Drug Approvals Update: Focus on 2022

Elizabeth A. Shlom PharmD, MBA, BCPS

CE Activity Objectives

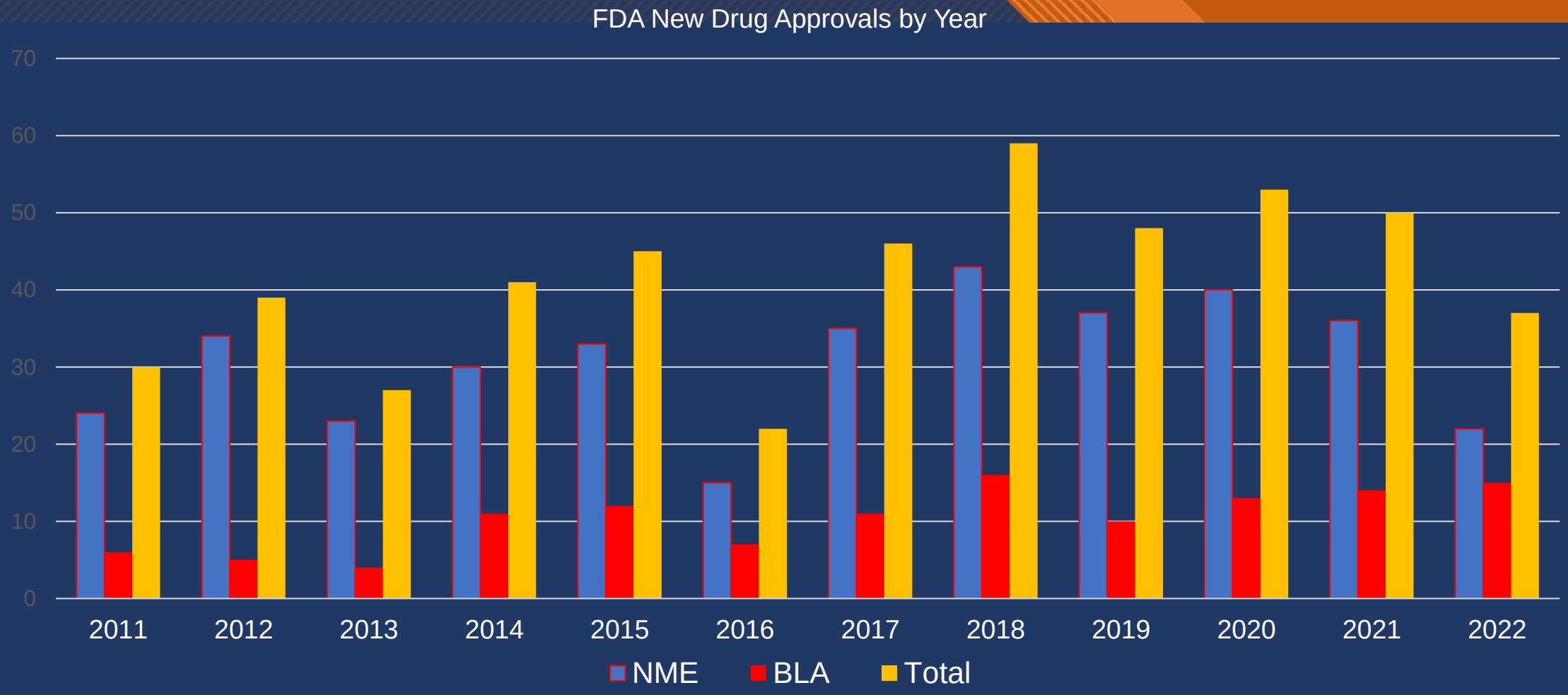
At the completion of this activity, pharmacists and pharmacy technicians will be able to*:*

1. Discuss new molecular entities approved by the FDA in 2022
2. Match a list of new medications with their indications
3. Describe safety concerns of new medications
4. Discuss the advancement of biologics and gene therapies

Disclosures

- I have no disclosures to report
- I will be using both generic and brand names of medications and may discuss both FDA-approved and non-FDA-approved indications

History of FDA Drug Approvals



2022: 37 total drugs approved; 22 non-biologics, 15 monoclonal antibodies

FDA Approval Designations

ORPHAN DRUG

O

Drug or biological product for a rare disease or condition

- Population of 200,000 or fewer patients

FIRST-IN-CLASS

FIC

Drug with a new mechanism of action

- Surrogate endpoints are permitted in clinical trials if drug fills an unmet medical need

	2018	2019	2020	2021	2022
Orphan Drug, N (%)	34 (58%)	21 (44%)	31 (58%)	26 (52%)	20 (54%)
First-in-Class, N (%)	19 (32%)	20 (42%)	21 (40%)	27 (54%)	21 (54%)

FDA Approval Designations

PRIORITY REVIEW

P

Expedited FDA review with action on the new drug application within 6 months

- Standard review is 10 months

BREAKTHROUGH THERAPY

B

Drug provides substantial improvement over current therapies

- Can be requested by manufacturer
- FDA might suggest after review of preliminary information

	2018	2019	2020	2021	2022
Priority Review, N (%)	43 (73%)	28 (58%)	30 (57%)	34 (68%)	21 (37%)
Breakthrough Therapy, N (%)	14 (24%)	13 (27%)	22 (42%)	14 (28%)	13 (35%)

New Anti-infectives

Lenacapavir (Sunlenca)

Oteseconazole (Vivjoa)

Lenacapavir (Sunlenca®) FIC P B

Indication: Multi-drug resistant HIV infection, in combination with other antiretrovirals

Mechanism of Action: Capsid inhibitor interfering with HIV-1 viral replication

Dosing:

927 mg SC injection (in abdomen) every 6 months after initiation regimen:

- Initiation Option #1: Day 1 - 927 mg SC injection + 600 mg PO; Day 2 - 600 mg PO

- Initiation Option #2: Day 1 - 600 mg PO; Day 2 – 600 mg PO; Day 8 - 300 mg PO; Day 15 - 927 mg SC

Safety Considerations:

Lenacapavir is a substrate of CYP3A, P-gp, UGT1A1:

- Avoid strong CYP3A inducers or combined inhibitors of CYP3A, P-gp, UGT1A1
- Possible increased risk of ADEs with drugs metabolized by CYP3A within 9 months of last SC injection

Immune Reconstitution Syndrome – an inflammatory response to indolent or residual opportunistic infections (e.g., MAI, CMV, PCP, TB, etc.)

Most Common Adverse Reactions

96% of adverse reactions are of mild or moderate severity

- Injection site reactions (65%)
- Nausea/GI ADEs (< 10%)

Lenacapavir (Sunlenca®) FIC P B

Capella Trial

***N Engl J Med* 2022;386:1793-803**

- Phase 2/3 study conducted at 42 sites in 11 countries
- Patients with resistance to ≥2 antiretroviral meds (from at least 3 of the 4 major classes) and HIV-1 RNA level ≥400 copies/mL for ≥ 8 weeks
- Cohort 1 (n=36): randomized 2:1 monotherapy with Lenacapavir vs Placebo + failing therapy
- Cohort 2 (n=36) open label Lenacapavir + optimized background therapy
- Week 26 – viral load <50 copies/mL in 81% of patients in Cohort 1 and 83% in Cohort 1
- Emerging mutations for resistance in 8 patients

Ongoing Trials

- Lenacapavir as a single agent for pre-exposure prophylaxis in people at risk for HIV
  - PURPOSE 1 and PURPOSE 2 (Multinational Phase 3 trials)
- Management of treatment-naïve HIV patients with baseline CD4 cell count of ≥ 200 cells/microliter
  - CALIBRATE trial (Phase 2 open-label trial)
- Oral Bictegravir/Lenacapavir combination in virologically suppressed, treatment-experienced HIV patients on complex regimens (Phase II/III trial)

Sunlenca [package insert]. Foster City, CA: Gilead Sciences Inc. 2022.

Oteseconazole (Vivjoa®) P

Indication: Recurrent vulvovaginal candidiasis (RVVC) in those *NOT* of reproductive potential

Mechanism of Action: Azole antifungal agent

Dosing:

Two dosing options:

#1. Day 1, 600mg, Day 2, 450mg, Day 14, 150mg once weekly x 11 weeks (Weeks 2-12)

#2. Days 1, 4 and 7, Fluconazole 150mg PO, Days 14-20, Oteseconazole 150mg daily, Starting on Day 28, Oteseconazole 150mg weekly to complete 11 weeks of treatment (Weeks 4-14)

Safety Considerations:

Embryofetal toxicity - Contraindicated in women of reproductive potential, pregnant or lactating

Drug interaction with substrates of breast cancer resistance protein (BCRP) increasing their exposure and ADEs

Not recommended in severe renal impairment, moderate or severe hepatic impairment

Most Common Adverse Reactions

Mild to moderate headache (7.4%) and nausea (3.6%)

Oteseconazole (Vivjoa®) P

VIOLET Trials

***NEJM Evid* 2022;1(8)**

Two R/MC/DB/PC/multi-national trials in women with ≥ 3 episodes of RVVC

- Treatments
  - 1) Induction phase: Fluconazole 150mg q72 hours (Days 1, 4, 7)
  - 2) Maintenance phase: 14 days after first fluconazole dose, patients randomized (2:1) to either 150mg Oteseconazole or Placebo x 7 days followed by 11 weekly doses
- Outcomes: proportion of patients with ≥ 1 culture-verified acute VVC episode or took medication known to treat VVC through week 48
  - Trial 1: (n=483)
    - Oteseconzole 27.3% vs Placebo 50.8% (p<0.001)
  - Trial 2: (n=425)
    - Otesconzole 21.3% vs Placebo 49.7% (p<0.001)

Vivjoa [package insert]. Durham, NC: Mycovia Pharmaceuticals Inc. 2022.

ultraVIOLET Trial

***Open Forum Infect Dis* 2021 Nov, 8(Suppl 1):S66-S67**

R/DB Trial in women with RVVC

- Treatments
  - 1) Induction phase: Oteseconazole 1050mg over two days (600mg on Day 1, 450mg on Day 2) or Fluconazole 150mg q 72 hours (Days 1, 4, 7)
  - 2) Maintenance phase: 150mg Oteseconazole or Placebo weekly for 11 weeks
- Outcomes:
  - Proportion of patients with > 1 culture-verified VVC through week 50 or unresolved VVC episode during induction
    - Oteseconazole 10.3% vs Fluconazole/Placebo 42.9% (p<0.001)
  - Proportion of patients with > 1 culture-verified VVC or took medication through week 50 or unresolved VVC episode during induction
    - Oteseconazole 43.5% vs Fluconazole/Placebo 59% (p=0.039)

New Medications for Blood Disorders

Sutimlimab-jome (Enjaymo®)

Mitapivat (Pyrukynd®)

Pacritinib (Vonjo®)

Sutimlimab-jome (Enjaymo®) FIC O P B

Indication: Treatment of hemolysis with cold agglutinin disease (CAD)

Mechanism of Action: Complement 1 (C1) inhibitor

Dosing:

Weight-based dosing weekly for 2 weeks, then every other week

- 6500mg if between 39kg and < 75 kg
- 7500mg if ≥ 75kg

Administer by IV infusion over 60 min (120 min in patients with cardiopulmonary disease)

Vaccinate against encapsulated bacteria at least 2 weeks prior to treatment per ACIP recommendations

Safety Considerations:

Potential for developing auto-immune diseases (e.g., systemic lupus erythematosus)

Recurrent hemolysis can occur if treatment is interrupted

No data on use in pregnancy, lactation, or pediatric patients

Most Common Adverse Reactions

Infections – UTI (38%), respiratory (25%), nasopharyngitis (21%), viral (25%)

Dizziness (29%), headache (21%), fatigue (33%), arthralgia (25%), hypertension (25%), nausea (25%), cough (25%)

Infusion-related reactions 17%

Sutimlimab-jome (Enjaymo®) FIC O P B

What is Cold Agglutinin Disease?

