MARCH 2023

NYS-ACCP Newsletter

VOLUME 9 | ISSUE 9

UNIVERSITY AT BUFFALO SCHOOL OF PHARMACY AND PHARMACEUTICAL SCIENCES

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Dr Collin Clark
PharmD, BCPS, BCGP

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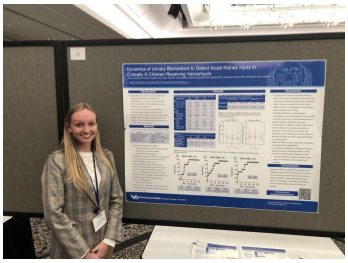
Dinner & Discussion

The SCCP E-Board held Dinner and Discussions with Dr. Maya Chilbert and Dr. Collin Clark over the past school year. Students gathered to hear Dr. Chilbert's and Dr. Clark's clinical experiences, pathway to pharmacy and advice on pharmacy school. This was a great opportunity for students to learn more about post-graduate training and career options through UB Pharmacy!

Journal Club Discussions

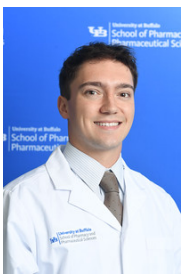
Liaisons Christina Cheng PharmD Candidate, Class of 2024 and Elisabeth Milk, PharmD Candidate, Class of 2025 and faculty advisor Dr. Calvin Meaney held several journal clubs to bring students together and discuss research. Journals included "**A Cluster-Randomized Trial of Blood-Pressure Reduction in Black Barbershops**" where accessibility to blood pressure management proved its value, "**The Role of Tirzepatide, Dual GIP and GLP-1 Receptor Agonist, in the Management of Type II Diabetes; the SURPASS Clinical Trials**" where tirzepatide was discussed as a new diabetes treatment, and "**Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC)**" where we conferred a shorter CAP treatment duration was non-inferior. We improved biostatistics, drug literature evaluation, and residency skills.

ACCP National Conference 2022 San Fran, CA



Autumn Spyhalsky PharmD/MS Candidate, Class of 2024, (pictured left) won the best student poster award at the ACCP Global Conference on Clinical Pharmacy in San Francisco, CA. Her poster titled 'Dynamics of Urinary Biomarkers to Detect Acute Kidney Injury in Critically Ill Children Receiving Vancomycin.' Her conclusions found that during the first 72 hours of vancomycin exposure in pediatric ICU patients, two specific biomarkers concentrations (being uNGAL and uKIM-1) were increased in those experiencing AKI compared to those that were not. These findings serve as a possible avenue to monitor and predict AKI incidence in future PICU patients.

Christina Cheng, PharmD Candidate, Class of 2024 (pictured right, third from the left), P3 liaison was appointed as a member at large for the ACCP National Student Network Advisory Committee. Her responsibilities consist of; reviewing and updating the ACCP student chapter guide, reviewing and editing student-related content on the ACCP website, and communicating any concerns or perspectives to the board of regents.

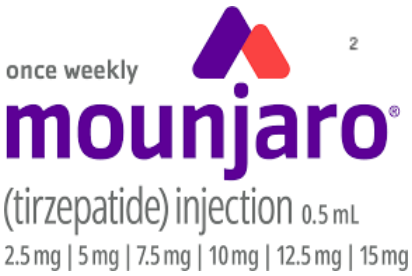


Clinical Research Challenge 2023

Austin Grzechowiak (left), Charly Schmitz (middle) and Nicole Kaym (right), all PharmD Candidates Class of 2026, passed the first round of the clinical skills competition. They are writing their letter of intent on clinical oncology for the second round!

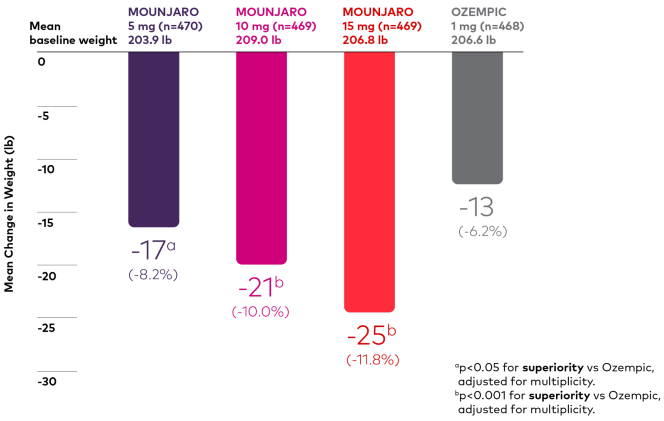
Jessica Weaver, PharmD Candidate, Class of 2024
Alexander Leidolf, PharmD Candidate, Class of 2024

