New Medications and FDA Updates 2016

Suzannah Kokotajlo, PharmD
Morristown Medical Center
May 11th, 2017
Suzannah.Kokotajlo@AtlanticHealth.org

ATLANTIC HEALTH SYSTEM

Atlantic Health System

Speaker Disclosure

Nothing to disclose

Pharmacist Objectives

- List the drugs that were brought to the market in 2016
- Describe the indications and mechanisms of action of the new medications
- Review adverse reactions and patient safety information for these new medications
- Relate new drugs approved in 2016 with those approved previously with similar indications
- Discuss important patient counseling and monitoring parameters for newly approved medications
- Identify drug safety warnings that were published by the FDA in 2016

New Medications of 2016

- **Adlyxin® (lixisenatide)**
- Anthim® (obiltoxaximab)
- Axumin™ (fluciclovine F-18)
- **Briviact® (brivaracetam)**
- **Cinqair® (reslizumab)**
- **Defitelio® (defibrotide sodium)**
- Epclusa® (sofsbuvir/velpatasvir)
- Eucrisa™ (crisaborole)
- **Exondys 51™ (eteplirsen)**
- Lartruvo™ (olaratumab)
- Netspot® (gallium Ga 68 dotatate)
- **Nuplazid™ (pimavanserin)**
- **Ocaliva® (obeticholic acid)**
- Rubraca™ (rucaparib)
- **Spinraza™ (nusinersen)**
- Taltz ® (ixekizumab)
- Tecentriq® (atezolizumab)
- Venclexta™ (venetoclax)
- Xiidra® (lifitegrast)
- Zepatier™ (elbasvir/grazoprevir)
- **Zinbryta™ (daclizumab)**
- **Zinplava™ (bezlotoxumab)**

Novel New Drugs 2016 Summary. Available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM536693.pdf. Accessed February 3, 2017.

Adlyxin® (lixisenatide)

- **Approval date**
  - July 2016
- **FDA approved indications**
  - Adjunctive therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- **Mechanism of action**
  - Glucagon-Like Peptide-1 receptor agonist
  - Increases glucose-dependent insulin release, decreases glucagon secretion, and slows gastric emptying
- **Dosing**
  - 10 mcg subcutaneously once daily for 14 days
  - 20 mcg subcutaneously once daily starting on day 15
- **Adverse reactions**
  - Anaphylaxis and serious hypersensitivity reactions
  - Pancreatitis
  - Hypoglycemia with concomitant use of sulfonylureas or basal insulin
  - Acute kidney injury
  - Immunogenicity

Adlyxin® (lixisenatide). Prescribing Information. Bridgewater, NJ. 2016.

Adlyxin® (lixisenatide)

- **Interactions**
  - Delays gastric emptying time and therefore rate of absorption of oral medications
  - Insulin
  - Sulfonylureas
- **Monitoring**
  - Glucose, hemoglobin A_1C
  - Renal function
  - Signs/symptoms of pancreatitis
- **Dosage forms available**
  - Starter pen 50 mcg/mL, 3 mL
    - Delivers 14 doses of 10 mcg
  - Maintenance pen 100 mcg/mL, 3 mL
    - Delivers 14 doses of 20 mcg
  - Storage
    - Before use: refrigerator
    - After first dose: 14 days room temperature
- **Counseling points**
  - Do not share pens with another person
  - Maintain adequate hydration to avoid risk of renal failure

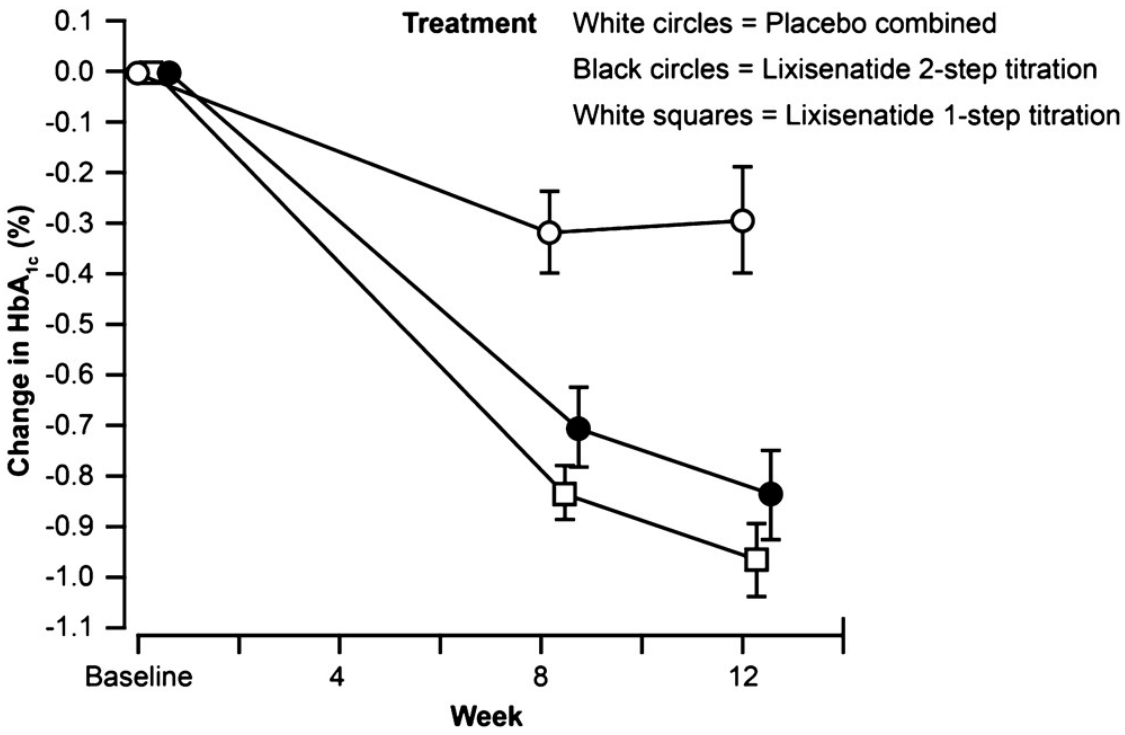
Adlyxin® (lixisenatide). Prescribing Information. Bridgewater, NJ. 2016.

Phase III Study

- Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group monotherapy trial
  - Group 1: lixisenatide 2-step dose increase
  - Group 2: lixisenatide 1-step dose increase
  - Group 3: placebo 2-step dose increase
  - Group 4: placebo 1-step dose increase
- Primary efficacy end point
  - Change in hemoglobin A_1C from baseline to study end
- Safety assessment
  - Physical examination
  - Blood pressure
  - Heart rate
  - 12-lead electrocardiogram
  - Standard laboratory measurements
  - Anti-lixisenatide antibodies
  - Adverse events

