Specialty Pharmaceuticals in Development

March 9, 2017

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- Discuss key specialty market trends and recent specialty drug approvals
- Identify high impact specialty medications that are likely to impact drug trends
- Discuss indications, efficacy, safety, and potential impact of new and emerging specialty medications

Key Specialty Market Trends

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Increased Competition

- Therapy Class Maturing
- Biosimilar Availability

Cancer Drug Development

- Record Number of FDA approvals for oncology drugs in 2015
- Innovation, targeted therapy, and novel mechanisms of action

Orphan Drug Development

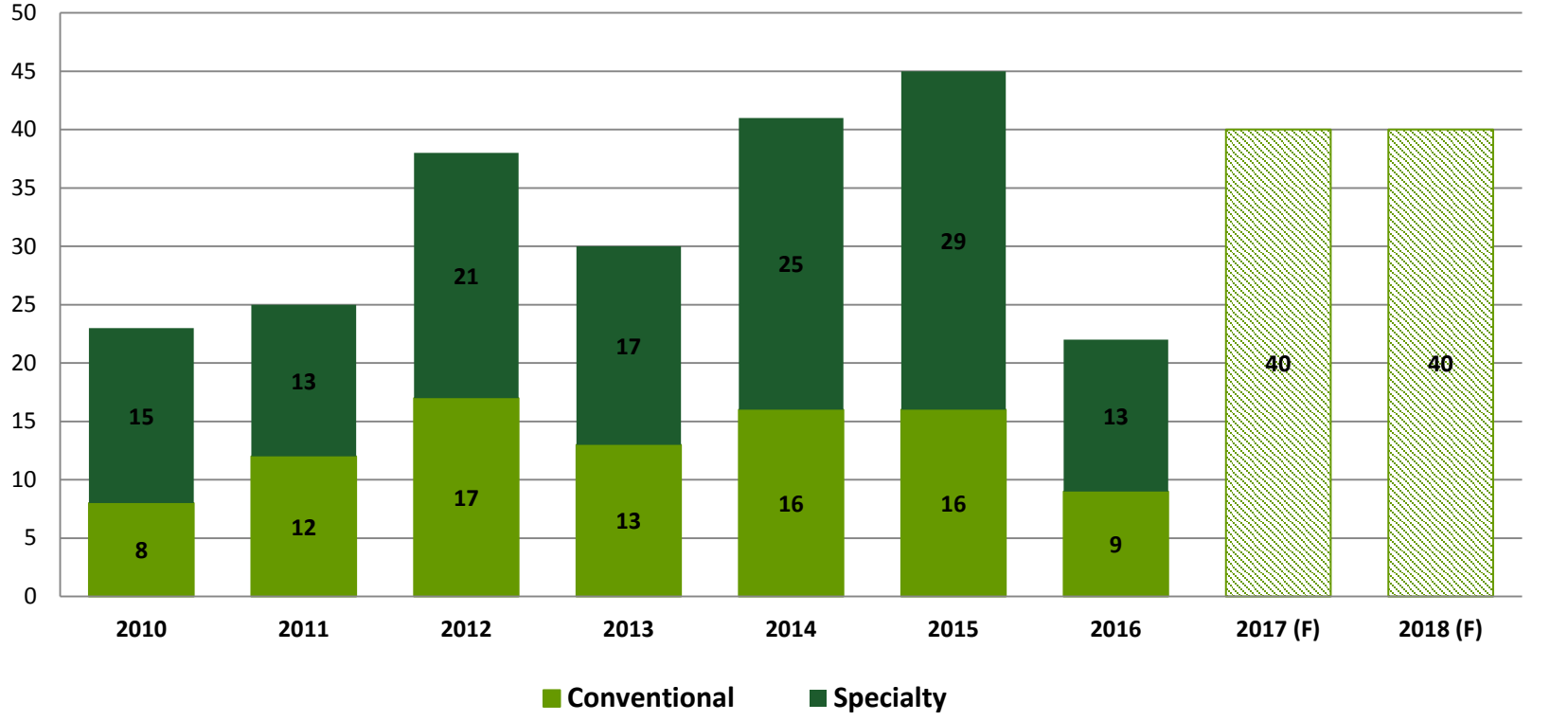
- Orphan drug spend is increasing at an alarming rate
- 41% of drugs approved by the FDA in 2016 had orphan drug designation