Diabetes Guideline Update & Mounjaro



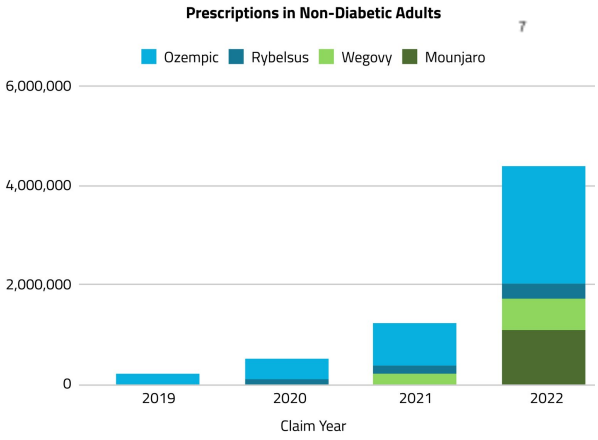
Mounjaro - How it Works

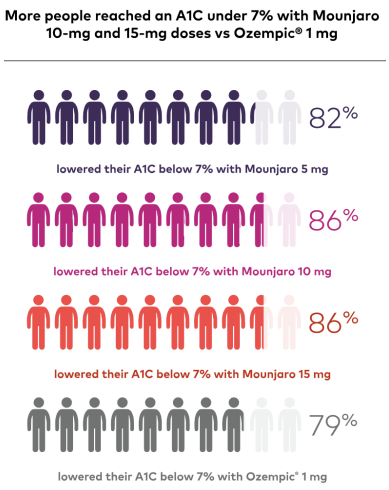
In May 2022, the FDA approved tirzepatide. This is a peptide-hormone with activity at both glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. It is the first dual GIP/GLP-1 receptor agonist to become available in the US and is indicated to improve glycemic control in adults with type 2 diabetes.[1]



Studies

Tirzepatide has also shown promising results when used for weight management in patients without diabetes; nevertheless, it has not yet received approval for this indication. In the SURPASS-1 trial, tirzepatide showed an average HbA1c reduction of 1.7% compared to placebo with more than 78% of patients achieving an HbA1C of less than 7%. In addition, average weight loss was also significant at the end of the 40 weeks at an average of 6.3-7.8 kg per patient.[3] Regarding competing injectables, semaglutide (Wegovy) was recently approved for chronic weight management, having demonstrated 10% placebo-subtracted weight loss, and qualifies as the first second-generation obesity medication which can also be used in non-diabetics. Because tirzepatide was found to induce superior weight loss than semaglutide for weight loss, there is significant reason to investigate its efficacy and safety in overweight or obese adults without diabetes for FDA approval.[4]





Supply & Demand

Drug shortage is on the rise among all pharmaceutical dosage forms. Sterile injectable products have a higher risk of shortage than other forms due to manufacturing of the pen itself, not the medication. The causes of shortage are multifactorial; including supply, demand, and regulatory issues. The surged demand for tirzepatide following the data on weight reduction contributes to supply issues as it continues to be used off-label by non-diabetics. In 2022, more than 5 million prescriptions for semaglutide subcutaneous, tirzepatide, semaglutide oral, or semaglutide for weight loss were written for weight management, compared with just over 230,000 in 2019.[5] The manufacturer coupon by Eli Lilly has made recent strides to combat misuse of it's patient access program by updating the guidelines for eligibility. In order to download a savings card the patient must confirm that they have obtained a tirzepatide prescription for type 2 diabetes.[6] These changes also include grandfathering in previous coupons if activated before November, 2022, and the new price for non-grandfathered savings cards reflecting prices in the hundreds of dollars. Previous to these changes, the discount program by Eli Lilly brought the cost down to $25 or less per month (after any existing deductible has been met). In the case of tirzepatide, a sudden demand for off-label usage could pose challenges for patients with diabetes who depend on the drugs for diabetes management.

Emily Bui, PharmD Candidate, Class of 2024
Farzaneh Hadji Esmaeili, PharmD Candidate, Class of 2025
Joan Wang, PharmD Candidate, Class of 2026

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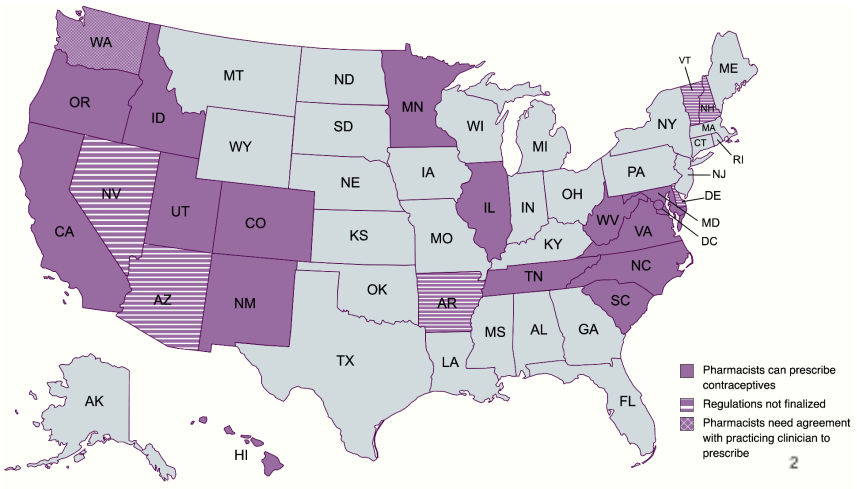
Advocacy: Expanding the Role of Pharmacy to Increase Access to Reproductive Healthcare

Pharmacists are some of the most trusted and accessible healthcare providers in the U.S., and with the growing responsibility that pharmacists have seen in these last couple of years, some states have developed laws that allow pharmacists to provide contraceptive care. These laws allow pharmacists to prescribe hormonal contraceptives, increasing access and bypassing difficulties accessing doctor's appointments. Following the decision made on Dobbs vs Jackson, increasing accessibility of contraceptives is more important than ever.



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Current Legislation and CPAs

Currently, there are 17 states and the District of Columbia with policies in place that allow pharmacists to prescribe hormonal contraceptives.[2] Hormonal contraceptives include birth control pills, the patch, the vaginal ring, and the injectable. Depending on the state, there may be varying requirements within their protocols including age limits, specific methods of contraceptives allowed to be prescribed, and the ability of the pharmacist to refuse this service. Currently in New York State, there is an active bill (S1043) that would allow pharmacists to prescribe contraception methods. The bill recently passed the senate and has yet to be delivered to the governor.[3]

Why is Birth Control Accessibility Important?