- Autoimmune disease with hemolytic anemia
  - Abnormal bone marrow cells produce antibodies called cold agglutinins. These attach to red blood cells and activate the complement pathway of the immune system to target the red blood cells and lead to hemolysis
  - C1 is the primary complement protein involved in CAD
  - Symptoms include fatigue, weakness, shortness of breath, dizziness, chest pain, irregular heartbeat, and bluish color and/or pain and discomfort of hands and feet
  - Cold temperatures or a compromised immune system can trigger the symptoms
- Most commonly seen in older adults; median age of onset is 65 years

Clinical Trials

- CARDINAL – 6-month open-label, single-arm trial in 24 CAD patients *N Engl J Med* 2021;384:1323-1334
  - 54% of patients had improved Hgb, no blood transfusions (Weeks 5-26), and no treatment beyond protocol (Weeks 5-26)
- CADENZA - 6-month placebo-controlled Phase III trial *Blood* 2022;14(9):990-991
  - Sutimlimab (n=22) significantly better than Placebo (n=20)
    - Combination of improved Hgb level, not receiving blood transfusions, and not receiving treatment for CAD beyond protocol
      - Sutimlimab 72.7% vs Placebo 15%
    - Improvement in symptoms and impacts of fatigue using FACIT-Fatigue assessment

Enjaymo [package insert]. Waltham, MA: Bioverativ USA Inc. 2023
Cold agglutinin disease - symptoms, causes, treatment: Nord. National Organization for Rare Disorders. https://rarediseases.org/rare-diseases/cold-agglutinin-disease/. Published November 17, 2020. Accessed March 14, 2023.

Mitapivat (Pyrukynd®) FIC O P

Indication: Hemolytic anemia in adults with pyruvate kinase (PK) deficiency

Mechanism of Action: Pyruvate kinase activator

Dosing:

Weeks 1-4: 5mg PO twice daily

Weeks 5-8: 20mg PO twice daily

Weeks 9 and beyond: 50mg PO twice daily

Increase dose based on Hgb levels and transfusion requirements

D/C if no response by 24 weeks

Safety Considerations:

Abrupt discontinuation/interruption can lead to acute hemolysis

Avoid with moderate or severe hepatic impairment

Drug interactions – avoid, monitor, and/or consider alternative agents concomitantly with mitpivat that are CYP3A inhibitors/inducers/substrates, or CYP2B6, CYP2C, UGT1A1, P-gp substrates

Most Common Adverse Reactions

Lab abnormalities include decreased estrone or estradiol (in males), increased urate

10% of trial patients had serious ADEs including atrial fibrillation, gastroenteritis, musculoskeletal pain

Back pain (15%), arthralgia (10%)

Mitapivat (Pyrukynd®) FIC O P

Orphan Disease

- RBC pyruvate deficiency is a rare autosomal recessive disease resulting in chronic hemolytic anemia
  - Most frequent symptoms: anemia (90-95%), splenomegaly (80-85%), jaundice (40-70%), gallstones (30-45%)
  - Lab abnormalities: low Hgb levels, elevated reticulocytes, elevated unconjugated bilirubin
- Supportive treatment with folic acid, B12 (if deficient), transfusions as needed
  - Splenectomy, after age 5 years, reduces transfusion requirements
  - Hematopoietic stem cell transplant may be of benefit but clinical trials are lacking
  - Gene therapy is under investigation

Pyrukynd [package insert]. Cambridge, MA: Agios Pharmaceuticals Inc. 2022
Journal of Blood Medicine 2022:13 461–471 .

Clinical Trials

- ACTIVATE: 24-week Phase III international R/DB/PC trial *N Engl J Med* 2022;386 (15):1432-1442
  - Adults (n=80) with PK deficiency not regularly transfused and with baseline Hgb < 10.0 g/dL
  - 40% of Mitapivat vs 0% of Placebo patients met the primary outcome of ≥1.5 g/dL increase in Hgb- from baseline
- ACTIVATE-T: 6-month open-label, single-arm, international Phase III trial *Blood* 2021;138(Suppl 1):924
  - Adults (n=27) with PK deficiency diagnosis and receiving regular transfusions (≥ 6 in past year)
    - 16-week dose optimization period and 24-week fixed-dose period
  - Primary Outcome: 37% with ≥33% reduction in RBC units transfused during fixed dose period compared to historical transfusion burden (p=0.0002)

Pacritinib (Vonjo®) O P

Indication: Myelofibrosis that is intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) and with a platelet count below 50 × 10^9/L

Mechanism of Action: Kinase inhibitor targeting JAK2 and FLT3 kinases

Dosing: 200mg orally twice daily with or without food

Safety Considerations:

Concomitant use of strong CYP3A4 inducers or inhibitors is contraindicated; avoid with moderate inducers or inhibitors

Can lead to severe bleeding and hemorrhage; hold prior to planned surgical procedures; avoid during active bleeding episodes

Avoid in patients with prolonged QT intervals, with moderate or severe hepatic impairment, with eGFR < 30 mL/min

Most Common Adverse Reactions

Diarrhea (48%), thrombocytopenia (34%), nausea (32%), anemia (24%), peripheral edema (20%), vomiting (20%), dizziness (15%), pyrexia (15%), epistaxis (12%)

Dose modifications for diarrhea, thrombocytopenia, hemorrhage, and prolonged QT interval are provided in the package insert

Pacritinib (Vonjo®) O P

Orphan Disease

- Myelproliferative neoplasms (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis) are rare with annual incidence of < 3 per 100,000
  - Myelofibrosis has median survival < 3 years with onset at ≥ 55 years of age; > 10 years in younger patients
  - Disease stratification (low, intermediate, or high risk) based on risk factors and is predictive of survival
  - Presence of thrombocytopenia is associated with higher symptom burden and shorter survival
- Myelofibrosis treatment options
  - Off-label use of agents including hydroxyurea, androgens, corticosteroids, erythropoietin stimulating agents, and others
  - Blood transfusions, radiation and splenectomy have been tried
  - Allogeneic hematopoietic stem cell transplantation has been used
  - JAK kinase inhibitors improve spleen size, symptoms and burden reduction and improve quality of life but have not demonstrated improved survival

Clinical Trials

***JAMA Oncol.* 2018 May 1;4(5):652-659**

- PERSIST-2: Phase III international MC/R/PC trial
  - Adults (n=311) with myelofibrosis and thrombocytopenia (platelet count ≤ 100 x 10^9/L)
  - 1:1:1 randomization to Pacritinib 400mg once daily, Pacritinib 200mg twice daily, or best available therapy (BAT) (including Ruxolitinib)
  - Primary Outcome:
    - Pacritinib (arms combined) were more effective than BAT at reducing spleen volume (SVR) by ≥ 35% but not at providing 50% reduction in total symptom score (TSS)
    - Pacritinib 200mg twice daily was more effective than BAT in both endpoints

Vonjo [package insert]. Seattle, WA: CTI BioPharma Corp. 2022.

New Cardiology Medication

Mavacamten (Camzyos®)

Mavacamten (Camzyos®) FIC O B

Indication: To improve functional capacity and reduce symptoms of symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (oHCM)

Mechanism of Action: Cardiac myosin inhibitor

Dosing:

Starting dose 5mg orally once daily, only with LVEF ≥55%

Titration of doses every 4 weeks based on LVEF and Valsalva left ventricular outflow tract (LVOT) gradient; after Week 12, monitor every 12 weeks

Available as 2.5mg, 5mg, 10mg, 15mg caps

Safety Considerations:

Boxed warning: Only use with LVEF >55%; monitor during treatment; interrupt treatment if worsening LVEF or symptoms

Concomitant drug contraindications:

- Moderate to strong CYP2C19 or strong CYP3A4 inhibitors
- Moderate to strong CYP2C19 or CYP3A4 inducers

Some concurrent illnesses (e.g., infection, arrhythmias) can increase risk of developing heart failure with Mavacamten

REMS PROGRAM

Camzyos REMS Program

- Drug is only available through REMS program with regular monitoring of heart function, concomitant medications, etc.
- Prescribers, patients, pharmacies must be enrolled
- Only available through certified pharmacies

Mavacamten (Camzyos®) FIC O B

What is Obstructive Hypertrophic Cardiomyopathy?

- Obstructive hypertrophic cardiomyopathy (cHCM)
  - Thickened and stiff heart muscle obstructs blood flow being pumped out to rest of the body
  - Symptoms: palpitations, shortness of breath, edema, decreased exercise capacity
- oHCM treatments
  - Medical treatments have included: beta blockers, non-dihydropyridine calcium channel blockers, disopyramide
  - Cardiac myosin inhibitors (e.g., mavacamten and aficamten) target the underlying pathophysiology of cHCM

Clinical Trials

***The Lancet* 2020;396(10253): 759-769**

- EXPLORER-HCM: Phase III MC/DB/R/PC international trial
  - Adults (n=251) with HCM (median LVEF 75% at baseline)
  - 1:1 randomization to Mavacamten 5-15mg once daily, or placebo; median duration of therapy 30 weeks (range 2-40 weeks)
  - Efficacy endpoints:
    - Mavacamten improved exercise capacity and symptoms in 37% of patients versus 17% of patients on placebo (p=0.0005)
    - 65% of Mavacamten patients improved by at least 1 NYHA class versus 31% of patients on placebo (p<0.0001)

Camzyos [package insert]. Princeton, NJ: Bristol-Myers Squibb. 2022.