Accelerated Approvals

- 73% of drugs approved by the FDA in 2016 had an expedited development or review method
- 95% of drugs approved by the FDA in 2016 were approved on their “first cycle” of review

Source(s): FDA Novel Drugs Summary 2016: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm534863.htm

- 22 New Molecular Entities were approved in 2016
  - 59% were specialty drugs & 41% were orphan drugs
- 2016 approval number was driven down by Complete Response Letters (CRL) and FDA approval delays into 2017 due to manufacturing concerns



Source(s): FDA Novel Drugs Summary 2016: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm534863.htm

Key 2016 Specialty Drug Approvals

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Drug	Manufacturer	Indication	FDA Approval	Approx. Cost	Comments
Zepatier	Merck	HepC	Jan 28	$975/mo	HCV 1&4 w/out ribavirin
Odefsey	Gilead	HIV	Mar 1	$2,500/mo	2nd TAF containing HIV drug
Evomela	Spectrum	Multiple Myeloma	Mar 15	$2,130/unit	1st in class for high-dose conditioning in MM
Taltz	Eli Lilly	Psoriasis	Mar 22	$4,500/mo	2nd in class IL-17 Inhibitor
Cinqair	Teva	Asthma	Mar 23	$84/ml	2nd in class IL inhibitor for eosinophilic asthma
Descovy	Gilead	HIV	Apr 4	$1560/mo	3rd TAF containing HIV drug
Venclexta	AbbVie	CLL	Apr 11	$6,800/mo	Indicated r/r 17P CLL
Cabometyx	Exelixis	Renal Cell Carcinoma	Apr 25	$13,750/mo	2nd line RCC after antiangiogenic therapy
Nuplazid	Acadia	Parkinson's Disease Psychosis	Apr 29	$1,950/mo	1st in class for PDP
Tecentriq	Genentech	Bladder Cancer	May 18	$12,500/mo	1st PD-L1 approved for bladder cancer

CLL=Chronic Lymphocytic Leukemia; RCC=Renal Cell Carcinoma
PDP=Parkinson's Disease Psychosis; MO=month

Source(s): FDA Novel Drugs Summary 2016: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm534863.htm

Key 2016 Specialty Drug Approvals

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Drug	Manufacturer	Indication	FDA Approval	Approx. Cost	Comments
Ocaliva	Intercept	Primary Biliary Cirrhosis	May 27	$5,800/mo	1st in class, farnesoid X receptor agonist for PBC
Zinbryta	Biogen/AbbVie	Relapsing Multiple Sclerosis	May 27	$6,800/mo	Inadequate response to two or more drugs
Epclusa	Gilead	HepC	Jun 28	$26,700/mo	1st pan-genotypic option; attractive for genotype 3
Cuvitru	Shire	Primary Immuno-deficiency	Sep 13	Patient specific dosing	Once monthly dosing
Exondys- 51	Sarepta	Duchenne Muscular Dystrophy	Sep 19	$115,000/dose*	1st in class for DMD
Lartruvo	Eli Lilly	Soft Tissue Sarcoma	Oct 19	$2,400/vial	1st new therapy for 1st line STS approved in >40 years
Rubraca	Clovis	Ovarian Cancer	Dec 19	$13,750/mo	PARP inhibitor, targeted therapy for BRCA+
Spinraza	Biogen	Spinal Muscular Atrophy	Dec 23	$125,000/dose	1st in class for SMA; administered intrathecally

*PBC=Primary Biliary Cirrhosis; DMD=Duchenne Muscular Dystrophy; SMA=Spinal Muscular Atrophy; STS=Soft Tissue Sarcoma; mo=Month; *=based on 50kg patient*

Pipeline: What is Coming

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- The majority of new chemical entities are specialty drugs
- Oncology remains the leading therapeutic category in development and accounts for more than half of specialty drugs in the pipeline
- Three times as many drugs for rare diseases in the pipeline compared to a decade ago

Drugs in Development for Selected Therapeutic Areas	
Therapeutic Area	Total Projects
Cancer	316
CNS	97
Infectious Disease	59
Diabetes	58
Immunological	58
Respiratory	58
Vaccines	57

Innovation

- Potential first-in-class medicines comprise up to 70% of the pipeline
- Second largest area of innovation is neurology – driven by multiple new therapeutic targets for Alzheimer's disease

