubrogepant	Allergan	Acute migraine treatment
Rimegepant	Biohaven Pharma	Acute migraine treatment

# Lasmiditan

- Lilly, CoLucid Pharmaceuticals
- M of A: 5-HT<sub>1F</sub> receptor agonist without vasoconstriction. Triptans are 5-HT<sub>1B/1D</sub> receptor agonist
- ADR: Dizziness, Fatigue, Vertigo, Paraesthesia, Somnolence
- Given orally
- Indications: Treatment of acute migraine
- Lilly plans to file an NDA later this year
- In an unpublished trial 39% were pain free at 2 hours compared to 21% with placebo. 49% were free of their most bothersome symptom at 2 hours compared to 34% with placebo.

# Self-Assessment Question #1

What is the biologic target for a new class drugs for prophylaxis of migraine headaches?

- A. Serotonin
- B. Calcitonin gene-related peptide
- C. Gamma-Aminobutyric acid
- D. Beta-adrenergic substances



# Self-Assessment Question #1

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# Dacomitinib

- Pfizer
- M of A: Epidermal growth factor receptor antagonists
- ADR: Nausea, vomiting
- Orally administered
- Indication: EGFR mutant Non-Small Cell Lung Cancer
- PDUFA: September 30, 2018
- Pfizer announced that in the Phase III, ARCHER trial, dacomitinib treatment resulted in progression free survival of 14.7 months and overall survival of 34 months compared to 9.2 months and 27 months with gefitinib. An FDA Advisory Committee recommended approval.

# MDR Antibiotics

Generic Name	Sponsor	Indication
Ceftobiprole	Basilea	Pneumonia
Cefiderocol	Shionogi	UTI, Pneumonia, Sepsis
Imipenem, Cilastatin, Relebactam	Merck & Co	Pneumonia, Abdominal Infections, UTI
Lefamulin	Nabriva Therapeutics	Pneumonia

# MDR Antibiotics

Generic Name	Sponsor	Indication
Fusidic acid	Cempra Pharmaceuticals	Skin and prosthetic joint infections
Eravacycline	Tetraphase Pharmaceuticals	Abdominal infection, UTI
Omadacycline	Paratek Pharmaceuticals	Skin infection, Pneumonia
Iclaprim	Motif BioSciences	Skin infection, Pneumonia

# Omadacycline

- Paratek Pharmaceuticals
- M of A: Ribosomal protein inhibitor (Tetracycline)
- ADR: Nausea and vomiting
- IV, Oral daily dosing
- Indication: Cap and skin infections
- PDUFA: October 4, 2018
- Parateck announced omadacycline was non-inferior to linezolid for skin infections and moxifloxacin for CAP. FDA advisory panel recommended approval for both indications.

# Duvelisib

- Infinity Pharmaceuticals
- M of A: Inhibits PI3K-delta and PI3K-gamma inhibiting cell growth
- ADR: Neutropenia, thrombocytopenia, anemia, diarrhea.
- Oral BID dosing
- Indication: Non-Hodgkin's Lymphoma, Chronic lymphocytic leukemia
- PDUFA: October 5, 2018
- Verastem announced that in the 319 patient, Phase III, DUO study, duvelisib treatment resulted in progression survival of 13.9 months compared to 9.9 months with ofatumumab.

# TTR amyloidosis

- Transthyretin (TTR) amyloidosis: Gradual progressive deposits of abnormal protein called amyloid (amyloidosis) in the body's organs and tissues, most often in the peripheral nervous system and sometimes the central nervous system.
- Treatment
  - Liver transplantation (sometimes with kidney or heart)
  - Some immunologic may decrease symptoms
  - Diflunisal reduced progression in a small trial
- Current treatments are very limited

# Patisiran

- Alnylam
- M of A: siRNA inhibitor targeting TTR
- ADR: Peripheral edema
- Intravenous Infusion administered every 3 weeks
- Approved for the treatment of Hereditary transthyretin-mediated amyloidosis (hATTR) polyneuropathy in August 2018
- Patisiran improved neuropathy impairment by 34 points compared to placebo in the 18-month, 225 patient hATTR APOLLO trial.