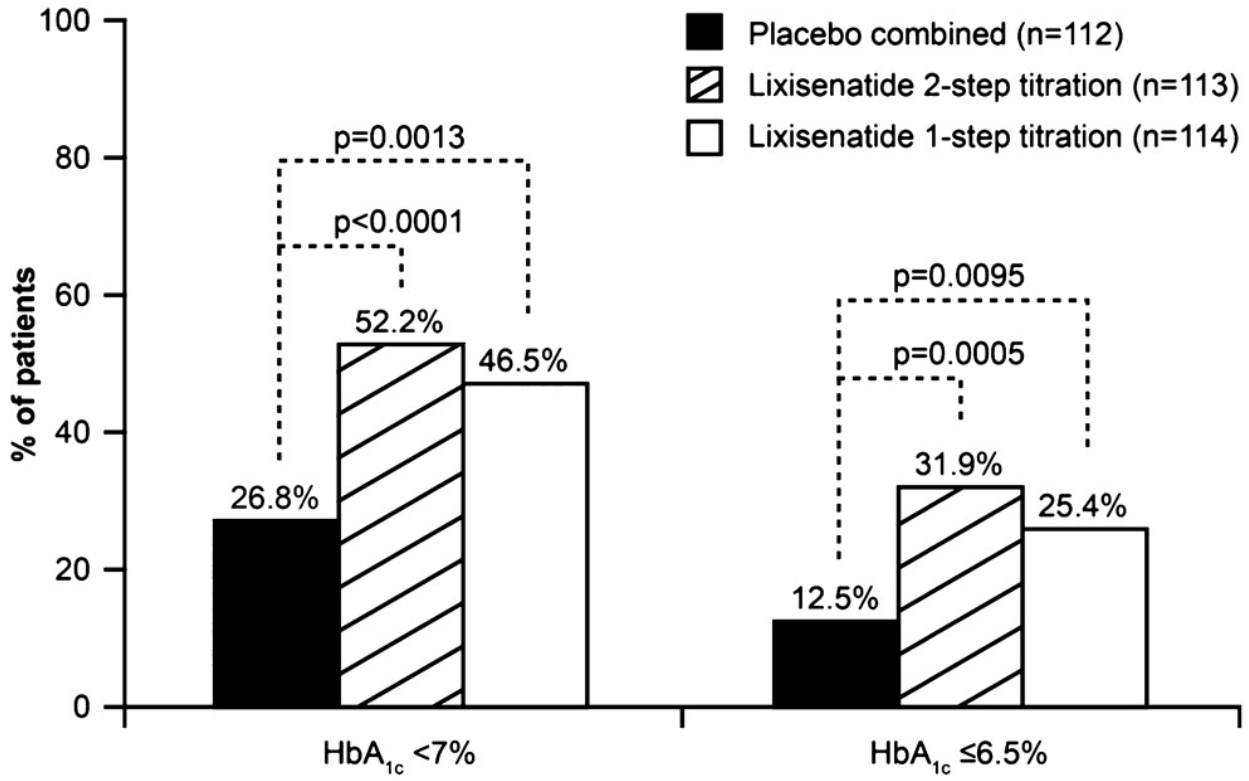
Fonseca VA, Alvarado-Ruiz R, Raccah D, et al. *Diabetes Care* 2012;35:1225-1231.

Results – Efficacy



Fonseca VA, Alvarado-Ruiz R, Raccah D, et al. *Diabetes Care* 2012;35:1225-1231.

Results – Efficacy



Fonseca VA, Alvarado-Ruiz R, Raccah D, et al. *Diabetes Care* 2012;35:1225-1231.

Results – Safety

Type of adverse event	Placebo combined (n = 122)	Lixisenatide 2-step dose increase (n = 120)	Lixisenatide 1-step dose increase (n = 119)	Lixisenatide combined (n = 239)
Any TEAE	55 (45.1)	63 (52.5)	65 (54.6)	128 (53.6)
Any serious TEAE	5 (4.1)	1 (0.8)	0	1 (0.4)
Discontinuation as a result of a TEAE	1 (0.8)	5 (4.2)	3 (2.5)	8 (3.3)
Gastrointestinal disorders (any)	17 (13.9)	39 (32.5)	38 (31.9)	77 (32.2)
Nausea	5 (4.1)	29 (24.2)	24 (20.2)	53 (22.2)
Headache	14 (11.5)	10 (8.3)	9 (7.6)	19 (7.9)
Vomiting	0	9 (7.5)	8 (6.7)	17 (7.1)
Dizziness	3 (2.5)	9 (7.5)	4 (3.4)	13 (5.4)
Nasopharyngitis	4 (3.3)	6 (5.0)	5 (4.2)	11 (4.6)
Symptomatic hypoglycemia	2 (1.6)	3 (2.5)	1 (0.8)	4 (1.7)

Data are n (%). TEAE: adverse events that developed or worsened during the on-treatment period (the time from the first dose of study medication up to 3 days after the last dose). The safety population comprised all randomized patients exposed to at least one dose of investigational drug.

Fonseca VA, Alvarado-Ruiz R, Raccah D, et al. *Diabetes Care* 2012;35:1225-1231.

Briviact® (brivaracetam)

- **Approval date**
  - February 2016
- **FDA approved indications**
  - Adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy
- **Mechanism of action**
  - Exact mechanism unknown
  - Displays a high and selective affinity for synaptic vesicle protein 2A in the brain
- **Dosing**
  - 50 mg twice daily
  - May increase to 100 mg twice daily
  - Adjust in hepatic impairment
    - Start at 25 mg twice daily
    - Maximum dose 75 mg twice daily
- **Adverse reactions**
  - Suicidal behavior and ideation
  - Neurological adverse reactions
  - Psychiatric adverse reactions
  - Hypersensitivity: bronchospasm and angioedema
  - Withdrawal of antiepileptic drugs

Briviact® (brivaracetam). Prescribing Information. Smyrna, GA. 2016.

Briviact® (brivaracetam)

- **Interactions**
  - Rifampin: decreases brivaracetam plasma concentrations; double the dose
  - Carbamazepine: increase exposure to carbamazepine-epoxide
  - Phenytoin: increase plasma concentrations; monitor levels
- **Monitoring**
  - CBC
  - Liver and renal function
  - Symptoms of depression and suicidality
- **Dosage forms available**
  - Tablets: 10 mg, 25 mg, 50 mg, 75 mg, 100 mg
  - Oral solution: 10 mg/mL
    - Discard 5 months after opening bottle
  - Injection: 50 mg/5 mL
- **Counseling points**
  - Tablets should be swallowed whole and should not be crushed or chewed
  - May take with or without food

Briviact® (brivaracetam). Prescribing Information. Smyrna, GA. 2016.

Phase III Fixed-Dose Study

- Phase III, prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose study
  - Group 1: placebo
  - Group 2: brivaracetam 5 mg/day divided BID
  - Group 3: brivaracetam 20 mg/day divided BID
  - Group 4: brivaracetam 50 mg/day divided BID
- Primary efficacy end point
  - Percent reduction of partial-onset seizure frequency/week for brivaracetam versus placebo during the 12 week treatment period
- Safety assessment
  - Adverse drug effects
  - Laboratory tests
  - Physical and neurologic examination
  - Vital signs
  - Body weight
  - Electrocardiogram

Biton V, Berkovic SF, Abou-Khalil B, et al. *Epilepsia* 2014;55:57-66.

Results – Efficacy

	Placebo	BRV 5 mg/day (N = 96)	BRV 20 mg/day (N = 99)	BRV 50 mg/day (N = 101)
Percent reduction over PBO in focal seizure frequency/week	--	– 0.9 (p = 0.885)	4.1 (p = 0.492)	12.8 (p = 0.025)
Median percent reduction from baseline in partial-onset seizure frequency/week	17.8%	20% (p = 0.991)	22.5% (p = 0.386)	30.5% (p = 0.003)
Responder rate of ≥ 50%	16.7%	21.9% (p = 0.353)	23.2% (p = 0.239)	32.7% (p = 0.008)
Seizure freedom	0%	1.1%	1%	4%

BRV = brivaracetam; PBO = placebo

Biton V, Berkovic SF, Abou-Khalil B, et al. *Epilepsia* 2014;55:57-66.