Accelerated Approvals

- 95% of NME applications received during 2016 were approved during the first review cycle
- 73% of drugs approved in 2016 had one or more expedited development or review designations
- 2012 average FDA review time was 10 months; 2015 average FDA review time was 8.5 months
- 41% of oncology drugs approved between 2013-2015 had breakthrough status

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Source(s): NRDD Impact of Breakthrough Designations; January 2013 Report on the Biopharmaceutical Pipeline; FDA.gov; Pharmaceutical Research and Manufacturers of America,
See more at http://www.phrma.org/innovation/meds-in-development#sthash.KZp0HZP4.dpuf
Drug development in Alzheimer's Disease : the path to 2025_10_26; EP World Preview 2016

- Robust cancer pipeline dominated with novel mechanisms of action, targeted therapy and oral routes of administration

Drug	Manufacturer	Indication	Route	Mechanism of Action	Potential FDA Approval
brigatinib	Ariad/Takeda Pharma	NSCLC	Oral	ALK/EGFR Inhibitor	4/29/2017
durvalumab	Astra Zeneca	Numerous tumor types	IV	PD-L1 Inhibitor	Q2:2017
avelumab	Pfizer	Merkel Cell Carcinoma	IV	PD-L1 Inhibitor	Q2:2017
CTL019	Novartis	DLBCL, ALL	IV	CAR-T	Q2:2017
AXI-CEL (KTE-C19)	Kite	DLBCL, MCL	IV	CAR-T	Q2:2017
neratinib	Puma Biotech	Breast Cancer	Oral	TKI	Q2:2017
niraparib	JNJ	Ovarian Cancer	Oral	PARP Inhibitor	Q2:2017
ribociclib	Novartis	Breast Cancer	Oral	CDK 4/6 Inhibitor	Q2:2017
abemaciclib	Eli Lilly	Breast Cancer	Oral	CDK 4/6 Inhibitor	Q3:2017
acalabrutinib	Astra Zeneca	CLL	Oral	BTK Inhibitor	Q3:2017
enasidenib	Celgene	AML	Oral	IDH2 Inhibitor	Q3:2017

brigatinib- *Takeda*

- Indication: 2nd line ALK-positive Non-Small Cell Lung Cancer (NSCLC)
- Route: oral once daily
- Comments: Potential to become 1st line therapy for the treatment of ALK-positive NSCLC

AXI-CEL (formerly KTE-C19)- *Kite Pharma*

- Indication: relapsed/refractory Diffuse Large B-cell Lymphoma, Mantle Cell Lymphoma
- Route: IV one time dose
- Comments: First potential CAR-T approved by the FDA

niraparib- *Tesaro*

- Indication: Ovarian Cancer
- Route: oral once daily
- Comments: PARP inhibitor; significantly reduced the risk of progression or death for patients with germline BRCA-positive platinum-sensitive, recurrent ovarian cancer

acalabrutinib- *AbbVie/Johnson & Johnson's*

- Indication: relapsed chronic lymphocytic leukemia
- Route: oral twice daily
- Comments: More specific BTK inhibitor with high response rate and durable remissions

Near Term Cancer Pipeline

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Drug	Manufacturer	Indication	Route	Mechanism of Action	Potential FDA Approval
midostaurin	Novartis	AML	Oral	FLT3 Inhibitor	Q3:2017
napabucasin	Sumitomo	Gastric Cancer	Oral	Stem Cell inhibitor	Q3:2017
Binimetinib/ encorafenib	Array	Melanoma	Oral	MEK/BRAF Inhibitor	Q3:2017
duvelisib	Verastem	CLL	Oral	PI3K Inhibitor	Q4:2017
entinostat	Syndax	Breast Cancer	Oral	HDAC Inhibitor	Q1:2018
AG-120	Celgene	AML	Oral	IDH1 Inhibitor	Q1:2018
ROVA-T	AbbVie	SCLC	IV	DLL3 Inhibitor	Q1:2018
veliparib	AbbVie	NSCLC	Oral	PARP Inhibitor	Q2:2018
volasertib	BI	AML	Oral	PLK1 Inhibitor	Q3:2018
inotuzumab	Pfizer	ALL	IV	ADC Conjugate	Q3:2018
JCAR017	Juno	ALL, DLBCL	IV	CAR-T	Q3:2018
pacritinib	CTI BioPharma	Myelofibrosis	Oral	JAK2/FLT3 Inhibitor	Q4:2018

napabucasin- *Sumitomo Dainippon*

- Indication: Gastric cancer
- Route: Oral once daily
- Comments: Potential first-in-class stem cell inhibitor approved by the FDA

binimetinib/encorafenib- *Array BioPharma*

- Indication: Melanoma
- Route: oral once to twice daily
- Comments: This combination significantly improved progression-free survival