These statewide protocols that expand the practice of community pharmacists are especially critical in rural areas, where access to OB/GYN providers are difficult. Out of the 14 states with the highest percentage of women in reproductive age in need of publicly funded contraceptive services and supplies, nine have rural populations exceeding a third of the state populations.[4] Pharmacists can help patients select a contraceptive method for long-term use to reduce the likelihood of unintended pregnancies and improve pregnancy planning.

Statistics

A national survey of 811 people who were at risk for unintended pregnancy revealed that 76% of the participants would benefit from pharmacists prescribing hormonal contraceptives instead of visiting and paying a clinician. 68% say they were likely to use pharmacy access to obtain hormonal contraceptives.[5] A 2019 cost-effectiveness analysis conducted of Oregon's Medicaid program estimated that pharmacists' ability to prescribe birth control resulted in 51 averted unintended pregnancies and saved $1.6 million dollars over the course of 2 years.[6] Although pharmacists charge a once annually consultation fee for this service, this fee is much more affordable than the cost of a clinician visit. This expansion of pharmacist's scope will positively benefit the general population and help lessen health disparities that affect access to contraception.

The Pharmacist's Scope

Expanding the scope of practice for pharmacists comes with tremendous benefits related to the patient's care as well as the healthcare system. Pharmacist's involvement in patient care helps ease the pressure and demand on physicians and other healthcare providers, and increases access for patients and helps to control health care costs.

Carmela Ruiz, PharmD Candidate, Class of 2024
Abigail Tarun, PharmD Candidate, Class of 2025
Nadia El Saghir, PharmD Candidate, Class of 2026

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Faculty Interview, Dr. Collin Clark PharmD, BCPS, BCGP, UB SCCP Chapter Founder

Michelle Maj: As the founder of the SCCP chapter at UB, how have you continued giving back to the organization now as a practicing pharmacist?

Collin Clark: Starting SCCP as a student, I have always looked at ACCP as my professional home. I have always tried to be involved in ACCP as much as possible, particularly in geriatrics practicing research networks (PRN). I have gotten involved in the committees as part of the PRN from the time I was in my residency training, through now, and I have been in the secretary treasurer role within the PRN, which has been a cool way to get involved with the organization more at a national level. I've also tried to still stay involved at the chapter level with what our students are doing; so I like to come back and participate in the events that the students are doing, encouraging students to do things like the Clinical Pharmacy Challenge. I've come back a few times and done some of the speaker events, as well as the dinner & discussions; so I come back for a few of those. I did one when I was a resident, which was really cool, and I did one again this year as faculty. So it's been kind of fun to come back at different stages in my career. You see what the chapter is doing and really stay connected.

Michelle Maj: You are the recipient of the 2023 New Investigator Award. I want to congratulate you on that. So what does this mean to you and the future of your practice now?

Collin Clark: This was an award through ACCP to help faculty start new areas of research. So I've been involved in doing some research related to transitions of care on the inpatient side as well as on the outpatient side with Dr. Slazak here at the school. We've sort of been doing two different transitions of care programs in their own little silos. This project is actually meant to sort of bring what we do at the hospital, along with what Dr. Slazak does in the clinic, together by creating a mechanism that would communicate the information from one clinical pharmacy team to the other; so, when patients go from inpatient to outpatient, there isn't as much confusion over what it is that patients are supposed to be doing. It takes a lot of the work that we've been doing independently and really studies a way that we can do it better.

Michelle Maj: How do you currently stay updated with the latest advances in pharmacy/clinical pharmacy? What are some things you do or recommend?

Collin Clark: I think one of the biggest things is being involved in professional organizations, which I'm very involved in ACCP. So I get a lot of community, especially in the practice and research networks. We're always sharing its articles, ideas for research projects, clinical practice, and things like that at the local level. I'm also involved in the Western New York Society of Health Systems Pharmacists. There's a lot of networking there, a lot of CE's and other really cool projects that clinical pharmacists as well as residents do around the area that is really good to stay up on. You know things that are happening nationally in clinical pharmacy but locally like within our health systems here in Western New York. I think those professional organizations are a big thing. As for the journals that I subscribe to in my discipline, I always have a table of contents forwarded to me. When it comes to new literature, I'm able to see those on a monthly basis or whenever it comes out, so I can go find the things that are interesting to me so I can stay up on it.

Michelle Maj: What experiences throughout your career and pharmacy have impacted you the most?

Collin Clark: I think the biggest things, especially early in my career, were a lot of really good patient interactions that I had that were really formative, especially where you can spend a lot of time with the patient and really see the lightbulb click in terms of what they're supposed to be doing with their medications or when you finally improve a patient that you've been working with for a long time. I used to do a lot of diabetes management when I was a resident, so seeing when you can finally get them to a place where they are feeling good about where they're at with their medications and to be able to share your expertise is great. I think those opportunities that I had are very formative and even today, working more on the inpatient side of things. The things that really stand out are when you're working with a really good team of clinicians, providers, and medical residents. You see the value that they put on having a pharmacist there and you know that they really appreciate what you bring to the team. I think those things are really formative and make me feel good about choosing to go into the clinical pharmacy field.

Michelle Maj: What's one thing you wish you knew when you were a student pursuing clinical pharmacy?

