Pipeline Preview 2019

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Introduction
Disclaimers and Disclosures

- Non-biased overview of the pipeline: **Not an all-inclusive** review of the pipeline
  - This CPE program **will** include discussion of non-FDA approved (off-label) medication use
- Maria Lowe, PharmD, BCPS declares that she has no financial relationships to disclose.
  - None of my statements today about drugs in the pipeline should be construed as indicating which, if any, of these agents may be reviewed by ICER in the future

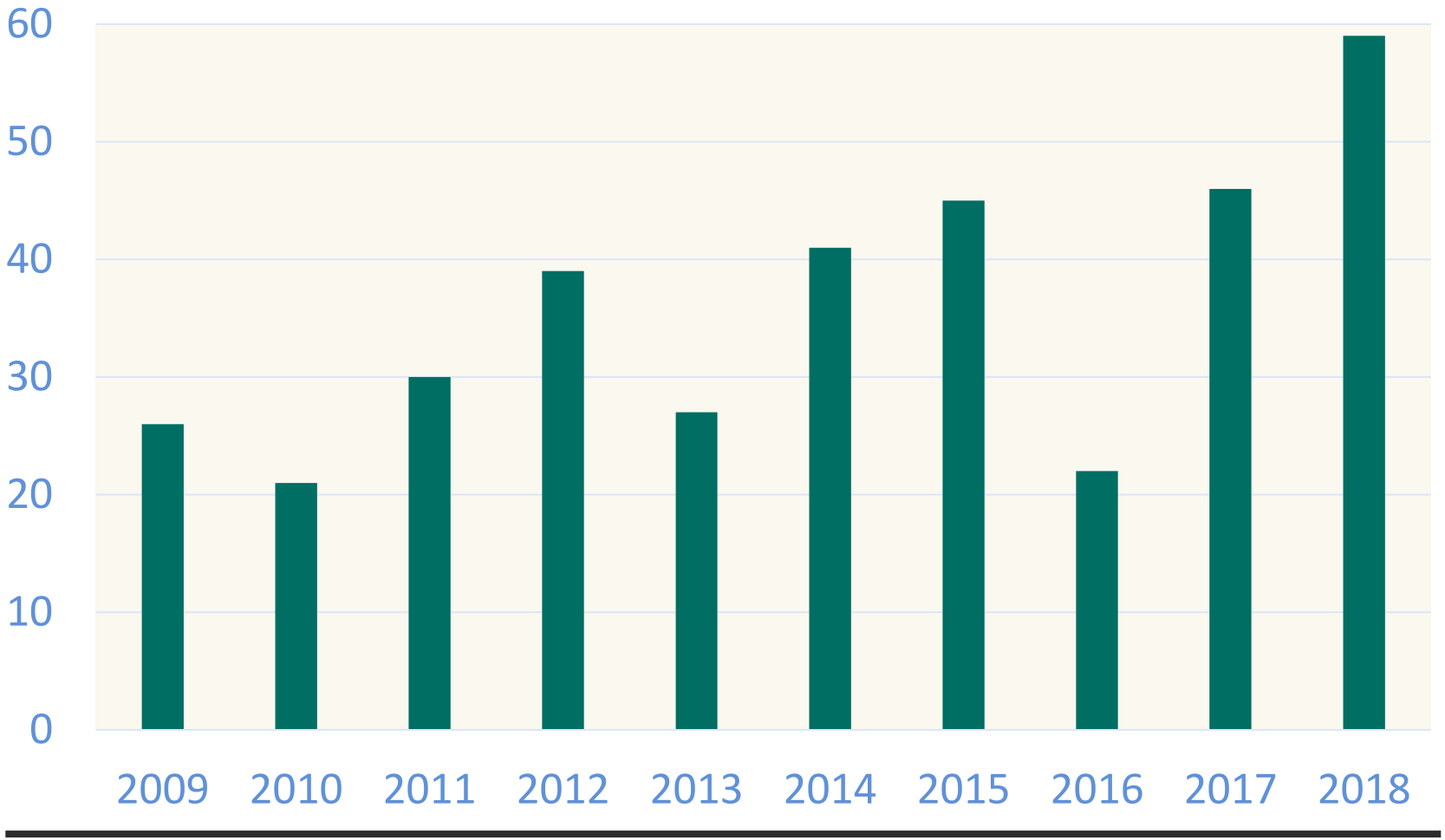
Objectives

By the end of this presentation, you should be able to…

1. Describe recent trends in the FDA approval process
2. Summarize late-stage pipeline agents across key therapeutic categories
3. Identify generic equivalents for commonly used brand-name products that will be introduced to the market over the next two years

Pipeline Trends

FDA-Approved Novel Drugs



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http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ucm121136.htm

Pipeline Trends
Themes of 2019

- **Number of novel drug approvals* remain high:** following a record-setting year in 2017, the FDA approved 59 novel drugs in 2018
  - Don't rely too much on those Advisory Committee decisions though…
- **Gene therapy is coming:** first two products already approved
  - FDA created regenerative medicine advanced therapy (RMAT) designation
  - Hemophilia expected to be next big market
    - And we thought paying for "normal" drugs was getting difficult…

*and falsified data in drug applications continues to be a **bad** idea

Immunology
Pipeline Trends

- **Robust pipeline:** >10 NMEs approved in 2018
  - Efforts appear consistent across psoriasis, rheumatoid arthritis, inflammatory bowel disease, lupus, and many other indications
- **Biosimilar market is expanding despite uncertainty:** 17 agents currently approved
  - FDA issues final guidance on interchangeability