New Dermatology Medications

Abrocitinib (Cibinqo®)

DaxibotulinumtoxinA-lanm (Daxxify®)

Anacaulase-bcdb (Nexobrid®)

Deucravacitinib (Sotyktu®)

Spesolimab-sbzo (Spevigo®)

Tapinarof (Vtama®)

Abrocitinib (Cibinqo®) P B

Indication: Atopic dermatitis in patients ≥ 12 years of age with disease that is refractory, moderate to severe

Mechanism of Action: Janus kinase (JAK) inhibitor

Dosing:

Usual dose is 100mg orally once daily ; can increase to 200mg once daily

Reduce dose in moderate/severe renal impairment or if CYP2C19 poor metabolizer to 50-100mg once daily

Avoid concomitant use of other JAK inhibitors, biologic immunomodulators or immunosuppressants

Safety Considerations:

Boxed Warnings – increased risk of infections, malignancies, thrombosis, major adverse cardiac events

Increased incidence of thrombocytopenia; avoid antiplatelet agents (except low-dose aspirin) during first 3 months of therapy

Avoid moderate/strong CYP2C19 and CYP2C9 inhibitors or strong CYP2C19 or CYP2C9 inducers

Avoid live vaccines before/during/after therapy

Most Common Adverse Reactions

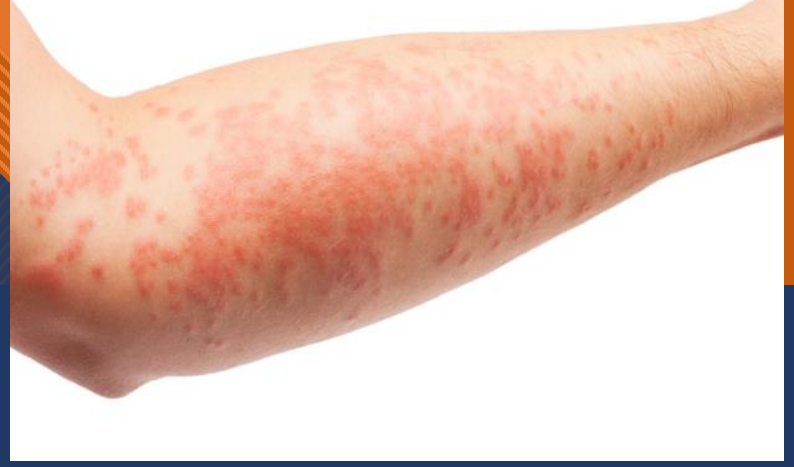
Nausea 14.5% (200mg/day) and 6% (100mg/day)

Nasopharyngitis 8.7% (200mg/day) and 12.4% (100mg/day)

Headache 7.8% (200mg/day) and 6% (100mg/day)

Other ADEs < 5%, Herpes simplex, increase CPK, dizziness, UTI, vomiting, acne, fatigue, etc.

Abrocitinib (Cibinqo®) P B



Phase III, R/DB/PC Clinical Trials

JADE MONO-1 (n=387) and JADE MONO-2 (n=331) with 12-weeks of monotherapy in subjects ≥12 years of age

- Abrocitinib 200mg QD, 100mg QD or placebo

Two Phase III trials used combination therapy

- JADE COMPARE (n=837) – Subjects ≥ 18 years of age; 16 weeks of Abrocitinib 200mg, 100mg QD or placebo plus Dupilumab Q2weeks SC
- JADE TEEN (n=285) – Subjects 12 to <18 years of age; 12 weeks of Abrocitinib 200mg, 100mg QD or placebo plus background topical medication

In all trials, significant response seen with abrocitinib 100mg and 200mg compared to placebo

Cibinqo [package insert]. New York, NY: Pfizer. 2023.

Place in Therapy

- Atopic dermatitis affects up to 10% of adults and 25% of children; disease is due to immune dysregulation and skin barrier disruption
- Treatment:
  - Mild-Moderate disease: topical corticosteroids and calcineurin inhibitors
  - Moderate-Severe disease: phototherapy, systemic immunosuppressives (e.g., cyclosporine, azathioprine, oral corticosteroids), biologics (dupilumab, tralokinumab), and JAK inhibitors (ruxolitinib, upadacitinib,abrocitinib)

DaxibotulinumtoxinA-lanm (Daxxify®)

Indication: Temporary improvement in moderate to severe frown lines in adult patients

Mechanism of Action: Acetylcholine release inhibitor and neuromuscular blocking agent

Dosing:

40 units per treatment session administered intramuscularly as 0.1mL (8 units) into each of five sites

Administer no more frequently than every 3 months

Safety Considerations:

Boxed warning for botulinum toxins – can spread to produce possibly life-threatening symptoms such as swallowing and breathing difficulties

Dosing of botulinum toxins is not interchangeable

Most Common Adverse Reactions

Headache (6%), eyelid ptosis (2%), facial paresis (1%)

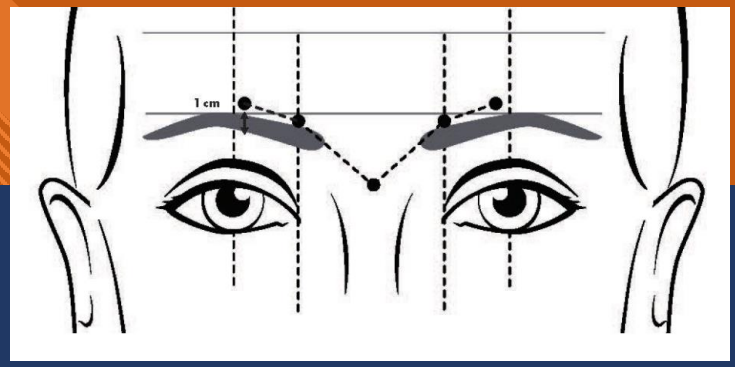
DaxibotulinumtoxinA-lanm (Daxxify®)

Two R/DB/MC/PC Clinical Trials

- SAKURA 1 (n=303) and SAKURA 2 (n=306) *Plastic & Reconstructive Surgery* 2020;145(1):45-58
- Mean age 50 years
- Efficacy based on investigator and subject assessment of frown wrinkle severity
  - Treatment success = achieving score of 0 or 1 (none or mild) and an improvement of ≥ 2 points from baseline for both investigator and subject assessment at Week 4

	Study 1		Study 2	
Treatment Success	Daxi	Placebo	Daxi	Placebo
	74%	0%	74%	0%
Median Duration of Response of DaxibotulinumtoxinA	28 weeks		26 weeks	

Daxxify [package insert]. Newark, CA: Revance Therapeutics, Inc. 2022.



Place in Therapy

- Botulinum toxin type A is most commonly used for cosmetic purposes
- Neuromodulators currently available:
  - OnabotulinumtoxinA (Botox Cosmetic)
  - AbobotulinumtoxinA (Dysport)
  - IncobotulinumtoxinA (Xeomin)
  - PrabotulinumtoxinA (Jeuveau)
  - DaxibotulinumtoxinA (Daxxify)
- DaxibotulinumtoxinA considerations
  - Duration of effectiveness approx. 6 months
  - No human or animal additives
  - Stored at room temp

Anacaulase-bcdb (NexoBrid®) O

Indication: Eschar removal in adults with deep partial thickness and/or full thickness thermal burns

Mechanism of Action: Proteolytic enzymes extracted from pineapple plant stems

Dosing:

Topical application (3mm thickness) to up to 15% of body surface area (BSA)

Second application at least 24 hours after first application; total treated area not to exceed 20% BSA

Product is prepared at bedside – lyophilized powder is aseptically mixed with gel included in package; use within 15 minutes

Apply ointment skin protectant barrier

Provide pain management as for dressing changes

Safety Considerations:

Not for use on chemical burns, burns on face/perineum/genitalia, burns on feet of patients with diabetes or occlusive vascular disease, circumferential burns, burns in patients with significant CV disease including inhalation injury

Avoid in patients with coagulation disorders or on medications that affect coagulation

Cross sensitivity with papayas and papain

Most Common Adverse Reactions

Pruritus (15%) and pyrexia (12%)

Anacaulase-bcdb (NexoBrid®) O

- Phase III DETECT clinical trial
  - Adult patients with deep partial-thickness and full-thickness thermal burns of 3%-30% of total body surface area (BSA)
  - Significant improvement with study endpoints:
    - Eschar removal
    - Shorter time to eschar removal
    - Lower incidence of surgical eschar removal compared to standard of care (SOC)
    - Non-inferiority in time to > 95% wound closure compared with patients treated with SOC
- U.S. is 44th country to approve use of anacaulase in thermal burns

NexoBrid [package insert]. Yavne, Israel: MediWound LTD. 2023.

Spesolimab-sbzo (Spevigo®) FIC O P B

Indication: Generalized pustular psoriasis (GPP) flares in adults

Mechanism of Action: humanized Interleukin-36 receptor antagonist

Dosing:

- 900mg single dose IV infusion over 90 minutes; diluted in 100mL NS
- If symptoms persist, a second 900mg dose can be administered 1 week after first dose

Safety Considerations:

- Increased risk of infections
- Hypersensitivity reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) and other infusion-related reactions

Most Common Adverse Reactions

- Asthenia, fatigue, nausea, vomiting, headache, pruritus, prurigo, infusion site hematoma and bruising, and urinary tract infection

Spesolimab-sbzo (Spevigo®) FIC O P B

What are GPP Flares?

- GPP is a rare and potentially life-threatening autoinflammatory skin disease
  - Flares - widespread eruption of sterile pustules with accompanying pain, fever, malaise, fatigue, sometimes arthritis and neutrophilic cholangitis
  - Can be relapsing with recurrent flares or persistent with intermittent flares
    - Flares can be spontaneous or triggered (e.g., by URIs, stress, medications, medication withdrawal, pregnancy, etc.)
  - Mortality 2-16%
    - Resulting from septic shock and cardiorespiratory failure
- Managed with cyclosporine, retinoids, methotrexate and biologic agents
- IL36 cytokines are overexpressed in GPP skin lesions

Spevigo [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2022.

