Pipeline Preview: 2015-2016

A Summary of the Pharmaceutical Pipeline

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Objectives

By the end of this presentation you will be able to:

- Describe recent trends in the FDA approval process
- Compare and contrast emerging pipeline agents with currently available therapeutic options
- Summarize generic availability of commonly used agents over the next two years

Introduction

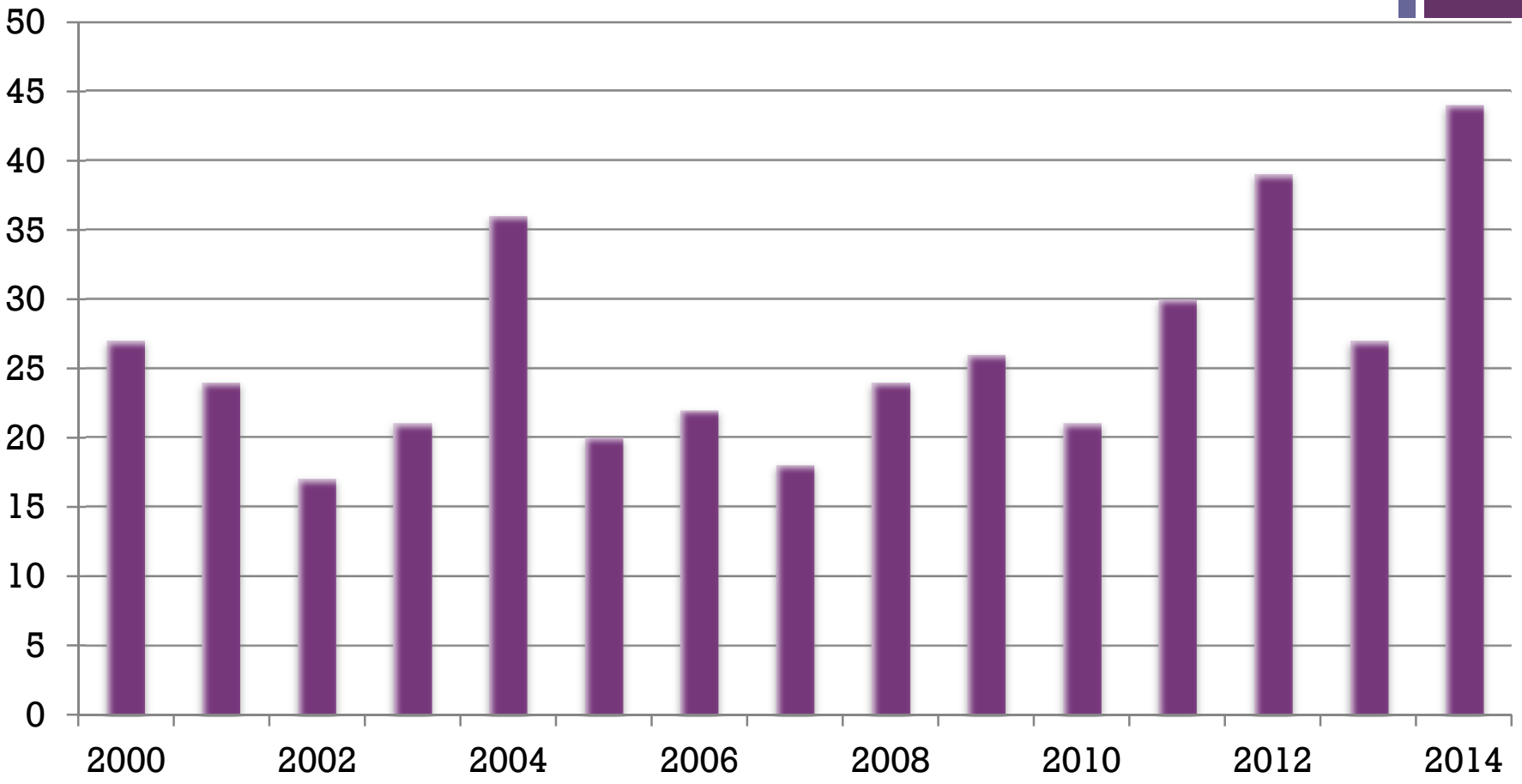
Disclaimer

- 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, Pharm.D., BCPS declares that she has **no** financial relationships with commercial interests. However, her employer, PatientsLikeMe, has received funding from a variety of sources including the following:

Accorda	Boehringer Ingelheim	Celgene	inVentiv Health	Patient Power
Actelion	Bristol-Meyer Squibb	CoPatient	Janssen Pharmaceuticals	Sanofi
AstraZeneca	Bupa	Curelator	Merck	Takeda
Avanir	Cancer Treatment Centers	EMD Serono	Novartis	UCB
Biogen Idec	of America	Genentech	NurseTogether	Walgreens

Pipeline Trends

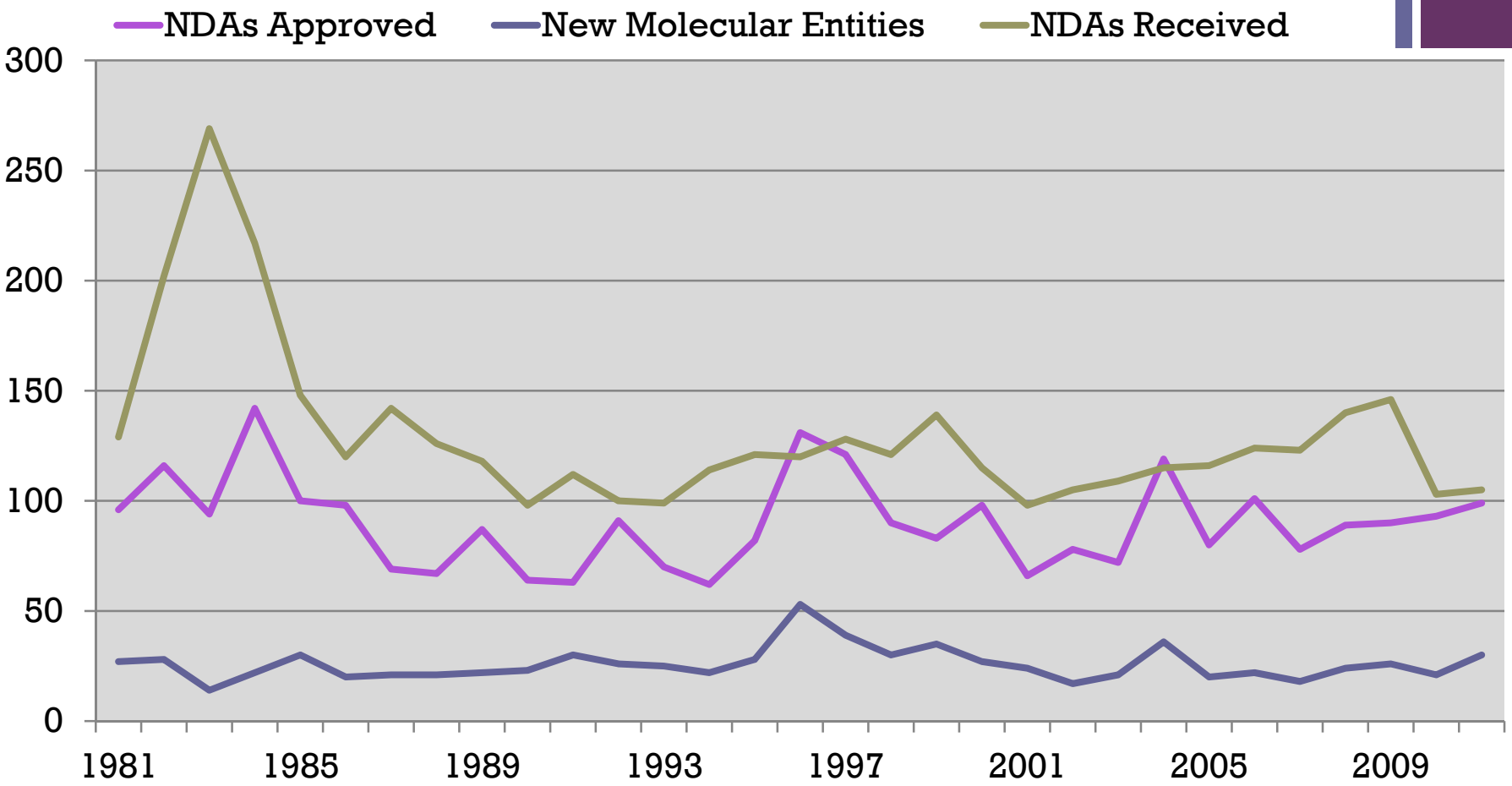
FDA Approved New Molecular Entities and Biologics