Rova-T- *AbbVie*

- Indication: Small Cell Lung Cancer (SCLC)
- Route: IV infusion every 3 weeks
- Comments: Potential first antibody-drug conjugate approved by the FDA for SCLC

veliparib-*AbbVie*

- Indication: NSCLC, Breast Cancer
- Route: oral twice daily
- Comments: Combination with backbone chemotherapy may become effective in treatment for multiple cancers

Select Orphan Drug Pipeline

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Drug	Manufacturer	Indication	Route	Mechanism of Action	Potential FDA Approval
Austedo (*deutrabenazine)*	Teva	HD, TD	Oral	VMAT Inhibitor	April 3, 2017
Brineura (*cerliponase alfa*)	BioMarin Pharmaceuticals	Batten Disease	ICV	RhTTP1 replacement therapy	April 17, 2017
Ingrezza (*valbenazine)*	Neurocrine Biosciences	TD, Tourette syndrome	Oral	VMAT 2 Inhibitor	April 29, 2017
Radicava (*edaravone)*	Mitsubishi Tanabe Pharma	ALS	IV	Lipoperoxide 15-HPETE inhibitor	June 16, 2017
CSL830	CSL Behring	HAE Prophylaxis	SC	C1 inhibitor	Q2:2017
voretigene neparvovec	Spark Therapeutics	RPE65 inherited retinal disorders	IO	RPE65 gene therapy	Q3:2017
emicizumab	Roche	Hemophilia A	SC	Factor IXa &X inhibitor	Q4:2017
DX2930	Dyax/Shire	HAE Prophylaxis	SC	Plasma kallikrein inhibitor	Q1:2018
Lupuzor (*rigerimod)*	Immupharma	Lupus	SC	Auto reactive lymphocyte destruction	Q2:2018
tirasemtiv	Cytokinetics	ALS	Oral	Troponin stimulant	Q2:2018
voclosporin	Aurinia	Lupus	Oral	Calcineurin Inhibitor	Q2:2018
anifrolumab	Astra Zeneca	Lupus	IV	IFNAR1 inhibitor	Q4:2018

HD= Huntington's Disease; TD=Tourette Syndrome
ALS=Amyotrophic Lateral Sclerosis; HAE=Hereditary Angioedema
ICV= intracerebroventicular SC=Subcutaneous, IO=Intraocular

Austedo- *Teva*

- Indication: Huntington's Disease and Tardive Dyskinesia
- Route: Oral daily
- Comments: Reformulated xenazine derivative with improved side effect profile

CSL-830-*CSL Behring*

- Indication: HAE prophylaxis
- Route: SC injection monthly
- Comments: First potential SC HAE prophylaxis drug approved by the FDA

emicizumab-*Roche*

- Indication: Hemophilia A with inhibitors
- Route: SC monthly
- Comments: Novel SC self administration and unique MOA to prevent inhibitor formation

Voretigene neparvovec-*Spark Therapeutics*

- Indication: RPE65 Inherited Retinal Disorders
- Route: IO once in each eye
- Comments: First potentially FDA approved gene therapy

- Robust pipeline dominated by interleukin inhibitors and selective JAK inhibitors

Drug	Manufacturer	Indication	Route	Mechanism of Action	Potential FDA Approval
Siliq (brodalumab)	Valeant	Psoriasis	SC	IL-17 inhibitor	approved 2/16/2017
tildrakizumab	Merck/Sun	Psoriasis	SC	IL-23 inhibitor	Q4:2017
guselkumab	Janssen	Psoriasis	SC	IL-23 inhibitor	Q4:2017
sarilumab	Regeneron/Sanofi	RA	SC	IL-6 inhibitor	3/2017
baricitinib	Incyte/Lilly	RA	Oral	JAK inhibitor	4/2017
sirukumab	GSK/Janssen	RA	SC	IL-6 inhibitor	9/2017
ABT-494	AbbVie	RA	Oral	JAK inhibitor	2018
filgotinib	Gilead/Galapagos	RA	Oral	JAK inhibitor	2019