- **Immunotherapy to counter select allergens:** potential for first FDA-approved treatment for peanut allergies

NME: new molecular entity

Immunology
Biosimilar Pipeline*

Product Name	Anticipated Biosimilar Launch
Mvasi® (bevacizumab-awwb)	7/2019
Ogivri® (trastuzumab-dkst)	Late 2019
Truxima® (rituximab-abbs)	Late 2019
Ontruzant® (trastuzumab-dttb)	12/2019-2020
Amjevita® (adalimumab-atto)	1/31/2023
Cyltezo® (adalimumab-adbm)	7/1/2023
Hymrioz® (adalimumab-adaz)	9/20/2023
Erelzi® (etanercept-szzs)	No launch estimate available

Please note: for the purposes of this table, proprietary names are utilized to distinguish patent expiration of the branded product
* All agents listed have FDA approval and are awaiting launch

Immunology
Agents in Development: Allergies

- **AR101**
  - Oral, peanut protein capsule
  - Seeking approval for the treatment of peanut allergies in children 4-17 years of age
  - Phase III **PALISADE trial** (N=551):
    - **67.2%** were able to ingest 600 mg or more of peanut protein (vs. **4.0%** in placebo group)
  - FDA decision expected by **1/2020**
- **Also in development:**
  - Viaskin Milk – patch; phase II
  - Viaskin Peanut – patch; **BLA resubmission expected in 2019**

BLA: biologic license application

Immunology
Agents in Development: Rheumatoid Arthritis

- **Upadacitinib**
  - Oral, inhibitor of Janus kinase 1 (JAK-1)
  - Seeking approval for moderate to severe RA
  - Phase III **SELECT trial** program:
    - ACR20 achieved by **56-66%** of patients (vs **28-36%** with placebo)
  - FDA decision expected **3Q2019**
    - Also in development for: ankylosing spondylitis, atopic dermatitis, Crohn's disease, psoriatic arthritis, ulcerative colitis
- **Also in development:**
  - Filgotinib – oral, JAK-1 inhibitor: **NDA expected in 2019**
  - Piclidenoson – oral, A3 adenosine receptor agonist (A3AR): Phase III

ACR20: 20% improvement in the American College of Rheumatology score, NDA: new drug application, RA: rheumatoid arthritis