Clinical Trials

***N Engl J Med* 2021;385:2431-40**

- EFFISAYIL-1: Phase II MC/DB/R/PC international trial (37 sites in 12 countries)
  - Adults (n=53) with a GPP flare
  - 2:1 randomization to Spesolimab 900mg IV dose or placebo; open-label dose of Spesolimab on day 8, open-label rescue med after day 8; followed for 12 weeks
  - Efficacy endpoints:
    - At end of Week 1, pustulation subscore of 0 (no visible pustules) in 54% of Spesolimab patients vs 6% with placebo ($p<0.001$)
    - At end of Week 1, pustulation total score of 0 or 1 (clear or almost clear skin) in 43% of Spesolimab patients vs 11% with placebo ($p=0.02$)
  - Infections in 17% of Spesolimab patients in Week 1, 47% by Week 12

Deucravacitinib (Sotyktu®) FIC

Indication: Moderate-to-severe plaque psoriasis in adults

Mechanism of Action: Tyrosine kinase 2 (TYK2) inhibitor

Dosing:

6mg orally once daily

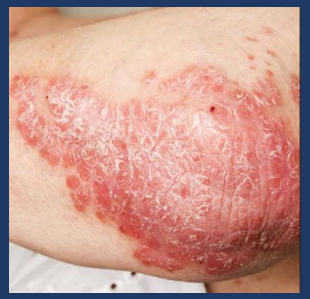
Safety Considerations:

- Increased risk of infection
- Evaluate for TB prior to treatment initiation
- Not to be used in combination with other potent immunosuppressants
- Not recommended in patients with severe hepatic failure

Most Common Adverse Reactions

- Upper respiratory tract infections, CPK levels increased, herpes simplex, mouth ulcers, folliculitis, acne

Deucravacitinib (Sotyktu®) FIC



Plaque Psoriasis Treatment

- 1st line: topical agents (corticosteroids, vitamin D3 analogues, retinoids, calcineurin inhibitors, coal tar, or anthralin)
- 2nd line: phototherapy or oral agents including methotrexate, cyclosporine, acitretin, apremilast
- 3rd line: biologics including etanercept, adalimumab, infliximab, ustekinumab, secukinumab, apremilast

Spevigo [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2022.

Phase III Clinical Trials

J Am Acad Dermatol 2023;88(1):P29-39

J Am Acad Dermatol 2023;88(1):P40-51

- POETYK PSO-1 and POETYK PSO-2
  - 52-week, R/DB/PC clinical trials
  - 666 patients in PSO-1; 1020 patients in PSO-2
- Both with 2:1:1 randomization to Deucravacitinib 6mg PO daily or placebo or Apremilast 30mg twice daily
  - Primary efficacy endpoints:
    - PASI 75** at Week 16, :
      - PSO-1: 58.4% with Deucravacitinib vs 12.7% with placebo and 35.1% with Apremilast (P<0.0001)
      - PSO-2: 53% with Deucravacitinib vs 9.4% with placebo (P<0.001) and 39.8% with Apremilast (P=0.0004)

** PASI 75: ≥75% reduction from baseline in Psoriasis Area and Severity Index

Tapinarof (Vtama®) FIC

Indication: Topical treatment of plaque psoriasis in adults

Mechanism of Action: Aryl hydrocarbon receptor agonist

Dosing:

- Each gram contains 10mg tapinarof
- Apply thin layer of cream to affected area once daily
- Not for oral, ophthalmic, or intravaginal use

Adverse Reactions:

Folliculitis (20%), nasopharyngitis (11%), contact dermatitis (7%), headache (4%), pruritus (3%), influenza (2%)

Phase 3 Clinical Trials

N Engl J Med 2021;385:2219-29

- 12-week, MC/R/DB/PC/Parallel group clinical trials
- 2:1 randomization to Tapinarof cream or placebo (vehicle cream) daily
  - Primary efficacy endpoints:
    - PGA (Physician's Global Assessment) response (PGA score 0/Clear or 1/Almost clear) and a decrease from baseline at Week 12:

Clinical Trials	Tapinarof Group	Vehicle Group	Significance
PSOARING 1 (n=510)	35.4% +/- 2.8	6.0% +/- 2.1	P<0.001
PSOARING 2 (n=515)	40.2% +/- 2.8	6.3% +/- 2.0	P<0.001

Vtama [package insert]. Long Beach, CA: Dermavant Sciences, Inc. 2022.

New Diagnostic Agents

Gadopiclenol (Elucirem®)

Xenon Sc 129 Hyperpolarized (Xenoview®)

Gadopiclenol (Elucirem®) P

Indication: For use with MRI to detect lesions with abnormal vascularity

Mechanism of Action: Macrocyclic gadolinium-based contrast agent (GBCA)

Dosing:

- 0.05 mmol/kg body weight IV bolus injection in patients aged 2 years and older

Boxed Warning:

- Risk of nephrogenic systemic fibrosis with GBCAs in patients with impaired renal function

Adverse Reactions:

Injection site pain, headache, nausea, injection site warmth or coldness, dizziness, localized swelling

Phase 3 Clinical Trials

- Two international R/DB/Controlled/Cross-over trials comparing Gadopiclenol 0.05 mmol/kg to Gadobutrol 0.1 mmol.kg
- PICTURE Trial – 256 patients with CNS lesions
  - Patents underwent two MRIs, with Gadopiclenol and Gadobutrol, separated by 2-14 days
  - Results: Gadopiclenol non-inferiority for all parameters (P<0.0001); enhancement percentage and lesion-background ratio were higher with Gadopiclenol for all three readers ((P<0.0001)
- PROMISE Trial – 304 patients with body lesions
  - Lesion visualization scores and number of lesions identified per patient were similar to those for gadobutrol

Elucirem [package insert]. Princeton, NJ: Guerbet LLC. 2022.

Source: *Investigative Radiology* ():10.1097/RLI.0000000000000944, December 19, 2022.

Xenon Sc 129 Hyperpolarized (Xenoview®) FIC

Indication: For use with MRI for evaluation of lung ventilation in patients ≥ 12 years

Mechanism of Action: Hyperpolarized contrast agent prepared from the Xenon Xe129 Gas Blend

Dosing:

- 75-100 mL Dose Equivalent (DE) of hyperpolarized xenon Xe 129 administered by oral inhalation of the entire contents of one dose delivery bag
- Administer dose within 5 min of DE measurement and initiate imaging immediately after inhalation
- Clear, colorless, odorless gas

Warnings:

- Supplemental oxygen administered simultaneously can degrade image quality
- Can cause transient hypoxia in susceptible patients

Adverse Reactions:

Adult patients: oropharyngeal pain, headache, dizziness

Pediatric patients: blood oxygen desaturation, heart rate elevation, numbness, tingling, dizziness, and euphoria

Xenoview [package insert]. Durham, NC: Polarean, Inc. 2022.

Phase 3 Clinical Trials

- Two MC/R/Open-label/Cross-over trials comparing Xenoview MRI to xenon Xe 133 scintigraphy in patients with pulmonary disorders
- Study 1 – 31 patients being evaluated for possible lung resection
  - Analysis: mean within-patient difference in predicted postoperative % of remaining lung ventilation between the two was within pre-specified equivalence interval
- Study 2 – 49 patients being evaluated for possible lung transplant surgery
  - Analysis: mean within-patient difference in percentage of overall lung ventilation was within a pre-specified equivalence interval

Source: https://www.globenewswire.com/news-release/2022/12/28/2580194/0/en/FDA-Approves-Polarean-s-XENOVIEW-xenon-Xe-129-hyperpolarized-for-use-with-MRI-for-the-Evaluation-of-Lung-Ventilation.html

New Medications for Endocrine Disorders

Tirzepatide (Mounjaro®)

Teplizumab-mxwv (Tzield®)

Tirzepatide (Mounjaro®) FIC

Indication:

Improves glycemic control in adults with type 2 diabetes mellitus, as an adjunct to diet and exercise

Mechanism of Action:

Dual agonist of glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor

- Decreases food intake; slows gastric emptying, increases insulin sensitivity; enhances first- and second-phase insulin secretion; and, reduces glycogen levels

Dosing:

- Initial dose: 2.5 mg SQ once weekly into abdomen, thigh or upper arm (rotate site with each dose); can be self-administered
- After 4 weeks, increase to 5 mg SQ once weekly; adjust dosage further in 2.5 mg increments after at least 4 weeks
- Max dose: 15 mg SQ once weekly

Safety Considerations:

- **Boxed Warnings**: risk of thyroid C-cell tumors; contraindicated in patients with history or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome
- Hypoglycemia with concomitant use of insulin or insulin secretagogues
- Delays gastric emptying and may impact the absorption of concomitantly administered oral meds

Most Common Adverse Reactions

- Nausea (12-18%), diarrhea (12-17), decreased appetite (5-11%, vomiting (5-9%), constipation (6-7%), dyspepsia (5-8%), abdominal pain (5-6%)

Mounjaro [package insert]. Indianapolis, IN: Lilly USA, LLC. 2022.