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

Pipeline Trends

New Molecular Entities vs. NDAs



http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SummaryofNDAApprovalsReceipts1938tothepresent/default.htm

NDA: New drug application

Pipeline Trends

Themes of 2015: Discussion

- What were some trends in the pipeline that you observed over the last year?

- What were/are the therapeutic categories you feel had/have the most growth or the potential for the greatest impact?

Pipeline Trends

Themes of 2015

Images available from:
http://www.forbes.com/sites/arleneweintraub/2015/02/27/gadfly-pharma-investor-shkreli-starts-anew-after-ousting-from-retrophin/
http://www.dailytimesgazette.com/addyi-the-first-female-libido-drug-has-been-approved-by-the-fda/30960/

Oncology

Pipeline Trends

- Continues to be a fast-paced area of development
  - 9 oncology approvals in 2014, 7 so far in 2015
  - Lots of movement with multiple myeloma and lung cancer
- Large price tags remain an issue
- First biosimilar approved: Zarxio® (filgrastim-sndz)
- Immuno-oncology targets remain a large focus
  - PD-1, CART

Oncology

Generic Pipeline

Product Name	Anticipated Generic Entry
Gleevec® (imatinib)	2/2016
Zytiga® (abiraterone acetate)	12/2016
Aloxi® (palonosetron)	9/2018
Emend® (fosaprepitant injection)	3/2019
Tarceva® (erlotinib)	5/2019
Sutent® (sunitinib)	2/2021
Alimta® (pemetrexed)	5/2022

Please note: for the purposes of this table, proprietary names are utilized to distinguish patent expiration of the branded product

Oncology

Lung Cancer

- Rociletinib vs. Osimertinib
  - Oral, tyrosine kinase inhibitors
  - Specifically targeting EGFR genes that carry the T790M mutation
  - Potential combination with PD-L1 inhibitors
  - Osimertinib [AZD-9291] – median PFS of 8.6 to 13.5 months
    - Safety concern: rash, diarrhea, interstitial lung disease
    - NDA submitted 6/2015
  - Rociletinib [CO-1686] – median PFS of 8 to 10.3 months
    - Safety concern: hyperglycemia
    - FDA decision expected **3/20/2016**

PD-L1:programmed death-ligand 1
PFS: progression-free survival

Oncology

Lung Cancer

- Necitumumab
  - IV, humanized monoclonal antibody, EGFR antagonist
  - Seeking approval in combination with gemcitabine and cisplatin for use in first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer
  - Phase III SQUIRE trial:
    - OS was 11.5 months in necitumumab combination group vs 9.9 months with gemcitabine/cisplatin alone (HR=0.84, p=0.01)
  - Safety concern: thromboembolism
  - FDA decision expected **late 2015**

EGFR: epidermal growth factor receptor, HR: hazard ratio, IV: intravenous OS: overall survival