Collin Clark: It would be related to the amount that providers really want to hear from pharmacy. Learning to be more proactive with recommendations rather than always waiting to be asked the question because I think a lot of things potentially could go unsaid. That was something that I learned over my career, like when to step in and say it instead of having the team talk about a patient, and then bringing it up after the fact when you have something to share and say this is what I actually think is going on. I realized you get a lot of respect for doing it that way.

Michelle Maj: Relating to the previous question, what are some tactics or how would you step in and say something?

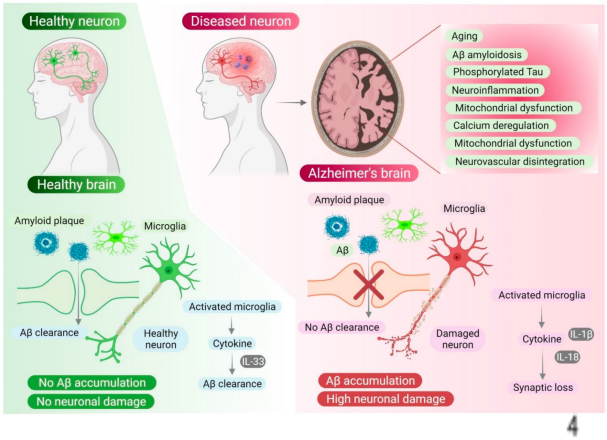
Collin Clark: What I learned was that it goes a lot into forming a trusting relationship with the providers that you're working with. I think a lot of it is in the delivery, in terms of how respectful you do it, and not trying to prove anyone wrong or say no that's a bad idea, this is what you should do. Learning it in a proactive way was one of the biggest things I had to realize. It was not what I anticipated the role of a pharmacist was going to be when I decided to go to pharmacy school.

Michelle Maj, PharmD Candidate, Class of 2024
Shirley Huang, PharmD Candidate, Class of 2025
Austin Grzechowiak, PharmD Candidate, Class of 2026

What is Lecanemab-irmb?

A humanized IgG1 monoclonal antibody injection approved by the FDA for the treatment of Alzheimer's disease using the Accelerated Approval Pathway on January 6th, 2023.[2]

MOA: Humanized IgG1 monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta. In Alzheimer disease, amyloid beta plaques accumulate which is believed to be the pathogenesis of the disease. Lecanemab-irmb binds with a high affinity to amyloid-beta protofibrils which are toxic to neurons.



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PKPD:

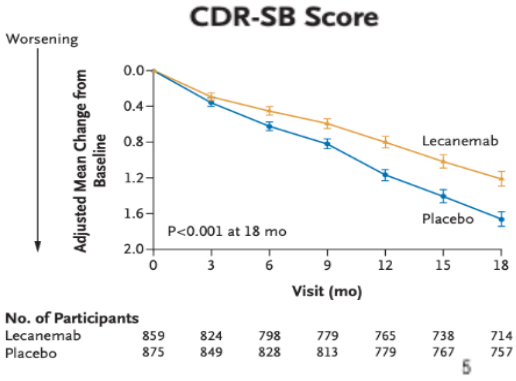
The half-life elimination of Lecanemab-irmb ranges from 5-7 days, along with a steady state volume of distribution of 3.22L. It is typically metabolized through proteolytic enzyme degradation. Lecanemab-irmb is not expected to undergo renal or hepatic metabolism.[3] Lecanemab-irmb was shown to reduce amyloid plaques at 53 and 73 weeks in a dose and time dependent manner. Higher exposure to lecanemab-irmb was associated with greater reductions in amyloid plaques and P-tau 181.

Adverse Effects:

Lecanemab-irmb most commonly can cause infusion-related reactions. Headaches, diarrhea, cough, and more seriously atrial fibrillation and brain edema are less common.[3] Lecanemab-irmb has also been associated with amyloid related imaging abnormalities (ARIA). These serious adverse effects are either characterized as ARIA with edema (ARIA-E) or as ARIA with hemosiderin deposition (ARIA-H). ARIA-E manifests itself as brain edema or sulcal effusion on MRI while ARIA-H manifests as microhemorrhage and superficial siderosis. Incidence of symptomatic and asymptomatic ARIA occurred in 12% of patients being treated with lecanemab-irmb.[3]

Clinical Trials:

Clarity AD was a phase 3, 18-month, multicenter, double-blind, placebo-controlled, parallel-group trial. Safety and efficacy of lecanemab-irmb was the main focus of this trial. Participants were those with early Alzheimer's disease and 50-90 years of age, and they were randomized in a 1:1 ratio with one group receiving lecanemab-irmb and the other receiving placebo. To test efficacy, the primary endpoint was a change in score from baseline to 18 months using the Clinical Dementia Rating-Sum of boxes (CDR-SB).[5] Secondary endpoints of the trial focused on the change over 18 months in amyloid plaques on a PET scan. At baseline, both groups had a mean CDR-SB score of 3.2. After 18 months, the group receiving lecanemab-irmb had a mean CDR-BS of 1.21 compared to a score of 1.66 in the placebo group. The baseline mean amyloid level in participants was 77.92 centiloids in the lecanemab-irmb group and 75.03 centiloids in the placebo group. After 18 months, the lecanemab-irmb group had a mean change of -55.48 centiloids from baseline and the placebo group had a mean change of 3.64 centiloids.[5] Overall, the Clarity AD phase 3 study concluded that lecanemab-irmb led to a lower decline in cognition and function compared to placebo and reduced amyloid plaque levels. However, a trial lasting longer than 18 months would be needed to further test the efficacy and safety of medication.