Immunology

Agents in Development: Atopic Dermatitis and Psoriasis

	Agent Name	Details	Also in Development For	Status
Atopic Dermatitis	**Abrocitinib**	Oral; targets JAK-1	N/A	Phase III
	Tradipitant	Oral, neurokinin 1 receptor antagonist	pruritis, emesis	Phase III
	Tralokinumab	SC; targets IL-13	asthma	Phase III
Psoriasis	**Bimekizumab**	IV, targets IL-17	psoriatic arthritis, axSpa, hidradenitis suppurativa	Phase III
	BMS-986165	Oral; tyrosine kinase 2 inhibitor	Crohn's disease, psoriatic arthritis, SLE, UC	Phase III
	Mirikizumab	IV and SC; targets IL-23	Crohn's disease, UC	Phase III

axSpA: axial spondyloarthritis, IL: interleukin, IV: intravenous, JAK: Janus kinase, SC: subcutaneous, SLE: systemic lupus erythematosus, UC: ulcerative colitis

Cardiovascular
Pipeline Trends

- **Development is picking up pace**: this could be an interesting area of the pipeline to watch
  - Developments continue in **lipid-lowering**, heart failure, and more
    - Vascepa (icosapent ethyl) expecting FDA decision on sNDA based on findings of REDUCE-IT trial
- **PCSK9 inhibitors**: cost, outcomes, access, and patents
  - What targets come after PCSK9?

PCSK9: Proprotein convertase subtilisin/kexin type 9, sNDA: supplemental new drug application

Cardiovascular
Generic Pipeline

Product Name	Anticipated Generic Entry
Brilinta® (ticagrelor)	7/2021*
Bystolic® (nebivolol)	9/2021*
Pradaxa® (dabigatran)	12/2021*
Livalo® (pitavastatin)	5/2023*
Xarelto® (rivaroxaban)	8/2024*
Multaq® (dronedarone)	4/2029*
Eliquis® (apixaban)	2/2031*

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* Or earlier

Cardiovascular
Agents in Development: Lipid-lowering

- **Bempedoic Acid**
  - Oral, once-daily – alone and in FDC with ezetimibe
  - Inhibits ATP-citrate lyase
  - Seeking approval for the treatment of hyperlipidemia
  - Phase III **CLEAR** clinical trial program is ongoing
    - ↓ LDL **18-31%** (alone or added to background statin)
    - ↓ LDL as much as **64%** when used in combination with ezetimibe and background statin therapy
  - FDA decision expected **2/2020**
- **Also in development**
  - Inclisiran – SC, once every 3 months; Phase III

FDC: fixed-dose combination, LDL: low-density lipoprotein

Cardiovascular

Agents in Development: Lipid-lowering

	Agent Name	Details	In Development For
Phase III	**Dalcetrapib**	• Oral • CETP inhibitor	• Cardiovascular event risk reduction in patients with recent ACS
Phase III	**Evinacumab**	• SC and IV • Inhibitor of angiopoietin-like protein 3	• HoFH, HeFH, severe hypertriglyceridemia
Phase II	**Gemcabene**	• Oral • Facilitates clearance of VLDL and inhibits production of cholesterol and triglycerides in the liver	• Severe hypertriglyceridemia, NASH, FH, and atherosclerotic cardiovascular disease
Phase II	**Resmetirom [MGL-3196]**	• Oral • Thyroid hormone receptor β-selective agonist	• Dyslipidemias and NASH

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ACS: acute coronary syndrome, CETP: cholesterol ester transfer protein, FH: familial hypercholesterolemia, HeFH: heterozygous familial hypercholesterolemia, HoFH: homozygous familial hypercholesterolemia, IV: intravenous, NASH: nonalcoholic steatohepatitis, SC: subcutaneous, VLDL: very low-density lipoprotein

Endocrine
Pipeline Trends

- **Insulin pricing:** average cost of insulin estimated to have tripled between 2002 and 2013
  - Where are the generics? (*authorized generics don't count)*
- **Building on the foundation of existing treatment options:** efforts focus on refining existing mechanisms of action
  - Dual SGLT1 and 2 inhibition, oxyntomodulins, and "twincretins"
- **NASH treatments are on the way**: several agents in development – but can they improve outcomes?