Oncology

Immuno-oncology: Multiple Myeloma

- Daratumumab
  - IV, humanized monoclonal antibody, CD38 antagonist
  - Seeking approval for the treatment of multiple myeloma in patients who have received at least 3 prior lines of therapy
  - Phase I/II GEN501 trial:
    - 36% overall response rate in patients with late-stage multiple myeloma
    - 65% of those who responded, had not experienced disease progression 12 months after the start of treatment
  - FDA decision expected **3/9/2016**

IV: intravenous

Oncology

Immuno-oncology: Multiple Myeloma

- Elotuzumab (Empliciti®)
  - IV, SLAMF7 antagonist
  - Seeking approval for the treatment of multiple myeloma in patients who have received one or more prior therapies
  - ELOQUENT2 Phase III trial:
    - Elotuzumab added to Revlimid® (lenalidomide) + dexamethasone (Ld) resulted in a 30% reduction in the risk of disease progression
      - ↑ PFS to 19.4 months vs 14.9 months with Ld alone (HR 0.70 [95% CI: 0.57, 0.85]; p = 0.0004)
  - FDA decision expected **2/29/2016**

CI: confidence interval, HR: hazard ratio, PFS: progression-free survival, SLAM: signaling lymphocyte activation molecule

Infectious Diseases

Pipeline Trends

- DAA Market is growing and changing quickly
  - Drug pricing has become the central issue
  - Discontinued production of older agents
    - Incivek® (telaprevir) and Victrelis® (boceprevir) by end of 2015
    - PegIntron® (peginterferon alfa-2b) and Rebetol® (ribavirin) by 2/2016
- Will hepatitis C become a thing of the past?
  - >95% SVR after 12 weeks of treatment
  - Cures within 6 weeks may not be far away
  - Focus expanding beyond genotype 1

DAA: direct acting antivirals, SVR: sustained virologic response

Infectious Diseases

Generic Pipeline

Product Name	Anticipated Generic Entry
Epzicom® (lamivudine/abacavir)	3/2016
Tamiflu® (oseltamivir phosphate)	8/2016
Kaletra® (lopinavir/ritonavir)	12/2016
Norvir® (ritonavir)	12/2016
Tygacil® (tigecycline)	4th quarter 2016
Sustiva® (efavirenz)	12/2017
Viread® (tenofovir)	12/2017
Atripla® (efavirenz/emtricitabine/tenofovir)	8/2018

Please note: for the purposes of this table, proprietary names are utilized to distinguish patent expiration of the branded product

Infectious Diseases

Hepatitis C

	Ingredients	Details	Dosing and Duration	Regulatory Status
Combination Products	Grazoprevir + elbasvir [MK-8742 + MK-5172]	NS3/4A protease inhibitor & NS5A inhibitor	Once daily for 12 weeks	FDA Decision expected 1/28/2016
	Velpatasvir + sofosbuvir [GS-5816 + GS-7977]	NS5A inhibitor & nucleotide analog polymerase inhibitor	Once daily for 12 weeks	NDA Submitted 10/2015
	Daclatasvir + asunaprevir + beclabuvir [BMS-791325]	NS5A inhibitor, protease inhibitor & non-nucleoside NS5B polymerase inhibitor	Twice daily for 12 weeks	Phase III

NDA: new drug application

Infectious Diseases

Hepatitis C

	Ingredients	Details	Dosing and Duration	Regulatory Status
Combination Products	Grazoprevir/elbasvir/MK-3682 [MK-8742/MK-5172/MK-3682]	NS3/4A protease inhibitor, NS5A inhibitor & NS5B polymerase inhibitor	Once daily for 8 weeks	Phase II
	Velpatasvir/sofosbuvir/GS-9857 [GS-5816/GS-7977/GS-9857]	NS5A inhibitor, nucleotide analog polymerase inhibitor & NS3/4A protease inhibitor	Once daily for 6-12 weeks	Phase II
	Odalasvir [ACH-3102]/sofosbuvir	NS5A inhibitor/nucleotide analog polymerase inhibitor	Once daily for 6 weeks	Phase II
	Daclatasvir/asunaprevir	NS5A inhibitor & protease inhibitor	N/A	NDA withdrawn