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Thomas Sulli, PharmD Candidate, Class of 2024
Callista Hipolito, PharmD Candidate, Class of 2023
Samantha Morales, PharmD Candidate, Class of 2024

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New Drug Update: XENOVIEW (xenon XE 129 hyperpolarized) - Hyperpolarized Contrast Agent for Lung MRI

Introduction

According to the American Lung Association, over 34 million Americans live with a chronic lung disease such as asthma and chronic obstructive pulmonary disease (COPD).[2] Currently, the imaging modality for the non-invasive, qualitative evaluation of chronic lung diseases is computed tomography (CT) of the chest. Conventional pulmonary magnetic resonance imaging (MRI) has been used less commonly because of complexities such as pulmonary MRI signals decaying rapidly as well as low proton density in healthy lungs which MRIs depend on. Due to these complications, pulmonary MRIs do not provide more information than a low-dose CT.[3] The use of hyperpolarized noble gasses makes lung MRIs feasible.

Xenon XE

In December 2022, the FDA approved XENOVIEW, a xenon XE 129 hyperpolarized contrast agent developed by Polarean, Inc. It is indicated for the evaluation of lung ventilation in adult and pediatric patients aged 12 years and older with the use of an MRI.[4] Xenon XE currently represents the first and only hyperpolarized contrast agent.

Mechanism of Action

Xenon XE is a gas that is orally inhaled and gets distributed in the lungs. A multi-nuclear capable MRI is used to visualize the distribution of the gas in the ventilated lungs.[5]

6

Dose

The recommended target dose of xenon XEis 75 - 100 mL Dose Equivalent (DE) of hyperpolarized xenon XE 129.[5]

Adverse Reactions

In the clinical trials, 12 out of 83 of the participants reported an adverse reaction. Of them, four participants reported oropharyngeal pain, two participants reported headache, and two patients reported dizziness.[5]

Clinical Trials

The approval was based on two clinical trials. Both trials were multicenter, randomized, open-label, cross-over Phase 3 studies that compared hyperpolarized 129Xe gas MRI to 133Xe scintigraphy for the evaluation of pulmonary function. One trial (NCT03417687) used subjects that were being evaluated for a lung resection surgery and had a total of 34 participants. The other trial (NCT03418090) used subjects that were being evaluated for a lung transplant surgery and had a total of 48 participants. Due to the vast differences in technique for obtaining hyperpolarized 129Xe MRI compared to 133Xe scintigraphy, blind study procedures were impossible. However, all image interpretations were performed by personnel blinded to the subject's medical history and all study assessments. In both trials, all subjects received both 129Xe MRI and 133Xe scintigraphy, but the order in which they received them was randomized. Both studies found that imaging produced using the hyperpolarized 129Xe gas MRI was equivalent to the imaging produced using 133Xe scintigraphy. The lung resection study found a mean within-subject difference between 129Xe and 133Xe of 1.4% (95% confidence interval, -0.8%, 3.6%). The lung transplant study found a mean within-subject difference between 129Xe and 133Xe of 1.6% (95% confidence interval, -3.7%, 0.5%).[4,7-8]

Jasmine Yeoh, PharmD Candidate, Class of 2025
Puteri Qisthina, PharmD Candidate, Class of 2025
Preston Lee, PharmD Candidate, Class of 2024

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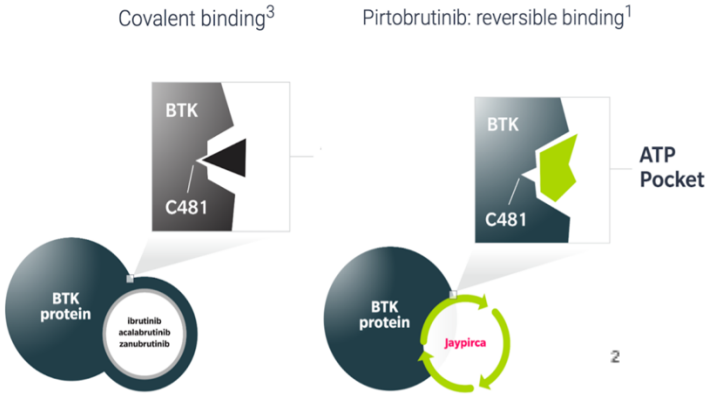
New Drug Review: Jaypirca (pirtobrutinib), first reversible BTK inhibitor by Eli Lilly

Overview: On January 27th of this year, Jaypirca (pirtobrutinib) was granted approval by the FDA for relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, one of which includes a Bruton's tyrosine kinase (BTK) inhibitor. pirtobrutinib is the first and only approved reversible BTK inhibitor. The accelerated approval of pirtobrutinib was largely due to the positive response rate in patients.[1] To further confirm the benefit of pirtobrutinib for this indication, clinical studies are ongoing.[1] A phase 3 trial (NCT04662255) is currently enrolling patients.