Tirzepatide (Mounjaro®) FIC

Phase 3 Randomized Controlled Trials in Adult Patients with Type 2 Diabetes Mellitus

TrialR/	N	Concomitant Therapy	Duration	Primary Outcome
SURPASS-1 (R/DB/PC)	478	None (treatment naïve patients)	40 weeks	TZP monotherapy 5mg, 10mg and 15 mg signif better than placebo at reducing HbA1c% from baseline; fasting serum glucose, bodweight and HbA1c targets of <7% and less than 5.7%
SURPASS-2 (open-label)	1879	Metformin (patients inadequately controlled on metformin alone)	40 weeks	TZP 5mg, 10mg or 15mg all demonstrating non-inferiority and superiority vs Semaglutide 1mg SQ once weekly in reducing HbA1c from baseline; Reductions in body weight also signif greater with TZP
SURPASS-3 (open-label)	1420	Metformin or Metformin + SGLT2i	52 weeks	TZP 5mg, 10mg or 15mg SQ once weekly demonstrated superiority vs dose-adjusted insulin degludec in reducing HbA1c at week 52 from baseline in insulin-naïve patients
SURPASS-4 (R/MC/OL/PG)	2002 with incre. CV risk	1-3 OAMs of Metformin, SGLT2i or Sulphonylurea medications	52 weeks	TZP 5mg, 10mg or 15mg SQ once weekly provided significant reduction in HB1Ac from baseline vs dose-adjusted insulin glargine; MACE-4 events not significantly different with TZP vs insulin glargine
SURPASS-5 (R/DB/PC)	472	Insulin glargine once daily with or without Metformin	40 weeks	TZP 5mg, 10mg or 15mg SQ once weekly provided significant reduction in HB1Ac from baseline vs placebo

- Obesity - SURMOUNT-1 Phase 3 clinical trial (n=2539) tirzepatide significantly reduced body weight (average loss of 15.0%, 19.5%, and 20.9%, with 5mg, 10mg, and 15mg, respectively) vs. 3.1% with placebo.
- A quick guide to the SURPASS and SURMOUNT trials | diabetes.medicinematters.com

The Lancet. 2021;398(10295):143-155; *N Engl J Med 2021;385:503-515*; *Diabetes 2021;70(Supplement_1):78-LB*; *The Lancet.* 2021;398(10313):1811-1824; *JAMA.* 2022;327(6):534-545; *N Engl J Med* 2022;387:205-16. TZP = tirzepatide; OAM = oral antidiabetic medications

Teplizumab-mzwv (Tzield®) FIC P B

Indication: to delay the onset of Stage 3 type 1 diabetes (T1D) in patients aged 8 years and older with Stage 2 T1D

Mechanism of Action: CD3-directed antibody

Dosing:

- Once daily infusion over at least 30 minutes; dilute in normal saline; 14 days of therapy
  - Day 1: 65 mcg/m2
  - Day 2: 125 mcg/m2
  - Day 3: 250 mcg/m2
  - Day 4: 500 mcg/m2
  - Days 5-14: 1030 mcg/m2
- Premedicate days 1-5 with NSAID or acetaminophen, an antihistamine, and/or an antiemetic

Safety Considerations:

- Teplizumab not recommended if patient's lymphocytes < 1000 lymphocytes/mcL, hemoglobin < 10 g/dL, platelets <150,000, ANC < 1500, elevated ALT or AST > 2 x ULN or bilirubin > 1.5 x ULN; evidence of acute infection with EBV or CMV
- Monitor for cytokine release syndrome, lymphopenia and hypersensitivity reactions

Most Common Adverse Reactions

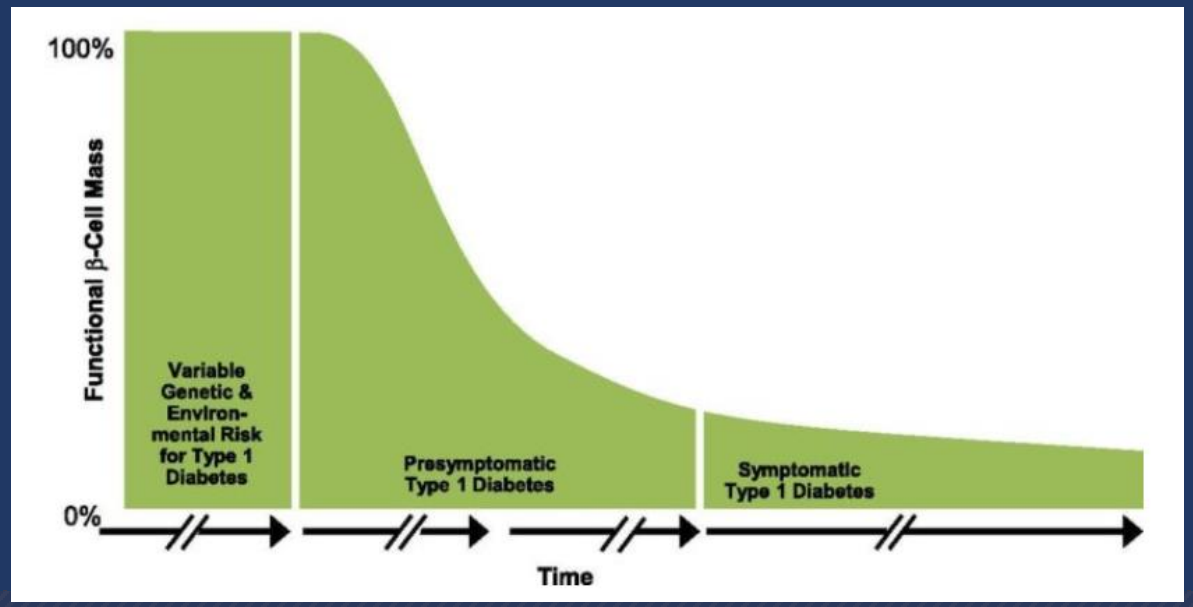
- Lymphopenia (73%)
- Rash (36%)
- Leukopenia (21%)
- Headache (11%)

Tzield [package insert]. Red Bank, NJ: Provention Bio, Inc. 2022.

Teplizumab-mzwv (Tzield®) FIC P B

Stages of Type 1 Diabetes

Stage 1	Stage 2	Stage 3
B-cell autoimmunity Normoglycemia Presymptomatic	B-cell Autoimmunity Dysglycemia Presymptomatic	B-cell autoimmunity Dysglycemia Symptomatic



Diabetes Care 2015;38(10):1964–1974,

Clinical Trials

- At Risk TN-10 Trial
  - *N Engl J Med* 2019;381(7):603-613
  - Conducted by TrialNet – a global network of T1D researchers
  - Phase 2 R/PC/DB trial in 76 relatives of patients with T1D and at high risk (72% ≤ 18 years of age)
  - Results
    - T1D diagnosis median time 48.4 months with teplizumab vs 24.4 months with placebo (P=0.0006)
    - Annualized rates of diagnosis of T1D was 14.9% per year with teplizumab vs 35.9% with placebo
    - Over a median follow-up period of 51 months, stage 3 T1D was diagnosed in 45% of teplizumab patients vs 72% of patients on placebo

New Medication for Gastrointestinal Disease

Vonoprazan/Amoxicillin/Clarithromycin (Voquezna®)

Vonoprazan/Amoxicillin/Clarithromycin (Voquezna®) FIC P

Indication: Treatment of *Helicobacter pylori (H. pylori)* infection in adults

Mechanism of Action: Vonoprazan is a potassium-competitive acid blocker (PCAB)

Dosing:

Triple PaK twice daily 12 hours apart x 14 days: Vonoprazan 20mg, amoxicillin 1000mg, clarithromycin 500mg

Dual PaK: Vonoprazan 20mg twice daily plus amoxicillin 1000mg three times a day x 14 days

Safety Considerations:

- Hypersensitivity and severe cutaneous adverse reactions
- *Clostridioides difficile*-associated diarrhea may occur
- Clarithromycin may be associated with QT prolongation, hepatotoxicity, drug interactions (strong CYP3A inhibitor), embryo-fetal toxicity and exacerbation of myasthenia gravis
- Drug interactions may occur due to reduced gastric acidity

Most Common Adverse Reactions

- Triple Pak: dysgeusia (4.6%), diarrhea (4%), vulvovaginal candidiasis (3.2%), headache (2.6%), abdominal pain (2.3%), hypertension (2%)
- Dual Pak: diarrhea (5.2%), abdominal pain (2.6%), vulvovaginal candidiasis (2%), nasopharyngitis (2%), headache (1.4%)

Vonoprazan/Amoxicillin/Clarithromycin (Voquezna®) FIC P

Phase 3 Clinical Trial

***Gastroenterology* 2022;163:608–619**

- 1046 patients with treatment-naïve *H. pylori* infection confirmed by positive ^{13}C-urea breath test
  - 14 days of treatment
    - Open-label Vonoprazan dual therapy –Vonoprazan 20mg twice daily, amoxicillin 1g 3 times daily
    - Double-blind triple therapy – either Vonoprazan 20mg or Lansoprazole 30mg, plus amoxicillin 1g, clarithromycin 500mg, all twice daily
- Results
  - Patients without clarithromycin or amoxicillin resistant strains:
    - Dual therapy (78.5%) and Vonoprazan Triple therapy (84.7%) non-inferior to Lansoprazole Triple therapy (78.8%) in 4-week post-treatment eradication rates
  - Patients with clarithromycin-resistant strains
    - Dual therapy (69.6%) and Vonoprazan Triple therapy (65.8%) superior to Lansoprazole Triple therapy (31.9%) in 4-week post-treatment eradication rates
  - All patients
    - Dual therapy (77.2%) and Vonoprazan Triple therapy (80.8%) superior to Lansoprazole Triple therapy (68.5%) in 4-week post-treatment eradication rates

H. pylori Treatment Options

- Clarithromycin triple therapy – PPI, clarithromycin, amoxicillin (or metronidazole if amoxicillin allergy)
  - 14 days of therapy
  - Only use if clarithromycin resistance is known to be < 15%
- Bismuth quadruple therapy – PPI or histamine-2 receptor antagonist, bismuth, metronidazole, and tetracycline
  - 10-14 days
  - Preferred regimen in areas with clarithromycin resistance or penicillin allergy
- Concomitant therapy – PPI, amoxicillin, clarithromycin, and a nitroimidazole (tinidazole or metronidazole)
  - 10-14 days
  - For patients with bismuth intolerance
- Sequential therapy – PPI and amoxicillin for 5-7 days, then PPI, clarithromycin, and a nitroimidazole for 5-7 additional days
- Hybrid therapy – PPI and amoxicillin for 7 days, then PPI, amoxicillin, clarithromycin, and a nitroimidazole for 7 days
- Levofloxacin-based triple therapy – PPI, levofloxacin, and amoxicillin for 114 days
- Fluoroquinolone sequential therapy – PPI and amoxicillin for 5-7 days, then PPI, fluoroquinolone and a nitroimidazole for 5-7 days

Voquesna [package insert]. Buffalo Grove, IL: Phathom Pharmaceuticals, Inc. 2022; *Amer J Gastroenterol* 2017;112(2):212-239;

New Medications for Genetic Diseases

Vutrisiran (Amvuttra®)

Olipudase alfa (Xenpozyme®)

Vutrisiran (Amvuttra®) O

Indication: treatment of polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis in adults

Mechanism of Action: a transthyretin-directed small RNA interference agent

Dosing:

- 25mg by subcutaneous injection every 3 months
- Administration is by a healthcare professions

Safety Considerations:

Reduced serum Vitamin A levels may occur

- Supplement with recommended daily allowance of Vitamin A
- Refer to ophthalmologist if ocular symptoms of Vitamin A deficiency occur

Most Common Adverse Reactions

- Pain in extremities (15%)
- Arthralgia (11%)
- Dyspnea (7%)
- Reduced level of Vitamin A (7%)

Amvuttra [package insert]. Cambridge, MA: Alnylam Pharmaceuticals, Inc. 2022.