NDA: new drug application

Cardiovascular

Pipeline Trends

- PCSK-9 inhibitors are here – now what?
  - Focus on cost and place in therapy
  - More competition in the lipid-lowering pipeline is yet to come
- 2015 also brought a number of other significant cardiovascular approvals
  - First antidote is here for newer oral anticoagulants
    - Praxbind® (idarucizumab)
      - More antidotes (and anticoagulants) on the way
  - Entresto® (sacubitril/valsartan) and Corlanor® (ivabradine) for heart failure

PCSK-9: proprotein convertase subtilisin/kexin-9

Cardiovascular

Generic Pipeline

Product Name	Anticipated Generic Entry
Crestor® (rosuvastatin)	5/2016
Azor® (olmesartan/amlodipine)	10/2016
Benicar® (olmesartan)	10/2016[a]
Zetia® (ezetimibe)	12/2016
Aggrenox® (aspirin/dipyridamole)	1/2017
Vytorin® (ezetimibe/simvastatin)	4/2017
Ranexa® (ranolazine)	2/2019

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a: also includes estimated generic entry of combination with hydrochlorothiazide

Cardiovascular

Heart Failure

- Finerenone
  - Oral, mineralocorticoid receptor antagonist
  - In development for the treatment of congestive heart failure
    - Phase II trials have shown decreased risk of death and hospitalization vs. Inspra® (eplerenone)
  - Currently in Phase III studies
- CardiAMP Therapy
  - Bone marrow-derived therapy for heart failure
    - Sample of cells extracted and tested; if patient is candidate for therapy, cells are processed and reintroduced
  - Currently in Phase III studies

Cardiovascular

Lipid-lowering Therapies

- Bempedoic acid [ETC-1002]
  - Oral, inhibitor of ATP-citrate lyase
  - In development for the treatment of hyperlipidemia
  - Phase II trials:
    - ↓ LDL **32-43%** in patients with diabetes
    - ↓ LDL **27-32%** in patients with history of statin intolerance
    - ↓ LDL **43-48%** in combination with Zetia® (ezetimibe)
    - ↓ LDL **22%** when added to atorvastatin 10 mg
  - Phase III trials beginning late 2015
    - Plans for development in fixed doze combination with ezetimibe

LDL: low density lipoprotein

Cardiovascular

Lipid-lowering Therapies

- Bococizumab
  - SC, humanized MAB that targets PCSK9
  - In development for the treatment of high cholesterol
  - Phase II trials:
    - In patients already on statin therapy, the addition of bococizumab resulted in a ↓ in LDL of **-53.4 mg/dL** and **-44.9 mg/dL** at 12 weeks for the twice- and once-monthly dosing, respectively
  - Currently in Phase III studies
    - Completion of cardiovascular outcomes studies expected in 2018

LDL: low density lipoprotein, MAB: monoclonal antibody, PCSK-9: proprotein convertase subtilisin/kexin-9

Cardiovascular

Lipid-lowering Therapies

- Cholesterol Transfer Protein Inhibitors
  - Long history of development within this class
    - Prior failure due to safety concerns (torcetrapib)
  - Shift in focus from HDL increasing properties to LDL decreasing properties
    - Anacetrapib – Phase III
    - Dalcetrapib – development terminated
    - Evacetrapib – development terminated
    - Torcetrapib – development terminated
    - TA-8995 – Phase II

Cardiovascular

Anticoagulant Antidotes

- Andexanet alfa [PRT4445]
  - Modified version of Factor Xa which can sequester direct inhibitors
    - Allows native Factor Xa to restore hemostasis
  - In development for use as antidote to betrixaban, Xarelto® (rivaroxaban) and Eliquis® (apixaban)
  - Phase III trials are ongoing
- Also in development
  - Ciraparantag [PER977] – Phase III
  - MEDI2452 – Pre-clinical