NASH: non-alcoholic steatohepatitis, SGLT: sodium glucose transport

Endocrine
Generic Pipeline

Product Name	Anticipated Generic Entry
Avandia® (rosiglitazone)	10/2020
Januvia® (sitagliptin)	7/2022*
Janumet® (sitagliptin/metformin)	7/2022*
Janumet XR® (sitagliptin/metformin ER)	7/2022*
Onglyza® (saxagliptin)	7/2023*
Qysmia® (phentermine/topiramate ER)	12/2024*
Tradjenta® (linagliptin)	5/2027*
Nesina® (alogliptin)	6/2028

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Endocrine
Agents in Development: Diabetes

- **Tirzepatide [LY3298176]**
  - SC, once-weekly
  - Dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist ("twincretin")
  - Phase III studies began in late 2018
  - Phase II: ↓ A1C from baseline **1.1%-2.4%**; weight loss of ~**11-25** lbs
- **Also in development:**
  - Oxyntomodulins
    - SAR425899 – SC, once-daily; *suspended due to GI toxicity*
    - MEDI0382 – SC, once-daily; phase II
    - Pegapamodutide – SC, once-weekly; phase II

GI: gastrointestinal, GLP1: glucagon-like peptide-1, lbs: pounds, SC: subcutaneous

Endocrine
Agents in Development: Diabetes

- **Sotagliflozin (Zynquista™)**
  - Oral, once-daily
  - Inhibits SGLT1 and SGLT2
    - **SGLT1:** regulates glucose absorption and incretin hormone release in the GI tract
    - **SGLT2:** helps regulate glucose reabsorption in the kidneys
  - Phase III **InTandem trials**: type 1 diabetes
    - ↓ A1C from baseline **0.25-0.31%** (placebo-adjusted, p<0.001)
    - ↓ daily bolus insulin use by **~5.5-15.3%**
  - FDA issued a Complete Response Letter **3/22/2019**
    - Phase III studies in type 2 diabetes

GI: gastrointestinal, SGLT: sodium glucose cotransport

Endocrine

Agents in Development: Diabetes

Class	Agent Name	Details	Status
GLP-1 Analogs	**Semaglutide**	Oral, once-daily	FDA decision expected **9/20/2019**
	ITCA-650	SC, implantable pump	NDA resubmission expected **mid-2019**
	Efpeglenatide	SC, once-weekly	Phase III
SGLT2	**Bexagliflozin**	Oral, once-daily	NDA possible **1H2020**

GLP1: glucagon-like peptide-1, NDA: new drug application, SC: subcutaneous, SGLT: sodium glucose cotransport

Endocrine

Agents in Development: Diabetes

Class	Agent Name	Details	Status
Insulin	**Follow-on insulin glargine** *(by Mylan and Biocon)*	Long-acting	CRL issued **6/2018**
	Ultra rapid lispro (URLi)	Ultra-rapid	NDA expected in **2019**
	Follow-on insulin glargine *(by Gan and Lee)*	Long-acting	Phase III
	Follow-on insulin aspart *(by Mylan and Biocon)*	Rapid-acting	Phase III
	Insulin tregopil	Oral; rapid-acting	Phase II/III
	ORMD-0801	Oral; regular insulin	Phase II

CRL: Complete Response Letter, NDA: new drug application

Endocrine
Agents in Development: NASH

- **Nonalcoholic fatty liver disease (NAFLD)**
  - Classified as either:
    - **Nonalcoholic fatty liver (NAFL)** – no inflammation present
    - **Nonalcoholic steatohepatitis (NASH)** – inflammation present, may cause damage to liver cells
  - NAFLD estimated to affect **30-40%** of US population
    - **3-12%** have NASH
  - Likely asymptomatic
    - NAFLD may not result in complications; NASH may result in **cirrhosis** and **liver failure**
  - Treatment options are currently limited