Results – Safety

- At least one treatment-emergent adverse event was reported during treatment period by
  - 71.1% in BRV 5 mg/day group
  - 79% in BRV 20 mg/day group
  - 75.2% in BRV 50 mg/day group
- Permanent discontinuation
  - 2% in PBO group
  - 8.2% in BRV 5 mg/day group
  - 4% in BRV 20 mg/day group
  - 5.9% in the BRV 50 mg/day group
- Severe adverse events
  - 5.1% in PBO group
  - 8.2% in BRV 5 mg/day group
  - 4% in BRV 20 mg/day group
  - 8.9% in BRV 50 mg/day group
- Two deaths occurred
- No clinically significant changes for laboratory markers, physical and neurologic examinations, vital signs, body weight, and EKG measurements

Biton V, Berkovic SF, Abou-Khalil B, et al. *Epilepsia* 2014;55:57-66.

Cinqair® (reslizumab)

- **Approval date**
  - March 2016
- **FDA approved indications**
  - Add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype
- **Mechanism of action**
  - Interleukin-5 antagonist
- **Dosing**
  - 3 mg/kg IV once every 4 weeks
  - Given as infusion over 25 to 50 minutes
- **Adverse reactions**
  - Anaphylaxis

Cinqair® (reslizumab). Prescribing Information. Frazer, PA. 2016.

Cinqair® (reslizumab)

- **Interactions**
  - None
- **Monitoring**
  - Anaphylaxis/hypersensitivity reaction
  - Pulmonary function tests
  - Signs of infection
- **Dosage forms available**
  - 100 mg/10 mL (10 mg/mL) vial
- **Counseling points**
  - Does not treat acute asthma symptoms or exacerbations
  - Do not reduce inhaled or oral corticosteroid use without consulting with physician

Cinqair® (reslizumab). Prescribing Information. Frazer, PA. 2016.

Phase III Trial

- Two multicenter, parallel, double-blind, randomized, placebo-controlled, phase III trials
  - Group 1: reslizumab 3 mg/kg IV every 4 weeks
  - Group 2: placebo infusion every 4 weeks
- Primary end point
  - Frequency of clinical asthma exacerbations per patient during the 52 week treatment period
- Safety assessment
  - Adverse effects

Castro M, Zangrilli J, Wechsler ME, et al. *Lancet Respir Med* 2015;3(5):355-66.

Results – Efficacy

	Study 1			Study 2			Pooled Data		
Primary End Point	**Placebo**	**Reslizumab**	**p-value**	**Placebo**	**Reslizumab**	**p-value**	**Placebo**	**Reslizumab**	**p-value**
Frequency of CAEs									
Patients with ≥ 1 CAE	132 (54%)	92 (38%)	--	105 (45%)	59 (25%)	--	237 (50%)	151 (32%)	--
Adjudicated CAE rate (events per patient year)									
All Episodes	1.80	0.9	< 0.0001	2.11	0.86	< 0.0001	1.81	0.84	< 0.0001
Episodes requiring systemic corticosteroids ≥ 3 days	1.60	0.72	< 0.0001	1.66	0.65	< 0.0001	1.54	0.66	< 0.0001
Episodes requiring hospital admission or ED treatment	0.21	0.14	0.257	0.05	0.03	0.402	0.12	0.077	0.510

CAE – clinical asthma exacerbation

Castro M, Zangrilli J, Wechsler ME, et al. *Lancet Respir Med* 2015;3(5):355-66.

Results – Safety

	Study 1		Study 2	
	Placebo (n = 243)	Reslizumab (n = 245)	Placebo (n = 232)	Reslizumab (n = 232)
All-grade adverse events	206 (85%)	197 (80%)	201 (87%)	177 (76%)
Asthma worsening	127 (52%)	97 (40%)	119 (51%)	67 (29%)
Upper respiratory tract infection	32 (13%)	39 (16%)	16 (7%)	8 (3%)
Nasopharyngitis	33 (14%)	28 (11%)	56 (24%)	45 (19%)
Sinusitis	29 (12%)	21 (9%)	10 (4%)	9 (4%)
Headache	30 (12%)	19 (8%)	17 (7%)	33 (14%)
Influenza	23 (9%)	18 (7%)	7 (3%)	6 (3%)
Serious adverse events	34 (14%)	24 (10%)	23 (10%)	18 (8%)
Asthma	13 (5%)	11 (4%)	6 (3%)	3 (1%)
Pneumonia	0	2 (< 1%)	6 (3%)	2 (< 1%)
Adverse events leading to discontinuation	8 (3%)	4 (2%)	9 (4%)	8 (3%)
Deaths	1 (< 1%)	0	0	0

Castro M, Zangrilli J, Wechsler ME, et al. *Lancet Respir Med* 2015;3(5):355-66.

Defitelio® (defibrotide sodium)

- **Approval date**
  - March 2016
- **FDA approved indications**
  - Treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD) with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation
- **Mechanism of action**
  - Not fully known
  - Stabilizes endothelial cells by reducing endothelial-cell activation and protecting these cells from further damage
    - Restores thrombo-fibrinolytic balance
- **Dosing**
  - 6.25 mg/kg IV every 6 hours for 21 days
- **Adverse reactions**
  - Hemorrhage
  - Hypersensitivity

Defitelio® (defibrotide sodium). Prescribing Information. Palo Alto, CA. 2016.

Defitelio® (defibrotide sodium)

- **Interactions**
  - Systemic anticoagulant or fibrinolytic therapy – avoid use
- **Monitoring**
  - Signs and symptoms of VOD
  - Hypersensitivity reactions
  - Bleeding
- **Dosage forms available**
  - 200 mg/2.5 mL (80 mg/mL) vial
- **Counseling points**
  - Immediately report any signs or symptoms of bleeding and allergic reaction

Defitelio® (defibrotide sodium). Prescribing Information. Palo Alto, CA. 2016.

Phase III Study

- Phase III, historically controlled, multicenter, open-label study
  - Patients received 25 mg/kg/day of defibrotide IV divided into 4 doses given over 2 hours every 6 hours for a minimum of 21 days
- Primary efficacy end point
  - Difference of survival rate at day + 100 post-HSCT between the treatment group and the historical control group
- Safety assessment
  - Adverse effects were evaluated

Richardson PG, Riches ML, Kernan N, et al. *Blood* 2016;127:1656-65.

Results – Efficacy

- Survival at day + 100 post HSCT
  - Defibrotide: 39 patients (38.2%)
  - Control: 8 patients (25%)
  - Between group difference: 23% (p = 0.0109)
- Complete response at day + 100 post HSCT
  - Defibrotide: 25.5%
  - Control: 12.5%
  - Between group difference: 19% (p = 0.0160)
- Survival at day + 180 post HSCT
  - Defibrotide: 33 patients (32.4%)
  - Control: 8 patients (25%)
  - Between group difference: p = 0.0669

Richardson PG, Riches ML, Kernan N, et al. *Blood* 2016;127:1656-65.

Results – Safety

- Eleven patients discontinued defibrotide prematurely for a possible drug-related toxicity (10.7%)
- All but 1 of the defibrotide-treated patients and all historical-control patients experienced at least 1 adverse event
- Most common adverse events in both groups were hypotension and diarrhea
- No difference in the incidence of common hemorrhagic adverse events between the two groups
- Most common fatal adverse event was pulmonary alveolar hemorrhage and this was observed with similar incidence between the two groups

Richardson PG, Riches ML, Kernan N, et al. *Blood* 2016;127:1656-65.