Central Nervous System

Pipeline Trends

- For pain management, emphasis remains on abuse-deterring opioids
  - FDA guidance released
- Migraine pipeline is all about calcitonin gene related peptides
  - Significant competition to become the first product
- Alzheimer's pipeline seems rejuvenated
- Behind recent approvals, MS pipeline seems to be slowing down

MS: multiple sclerosis

Central Nervous System

Generic Pipeline

Product Name	Anticipated Generic Entry
Frova® (frovatriptan)	11/2015
OxyContin® (oxycodone)	1/2016[a]
Nuvigil® (armodafinil)	6/2016
Seroquel XR® (quetiapine ER)	11/2016
Relpax® (eletriptan hydrobromide)	12/2016
Azilect® (rasagiline mesylate)	2/2017
Strattera® (atomoxetine)	5/2017
Treximet® (sumatriptan/naproxen)	2/2018

Please note: for the purposes of this table, proprietary names are utilized to distinguish patent expiration of the branded product
a: new formulation

ER: extended release

Central Nervous System

Pain Management: Abuse-deterring Formulations

- Guidance issued in 2015:
  - "The FDA is encouraging manufacturers to develop abuse-deterrent drugs that work correctly when taken as prescribed, but, for example, may be formulated in such a way that deters misuse and abuse"
    - http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm440713.htm
- Examples of products in the pipeline:
  - Oxycodone/naltrexone ER [ALO-02]
  - Avridi® (IR oxycodone)
  - Arymo® (ER morphine)
  - ER oxycodone (Oxycodone DETERx®)
  - AVERSION hydrocodone/APAP (AVERSION H/A)
  - ER hydrocodone/APAP [MNK-155]
  - ER hydrocodone (CEP-33237, DETERx hydrocodone)

APAP: acetaminophen, ER: extended release,
HYD: hydrocodone bitartrate tablets, NDA: new drug application

Central Nervous System

Migraine Prevention

- Calcitonin gene-related peptides (CGRP)
  - Monoclonal antibodies that block activity of CGRP to minimize the vasodilation and neuroinflammation that leads to migraines
  - First preventative therapy specific to migraines
    - AMG334 – Phase III
    - ALD403 – Phase III
    - MK-1602 – Phase III
    - LY2951742 – Phase III
    - TEV-48125 – Phase II
    - MK-8031 – Phase II

Central Nervous System

Alzheimer's Disease

Mechanism/Class	Agent Name	Phase of Development	Dosing
Beta amyloid protein antagonist	Gantenerumab	Phase III	SC
	Solanezumab	Phase III	IV
	Aducanumab	Phase III	IV
Advanced glycosylation end product receptor antagonist	Azeliragon	Phase III	Oral
BACE inhibitor	MK-8931	Phase III	Oral
	AZD-3293	Phase III	Oral
5-Hydroxytryptamine 6 receptor antagonist	RVT-101	Phase III	Oral
	Idalopirdine	Phase III	Oral

BACE: beta-site amyloid precursor protein cleaving enzyme,
IV: intravenous, SC: subcutaneous

Central Nervous System

Multiple Sclerosis

- Laquinimod (Nerventra®)
  - Oral, immunomodulator with anti-inflammatory and neuroprotective properties
  - In development for the treatment of MS
    - Possible emphasis on PPMS and disability progression
  - Conflicting data regarding impact on relapse rate
    - ALLEGRO: ~23% ↓ ARR vs. placebo
    - BRAVO: unable to demonstrate ↓ ARR vs. placebo
  - Phase III CONCERTO and ARPEGGIO trials
    - Phase II for PPMS

ARR: annualized relapse rate, MS: multiple sclerosis,
PPMS: primary progressive multiple sclerosis