2



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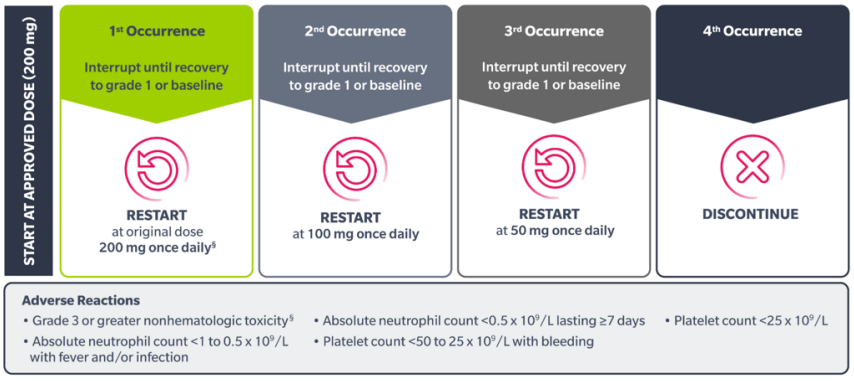
MOA: Pirtobrutinib is a small molecule that noncovalently (reversibly) inhibits BTK. BTK is a signaling protein in B-cells that results in proliferation, trafficking, chemotaxis, and adhesion.[2] Pirtobrutinib reversibly binds to wild type BTK and BTK harboring C481 mutations to prevent activation of the different B-cell pathways.[2] (Image 1)

Clinical Trials: Pirtobrutinib had received priority review and fast track designation for approval to treat mantle cell lymphoma (MCL) based on the BRUIN clinical trial (NCT03740529). Efficacy assessment was based on 120 patients with MCL who were treated with pirtobrutinib 200mg daily until disease progression or toxicity. The overall response rate (ORR) was 50%, with a confidence interval between 41-59. Of the 120 patients, 45 (38%) had a partial response, and 15 (13%) had a complete response. The time to response was a median of 1.8 months. Most common adverse reactions were decreased neutrophil count, decreased hemoglobin, decreased platelet count, fatigue, musculoskeletal pain, decreased lymphocyte count, bruising, and diarrhea.[3]

Clinical Pearls:

Pirtobrutinib's recommended dose is 200mg by mouth daily, with or without food. Patients should be monitored for signs of bleeding while taking pirtobrutinib and the risk/benefit of co-administration of antithrombotics with pirtobrutinib should be considered. Serious adverse reactions occurred in 38% of patients, including pneumonia, COVID-19, musculoskeletal pain, hemorrhage, pleural effusion, and sepsis. Pirtobrutinib also carries the risk of atrial flutter, occurring in 3.9% of patients.Manufacturer guidelines recommend discontinuing therapy after four occurrences of certain adverse reactions including non hematologic toxicity, and decreased absolute neutrophil or platelet counts. (Image 2).[3-5]



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PKPD: Patients with severe renal impairment (eGFR < 15-29ml/min) should be reduced to 100mg daily. There is no dose adjustment required for patients with mild to moderate renal impairment. Concomitant use of pirtobrutinib with strong CYP3A4 inhibitors should either be avoided, the pirtobrutinib dose reduced by 50mg, or discontinued for the duration of CYP3A4 inhibitor use. Concomitant administration with CYP3A4 inducers should also either be avoided, or the pirtobrutinib dose should be increased from 200mg to 300mg or if the current dose is 50mg or 100mg, increase by 50mg.

Elaine Marji PharmD Candidate, Class of 2024
Jordan Reyes, PharmD Candidate, Class of 2025

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New Drug Approval: Brenzavvy™ (Bexagliflozin)

What Is It

Bexagliflozin was developed by the company TheracosBio and approved by the FDA on January 23rd, 2023. It is an SGLT-2 transporter inhibitor that works by preventing reabsorption of glucose from the renal glomerular filtrate in the renal proximal tubule. Therefore, by inhibiting that transporter it prevents the reabsorption of glucose and also lowers the renal threshold for glucose to increase urinary glucose excretion.[1] This ultimately lowers blood sugar and improves glycemic control. Bexagliflozin is now the fifth SGLT-2 Inhibitor approved in the US.

2

What Does It Treat

Bexagliflozin is a new medication approved for the treatment for Type 2 Diabetes to help lower blood sugar and improve diabetes control. While using this medication it is recommended to implement lifestyle modifications consisting of diet and exercise.

4

Clinical Pearls

Bexagliflozin is given as a 20mg oral tablet taken once daily. Side effects include urinary tract infections, vaginal yeast infections, dizziness or headache.[1] Bexagliflozin is not recommended in patients with Type I Diabetes as it may increase their risk of diabetic ketoacidosis. Bexagliflozin is also contraindicated in patients that are on dialysis or have a history of hypersensitivity reactions to SGLT-2 Inhibitors.[3]

5

New Drug Updates

Bexagliflozin was first approved by the FDA for animal use on December 8th, 2022. It was originally indicated for felines diagnosed with diabetes mellitus and was marketed as Bexacat (bexagliflozin). Shortly after, bexagliflozin was FDA approved for human use on January 23, 2023.[5]

New Clinical Trials/Guidelines

Bexagliflozin was approved based on the results from 23 clinical trials. One trial was the BEST trial which enrolled 1700 participants with T2DM and elevated risk of cardiovascular events. It looked at the effect of bexagliflozin on A1C levels over 24 weeks. Results showed that this medication compared to placebo was able to reduce A1C levels by 0.85%.[6]

Arm/Group Title	Bexagliflozin Tablets, 20 mg	Placebo Tablets
Arm/Group Description	Each subject will receive bexagliflozin 20 mg once daily for the duration of the study. Bexagliflozin: 20 mg, tablet	Each subject will receive placebo (inactive tablet) once daily for the duration of the study. Placebo: 20 mg tablet to match active comparator Show less
Overall Number of Participants Analyzed	1046	531
Least Squares Mean (95% Confidence Interval) | Unit of Measure: percentage of glycated hemoglobin	-0.85 (-0.90 to -0.80)	-0.37 (-0.44 to -0.30)

6

Natalie Peunic, PharmD Candidate, Class of 2025
Michelle Hui, PharmD Candidate, Class of 2025
Patrick Mueller, PharmD Candidate, Class of 2026