Vutrisiran (Amvuttra®) O

Polyneuropathy of hATTR Amyloidosis

Peripheral sensory, motor, and/or autonomic nerves affected

- Degeneration and dysfunction of the nerves
- Altered sensation, difficulty walking, carpal tunnel syndrome, weight loss, orthostatic hypotension and falls

Treatments to suppress production of TTR in liver

- Orthotopic liver transplant –removes primary source of variant TTR
- Patisiran (Onpatrro®) - small interfering ribonucleic acid (siRNA) that prevents production of TTR protein
- Inotersin (Tegsedi®) - transthyretin-directed antisense oligonucleotide prevents production of TTR protein

HELIOS-A Clinical Trial

Amyloid 2022;30(1):109-118

- Phase 3 global, open-label trial comparing vutrisiran with external placebo (n=77) group in APOLLO study
  - Adults (n=164) with documented TTR variant and neuropathy
  - 3:1 randomization to vutrisiran (n=122) 25mg SC every 3 months or patisiran (n=42) 0.3mg/kg IV every 3 weeks
  - Outcomes:
    - Change in neuropathy from baseline to 9 months was signif improved for vutrisiran vs placebo
    - Signif improvement in QOL, 10-meter walk test and other secondary endpoints with vutrisiran vs placebo
    - Primary and secondary endpoints, TTR reduction non-inferior with vutrisiran vs patisiran

Olipudase alfa (Xenpozyme®) FIC O P B

Indication: treatment of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients without CNS manifestations of the disease

Mechanism of Action: hydrolytic lysosomal sphingomyelin-specific enzyme for replacement

Dosing:

- Starting dose
  - Adults: 0.1 mg/kg IV infusion
  - Pediatrics: 0.03 mg/kg IV infusion
  - Use adjusted body weight if BMI ≥ 30
- Maintenance dose: 3 mg/kg IV infusion every 2 weeks
- Dose escalation through week 14 (week 16 for pediatric patients) with doses every 2 weeks

Safety Considerations:

- Boxed warning: severe hypersensitivity reactions; have support measures available during infusion
- Possible infusion associated reactions, elevated transaminases, fetal malformations
- Pretreat with antihistamines, antipyretics, and/or corticosteroids to prevent severe hypersensitivity reactions
- Obtain baseline transaminase levels and pregnancy test for female patients of child-bearing age

Most Common Adverse Reactions

- Adult patients: headache (54%), cough (31%), diarrhea (15%), hypotension (15%), ocular hyperemia (15%)
- Pediatric patients: pyrexia (100%), cough (75%), diarrhea (75%), rhinitis (75%), abdominal pain (63%), vomiting (50%), headache (50%), urticaria (50%), nausea (38%), rash (38%), arthralgia (38%), pruritus (25%), fatigue (25%), pharyngitis (25%)

Xenpozyme [package insert].Cambridge, MA: Genzyme Corporation. 2023.

Olipudase alfa (Xenpozyme®) FIC O P B

Acid Sphingomyelinase Deficiency (ASMD)

Lysosomal storage disease

- Autosomal recessive disease – rare, progressive and often fatal disease
- Genetic variant results in reduced activity of the enzyme acid sphingomyelinase (ASM)
  - Intra-lysosomal accumulation of sphingomyelin, cholesterol and other lipids in tissues
  - Interstitial lung disease, pulmonary dysfunction, splenomegaly, hepatomegaly, dyslipidemia, thrombocytopenia, anemia

Treatments

- Supportive care
- Olipudase alfa is first treatment - provides an exogenous source of ASM

Clinical Trials

- ASCEND trial – M/R/DB/PC Phase 2/3 *Genet Med* 2022; Jul;24(7):1425-1436
  - 52-week primary analysis period
    - 31 adult patients, median age 34 years
    - Olipudase alfa significantly improved mean % predicted diffusion capacity of the lungs for carbon monoxide, and reduced spleen volume vs placebo
- ASCEND-Peds trial – MC/OL Phase 1/2 *Genet Med* 2021 Aug;23(8):1543-1550
  - 64-week
    - 20 patients, age range 1-17 years
    - Olipudase alfa provided significant improvements in mean % predicted diffusion capacity of the lungs for carbon monoxide, reduced spleen and liver volumes, platelet count and linear growth compared to baseline
- Open-label extension trials for both continued to show improvements

New Medication for Kidney Disease

Terlipressin (Terlivaz®)

Terlipressin (Terlivaz®) FIC O P

Indication: treatment of adults with hepatorenal syndrome and rapid reduction in kidney function

Mechanism of Action: vasopressin receptor agonist

Dosing:

- Days 1-3: 0.85 mg IV every 6 hours
- Day 4: assess SCr vs baseline
  - if at least 30% reduction in SCr, continue 0.85 mg IV every 6 hours
  - If decreased less than 30%, increase dose to 1.7 mg every 6 hours
  - If at or above baseline, d/c terlipressin
  - Continue until 24 hours after two consecutive SCr values < 1.5 mg/dL
- Patients with SCr > 5 mg/dL are unlikely to benefit from terlipressin

Safety Considerations:

- Boxed warning – may cause severe or fatal respiratory failure especially in patients with volume overload or acute-on-chronic-liver failure grade 3
- Avoid in patients with hypoxia or worsening respiratory symptoms
- Avoid in patients with ongoing coronary, peripheral or mesenteric ischemia

Most Common Adverse Reactions

- Abdominal pain (19.5%)
- Nausea (16%)
- Respiratory failure (15.5%)
- Diarrhea (13%)
- Dyspnea (12.5%)

Terlivaz [package insert].Bedminster, NJ: Mallinckrodt Hospital Products, Inc.. 2022.

Terlipressin (Terlivaz®) FIC O P

CONFIRM Clinical Trial

N Engl J Med 2021;384:818-28

- MC/DB/R/PC Phase 3 study; 2:1 randomization; max 14 days of treatment
- 300 patients with hepato-renal syndrome with rapidly progressive worsening in renal function (HRS-AKI)
- Most patients in the trial also received albumin (83% with terlipressin; 91% with placebo)
- Results
  - Primary efficacy endpoint - 29.1% with terlipressin had 2 consecutive SCr values of ≤ 1.5 mg/dL obtained at least 2 hours apart by Day 14 or discharge vs 15.8% with placebo (P=0.012)
  - Durability of reversal – 31.7% with terlipressin vs 15.8% with placebo (P=0.003)
  - Incidence of reversal without recurrence by day 30 – 24.1% with terlipressin vs 15.8% with placebo (P=0.092)
- Safety endpoints have led to some controversy
  - Death by 90 days: 51% with terlipressin; 45% with placebo
  - Respiratory failure: 10% with terlipressin; 3% with placebo

Place in Therapy

- Hepatorenal syndrome type 1 (HRS-1) is a form of acute kidney injury (AKI) in cirrhosis; 3-month survival is 20-40%
- Terlipressin has been in use in EU for 30 years
- HRS management in U.S.
  - Vasoconstrictors (off-label use prior to terlipressin)
  - Albumin
  - Renal replacement therapy
  - Liver transplantation
- U.S. Society Guidelines have added terlipressin for medical management of HRS-AKI
  - ACG – terlipressin (or norepinephrine) suggested for hospitalized patients with cirrhosis and HRS-AKI without high grade of acute on chronic liver failure (ACLF) or major cardiopulmonary of vascular disease
  - AASLD – terlipressin is preferred vasoconstrictor in combination with albumin to treat HRS-AKI

New Medications for Neurological and Neuromuscular Disorders

Ublituximab-xiiy (Briumvi®)
Sodium Phenylputyrate and Taurursodiol (Relyvrio®)
Daridorexant (Quviviq®)
Ganaxolone (Ztalmy®)

Ublituximab-xiiv (Briumvi®)

Indication: treatment of relapsing forms of multiple sclerosis in adults (e.g., clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease)

Mechanism of Action: CD20-directed cytolytic recombinant monoclonal antibody

Dosing:

- First Dose: 150mg by IV infusion
- Second Dose: 450mg IV infusion 2 weeks after first dose
- Subsequent Doses: 450 mg IV infusion 24 weeks after first dose and then every 24 weeks
- Screen for Hepatits B and serum immunoglobulins prior to first dose
- Premedicate with corticosteroid and an antihistamine prior to each infusion

Safety Considerations:

- Contraindicated with active Hepatitis B infection
- Infusion reactions - Monitor for infusion reactions for at least 60 minutes after first 2 infusions
- Serious infections, and reductions in immunoglobulins may occur
- Vaccines should be administered 4 weeks (live vaccines) or 2 weeks (non-live) before treatment
- Can cause fetal harm

Most Common Adverse Reactions

- Infusion reactions (48%)
- Upper respiratory tract infections (45%)

Briumvi [package insert].Morrisville, NC: TG Therapeutics, Inc. 2022.