Central Nervous System

Multiple Sclerosis

- Sphingosine-1 phosphate receptor modulators
  - Ponesimod
    - Phase III OPTIMUM trial initiated 2015 – head-to-head vs Aubagio® (teriflunomide)
      - Also in Phase II for psoriasis and graft-versus-host disease
  - Ozanimod
    - Phase III RADIANCE trial completed enrollment in 2015
      - Also in Phase III for ulcerative colitis and Phase II for Crohn's disease

Endocrine

Pipeline Trends

- New insulin options available with more coming
  - Toujeo Solostar® (insulin glargine recombinant), Tresiba® (insulin degludec), Ryzodeg 70/30® (insulin degludec and insulin aspart)
- Continued growth in existing therapeutic categories
  - No new mechanisms – focus on new combinations and formulations
- FDA continues to emphasize safety
  - New safety concerns for DPP-4 inhibitors and SGLT2 products

Endocrine

Generic Pipeline

Product Name	Anticipated Generic Entry
Glumetza® (metformin ER)	2/2016
Lantus® (insulin glargine)	2nd Half 2016[a]
Januvia® (sitagliptin)	7/2022
Janumet® (sitagliptin/metformin)	7/2028
Onglyza® (saxagliptin)	11/2028

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a: date when biosimilar entry will be allowed, will not be a standard generic

Endocrine

Type 2 Diabetes

Class	Agent Name	Phase of Development	Dosing
GLP-1 Agonists	Lixisenatide (Lyxumia®)	NDA submitted 9/2015	Once-daily
	Semaglutide	Phase III Also in Phase II as oral formulation	Once-weekly Oral formulation: once-daily
	ITCA 650 (exenatide DUROS)	Phase III	Once- or twice-yearly
DPP-4 Inhibitors	Evogliptin	Phase III	Oral, once-daily
	Gosogliptin	Phase III	Oral, once-daily
	Retagliptin	Phase III	Oral, once-daily
SGLT2 Inhibitors	Bexagliflozin	Phase III	Oral, once-daily
	Ertugliflozin	Phase III	Oral, once-daily
	Sotagliflozin	Phase III	Oral, once-daily

DPP-4: dipeptidyl peptidase-4, NDA: new drug application
SC: subcutaneous, SGLT2: sodium/glucose co-transporter 2

Endocrine

Type 2 Diabetes

Class	Agent Name	Phase of Development	Dosing
Insulin	Basaglar [LY2963016]	8/2014: FDA grants tentative approval	Once-daily, basal
	Insulin peglispro	Phase III – NDA submission delayed	Once-daily, basal
	Buccal insulin spray (Oral-lyn™)	Phase III	Meal-time
	BioChaperone® Lispro	Phase II	Meal-time
	Oral insulin capsule (ORMD-0801)	Phase II	Once-daily

NDA: new drug application

Endocrine

Type 2 Diabetes

Class	Agent Name	Phase of Development	Dosing
Combination Products	Saxagliptin/dapagliflozin	NDA submitted	Once-daily
	Ertugliflozin/sitagliptin	Phase III	Once-daily
	Canagliflozin/teneligliptin	Phase III	Once-daily
	Linagliptin/metformin ER	NDA submitted	Once-daily
	Gemigliptin/rosuvastatin	Phase III	Once-daily
	Lixisenatide/insulin glargine (LixiLan)	NDA expected for 2015	Once-daily
	Liraglutide/insulin degludec (Xultophy)	Phase III	Once-daily

ER, extended release, NDA: new drug application

Pipeline Trends

Themes of 2015: Discussion

- What were some trends in the pipeline that you observed over the last year?

- What were/are the therapeutic categories you feel had/have the most growth or the potential for the greatest impact?