# Inotersen

- Ionis Pharma, Akcea Therapeutics
- M of A: Transthyretin-targeting antisense drug
- ADR: Thrombocytopenia
- Weekly subcutaneous injection
- Indication: hATTR polyneuropathy
- PDUFA: October 6, 2018 (moved from 7/6/18)
- Inotersen improved the mNIS+7 score, which, measures neuropathy impairment by 20 points compared to placebo in a 15-month, 172 hATTR patient NEURO-TTR trial.

# Tafamidis

- Pfizer
- M of A: Stabilizes TTR strands, which can unravel and harm neurons
- ADR: Diarrhea, Urinary tract infection Vaginal infection
- Daily oral dose
- Indication: TTR amyloid cardiomyopathy, dose
- PDUFA: No date set. FDA rejected the drug in 2012 due to a limited efficacy
- Pfizer announced that in a 30-month trial, tafamidis reduced all-cause mortality (30% vs 43%) compared to placebo. Tafamidis also cardiovascular-related hospitalizations.

# Self-Assessment Question #2

Which drug is not being developed to treat TTR amyloidosis?

- A. Tafamidis
- B. Inotersen
- C. Dacomitinib
- D. Patisiran

# Self-Assessment Question #2

Which drug is not being developed to treat TTR amyloidosis?

- A. Tafamidis
- B. Inotersen
- C. Dacomitinib**
- D. Patisiran

# Sarecycline (Seysara)

- Almirall, Paratek Pharmaceuticals
- M of A: Ribosomal protein inhibitor (Tetracycline)
- ADR: Nausea, Nasopharyngitis, Headache
- Oral daily dosing
- Indication: Moderate to severe acne
- PDUFA: October 19, 2018
- Sarecycline reduced the Investigators Global Assessment (IGA) scale score and inflammatory lesion score count in two 12 week trials of moderate to severe acne patients.

# Cemiplimab

- Regeneron, Sanofi
- M of A: PD-1 antibody
- ADR: Diarrhea, fatigue, nausea, constipation, rash
- IV
- Indication: Cervical cancer, NSCLC, cutaneous squamous cell cancer
- PDUFA: October 28, 2018
- Regeneron announced that cemiplimab has shown a 46-47% overall response rate in two Phase II metastatic cutaneous squamous cell carcinoma trials.

# Oliceridine

- Trevena
- M of A: Mu opioid receptor modulator
- ADR: Nausea, Vomiting, Headache, Dizziness
- 2 IV loading doses 10 min apart, followed by on demand doses
- Indication: Post-op pain
- PDUFA: November 2, 2018
- Trevena announced that oliceridine was similar to morphine in a Phase IIb trial and superior to placebo in Phase III trials. Oliceridine likely be C-II drug.

# Revefenacin

- Mylan, Theravance
- M of A: Muscarinic receptor antagonist
- ADR: Nasopharyngitis, URTI, Cough
- QD nebulized inhalation
- Indication: COPD
- PDUFA: November 13, 2018
- Theravance announced that revefenacin improved trough FEV1 compared to placebo in 2 Phase III trials involving 1,250 moderate-to-severe COPD and had a comparable COPD exacerbation rate to MDI tiotropium in a 1,055 patient, safety trial.



# Rifamycin-SV

- Salix, Cosmo
- M of A: Inhibition of DNA dependent RNA synthesis
- ADR: Similar to placebo
- Oral BID
- Indication: Traveler's diarrhea
- PDUFA: November 16, 2018
- Cosmo announced that rifamycin-DV was non-inferior to ciprofloxacin and superior to placebo in treating patients with travelers' diarrhea. Cosmo also announced the drug was non-inferior to single doses of ciprofloxacin and levofloxacin in treating military personnel with travelers' diarrhea.

# Larotrectinib

- Loxo Oncology, Bayer
- M of A: Selective inhibitor of tropomyosin receptor kinase
- ADR: Fatigue, Constipation, Dizziness
- Oral BID
- Indication: Tumors with NTRK-fusion proteins
- PDUFA: November 26, 2018
- Data is only available from small early trials that demonstrated a high percentage of overall response and progression-free survival. Loxo estimates 3,000 to 10,000 late-stage cancer patients in the US and Europe with this mutation.