Ublituximab-xiiv (Briumvi®)

ULTIMATE I and II Trials

N Engl J Med 2022;387(8):704-714

- 2 identical DB/DD/R Phase 3 trials
- 1:1 randomization: IV ublituximab (Day 1:150mg; then 450mg IV on Day 15 and at weeks 24, 48 and 72) vs oral placebo or oral teriflunomide (14mg once daily) and IV placebo

	Primary End Point	Ublituximab	Teriflunomide	P Value
ULTIMATE I (n=545)	Adj annualized relapse rate (95% CI)	0.08 (0.04 to 0.14)	0.19 (0.12 to 0.28)	
	Rate ratio (95% CI)	0.41 (0.27 to 0.62)		< 0.001
ULTIMATE II (n=544)	Adj annualized relapse rate (95% CI)	0.09 (0.05 to 0.17)	0.18 (0.11 to 0.29)	
	Rate ratio (95% CI)	0.51 (0.33 to 0.78)		0.002

Place in Therapy

Disease-modifying therapies for multiple sclerosis

- Monoclonal antibodies (considered most effective)
  - Natalizumab
  - Ocrelizumab
  - Rituximab
  - Ofatumumab
  - Alemtuzumab
  - Ublituximab
- Oral therapies – Fumarates, Sphingosine 1-phosphate receptor modulators, Teriflunomide, Cladribine
- Injectable therapies – recombinant human interferon beta-1b, recombinant human interferon beta-1a, Glatiramer acetate

Sodium Phenylbutyrate and Taurursodiol (Relyvrio®) O P

Indication: treatment of amyotrophic lateral sclerosis (ALS) in adults

Mechanism of Action: prevents nerve cell death by blocking stress signals within mitochondria and endoplasmic reticulum

Dosing:

- 1 packet orally daily for first 3 weeks then 1 packet twice daily
  - 1 packet contains 3 g sodium phenylbutyrate and 1 g taurursodiol
- Empty packet into 8 ounces of room temp water and take within 1 hour of preparation
  - Administer before a snack or meal

Safety Considerations:

- High sodium content
- Drug interactions
  - Avoid concomitant use of bile acid sequestering agents or transporters, aluminum-based antacids, probenecid, phenylbutyrate, OATP1B3 inhibitors
  - Avoid drugs that are substrates for OAT1, PgP, BCRP, CYP450 isoenzymes and have a narrow therapeutic index
- Patients with enterohepatic circulation disorders, pancreatic disorders or intestinal disorders may have decreased absorption of the medication

Most Common Adverse Reactions

- Diarrhea (25%)
- Abdominal pain (21%)
- Nausea (18%)
- Upper respiratory infections (18%)

Relyvrio [package insert].Cambridge, MA: Amylyx Pharmaceuticals.. 2022.

Sodium Phenylbutyrate and Taurursodiol (Relyvrio®) O P

CENTAUR Trial

N Engl J Med 2020;383(10):919-930

- MC/R/DB/PC Phase 2 trial conducted at 25 centers of the Northeast Amyotrophic Lateral Sclerosis Consortium
- 2:1 randomization: PO 3g sodium phenylbutyrate and 1g taurursodiol or placebo mixed in water and taken daily x 3 weeks, then twice daily to complete 24 weeks of treatment
- Outcomes (n=135)
  - Mean change in rate of decline of Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised score with active drug (-1.24 per month) was significantly less than with placebo (-1.66 per month) (P=0.03)
  - 0.53 Cumulative hazard ratio (death, tracheostomy, hospitalization) with active drug vs placebo
  - GI adverse events (nausea, diarrhea, abdominal pain) more frequent with active drug than placebo in first 3 weeks

Place in Therapy

ALS – disorder of motor neuron degeneration leading to progressive muscle weakness

- Median survival is 3-5 years from symptom onset; 10-20% survive > 10 years
- Most common cause of death – respiratory failure

FDA approved disease modifying treatments

- Riluzone (Rilutek®, Tiglutik®, Exservan®) - oral, thickened oral solution, and oral film
- Edaravone (Radicava®) – IV, PO

Investigational treatments

- Stem cell therapy
- Gene therapy

Daridorexant (Quviviq®)

Indication: insomnia in adults with difficulties in sleep onset and/or sleep maintenance

Mechanism of Action: dual orexin receptor antagonist

Dosing:

- 25 – 50 mg orally once nightly within 30 minutes of bedtime and at least 7 hours prior to planned awakening
  - If taken with food, sleep onset may be delayed
- Hepatic impairment
  - 25mg recommended as highest dose with moderate hepatic impairment
  - Not recommended with severe hepatic impairment
- Drug interactions
  - Avoid concomitant use of CYP3A4 inhibitors or moderate/strong CYP3A4 inducers

Safety Considerations:

- Schedule IV controlled substance
- CNS depressant effects and impaired alertness may continue the morning after taking
- Worsening of depression and suicide ideation may occur
- Sleep paralysis, sleep-related hallucinations, cataplexy-like symptoms may occur
- Discontinue if complex sleep behaviors occur – sleepwalking, sleep driving, etc.

Most Common Adverse Reactions

- Headache (6-7%)
- Somnolence or fatigue (5-6%)

Quviviq [package insert].Radnor, PA: Idorsia Pharmaceuticals US Inc. 2023.

Daridorexant (Quviviq®)

Phase 3 Trials

Lancet Neurol 2022;21:125-139

- Two MC/R/DB/PC trials conducted at 156 centers in 18 countries
- 1:1:1 randomization: oral dosing every evening x 1 month
  - Study 1: 50mg daridorexant, 25mg daridorexant, or placebo
  - Study 2: 25mg daridorexant, 10mg daridorexant, or placebo
- Outcomes at Months 1 and 3
  - Study 1 (n=930) – Latency to Persistent Sleep (LPS) and Wake After Sleep Onset (WASO) were significantly improved for 25mg and 50mg daridorexant vs placebo
  - Study 2 (n=924) – LPS and WASO were only significantly improved over placebo with the 25mg daridorexant dose

Place in Therapy

1. Benzodiazepine receptor agonists
   a. Non-benzodiazepines - eszopiclone, zaleplon, zolpidem
   b. Benzodiazepines – estazolam, flurazepam, temazepam, triazolam, quazepam
2. Dual orexin receptor antagonists
   a. Lemborexant (Dayvigo®)
   b. Suvorexant (Belsomra®)
   c. Daridorexant
3. Histamine receptor antagonists - Low-dose doxepin
4. Melatonin receptor agonists - Ramelteon

Ganaxolone (Ztalmy®) FIC O P

Indication: treatment of seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in patients 2 years of age and older

Mechanism of Action: neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator

Dosing:

- Available as oral suspension 50 mg/mL
- Dosage for patients ≤ 28 kg
  - Starting dose: 6 mg/kg orally three times daily; titrate gradually
  - Max dose: 21 mg/kg three times daily
- Dosage for patients > 28 kg
  - Starting dose: 150 mg three times daily
  - Max dose: 600 mg three times daily
- Take with food

Safety Considerations:

- Schedule 5 controlled substance
- Monitor for somnolence and sedation
- Drug interactions – avoid concomitant use of moderate or strong CYP3A4 inducers
- Monitor for suicidal behavior and ideation
- Withdraw gradually to avoid risk of increased seizure activity

Most Common Adverse Reactions

- Somnolence (38%)
- Pyrexia (18%)
- Upper respiratory tract infection (10%)
- 22% of patients interrupted dosing or reduced dosage due to adverse effects vs 18% of patients on placebo

Ztalmy [package insert].Radnor, PA: Marinus Pharmaceuticals, Inc.. 2022.

Ganaxolone (Ztalmy®) FIC O P

Marigold Trial

***Lancet Neurol* 2022;21(5):417-427**

- MC/R/DB/PC Phase 3 trial conducted at 39 outpatient clinics in 8 countries in CDD patients ages 2-21 years
- 1:1 randomization: ganaxolone or placebo three times a day to complete 17 weeks of treatment
- Outcomes (n=101)
  - Median change in 28-day major motor seizure frequency was -30.7% with ganaxolone vs -6.9% with placebo (p=0.0036)
  - Treatment-emergent adverse events occurred at similar rates with active drug and placebo

What is CDKL5 Deficiency Disorder?

- CDKL5 genetic mutations lead to deficient proteins essential for normal brain development
- Approx 1200 cases worldwide
- Refractory seizures beginning in infancy
- Severe impairment in neurologic development
- Affected children can't walk, talk or care for themselves
- Disease modifying treatments are in development

From: Amicus Therapeutics Corporate Overview, Sept 2016

New Medications for Eye Diseases

Omidenepag isopropyl ophthalmic solution (Omlonti®)
Faricimab-svoa(Vabysmo®)

Omidenepag isopropyl ophthalmic solution (Omlonti®)

Indication: to reduce elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Mechanism of Action: prostaglandin E2 (EP2) receptor agonist

Dosing:

- One drop of 0.002% solution in affected eye once daily in the evening

Safety Considerations:

- Can cause increased pigmentation of the iris, periorbital tissue and eyelashes; eyelash changes; ocular inflammation; and, macular edema

Most Common Adverse Reactions

- Conjunctival hyperemia (9%), photophobia (5%), vision blurred (4%), dry eye (3%), instillation site pain (3%), eye pain (2%), ocular hyperemia (2%), punctate keratitis (2%), headache (2%), eye irritation (1%), and visual impairment (1%)

Phase 3 trials: omidenepag isopropyl reduced IOP from 5-7 mm Hg in three 3-month, double-masked trials (average baseline IOP 24-26 mm Hg) while timolol and latanaprost arms reduced IOP 5-7 mm Hg and 6-8 mm Hg, respectively

Omlonti [package insert].Emeryville, CA: Santen Inc.. 2022.

Faricimab-svoa (Vabysmo®)

Indication: Neovascular (Wet) age-related macular degeneration (nAMD) and diabetic macular edema (DME)

Mechanism of Action: vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) bispecific antibody

Dosing:

nAMD: 6 mg (0.05 mL) by intravitreal injection every 4 weeks x 4 doses

- Conduct optical coherence tomography and visual acuity evaluations 8 and 12 weeks after last dose
- Additional doses (8, 12 or 16 week intervals) to be given based on assessment results

DME: two dosing options

1. 6 mg by intravitreal injection every 4 weeks x at least 4 doses
    - Conduct optical coherence tomography and visual acuity evaluations to guide further dosing
2. 6 mg every 4 weeks x 6 doses, then 6 mg every 8 weeks

Safety Considerations:

- Intravitreal injections can lead to endophthalmitis and retinal detachment
- Intraocular pressure may increase transiently beginning within 60 minutes of injection
- Risk of arterial thromboembolic events with VEGF inhibition

Most Common Adverse Reactions

- Cataracts (15%)
- Conjunctival hemorrhage (8%)

Vabysmo [package insert].South San Francisco, CA: Genentech, Inc.. 2023.