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New Drug Review: Filspari™ (Sparsentan): Tablets to Reduce Proteinuria in Adults with Primary Immunoglobulin A Nephropathy (FDA Accelerated Approval February, 2023)

Background

There are five different types of immunoglobulin (Ig) antibodies (IgG, IgM, IgA, IgD, IgE). IgA acts mainly against bacterial infections. IgAN (Immunoglobulin A Nephropathy), also known as Berger's disease, is a rare autoimmune disease in which the ileum (Peyer's Patches) produces abnormal structured IgA proteins that the body recognizes as a foreign antigen, causing the formation of antigen-antibody complexes. These complexes accumulate in the kidney leading to inflammation and damage to the glomeruli. Red blood cells and protein then leak into the urine. Over time, this causes irreversible damage to the kidney and kidney failure. There is no cure for this disease as the exact cause of abnormal IgA production is still unknown. Hence, treatment is focused on preventing disease severity, further glomeruli damage, and delaying kidney failure. These preventative treatments include both immunosuppressive agents (prednisone) and non-immunosuppressive agents, which reduce inflammatory damage to the glomeruli. Due to the potential side effects of corticosteroids, this is reserved for patients with severe cases. Filspari™ (sparsentan) is the first and only non-immunosuppressive therapy to reduce proteinuria in patients with IgAN and a urine protein creatinine ratio (UPCR) of ≥1.5 g/g.[1]

TRAVERE™ THERAPEUTICS

1

FILSPARI™ (Sparsentan) 200mg & 400mg Tablets

2

Mechanism of Action

1

Sparsentan is an endothelin-1 and angiotensin-II antagonist. It is available as 200mg & 400mg film-coated immediate-release tablets. Per recommendation, treatment is initiated with 200mg tablets once daily for the first 14 days, then increased to 400mg daily.[1] Sparsentani has a high affinity for both the endothelin type A receptor (ETAR) and angiotensin-II type 1 receptor (AT1R). Sparsentan selectively antagonizes endothelin-1 & angiotensin-II, leading to an overall reduction of blood pressure and to the kidneys themselves. This reduces the amount of proteinuria and inflammatory damage to the glomeruli ultimately slowing disease progression.[3]

Pharmacokinetics

Sparsentan is a highly protein-bound drug (plasma protein binding is >99%) that reaches steady-state within 7 days following the first dose. It is predominantly metabolized by CYP3A and undergoes autoinduction requiring its' dose to be increased after 14 days of treatment. Following a 400mg oral dose of sparsentan the mean Cmax and AUCs were 6.97 g/ml and 83 g X h/ml and peak plasma concentrations were reached within 2-8 hours. Sparsentan has a half-life of 9.6 hours and is mainly excreted fecally (>80%) and minimally in urine (2%). Sparsentan has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and eGFR <30 mL/min/1.73 m2.[4]

Warning & Precautions

Sparsentan is only available through a REMS (Risk Evaluation Mitigation Strategies) program due to the risks of hepatotoxicity and embryo-fetal toxicity (both are black box warnings). Risks to the fetus can persist for one month after discontinuation of sparsentan which elicits consideration if one is planning a pregnancy. Therapy should be discontinued in patients who develop reduced kidney function to prevent acute kidney injury (AKI). Sparsentan should be avoided in patients with elevated aminotransferases (>3X and ≤8X) ULN (Upper limit normal) at baseline. It is recommended to avoid the use of moderate-strong CYP3A inhibitors and inducers while on sparsentan. Concomitant use with potassium-sparing drugs may cause hyperkalemia and requires dosage adjustment or discontinuation of sparsentan. Eliminating or adjusting other antihypertensive drugs should be considered while on sparsentan as side effects (e.g. dizziness) may be increased. Fluid retention may develop and warrants dose adjustment. Use of renin-angiotensin-aldosterone system inhibitors, endothelin receptor antagonists, and/or aliskiren is contraindicated when using sparsentan.[4]

Adverse Events

Peripheral edema is the most common adverse reaction (≥5%) reported. Hypotension (including orthostatic hypotension), dizziness, hyperkalemia, acute kidney injury, embryo-fetal toxicity, hepatotoxicity, and anemia may also occur.[4]

Clinical Trials

The ongoing PROTECT trial and Travere Therapeutics were granted accelerated approval from the FDA on February 17, 2023.[1] The goal is to assess the efficacy of sparsentan in decreasing proteinuria in those at high risk of progressing to renal failure. On day one of randomization, patients were assigned to the sparsentan group of 200 mg or the irbesartan group of 150 mg. Both groups have a titration schedule of up to 400 mg per day in the sparsentan group and 300 mg per day in the irbesartan group. The primary analysis is the change in UPCR from baseline at week 36. The secondary analysis looked at changes in eGFR annually. This trial will continue to evaluate secondary outcomes on eGFR.[2] In patients receiving sparsentan, there was a 49.8% mean reduction of proteinuria from baseline with only a 15.1% mean reduction of proteinuria in the irbesartan group at the week 36 mark.[2] These results are what led to the accelerated approval and likelihood of patients receiving this disease-mitigating treatment.