GI: gastrointestinal, SGLT: sodium glucose cotransport

Endocrine

Agents in Development: NASH

Agent Name	Details	Status
Belapectin [GR-MD-02]	• IV, every other week • **Targets galectin-3**	Phase III
Cenicriviroc	• Oral, once-daily • **Inhibits CCR2 and CCR5**	Phase III
Elafibranor	• Oral, once-daily • **Dual agonist of the PPARα and PPARδ**	Phase III
Obeticholic acid	• Oral, once-daily • **selective farnesoid X receptor (FXR) agonist**	Phase III
Resmetirom [MGL-3196]	• Oral, once-daily • **Thyroid hormone receptor β-selective agonist**	Phase III
Selonsertib	• Oral, once-daily • **ASK-1 inhibitor**	Phase III

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ASK-1: apoptosis signal-regulating kinase 1, CCR: chemokine receptor, DPP-4: dipeptidyl peptidase 4, IV: intravenous, NASH: non-alcoholic steatohepatitis, PPAR: peroxisome proliferator-activated receptors

Infectious Diseases
Pipeline Trends

- **HIV treatment options continue to expand:** new options and new mechanisms result in shift in treatment guidelines
- **Concerns mount regarding scope of antimicrobial resistance:** how to incentivize drugs in light of development paradox
  - FDA announces 2019 strategic approach for combating antimicrobial resistance

HIV: human immunodeficiency virus

Infectious Diseases
Generic Pipeline

Product Name	Anticipated Generic Entry
Factive® (gemifloxacin)	9/2019
Moxeza® (moxifloxacin ophthalmic solution)	3/2020*
Kaletra® (lopinavir/ritonavir)	11/2020
Mycamine® (micafungin)	1/2021*
Selzentry® (maraviroc)	8/2021*
Atripla® (efavirenz/emtricitabine/tenofovir disoproxil fumarate)	9/2021*
Emtriva® (emtricitabine)	9/2021
Truvada® (emtricitabine/tenofovir disoproxil)	9/2021

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Infectious Diseases

Agents in Development: HIV Treatment and Prevention

Agent Name	Details	Status
Tenofovir alafenamide + emtricitabine (Descovy®)	• Oral, once-daily • Seeking approval for pre-exposure prophylaxis (PrEP) • **Reverse transcriptase inhibitor + NRTI**	FDA decision expected **10/5/2019**
Cabotegravir + rilpivirine	• IM, every 4-8 weeks • Oral tablet for lead-in treatment also under review • **Integrase inhibitor + NNRTI**	FDA decision expected **12/29/2019**
Fostemsavir	• Oral, twice-daily • **Attachment inhibitor**	NDA submission expected before end of **2019**
Leronlimab [PRO 140]	• SC, once-weekly • **Viral entry inhibitor (targets CCR5)** • In development as an add-on to ART to treat resistance as well as a monotherapy agent for maintenance of remission	Rolling BLA submission expected to be complete by **3Q2019**

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ART: antiretroviral therapy, BLA: biologic license application, HIV: human immunodeficiency virus , IM: intramuscular, NDA: new drug application, NNRTI: nonnucleoside reverse transcriptase inhibitor, NRTI: nucleotide reverse transcriptase inhibitor, SC: subcutaneous

Central Nervous System
Pipeline Trends

- **Depression treatment:** spotlight on ketamine-like drugs and the NMDA receptor
  - Does psilocybin also have a role to play?
  - First agent approved to treat postpartum depression
- **CGRPs and migraine treatment:** from migraine prevention to acute migraine treatment
- **Opioid crisis and pain management:** growing need to move beyond opioids
  - FDA hoping to facilitate OTC transition for naloxone
  - Alzheimer's Disease: development continues to be unsuccessful

CGRP: calcitonin gene-related peptide, NMDA: N-methyl-D-aspartate, OTC: over-the-counter

Central Nervous System
Generic Pipeline

Product Name	Anticipated Generic Entry
Edluar® (zolpidem SL)	9/2019
Silenor® (doxepin)	1/2020*
Chantix® (varenicline)	5/2020
Ofirmev® (acetaminophen injection)	12/2020
Saphris® (asenapine)	12/2020
Zomig® (zolmitriptan nasal spray)	5/2021
Fycompa® (perampanel)	6/2021
Vimpat® (lacosamide)	3/2022