RA=Rheumatoid Arthritis
SC=Subcutaneous

Siliq-*Valeant*

- Indication: Psoriasis
- Route: SC injection every 2 weeks
- Comments: REMS and Black Box warning for suicidal ideation and behavior and contraindicated in patients with Crohn's Disease

tildrakizumab- *Merck/Sun*

- Indication: Psoriasis
- Route: SC injection every 8 or 12 weeks
- Comments: IL-23 inhibitor; dosing advantage compared to Cosentyx/Taltz

guselkumab-*Janssen*

- Indication: Psoriasis
- Route: SC injection every 8 weeks
- Comments: IL-23 inhibitor and advantageous dosing every 8 weeks compared to Cosentyx and Taltz (IL-17 inhibitors)

sarilumab-*Regeneron/Sanofi*

- Indication: RA
- Route: SC injection every 2 weeks
- Comments: FDA delay due to manufacturing concerns

baricitinib- *Incyte/Lilly*

- Indication: RA
- Route: oral daily
- Comments: Selective JAK 1/2 inhibitor; similar efficacy to Xeljanz with potentially better SE profile; significantly better ACR50 compared to Humira

- Pipeline is focused on Primary Progressive and Secondary Progressive Multiple Sclerosis due to large unmet need

Drug	Manufacturer	Indication	Route	Mechanism of Action	Potential FDA Approval
Ocrevus (*ocrelizumab*)	Genentech/ Roche	PPMS & RRMS	IV	Mab targeting CD20+ B-cells	March 28, 2017
siponimod	Novartis	SPMS	Oral	S1P1 inhibitor	Q2:2018
MD-1003	MedDay	SPMS	Oral	ACC1&2 and Kreb Cycle activator	Q3:2018
ozanimod	Celgene	RRMS	Oral	S1P1 inhibitor	Q4:2018
laquinimod	Active Biotech/Teva	PPMS & RRMS	Oral	Unknown	2019+
ibudilast	MedicNova	PPMS&SPMS	Oral	Non-selective PDE inhibitor	2019+

PPMS=Primary Progressive Multiple Sclerosis
RRMS=Relapsing Remitting Multiple Sclerosis
SPMS=Secondary Progressive Multiple Sclerosis

Ocrevus- *Genentech/Roche*

- Indication: Primary Progressive & Relapsing Remitting Multiple Sclerosis
- Route: IV infusion every 6 months
- Comments: FDA delay due to manufacturing concerns; potential 1st in class PPMS treatment

siponimod- *Novartis*

- Indication: Secondary Progressive Multiple Sclerosis
- Route: oral daily
- Comments: Positive phase III date; potentially registrational; potential 1st in class SPMS treatment

- Pipeline dominated by interleukin inhibitors and first in class biologic for atopic dermatitis

Drug	Manufacturer	Indication	Route	Mechanism of Action	Potential FDA Approval
Eucrisa™ (*crisaborole*)	Pfizer	Atopic Dermatitis	Topical	PDE-4 inhibitor	FDA approval 12/14/2016
Dupixent (*dupilumab*)	Regeneron/ Sanofi	Atopic Dermatitis	SC	IL-4&13 inhibitor	March 29, 2017
benralizumab	Astra Zeneca	Eosinophilic Asthma	SC	IL-5 inhibitor	Q4:2017
lebrikizumab	Genentech/ Roche	Severe Asthma	SC	IL-13 inhibitor	Q4:2017
tralokinumab	Astra Zeneca	Severe Asthma	SC	IL-13 inhibitor	2019+
AR101	Aimmmune	Peanut Allergy	Oral	Immunotherapy	Q3:2018
Viaskin	DBV Technology	Peanut Allergy	Patch	Immunotherapy	Q3:2018

SC=Subcutaneous

- Pipeline dominated by CGRP antagonists and drugs targeting episodic and chronic migraine prevention