Faricimab-svoa(Vabysmo®)

nAMD Clinical Trials

***Lancet* 2022;399(10326):729-740**

- TENAYA (n=334) and LUCERNE (n=337) Phase 3 trials - identical Global/MC/R/Parallel-group/Double-masked non-inferiority trials in treatment naïve patients
- Primary trial outcomes - Mean change in BCVA (best-corrected visual acuity) from baseline averaged over weeks 40, 44, and 48 was non-inferior for faricimab 6 mg up to Q16W versus aflibercept 2 mg Q8W

Table 1 FDA Approved Anti-VEGF Medications for Wet AMD

Medication	Dosage	Maximum Approved Interval	Mechanism of Action
Pegaptanib*	0.3 mg/ 90mcl	Q6weeks	Pegylated aptamer that binds to VEGF165
Bevacizumab**	1.25 mg /0.05 mL	Q4weeks	Monoclonal antibody that binds to VEGF-A
Ranibizumab	0.5 mg/ 0.05 mL	Q4weeks	Monoclonal antibody fragment that binds to VEGF-A
Aflibercept	2 mg/ 0.05 mL	Q8weeks	Fusion protein that that binds to VEGF-A, VEGF-B, and placental growth factor
Brolucizumab	6 mg/ 0.05 mL	Q12weeks	Humanized, single-chain variable fragment that three major isoforms of VEGF-A (VEGF 110, VEGF 121, and VEGF 165)
Faricimab	6 mg/ 0.05 mL	Q16weeks	Bispecific monoclonal antibody that inhibits both VEGF-A and angiopoietin 2 (Ang-2)

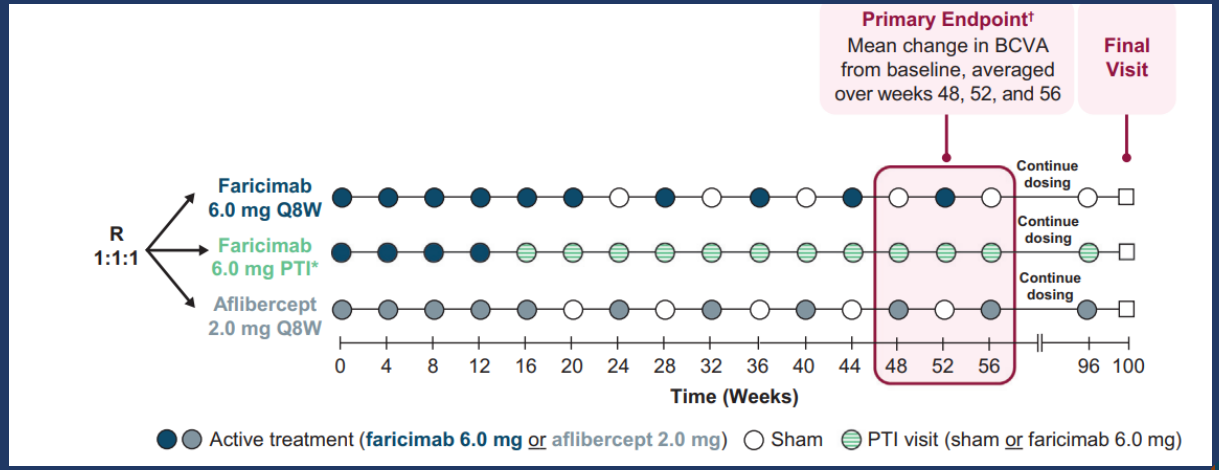
Notes: *No longer commercially available in the US. **Not FDA approved but used commonly in retina practices based on the CATT trial.

From: *Drug Design, Development and Therapy* 2022:16 3395–3400

DME Clinical Trials

***Lancet* 2022;399(10326):741-755**

- YOSEMITE (n=940) and RHINE (n=951) Phase 3 trials - identical Global/MC/R/Parallel-group/Double-masked non-inferiority trials



- Primary outcome – BCVA (best corrected visual acuity) difference from baseline to 1 year was non-inferior with faricimab every 8 weeks or PTI (personalized treatment interval) versus aflibercept every 8 weeks

New Oncology Medications

New Oncology Medications – Injectable Biologics

Generic Name	Trade Name	Drug Class	Indication(s)
Mirvetuximab soravtansine-gynx	Elahere O FIC P	Antibody-drug conjugate: folate receptor alpha (FRalpha) directed antibody and microtubule inhibitor conjugate	Epithelial ovarian, fallopian tube, or primary peritoneal cancer that is FRalpha positive, platinum resistant, and after 1-3 prior systemic treatments
Tremelimumab-actl	Imjudo O	Cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody	1) Unresectable hepatocellular carcinoma, in combination with durvalumab (Imfinzi®), a PD-L1 inhibitor 2) Metastatic non-small cell lung cancer, in combination with durvalumab and platinum-based chemotherapy
Tebentafusp-tebn	Kimmtrak O FIC B P	Bispecific gp100 peptide-HLA-directed CD3 T-cell engager	Uveal melanoma that is is unresectable or metastatic, in adult patients who are HLA-A*02:01 positive

New Oncology Medications - Biologics

Generic Name	Trade Name	Drug Class	Indication(s)
Mosunetuzumab -axgb	Lunsumio O FIC B P	Bispecific CD20-directed CD3 T-cell engager	Follicular lymphoma that is relapsed/refractory, and patient has had at least 2 lines of systemic therapy
Nivolumab and relatlimab-rmbw	Opdualag O FIC P	Programmed death receptor-1 blocking antibody (nivolumab) and lymphocyte activation gene-3 blocking antibody (relatlimab)	Advanced melanoma that is unresectable or metastatic, in patients 12 years and older
Eflapegrastim-xnst	Rolvedon	Recombinant human granulocyte growth factor	To decrease incidence of infection and febrile neutropenia in adult patients with non-myeloid cancers, receiving myelosuppressive drugs associated with significant incidence of febrile neutropenia
Teclistamab-cqyv	Tecvayli REMS	Bispecific B-cell maturation agent (BCMA)-directed	Multiple myeloma, relapsed or refractory, after at least 4 prior lines of therapy

Other New Oncology Medications

Generic Name	Trade Name	Drug Class	Indication(s)
Adagrasib	Krazati O B	RAS GTPase inhibitor	Non-small cell lung cancer that is KRAS G12C-mutated locally advanced or metastatic, in adult patients who have received at least one prior systemic therapy
Futibatinib	Lytgobi O B P	Kinase inhibitor	Intrahepatic cholangiocarcinoma that is previously treated, unresectable, locally advanced or metastatic, and harbors fibroblast growth receptor 2 gene fusions
Lutetium (177Lu) vipivotide tetraxetan	Pluvicto FIC B P	Radioligand therapeutic agent	Prostate cancer that is metastatic, castration-resistant, and positive for prostate-specific membrane antigen
Olutasidenib	Rezlidhea O	Isocitrate dehydrogenase-1 (IDH1) inhibitor	Acute myeloid leukemia in adults, that is relapsed or refractory, and with susceptible isocitrate dehydrogenase-1 mutation

Notable CBER Drug Approvals in 2022

CBER Drug Approvals

- FDA Center for Biologics Evaluation and Research
  - Regulates biological products
    - Vaccines, blood and blood products, and cells, tissues, and gene therapies for prevention, treatment and diagnosis
  - Biologics license application (BLA)
- Human gene therapies
  - Replace a disease-causing gene with a healthy copy of the gene
  - Inactivate a disease-causing gene
  - Introduce a new or modified gene to help treat a disease
- Gene therapies include viral vectors, human gene editing technology, patient-derived cellular gene therapy products
  - CAR T-cell immunotherapy (Chimeric antigen receptor T-cells)

Notable CBER Drug Approvals

Generic Name	Trade Name	Drug Class	Indication(s)
Nadofaragene firadenovec-vncg	Adstiladrin	Non-replicating adenoviral vector-based gene therapy	Bladder cancer that is BCG-unresponsive, non-muscle invasive, and with carcinoma in situ with or without papillary tumors
Ciltacabtagene autoleucel	Carvykti	B-cell maturation antigen (BCMA) directed genetically modified autologous T cell immunotherapy	Multiple myeloma that is relapsed/refractory after 4 or more lines of therapy
Etranacogene dezaparvovec-drib	Hemgenix	Adeno-associated virus vector-based gene therapy	Hemophilia B

Notable CBER Drug Approvals

Generic Name	Trade Name	Drug Class	Indication(s)
Elivaldogene autoleucel	Skysona	Cell suspension	To slow progression of neurologic dysfunction in boys 4-17 years old with early, active cerebral adrenoleukodystrophy
Betibeglogene autotemcel	Zynteglo	Autologous hematopoietic stem cell-based gene therapy	Beta-thalassemia in adult and pediatric patients who require regular red blood cell transfusions
Fecal microbiota, live-jslm	Rebyota	Fecal microbiota	Prevention of recurrence of *Clostridioides difficile* infection (CDI) in adults following antibiotic treatment for recurrent CDI

Learning Assessment Questions

Question 1

- Which one of the following is true regarding new medications with REMS programs?

A. 10 new medications approved in 2022 have REMS programs
B. Mavacamten (Camzyos®) is only available through a REMS program to allow for regular monitoring of heart function, concomitant medications, etc.
C. Terlipressin (Terlivaz®) is only available through a REMS program to make sure it is only used for patients with hepatorenal syndrome and rapid reduction in renal function
D. DaxibotulinumtoxinA-lanm (Daxxify®) is only available through a REMS program to monitor for life-threatening swallowing and breathing difficulties

Question 2

- Which of the following is correct regarding the new medications of 2022?

A. There were only 2 new oncology medications approved in 2022
B. 5 of the 37 new medications approved through CDER were monoclonal antibodies
C. More than half of the new drugs approved in 2022 were orphan drugs
D. Nearly all of the new drugs of 2022 were priority review and breakthrough drugs

Question 3

- Which of the following statements is FALSE regarding new gene therapies?

A. CAR T-cell therapies are gene therapies approved by FDA's Center for Biologics Evaluation and Research

B. Gene therapies are inexpensive treatments that are easy to administer

C. Gene therapies are primarily used for cancers and genetic diseases

D. Early adoption of gene therapies is hampered by getting payers on board, risk-benefit of the drugs, and uncertain safety concerns

Question 4

- Which one of the following new drugs and indications is NOT CORRECT?

A. Lenacapavir (Sunlenca®) – multi-drug resistant HIV
B. Gadopiclenol (Elucirem®) – contrast agent for MRI
C. Tirzepatide (Mounjaro®) – Type 2 diabetes
D. Ublituximab-xiiv (Briumvi®) - insomnia

Question 5

- Which one of the following orphan drugs and indications is NOT CORRECT?

A. Sutimlimab-jome **(Enjaymo®)** – hemolysis with Cold Agglutinin Disease
B. Sodium Phenylbutyrate and Taurursodiol (Relyvrio®) – generalized pustular psoriasis (GPP) flares
C. Ganaxolone (Ztalmy®) – seizures with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD)
D. Vutrisiran (Amvuttra®) - polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis

Thank you for your Attention!

Questions?

Elizabeth A. Shlom, PharmD, MBA, BCPS
lizshlom@yahoo.com