Pipeline Trends

Conclusion

- Drug prices continue to be a hot topic
- Oncology remains an area of significant and rapid growth
  - Keep an eye on immuno-oncology agents
- PCSK-9 inhibitors may not be the end of advances in lipid-lowering therapies
- Still more developments expected for HCV
- Lots of excitement in the CNS pipeline
  - Specifically with Alzheimer's and migraine prevention

References

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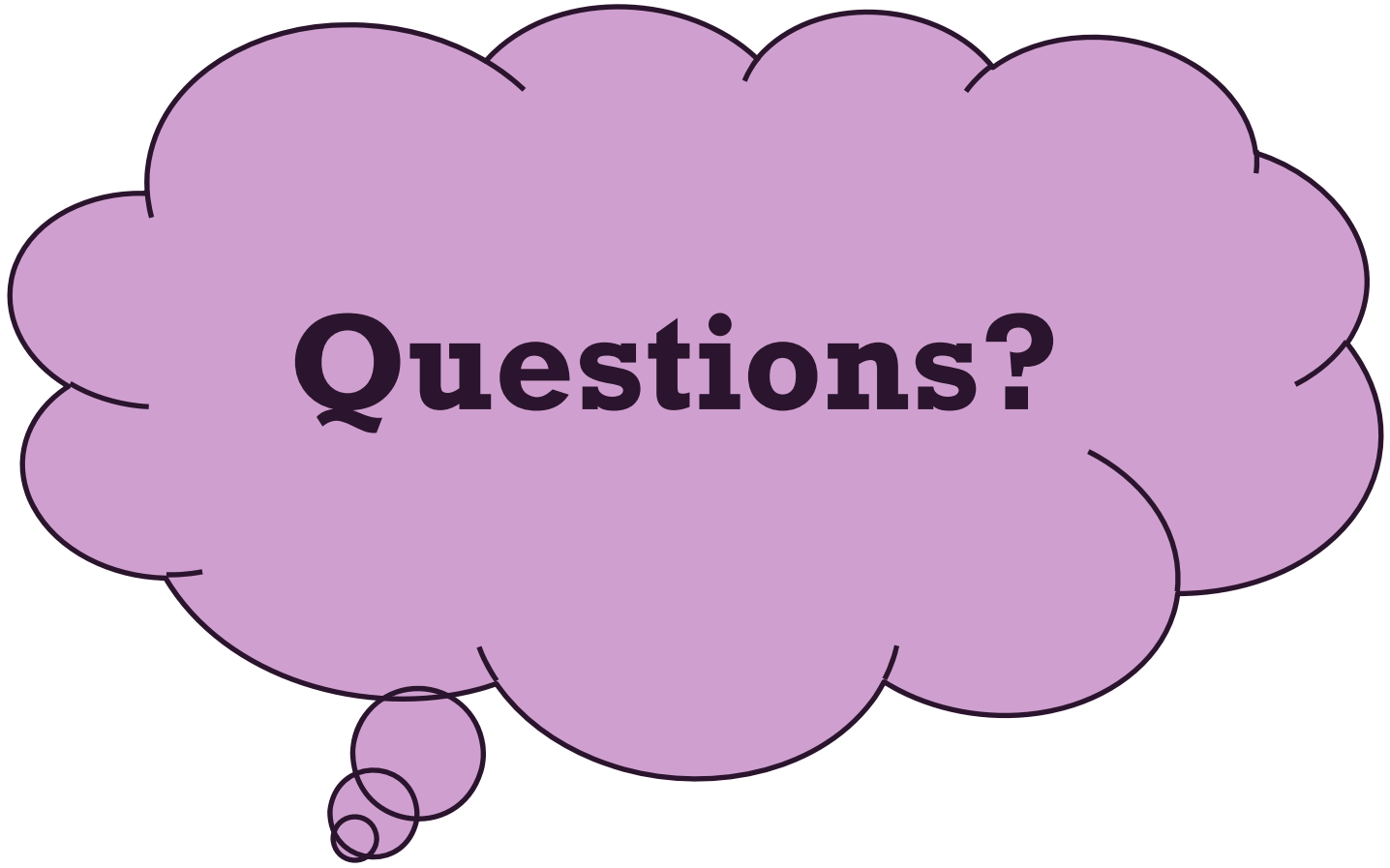
Questions?