Exondys 51™ (eteplirsen)

- **Approval date**
  - September 2016
- **FDA approved indications**
  - Treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping
- **Mechanism of action**
  - Binds to exon 51 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing
  - Skipping allows for production of an internally truncated dystrophin protein
- **Dosing**
  - 30 mg/kg IV once weekly
- **Adverse reactions**
  - Balance disorder
  - Vomiting
  - Facial flushing
  - Erythema

Exondys 51™ (eteplirsen). Prescribing Information. Cambridge, MA. 2016.

Exondys 51™ (eteplirsen)

- **Interactions**
  - None
- **Monitoring**
  - None
- **Dosage forms available**
  - 100 mg/2 mL and 500 mg/10 mL (50 mg/mL) vials
- **Counseling points**
  - Not a cure, will have to receive life long therapy

Exondys 51™ (eteplirsen). Prescribing Information. Cambridge, MA. 2016.

Study 201 and Study 202

- Study 201
  - Phase IIB, double-blind, placebo-controlled
    - Cohort 1: eteplirsen 30 mg/kg/week
    - Cohort 2: eteplirsen 50 mg/kg/week
    - Cohort 3: placebo
- Study 202
  - Open-label, long-term safety and efficacy study
    - Cohort 1: eteplirsen 30 mg/kg/week
    - Cohort 2: eteplirsen 50 mg/kg/week
- Efficacy end points
  - Dystrophin production
  - 6-minute walk test (6MWT)
- Safety assessment
  - Vital signs
  - Physical examinations
  - Monitoring for injection site reactions
  - Electrocardiograms / echocardiograms
  - Clinical laboratory testing
  - Kidney function

Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. *Ann Neurol* 2013;74:637-647.

Results – Efficacy (Dystrophin)

- 12 week
  - Cohort 2 (50 mg/kg)
    - No increases in percentage of dystrophin-positive fibers compared to pretreatment
    - Change from baseline was not statistically different compared to placebo cohort
- 24 week
  - Cohort 1 (30 mg/kg)
    - 22.9% increase from pretreatment compared to placebo ($p < 0.002$)
- 48 week
  - Cohorts 1 (30 mg/kg) and 2 (50 mg/kg) showed significant increases in percentage of dystrophin-positive fibers (mean 47.3%)

Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. *Ann Neurol* 2013;74:637-647.

Results – Efficacy (6MWT)

- Mean baseline 6MWT distance for all subjects was 381.9 m
- 6MWT from baseline to week 24
  - Cohort 1 (30 mg/kg): – 128.2 m (± 31.6 m)
    - 14.2 m (± 14.4 m)
  - Cohort 2 (50 mg/kg): – 0.3 m (± 31.2 m)
  - Cohort (placebo): – 25.8 m (± 30.6 m)
- 6MWT from baseline to week 48
  - Cohort 1 (30 mg/kg): – 153.4 m (± 38.7 m)
    - 31.5 m (± 19.9 m)
  - Cohort 2 (50 mg/kg): 21 m (± 38.2 m)
  - Cohort (placebo): – 68.4 m (± 37.6 m)

Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. *Ann Neurol* 2013;74:637-647.

Results – Safety

- Well tolerated
- No treatment-related adverse effects
- Mild and transient proteinuria was observed in a single placebo-treated patient

Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. *Ann Neurol* 2013;74:637-647.

Nuplazid™ (pimavanserin)

- **Approval date**
  - April 2016
- **FDA approved indications**
  - Treatment of hallucinations and delusions associated with Parkinson's Disease psychosis
- **Mechanism of action**
  - Unknown
  - Could be mediated through a combination of inverse agonist and antagonist activity at serotonin receptors
- **Dosing**
  - 34 mg by mouth once daily
- **Adverse reactions**
  - BLACK BOXED WARNING: Increased mortality in elderly patients with dementia-related psychosis
  - QT interval prolongation

Nuplazid™ (pimavanserin). Prescribing Information. San Diego, CA. 2016.

Nuplazid™ (pimavanserin)

- **Interactions**
  - Strong CYP3A4 inhibitors (ketoconazole): reduce dose to 17 mg by mouth once daily
  - Strong CYP3A4 inducers: dose escalation may be needed
  - Other QT prolonging medications
- **Monitoring**
  - Mental status
  - Renal and liver function
- **Dosage forms available**
  - 17 mg tablets
- **Counseling points**
  - Speak with healthcare professional if there are any changes in prescription or OTC medications due to potential for drug interactions
  - May administer without regard to food

Nuplazid™ (pimavanserin). Prescribing Information. San Diego, CA. 2016.

Phase III Study

- Phase III, randomized, double-blind, parallel group, placebo-controlled trial
  - Group 1: pimavanserin 40 mg daily (2 x 20 mg tablets)
  - Group 2: placebo
- Primary efficacy end point
  - Change in total SAPS-PD score (scale for assessment of positive symptoms – Parkinson's Disease-adapted) from baseline to day 43
- Safety assessment
  - Review of concomitant drug use
  - Adverse effects
  - Physical examination findings
  - Clinical laboratory measures
  - Vital signs
  - Electrocardiogram results

Cummings J, Isaacson S, Mills R, et al. *Lancet* 2014;383;533-40.

Results – Efficacy

- Primary efficacy end point
  - SAPS-PD
    - Pimavanserin: – 5.79 compared to baseline
    - Placebo: – 2.73 compared to baseline
    - p = 0.0014
- Secondary efficacy end point
  - SAPS-PD percentage change
    - Pimavanserin: 37%
    - Placebo: 14%
    - p = 0.0006

Cummings J, Isaacson S, Mills R, et al. *Lancet* 2014;383;533-40.

Results – Safety

	Placebo (n = 94)	Pimavanserin 40 mg (n = 104)
Nausea	6 (6%)	6 (6%)
Peripheral edema	3 (3%)	7 (7%)
Urinary tract infection	11 (12%)	14 (13%)
Fall	8 (9%)	11 (11%)
Confusional state	3 (3%)	6 (6%)
Headache	5 (5%)	1 (1%)
Hallucination	4 (4%)	7 (7%)

Cummings J, Isaacson S, Mills R, et al. *Lancet* 2014;383;533-40.

Ocaliva® (obeticholic acid)

- **Approval date**
  - May 2016
- **FDA approved indications**
  - Treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA
- **Mechanism of action**
  - Farnesoid X receptor agonist; activation of FXR suppresses de novo synthesis of bile acids from cholesterol and increases transport of bile acids out of the hepatocytes, limiting the overall size of the circulating bile acid pool while promoting choleresis
- **Dosing**
  - 5 mg by mouth once daily: after 3 months, may increase to 10 mg by mouth once daily if adequate effects have not been achieved
  - Intolerable pruritus: 5 mg by mouth every other day
  - Hepatic impairment: 5 my by mouth once weekly; can increase to 5 mg by mouth twice weekly and then 10 mg by mouth twice weekly
- **Adverse reactions**
  - Liver-related: jaundice, ascites, primary biliary cholangitis flare
  - Severe pruritus
  - Reduction in HDL-C

Ocaliva® (obeticholic acid). Prescribing Information. New York, NY. 2016.