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Central Nervous System
Agents in Development: Depression

	Agent Name	Details	Status
Other	**Buprenorphine + samidorphan [ALKS-5461]**	• Oral, once-daily • **Partial mu-receptor agonist and kappa-receptor antagonist + mu-receptor antagonist**	**2/4/2019** FDA issues Complete Response Letter
N-methyl-D-aspartate (NMDA)	**Bupropion + dextromethorphan [AXS-05]**	• Oral, once-daily • **Antagonist**	NDA expected in **2020**
	Rapastinel	• IV, every 1-2 weeks • **Partial agonist**	Phase III; *results expected in 2019*
	Apimostinel	• Oral, once-daily • **Partial agonist**	Phase II
	AV-101	• Oral, once-daily • **Inhibits glycine B receptor**	Phase II

IV: intravenous, NDA: new drug application

Central Nervous System

Agents in Development: Bipolar Disorder + Schizophrenia

Agent Name	Details	Status
Ketamine [NRX-100] & D-cycloserine + lurasidone [NRX-101]	• NRX-100: IV, single infusion • NRX-101: oral, once-daily • **NMDA antagonists (plus antagonist at D2-5HT2A)**	Phase III
Samidorphan + olanzapine [ALKS 3831]	• Oral, once-daily • **mu-receptor antagonist + atypical antipsychotic** • Also in development for schizophrenia	NDA expected in **4Q2019**
Lumateperone	• IV, Oral • **Atypical antipsychotic that modulates serotonin, dopamine, and glutamate** • Also in development for bipolar disorder	FDA decision on NDA (schizophrenia) expected **12/27/2019**
HP-3070	• Transdermal patch containing asenapine • **Atypical antipsychotic**	FDA decision expected **10/2019**

IV: intravenous, NDA: new drug application

Central Nervous System

Agents in Development: Migraine

	Agent Name	Use	Dosing	Status
CGRP Inhibitors	**Eptinezumab**	Prevention	IV, every 3 months	FDA decision expected **2/2020**
	Ubrogepant	Acute treatment	Oral	FDA decision expected in **12/2019**
	Rimegepant	Acute treatment	Oral	FDA decision expected **2/2020**
	Atogepant	Prevention	Oral, once-daily	Phase III
Triptans	**Rizatriptan oral film (Rizaport)**	Acute treatment	Oral film	Response to CRL expected in **3Q2019**
	Lasmiditan	Acute treatment	Oral	FDA decision expected **11/2019**
	Meloxicam + rizatriptan	Acute treatment	Oral	NDA expected in **1H2020**
	Zolmitriptan (Qtrypta)	Acute treatment	Microneedle system	NDA expected in **4Q2019**

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BLA: biologic license application, CRL: complete response letter, CGRP: calcitonin gene-related peptides, IV: intravenous, NDA: new drug application

Central Nervous System
Agents in Development: Opioid Use Disorder

- **Buprenorphine depot [CAM2038] (Brixadi)**
  - SC, once-monthly and once-weekly
  - Also in development for the treatment of chronic low back pain
  - Phase III trials
    - Demonstrated **superiority vs sublingual buprenorphine** on % of illicit opioid-negative urine tests and self-reports over 24 weeks
  - FDA granted tentative approval **12/23/2018**
- **Also in development:**
  - Pre-filled naloxone syringe – FDA decision expected **10/2019**
  - Intranasal naloxone – FDA decision expected **3/2020**

SC: subcutaneous

Central Nervous System
Agents in Development: Pain

- **Tanezumab**
  - SC, nerve growth factor inhibitor
  - In development for the treatment of osteoarthritis pain, chronic low back pain, cancer pain
  - **Potential safety concern within class:** joint damage
  - Phase III trials are ongoing
    - BLA possible in **4Q2019-early 2020**
- **Also in development:**
  - Fasinumab – SC; phase III