Drug	Manufacturer	Indication	Route	Mechanism of Action	Potential FDA Approval
lasmiditan	CoLucid/Lilly	Acute Migraine Treatment	Oral	5-HTF-1 agonist	Q3:2018
ubrogepant	Merck/Allergan	Acute Migraine Treatment	Oral	CGRP substrate antagonist	Q4:2018
AL-403	Alder	Episodic/Chronic Migraine Prevention	IV	CGRP substrate antagonist	Q4:2017
erenumab	Amgen/Novartis	Episodic/Chronic Migraine Prevention	SC	CGRP receptor antagonist	Q4:2017
galcanezumab	Lilly	Episodic/Chronic Migraine Prevention & Cluster Headaches	SC	CGRP substrate antagonist	Q4:2017
TEV-48125	Teva	Episodic/Chronic Migraine Prevention	SC	CGRP substrate antagonist	Q4:2018

SC=Subcutaneous

- Pipeline dominated by novel mechanisms of action for treatment resistance, injectable therapies and novel combinations to reduce pill burden

Drug	Manufacturer	Indication	Route	Mechanism of Action	Potential FDA Approval
Ibalizumab	TaiMed	Treatment resistant HIV	IV	HIV Entry Inhibitor	Q4:2017
PRO-140	CytoDyn	Treatment resistant HIV	SC	HIV Entry Inhibitor	Q1:2018
dolutegravir/ rilpivirine	ViiV Healthcare/Janssen	HIV maintenance treatment	Oral	Integrase Inhibitor/NNRTI	Q2:2018
bictegravir/ FTC/TAF	Gilead	Treatment naiive HIV treatment	Oral	Integrase Inhibitor/NRTI/NRTI	Q3:2018
fostemsavir	ViiV Healthcare	HIV maintenance treatment	Oral	Attachment Inhibitor	Q3:2018

SC=Subcutaneous

Disease Modifying Alzheimer's Disease Pipeline

- Disease of unknown etiology with large economic burden on the healthcare system
- Large potential market with treatment options limited to symptomatic therapy
- 99.9% of phase III Alzheimer's Disease drugs have failed clinical trials

Drug	Manufacturer	Indication	Route	Mechanism of Action	Potential FDA Approval
aducanumab	Biogen	Mild AD	IV	Amyloid B mAB	2019+
AZD-3293	AZ/Lilly	Mild AD	Oral	BACE inhibitor	2019+
Verubecestat	Merck	Prodromal AD	Oral	BACE inhibitor	2019+
crenezumab	Roche	Mild AD	IV	Amyloid B mAB	2019+
gantenerumab	Roche	Mild AD	IV	Amyloid B mAB	2019+
BAN-2401	Biogen/Eisai	Prodromal/Mild AD	IV	Amyloid B mAB	2020+
CNP-520	Amgen/ Novartis	Mild AD	Oral	BACE inhibitor	2020+
JNJ-54861911	Shionogi/ Janssen	Mild AD	Oral	BACE inhibitor	2020+

adacanumab-*Biogen*

- Indication: Mild AD
- Route: IV every 4 weeks
- Comments: Phase I data showed reduction in plaque volume; ENGAGE & EMERGE data expected 2019

AZD-3293- *AZ/Lilly*

- Indication: Mild AD
- Route: oral daily
- Comments: AMARANTH trial data expected 2019

verubecestat-*Merck*

- Indication: Prodromal AD
- Route: oral daily
- Comments: Failed phase III EPOCH trial in mild to moderate Alzheimer's Disease. EPOCH trial had no safety concerns so the APECS trial will continue in prodromal AD patients with data expected 2019

- Large potential market with limited treatment options currently such as weight control and treatment of concurrent conditions
- Therapy will be characterized by a multi-drug regimen with varying mechanisms of action

Drug	Manufacturer	Indication	Route	Mechanism of Action	Potential FDA Approval
obeticholic acid (OCA)	Intercept Pharmaceuticals	NASH	Oral	FXR agonist	Q2:2019
elafibranor	Genefit	NASH	Oral	PPAR alpha agonist	2019+
cenicriviroc	Tobira/Takeda	NASH	Oral	CCR2&5 inhibitor	2019+
aramchol	Galmed Pharmaceuticals	NASH	Oral	SCD1 inhibitor	2019+
emricasen	Conatus Pharmaceuticals	NASH	Oral	Caspase inhibitor	2019+
selonsertib	Gilead	NASH	Oral	ASK1 inhibitor	2019+
tipelukast	MedicNova	NASH	Oral	LOXL2, phosphodiesterase & 5-lipoxygenase inhibitor	2019+

Questions?

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