Ocaliva® (obeticholic acid)

- **Interactions**
  - Bile acid binding resins
  - Warfarin
  - CYP1A2 substrates with narrow therapeutic index
- **Monitoring**
  - Liver function tests
  - Lipid profile
  - Signs/symptoms of pruritus
- **Dosage forms available**
  - 5 mg and 10 mg tablets
- **Counseling points**
  - May administer without regard to food
  - If taking a bile acid binding resin, take obeticholic acid at least 4 hours before or 4 hours after taking the bile acid binding resin

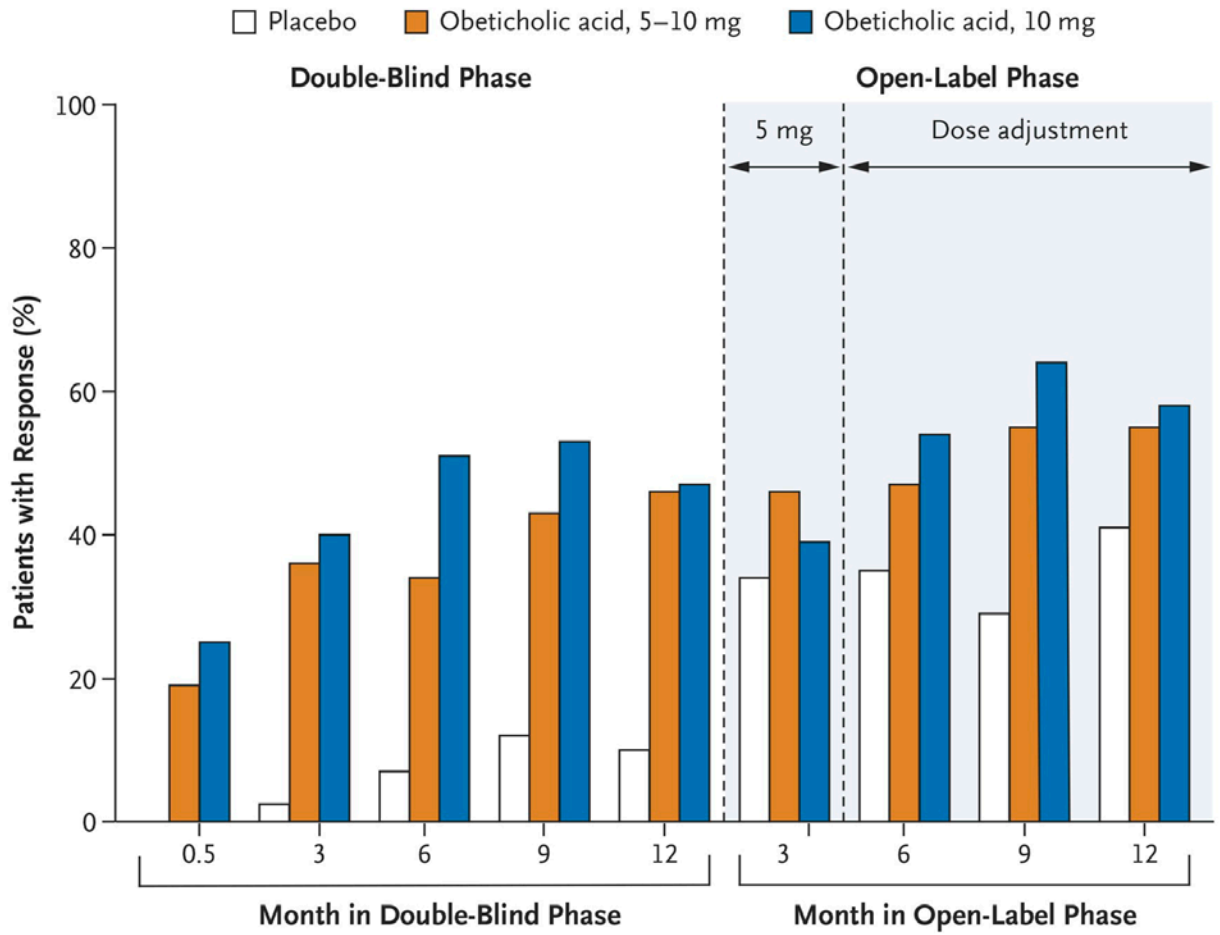
Ocaliva® (obeticholic acid). Prescribing Information. New York, NY. 2016.

Phase III Study

- Randomized, double-blind, placebo-controlled, parallel-group, 12-month phase III trial
  - Group 1: placebo orally once daily
  - Group 2: obeticholic acid 5 mg, then 10 mg orally once daily
  - Group 3: obeticholic acid 10 mg orally once daily
- Primary composite end point
  - Alkaline phosphatase level of less than 1.67 times the upper limit of the normal range, with a reduction of at least 15% from baseline and a total bilirubin level at or below the upper limit of normal at 12 months
- Safety assessment
  - Adverse effects

Nevens F, Andreone P, Mazzella G, et al. *N Engl Med* 2016;375:631-43.

Results – Efficacy



Nevens F, Andreone P, Mazzella G, et al. *N Engl Med* 2016;375:631-43.

Results – Safety

Event	Double-Blind Phase			Open-Label Extension
	Placebo (N = 73)	Obeticholic Acid, 5–10 mg (N = 70)	Obeticholic Acid, 10 mg (N = 73)	Total Obeticholic Acid (N = 193)
	number of patients (percent)			
Pruritus	28 (38)	39 (56)	50 (68)	138 (72)
Nasopharyngitis	13 (18)	17 (24)	13 (18)	45 (23)
Headache	13 (18)	12 (17)	6 (8)	36 (19)
Fatigue	10 (14)	11 (16)	17 (23)	50 (26)
Nausea	9 (12)	4 (6)	8 (11)	28 (15)
Diarrhea	8 (11)	2 (3)	8 (11)	17 (9)
Back pain	8 (11)	4 (6)	4 (5)	24 (12)
Upper respiratory tract infection	8 (11)	4 (6)	4 (5)	20 (10)
Urinary tract infection	8 (11)	4 (6)	4 (5)	31 (16)
Dyspepsia	8 (11)	4 (6)	0	10 (5)
Arthralgia	3 (4)	4 (6)	7 (10)	32 (17)
Serious adverse event	3 (4)	11 (16)	8 (11)	27 (14)

Nevens F, Andreone P, Mazzella G, et al. *N Engl Med* 2016;375:631-43.

Spinraza™ (nusinersen)

- **Approval date**
  - December 2016
- **FDA approved indications**
  - Treatment of spinal muscular atrophy (SMA) in pediatric and adult patients
- **Mechanism of action**
  - Antisense oligonucleotide (ASO) designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency
  - It increases exon 7 inclusion in SMN2 messenger ribonucleic acid transcripts and production of full-length SMN protein
- **Dosing**
  - 12 mg (5 mL) intrathecally
  - 3 loading doses 14 days apart, then 4th loading dose 30 days after 3rd, then every 4 months
- **Adverse effects**
  - Thrombocytopenia and coagulation abnormalities
  - Renal toxicity

Spinraza™ (nusinersen). Prescribing Information. Cambridge, MA. 2016.

Spinraza™ (nusinersen)

- **Interactions**
  - None
- **Monitoring**
  - CBC and coagulation tests
  - Urine protein
- **Dosage forms available**
  - 12 mg/5 mL (2.4 mg/mL) vial
- **Counseling points**
  - This is not a cure, life long therapy is needed
  - Important to obtain necessary laboratory values prior to each administration

Spinraza™ (nusinersen). Prescribing Information. Cambridge, MA. 2016.

Phase II Dose-Escalation Study

- Phase II, open-label, dose-escalation study
  - 6 – 12 mg group: 6 mg on days 1, 15, 85, and then 12 mg on days 253 and then every 4 months thereafter
  - 12 mg group: 12 mg on days 1, 15, 85, 253 and then every 4 months thereafter
- Clinical efficacy assessments
  - Change from baseline in two assessments of motor function
    - Hammersmith Infant Neurological Exam – Part 2 (HINE-2)
    - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)
- Safety assessments
  - Adverse events
  - Physical and neurological examinations
  - Vital signs
  - Clinical laboratory tests
  - CSF tests
  - Electrocardiographs

Finkel RS, Chirboga CA, Vajsar J, et al. *Lancet* 2016;388:3017-26.