BLA: biologic license application, SC: subcutaneous

Central Nervous System
Agents in Development: Pain (Opioids)

Agent Name	Details	Status
Oliceridine (Olinvo™)	• IV, mu-receptor G protein pathway selective modulator • **Seeking approval for:** moderate-to-acute pain	Response to CRL possible in **early 2020**
NKTR-181	• Oral, full mu-opioid receptor agonist • **In development for:** the treatment of moderate-to-severe chronic low back pain	FDA Decision Expected by **8/29/2019**
Difelikefalin [CR-845] (Korsuva™)	• Oral and IV, peripheral kappa opioid receptor agonist • **In development for:** acute and chronic pain	Phase III; *oral formulation in Phase II*
Tramadol	• IV, selective mu-opioid receptor agonist • **In development for:** moderate-to-moderately-severe postoperative pain	NDA expected in 12/2019

CRL: complete response letter, IV: intravenous, NDA: new drug application

Central Nervous System
Agents in Development: Pain (Non-Opioids)

Agent Name	Details	Status
Meloxicam	• IV and IM, COX-2 inhibitor • **In development for:** moderate to severe pain	**3/22/2019** FDA issued CRL
HTX-011 (bupivacaine and meloxicam)	• Local application to surgical site, local anesthetic and anti-inflammatory • **In development for:** reduce postoperative pain and the need for opioid analgesics for 72 hours	**4/30/2019** FDA issued CRL
CNTX -4975	• Intra-articular injection, targets capsaicin receptor • **In development for:** osteoarthritis pain	Phase III
Disodium zoledronate tetrahydrate	• Oral, osteoclast inhibitor • **In development for:** treatment of CRPS, knee osteoarthritis, and chronic lower back pain	Phase III
SP-102	• Epidural injection, non-opioid steroid injection • **In development for:** management of sciatica	Phase III

COX: cyclooxygenase, CRL: complete response letter, CRPS: complex regional pain syndrome, IM: intramuscular, IV: intravenous

Pipeline Trends

But what about…

- Brolucizumab
- Crizanlizumab
- DS-8201
- Elexacaftor + tezacaftor + ivacaftor
- Enfortumab Vedotin
- Golodirsen
- Idecabtagene vicleucel "Ide-cel")
- Lentiviral beta-globin gene transfer (Zynteglo)
- Lisocabtagene maraleucel ("Liso-cel")
- Luspatercept
- Ozanimod
- Ponesimod
- Relugolix
- Voxelotor

HIV: human immunodeficiency virus

Pipeline Trends
Conclusions

- **The pipeline is getting harder to summarize and generalize:** orphan and specialty drugs are likely to be new normal
  - Don’t forget about gene and cell therapies
- **Treatments are coming in all shapes and sizes:** keep an open mind
  - Cannabinoids for seizures, ketamine for depression, or long-acting injectables for HIV, potential cures
- **Drug pricing continues to be a concern:** cost is a crucial element in risk-benefit evaluations

HIV: human immunodeficiency virus

Questions?

Pipeline Trends
References

- Anticipated availability of first-time generics [webpage on the Internet]. Stockton (CA): Pharmacist's Letter; 2019 [cited 2019 Aug 2]. Available from: http://pharmacistsletter.therapeuticresearch.com/pl/ArticlePDF.aspx?s=PL&DetailID=280401
- Drugs@FDA [homepage on the Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2019 [cited 2019 Aug 2]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
- PipelineReview.com [homepage on the Internet]. Stuttgart, Germany: LaMerie Business Intelligence; 2019 [cited 2019 Aug 2]. Available from: http://www.pipelinereview.com/
- FierceBiotech [homepage on the Internet]. FierceMarkets; 2019 [cited 2019 Aug 2]. Available from: http://www.fiercebiotech.com/
- ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2019 Aug 2]. Available from: http://clinicaltrials.gov
- Pharmaceutical Databank BioPharmCatalyst [homepage on the Internet]. BioPharmCatalyst; 2010- [cited 2019 Aug 2]. Available from: http://www.biopharmcatalyst.com/.