# Amifampridine (Firdapse)

- Catalyst, BioMarin
- M of A: Potassium channel blocker that allows an increases in acetylcholine release
- ADR: Digital parenthesis, Nausea, Headache
- Oral
- Indication: Lambert-Eaton Myasthenic Synd, Spinal Muscular Atrophy
- PDUFA: November 28, 2018
- Available in EU since 2010, FDA required more data. Derivative of 3,4-DAP that Jacobus Pharm would gives away. If Jacobus is not successful in receiving approval, amifampridine may have a large price tag.

# Gilteritinib

- Astellas, Kotobuki
- M of A: Receptor tyrosine kinase inhibitor of FLT3 and AXL
- ADR: Febrile neutropenia, anemia, thrombocytopenia, sepsis, pneumonia
- Oral
- Indication: AML, NSCLC
- PDUFA: November 29, 2018
- In the 252 patient, Phase I/II CHRYSALIS trial, gilteritinib treatment resulted in a 40% overall response rate.

# Lorlatinib

- Pfizer
- M of A: ALK/ROS1 tyrosine kinase inhibitor
- ADR: Increased lipids, peripheral neuropathy, weight increase, cognitive effects, mood effects, fatigue, diarrhea, arthralgia
- Oral
- Indication: Anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC)
- PDUFA: November 30, 2018
- Pfizer announced that in a 275 patient, Phase II trial, lorlatinib had an ORR of 39% in 111 ALK-positive patients with NSCLC that had previously been treated with 2 or 3 ALK inhibitors and 90% in treatment naive patients.

# Talazoparib

- Medivation
- M of A: Poly ADP ribose polymerase (PARP) inhibitor
- ADR: Anemia, Thrombocytopenia, Leukopenia, Fatigue, Nausea, Alopecia
- Oral
- Indication: metastatic breast cancer with + BRCA 1 or BRCA 2
- PDUFA: December 7, 2018
- Pfizer announced that treatment with talazoparib in BRCA1/2 + breast cancer, resulted in a PFS of 8.6 months compared to 5.6 months with standard chemotherapy and an overall response rate of 65% vs 27%.

# Brexanolone

- Sage Therapeutics
- M of A: GABA A receptor modulator
- ADR: Headache, nausea, dizziness, infusion site pain
- Intravenous Infusion given over 60 hours
- Indication: Postpartum depression
- PDUFA: December 19, 2018
- Sage announced that in 2 Phase III trials, brexanolone improved HAM-D scores at 60 hours, which was maintained at 30 days in women with severe or moderate post-partum depression.

# Solriamfetol

- Jazz
- M of A: Selective Norepinephrine and Dopamine Reuptake Inhibitor
- ADR: Anxiety, nausea and vomiting
- Oral
- Indication: Narcolepsy, Excessive Daytime Sleepiness in COPD
- PDUFA: December 20, 2018
- Jazz announced results from 3 Phase III trials, where solriamfetol increased wakefulness in both narcolepsy and COPD. Jazz announced that solriamfetol maintained efficacy for 50 weeks in the open label TONES 5 trial.



# Baloxavir Marboxil

- Genentech, Shionogi
- M of A: Inhibit the cap-dependent endonuclease protein restricting viral replication.
- ADR: Nausea (less than oseltamivir in trials)
- Single oral dose
- Indication: Influenza infection
- PDUFA: December 24, 2018
- In the Phase III, CAPSTONE-1 trial, a single dose of baloxavir marboxil was similar to 5 days of oseltamivir in the time to alleviate symptoms.

# Self-Assessment Question #3

What is unique about administering Baloxavir Marboxil?