Results – Efficacy

- Incremental improvements in developmental motor milestones on HINE-2 observed for 16 of 19 patients
  - 1/4 of 6 – 12 mg group ($p = 0.0002$)
  - 15/15 of 12 mg group ($p < 0.0001$)
- Motor function, assessed using CHOP-INTEND, showed mean increase of 11.5 points with 14 of 18 infants having improvement ($p = 0.008$)
- Median age of death or permanent ventilation has not been reached because most participants were surviving without permanent ventilation
- Electrophysiological assessment using CMAP in 12 mg group
  - Peroneal CMAP: all participants showed improvement
    - 742% increase ($p < 0.0001$)
  - Ulnar CMAP: 12/15 participants showed improvement
    - 377% increase ($p = 0.0103$)

Finkel RS, Chirboga CA, Vajsar J, et al. *Lancet* 2016;388:3017-26.

Results – Safety

- All participants experienced adverse events
  - Mild: 359
  - Moderate: 153
  - Severe: 77
    - All considered not related or unlikely related to the study drug
- No changes in
  - Neurological examination findings
  - Laboratory assessments
  - Vital signs
  - Electrocardiogram parameters
  - CSF parameters
- No safety concerns with intrathecal injection

Finkel RS, Chirboga CA, Vajsar J, et al. *Lancet* 2016;388:3017-26.

Zinbryta™ (daclizumab)

- **Approval date**
  - May 2016
- **FDA approved indications**
  - Treatment of adult patients with relapsing forms of multiple sclerosis
- **Mechanism of action**
  - Exact mechanism unknown
  - Presumed to involve modulation of interleukin-2 mediated activation of lymphocytes through binding to CD25
- **Dosing**
  - 150 mg subcutaneously once monthly
- **Adverse effects**
  - BLACK BOX WARNING
    - Hepatic injury, including autoimmune hepatitis
    - Other immune-mediated disorders
  - Acute hypersensitivity
  - Infections
  - Depression and suicide

Zinbryta™ (daclizumab). Prescribing Information. Cambridge, MA. 2016.

Zinbryta™ (daclizumab)

- **Interactions**
  - Live vaccines
  - Other hepatotoxic medications
- **Monitoring**
  - Liver function tests at baseline and monthly prior to each injection
- **Dosage forms available**
  - 150 mg/mL single use pen
- **Counseling points**
  - REMS program
  - Report any signs or symptoms of depression
  - Seek medical help if signs or symptoms of allergic reaction
  - Self-injection

Zinbryta™ (daclizumab). Prescribing Information. Cambridge, MA. 2016.

DECIDE Trial

- Phase III, randomized, double-blind, active-controlled trial
  - Group 1: daclizumab 150 mg subcutaneous every 4 weeks and intramuscular placebo once weekly
  - Group 2: interferon beta-1a 30 mcg intramuscularly once weekly and subcutaneous placebo every 4 weeks
- Primary efficacy endpoint
  - Annualized relapse rate over a period of 144 weeks
- Safety assessment
  - Adverse effects
    - Infections
    - Cutaneous events
    - Laboratory abnormalities

Kappos L, Wiendl H, Selmaj K, et al. *N Engl J Med* 2015;373:1418-28.

Results – Efficacy

End Point	Interferon Beta-1a (N=922)	Daclizumab HYP (N=919)	P Value
Primary end point			
Adjusted annualized relapse rate			
Rate (95% CI)	0.39 (0.35–0.44)	0.22 (0.19–0.24)	<0.001
Percent reduction vs. interferon beta-1a (95% CI)	45 (36–53)		
Secondary end points†			
New or newly enlarged hyperintense lesions on T_2-weighted images over period of 96 wk‡			
Adjusted mean no. (95% CI)	9.4 (8.5–10.5)	4.3 (3.9–4.8)	<0.001
Percent reduction vs. interferon beta-1a (95% CI)	54 (47–61)		
Disability progression confirmed at 12 wk at wk 144			
Estimated percent of patients§	20	16	0.16
Hazard ratio, daclizumab HYP vs. interferon beta-1a (95% CI)	0.84 (0.66–1.07)		
Proportion of patients free from relapse at wk 144			
Estimated percent of patients§	51	67	—
Hazard ratio for relapse, daclizumab HYP vs. interferon beta-1a (95% CI)	0.59 (0.50–0.69)		
Clinically meaningful worsening on the MSIS-29 physical subscale score at wk 96¶			
Estimated percent of patients with worsening	23	19	—
Percent reduction in the odds of worsening vs. interferon beta-1a (95% CI)	24 (5–40)		

Kappos L, Wiendl H, Selmaj K, et al. *N Engl J Med* 2015;373:1418-28.

Results – Safety

Event	Interferon Beta-1a (N=922)	Daclizumab HYP (N=919)
	number (percent)	
Adverse event		
Any event	842 (91)	838 (91)
Any event, excluding multiple sclerosis relapse	816 (89)	823 (90)
Serious adverse event		
Any event	194 (21)	221 (24)
Any event, excluding multiple sclerosis relapse	88 (10)	142 (15)
Treatment discontinuation		
Due to adverse event	112 (12)	142 (15)
Due to adverse event, excluding multiple sclerosis relapse	84 (9)	131 (14)
Death*	4 (<1)	1 (<1)
Adverse events according to severity		
Mild	239 (26)	228 (25)
Moderate	495 (54)	483 (53)
Severe	108 (12)	127 (14)
Adverse events in ≥10% of either treatment group, excluding multiple sclerosis relapse		
Nasopharyngitis	197 (21)	226 (25)
Headache	175 (19)	159 (17)
Upper respiratory tract infection	124 (13)	149 (16)
Pyrexia	134 (15)	104 (11)
Injection-site pain	102 (11)	96 (10)
Urinary tract infection	98 (11)	96 (10)
Influenza-like illness	346 (38)	88 (10)
Adverse events of special interest		
Infection†	523 (57)	595 (65)
Serious infection	15 (2)	40 (4)
Cutaneous event†	176 (19)	344 (37)
Serious cutaneous event	1 (<1)	14 (2)
Hepatobiliary disorder†	16 (2)	26 (3)
Serious hepatobiliary disorder	4 (<1)	7 (1)
Hepatic event‡	130 (14)	144 (16)
Serious hepatic event‡	4 (<1)	6 (1)
Hepatic laboratory abnormality§		
Alanine aminotransferase or aspartate aminotransferase ≥3× ULN	80 (9)	96 (10)
Alanine aminotransferase or aspartate aminotransferase >5× ULN	31 (3)	59 (6)
Alanine aminotransferase or aspartate aminotransferase ≥3× ULN and total bilirubin >2× ULN	1 (<1)	7 (1)
Met criteria of Hy's law	1 (<1)	1 (<1)
Malignant condition¶	8 (1)	7 (1)

Kappos L, Wiendl H, Selmaj K, et al. *N Engl J Med* 2015;373:1418-28.

Zinplava™ (bezlotoxumab)

- **Approval date**
  - October 2016
- **FDA approved indications**
  - Reduce recurrence of *Clostridium difficile* infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence
- **Mechanism of action**
  - Human monoclonal antibody that binds to *C. difficile* toxin B and neutralizes its effects
- **Dosing**
  - 10 mg/kg IV once
- **Adverse effects**
  - Heart failure
  - Infusion related reactions

Zinplava™ (bezlotoxumab). Prescribing Information. Whitehouse Station, NJ. 2016.