Zach Walker, PharmD Candidate, Class of 2024
Nusrat Samiya Mithila, PharmD Candidate, Class of 2026
Pooyan Esmaeilishayeh, PharmD Candidate, Class of 2026

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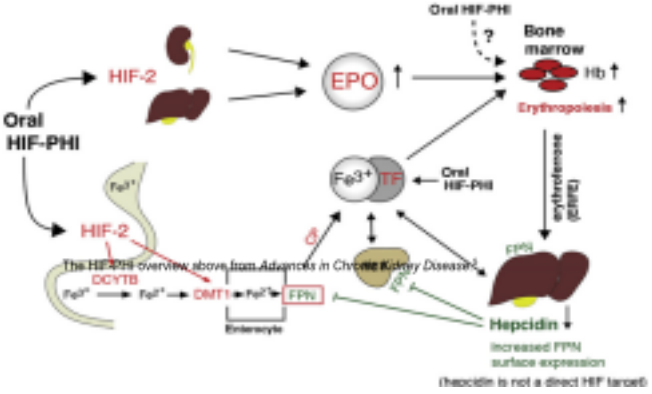
What is it?

Jesduvroq (daprodustat) tablets
1 mg • 2 mg • 4 mg • 6 mg • 8 mg

Released on February 1st, 2023, Jesduvroq (daprodustat) is the first ***oral treatment*** for anemia caused by chronic kidney disease (CKD); it is available in 1 mg, 2 mg, 4 mg, 6 mg, and 8 mg tablet strengths.[1] Daprodustat treats anemia caused by chronic kidney disease .[2] Anemia is defined as "a condition in which your blood has a lower than normal amount of red blood cells or hemoglobin". In chronic kidney disease, there is less erythropoietin (EPO) that is produced, a hormone that signals to the bone marrow to generate more red blood cells. Due to the reduced red blood cells in the body, this induces hypoxia causing less oxygen to be delivered to the organs and tissues.[3]

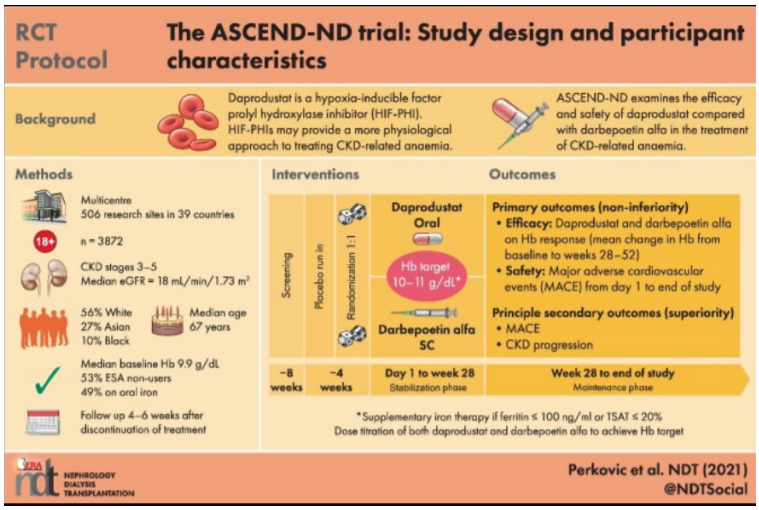


MOA

Daprodustat belongs to a category of drugs called **hypoxia-inducible factor prolyl hydroxylase inhibitors** also known as: **HIF-PHI**. It is noted that, "inhibition of oxygen-sensing prolyl hydroxylase enzymes stabilizes hypoxia-inducible factors, which can lead to transcription of erythropoietin and other genes involved in the correction of anemia".[2] In other words, daprodustat works by inhibiting the factors that stop the production of erythropoietin. This then increases erythropoietin and signals to the bone marrow to generate new red blood cells.

PKPD

If the hemoglobin (Hgb) reaches the threshold of increasing greater than 1 g/dL over 2 weeks (or 2 g/dL over 4 weeks) or exceeds 11 g/dL after therapy initiation, then the dose should be decreased. The pharmacokinetic aspect reveals that the drug follows a dose-proportional trend, and steady-state concentrations are reached within 24-hours. The medication is primarily metabolized by CYP2C8 and is contraindicated with concomitant strong CYP2C8 inhibitors.[7] Greater than 99% of the drug is excreted as oxidative metabolites discovered mostly in the feces. After taking daprodustat for 52 weeks, studies reveal the drug also increased serum transferrin and total iron binding capacity.[6]



Adverse Effects

Daprodustat carries a BBW for increased risk of death, myocardial infarction, stroke, venous thromboembolism, and thrombosis of vascular access. Patients with cardiovascular disease have a higher risk of these events.[6]

Studies Involved

The ASCEND-ND trial was a Phase 3, 1:1 randomized, open-label, sponsor-blinded, multicenter trial. It assessed the safety and efficacy of daprodustat versus darbepoetin alfa in patients with anemia secondary to CKD.[8] The primary outcome results showed a Hgb level difference of 0.74 ∓ 0.2 g/dL for the Daprodustat group and 0.66 ∓ 0.02 g/dL for the darbepoetin alfa group between weeks 28 to 52. The first MACE happened in 378/1937 patients in the daprodustat group and happened in 371/1935 in the darbepoetin alfa group, illustrating a hazard ratio of 1.03, and 95% CI 0.89 to 1.19. Overall, the authors determined that daprodustat when compared to darbepoetin alfa is effective in treating anemia related CKD and shown to be non-inferior when assessing CV safety.[9] Due to daprodustats' oral, once a day treatment regimen, it is able to provide a new and convenient way for already pill-burdened CKD patients. Daprodustat is a drug to be on the lookout for in the near future!

Livia Chase, PharmD Candidate, Class of 2024
Elisabeth Milk, PharmD Candidate, Class of 2025
Linda Chen, PharmD Candidate, Class of 2025

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