- A. Sub-Q dose
- B. Given TID
- C. Single oral dose
- D. Sublingual dose given for 5 days

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# Glasdegib

- Pfizer
- M of A: Smoothened inhibitor that disrupts the Hedgehog pathway
- ADR: Anemia, febrile neutropenia, nausea, decreased appetite, fatigue, and thrombocytopenia
- Oral
- Indication: Acute myeloid leukemia, Myelodysplastic syndrome
- PDUFA: December 27, 2018
- Pfizer announced that in Phase II trials, the addition of gladegib to cytarabine or cytarabine/daunorubicin increased overall survival in patients with AML or high-risk myelodysplastic syndrome

# Sacituzumab govitecan

- Immunomedics, Seattle Genetics
- M of A: Topoisomerase Inhibitor
- ADR: Neutropenia, Leukopenia, Anemia, Diarrhea, Febrile neutropenia
- Intravenous Infusion
- Indication: Triple-negative breast cancer
- PDUFA: January 18, 2018
- In a 16-month, 69 patient, phase II trial, 30% of patients treated with sacituzumab govitecan had an overall response and 69.5% experienced a reduction in tumor burden.

# Samidorphan/Buprenorphine (ALKS 5461)

- Alkremes
- M of A: Mu opioid receptor agonist & Kappa opioid receptor antagonist
- ADR: Nausea, Dizziness, Fatigue
- Oral, give QD
- Indication: Major Depressive Disorder
- PDUFA: January 31, 2018
- Alkremes announced that ALKS 5461 was similar to placebo in 2 Phase III trials (FORWARD-3 and 4). A post hoc analysis of FORWARD-4 suggested an improvement in the MADRS score. ALKS 5461 improved the MADRS 6 score compared to placebo in the Phase III FORWARD-5 trial.

# Iclaprim

- Motif Bio
- M of A: Dihydrofolate reductase (DHFR) inhibitor
- ADR: Headache, nausea, vomiting, fatigue
- IV Infusion over 2 hours Q12 hr
- Indications: Skin infections and hospital acquired pneumonia
- PDUFA: February 13, 2019
- Covers only Gram + bacteria. Motif announced that iclaprim was non-inferior to vancomycin in two Phase III skin infection trials and was non-inferior to linezolid in one Phase III skin infection trial, but did not reach non-inferiority in a second trial.

# Ravulizumab

- Alexion Pharmaceuticals
- M of A: Complement C5 inhibitor
- ADR: Headache, pyrexia, similar to eculizumab
- IV bolus every 2 months
- Indications: Paroxysmal nocturnal hemoglobinuria
- PDUFA: February 18, 2019
- Being developed to replace eculizumab. Alexion announced that ravulizumab was noninferior to eculizumab in Phase III trials. Eculizumab patients switched to ravulizumab maintained LDH levels. Analysts have expressed concerns over potential cost.



# Semaglutide (Ozempic)

- Novo Nordisk
- M of A: GLP-1 receptor agonist
- The weekly subcutaneous Injection was approved on 12/5/17
- PDUFA: March 22, 2018
- In a Phase II dose ranging study, a 40mg oral dose was similar to the weekly injection in lowering HbA1c, weight loss and ADR occurrence.
- In the unpublished Phase III Pioneer-1 trial, oral semaglutide lowered HbA1c 0.8% (3mg), 1.3% (7mg) & 1.5% (14mg) vs 0.1% with placebo.

# Bremelanotide

- AMAG Pharmaceuticals
- M of A: Melanocortin 4 receptor agonist
- ADR: Nausea, Flushing, Headache
- Subcutaneous Injection
- Indication: Hypoactive sexual desire disorder
- PDUFA: March 23, 2018
- AMAG reported that in 2 Phase III, trials with over 1,200 female patients with hypoactive sexual desire disorder, bremelanotide increased desire and lowered distress compared to placebo.

# NKTR-181

- Nektar
- M of A: Selective mu-opioid agonist
- ADR: Nausea, Constipation
- Oral
- Indication: Moderate to severe chronic low back pain
- PDUFA: May 28, 2018
- Nektar announced that NKTR-181 reduced pain compared to placebo in 600 opioid-naive patients with moderate to severe chronic low back pain. A small trial suggested that NKTR-181 had a lower abuse potential than oxycodone.

# Self-Assessment Question #4

What new dosage form is being developed for semaglutide?

- A. Transdermal
- B. Intramuscular depot injection
- C. Intravenous infusion
- D. Oral

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Questions