Zinplava™ (bezlotoxumab)

- **Interactions**
  - None
- **Monitoring**
  - None
- **Dosage forms available**
  - 1,000 mg/40 mL (25 mg/mL) vial
- **Counseling points**
  - This medication does not take the place antibacterial treatment – must continue their antibiotic

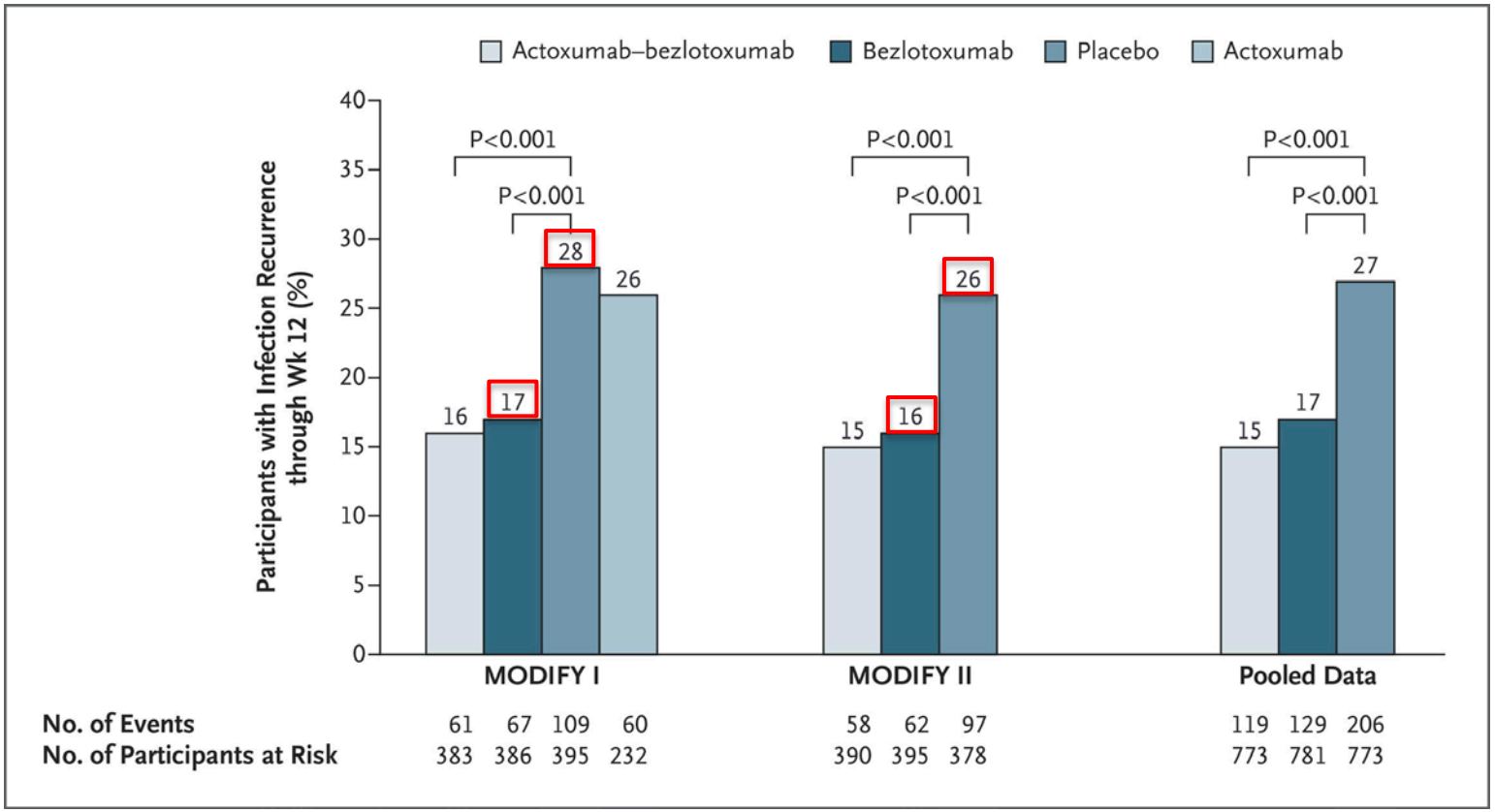
Zinplava™ (bezlotoxumab). Prescribing Information. Whitehouse Station, NJ. 2016.

MODIFY I and MODIFY II

- Phase III, double-blind, placebo controlled trials
  - Group 1: bezlotoxumab 10 mg/kg IV x 1
  - Group 2: actoxumab plus bezlotoxumab 10 mg/kg IV x 1
  - Group 3: placebo IV x 1
  - Group 4: actoxumab 10 mg/kg IV x 1 (MODIFY I only)
- Primary efficacy end point
  - Proportion of participants with recurrent *C. difficile* infection during 12 weeks of follow-up
- Safety assessment
  - Adverse effects

Wilcox MH, Gerding DN, Poxton IR, et al. *N Engl J Med* 2017;376:305-17.

Results – Efficacy



Wilcox MH, Gerding DN, Poxton IR, et al. *N Engl J Med* 2017;376:305-17.

Results – Safety

Table 2. Clinical Adverse Events in the As-Treated Population in Both Trials.

Time Period and Event	Actoxumab plus Bezlotoxumab (N=777)	Bezlotoxumab (N=786)	Actoxumab (N=235)	Placebo (N=781)
		number of participants (percent)		
During the 24 hours after infusion				
Infusion-specific reaction*	62 (8.0)	81 (10.3)	26 (11.1)	59 (7.6)
Treatment stopped because of an adverse event	0	1 (0.1)	1 (0.4)	0
During the 4 weeks after infusion				
One or more adverse events	455 (58.6)	485 (61.7)	158 (67.2)	478 (61.2)
Serious adverse event	123 (15.8)	156 (19.8)	65 (27.7)	167 (21.4)
Death	28 (3.6)	32 (4.1)	14 (6.0)	32 (4.1)
Drug-related adverse event†	50 (6.4)	59 (7.5)	17 (7.2)	46 (5.9)
Serious drug-related adverse event‡	5 (0.6)	4 (0.5)	3 (1.3)	2 (0.3)
Most common adverse events§				
Abdominal pain	32 (4.1)	34 (4.3)	15 (6.4)	34 (4.4)
Diarrhea	46 (5.9)	47 (6.0)	13 (5.5)	45 (5.8)
Nausea	47 (6.0)	52 (6.6)	28 (11.9)	39 (5.0)
Vomiting	24 (3.1)	31 (3.9)	10 (4.3)	21 (2.7)
Fatigue	21 (2.7)	18 (2.3)	11 (4.7)	12 (1.5)
Pyrexia	31 (4.0)	36 (4.6)	11 (4.7)	27 (3.5)
C. difficile infection¶	27 (3.5)	23 (2.9)	20 (8.5)	48 (6.1)
Urinary tract infection	24 (3.1)	32 (4.1)	13 (5.5)	35 (4.5)
Headache	33 (4.2)	35 (4.5)	14 (6.0)	24 (3.1)
During the 12 weeks after infusion				
Serious adverse event‖	212 (27.3)	231 (29.4)	104 (44.3)	255 (32.7)
Death	51 (6.6)	56 (7.1)	27 (11.5)	59 (7.6)

Wilcox MH, Gerding DN, Poxton IR, et al. *N Engl J Med* 2017;376:305-17.

FDA Updates 2016

ATLANTIC HEALTH SYSTEM

Atlantic
Health System

Noxafil® (posaconazole): Dosing Errors

- January 4th, 2016
- Differences in dosing regimens between the two oral formulations of Noxafil® (posaconazole) have resulted in dosing errors
  - Oral suspension and tablets cannot be directly substituted for each other – requires a dosage change
  - Outer carton was changed in addition to the prescribing information and patient information
- Recommendation
  - Prescribers
    - Specify the dosage form, strength, and frequency on all posaconazole prescriptions
  - Pharmacists
    - Request clarification when the dosage form, strength, or frequency are not specified
  - Patients
    - Talk to their healthcare professional before switching from one oral formulation to another

FDA Drug Safety Communication: Noxafil (posaconazole): Dosing Errors when Switching between Different Oral Formulations; Label Changes Approved. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm479782.htm. Accessed February 7, 2017.

Opioid Pain Medications

- March 22nd, 2016
- Several new safety issues that have lead the FDA to require changes to the labels of all opioid drugs
  - Opioids can interact with antidepressants and migraine medications and cause serotonin syndrome
    - Recommendation: discontinue opioid treatment; use a different medication
  - Taking opioids may lead to a serious condition in which the adrenal glands do not produce adequate amounts of cortisol
    - Recommendation: perform diagnostic testing; treat with steroids and wean the patient off the opioid
  - Long terms use of opioids may be associated with decreased sex hormone levels
    - Recommendation: conduct laboratory evaluation

FDA Drug Safety Communication: Opioid Pain Medicines: New Safety Warnings Added to Prescription Opioid Medications. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm491715.htm. Accessed February 7, 2017.

Saxagliptin and Alogliptin

- April 5th, 2016
- Medications containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease
  - New warnings to the drug labels have been added for these medications
- Recommendation
  - Healthcare Professionals
    - Consider discontinuing medications containing saxagliptin and alogliptin in patients who develop heart failure
  - Patients
    - Contact healthcare professionals immediately if develop signs of heart failure

FDA Drug Safety Communication: Diabetes Medications Containing Saxagliptin and Alogliptin: Risk of Heart Failure. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm494252.htm. Accessed February 7, 2017.

Brintellix® (vortioxetine) → Trintellix®

- May 2nd, 2016
- FDA approved the brand name change for the antidepressant Brintellix® (vortioxetine) to decrease risk of prescribing errors due to name confusion with the blood-thinning medication Brilinta® (ticagrelor)
  - The new brand name is Trintellix®
- Recommendation
  - Healthcare professionals
    - Use generic name as well as brand name and indication when prescribing
  - Patients
    - Double check that they have received the correct medication; Trintellix® tablets will be identical to Brintellix® tablets

FDA Drug Safety Communication: Brintellix (vortioxetine): Brand Name Change to Trintellix, to Avoid Confusion With Antiplatelet Drug Brilinta (ticagrelor). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm498607.htm. Accessed February 7, 2017.

Fluoroquinolone Antibiotic Safety Updates

- May 12th, 2016 and July 26th, 2016
- FDA advising that serious side effects associated with systemic fluoroquinolone antibiotics may outweigh benefits in patients with certain uncomplicated infections
  - Side effects can be disabling and potentially permanent and can involve the tendons, muscles, joints, nerves, and central nervous system
  - Labels of all fluoroquinolone antibiotics were updated to reflect the new safety warnings
- Recommendation
  - Healthcare professionals
    - Do not prescribe systemic fluoroquinolone therapy for patients who have other treatment options; stop therapy if patient exhibits symptoms
  - Patients
    - Contact healthcare professional if experience any serious side effects while taking a fluoroquinolone

FDA Drug Safety Communication: Fluoroquinolone Antibacterial Drugs: FDA Advises Restricting Use for Certain Uncomplicated Infections. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm500665.htm. Accessed February 7, 2017.
FDA Drug Safety Communication: Fluoroquinolone Antibacterial Drugs for Systemic Use: Warnings Updated Due to Disabling Side Effects. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm513065.htm. Accessed February 7, 2017.

Loperamide and Serious Heart Problems

- June 7th, 2016
- FDA is warning that taking higher than recommended doses of loperamide may cause serious heart problems and can lead to death
  - QT prolongation, Torsades de Pointes, other ventricular arrhythmias, syncope, cardiac arrest
- Recommendations
  - Healthcare professionals
    - Be aware of this serious side effect and consider it if there are unexplained cardiac issues
  - Patients
    - If taking loperamide OTC and diarrhea lasts more than 2 days, stop taking it and contact your healthcare professional

FDA Drug Safety Communication: Loperamide (Imodium): Serious Heart Problems With High Doses From Abuse and Misuse. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm505303.htm. Accessed February 7, 2017.

Canagliflozin and Dapagliflozin

- June 14th, 2016
- FDA has strengthened the existing warning about the risk of acute kidney injury for canagliflozin and dapagliflozin
- Recommendation
  - Healthcare professionals
    - Consider factors that may predispose patients to acute kidney injury prior to starting them on these medications; monitor kidney function prior to starting and periodically thereafter
  - Patients
    - Seek medical attention immediately if experience signs and symptoms of acute kidney injury

FDA Drug Safety Communication: Canagliflozin (Invokana, Invokamet) and Dapagliflozin (Farxiga, Xigduo XR): Strengthened Kidney Warnings. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm506554.htm. Accessed February 7, 2017.

Opioid Pain or Cough Medications and Benzodiazepines

- August 31st, 2016
- Use of opioid medications with benzodiazepines has resulted in serious side effects, including slowed or difficult breathing and deaths
  - FDA is adding boxed warnings to the drug labeling of prescription opioid pain and prescription opioid cough medications and benzodiazepines
- Recommendations
  - Healthcare professionals
    - Limit prescribing opioid pain medications with benzodiazepines or other CNS depressants; limit dosages and duration
    - Avoid prescribing prescription opioid cough medications for patients taking benzodiazepines
  - Patients
    - Seek medical attention immediately if experience symptoms of unusual dizziness or lightheadedness, extreme sleepiness, slowed or difficult breathing, or unresponsiveness

FDA Drug Safety Communication: Opioid Pain or Cough Medicines Combined With Benzodiazepines: FDA Requiring Boxed Warning About Serious Risks and Death. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm518710.htm. Accessed February 7, 2017.

General Anesthetic and Sedation: Young Children and Pregnant Women

- December 14th, 2016
- FDA is warning that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or in pregnant women during their third trimester may affect the development of children's brains
  - Warnings are being added to the labels of general anesthetic and sedation drugs
- Recommendations
  - Healthcare professionals
    - Balance the benefits of appropriate anesthesia in young children and pregnant women against the potential risks
  - Parents/Pregnant Women
    - Discuss with healthcare professional the potential adverse effects of anesthesia on brain development

FDA Drug Safety Communication: General Anesthetic and Sedation Drugs: New Warnings for Young Children and Pregnant Women. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm533195.htm. Accessed February 7, 2017.

Conclusion

- In 2016 …
  - Only 22 novel drugs approved
    - 8 first in class
    - 9 to treat rare diseases
  - 4 new medications for cancer
  - 2 new medications to treat hepatitis C
  - 2 new diagnostic agents
  - Multiple FDA updates

New Medications and FDA Updates 2016

Suzannah Kokotajlo, PharmD
Morristown Medical Center
May 11th, 2017
Suzannah.Kokotajlo@AtlanticHealth.org

ATLANTIC HEALTH SYSTEM

Atlantic Health System