SCRIP
CITELINE COMMERCIAL

15 Nov 2022 | **Analysis**

# IBD Market Snapshot: New Medicines Try To Address Patient, Physician Demands

*Oral Drugs, Novel Biologics Offer New Options*

by Mandy Jackson

Remission rates with existing therapies leave much room for improvement, so a variety of treatments are needed – leaving major players attempting to carve unique paths in a crowded market.

New drugs are looking to enter the mature inflammatory bowel disease market by focusing on the remaining unmet needs, with clinical development programs aimed at improving remission rates beyond what is possible with existing therapies and maintaining remission for longer periods of time, while providing relief in the near-term from symptoms that patients describe as debilitating aspects of ulcerative colitis and Crohn's disease that impact their daily lives, such as bowel urgency.

*Click here to explore this interactive content online*

Oral JAK inhibitors and S1P receptor modulators are just the start for novel mechanisms coming to inflammatory bowel disease (IBD), a market currently dominated by anti-TNF antibodies and other biologics after ulcerative colitis (UC) and Crohn's disease (CD) patients progress on conventional therapies. Advanced therapies going forward will include additional drugs targeting JAK and S1P as well as interleukin-23 (IL-23) inhibitors and other novel biologics hoping to fill big gaps in the market.

*AbbVie Inc.*'s Humira (adalimumab) and Johnson & Johnson's Remicade (infliximab) are among the TNF inhibitors used in IBD, along with J&J's IL-12/23 inhibitor Stelara (ustekinumab) and *Takeda Pharmaceutical Co. Ltd.*'s integrin inhibitor Entyvio (vedolizumab). However, those and other companies are angling to provide new mechanisms to treat UC and CD because patients still unable to achieve remission or manage difficult symptoms, such as bowel urgency, with

available advanced therapies.

*Pfizer Inc.* had the first JAK inhibitor approved for UC in 2018 with Xeljanz (tofacitinib). (Also see "*Pfizer's Xeljanz Pushed By New Tailwind From Approval In Ulcerative Colitis*" - Scrip, 30 May, 2018.) However, the JAK class has since been relegated to post-biologic use in the US due to safety concerns. (Also see "*FDA Warnings And Restrictions On JAKs Curb Growth Potential Of Big Brands*" - Scrip, 1 Sep, 2021.) Now, the company is working to bring its second oral therapy for UC to market with the S1P modulator etrasimod for moderate-to-severe disease both for biologic-naïve and biologic-experienced patients. Pfizer plans to provide an update on its US Food and Drug Administration filing plans for etrasimod in UC in the coming months; the drug is in Phase II/III for Crohn's disease.

*Bristol Myers Squibb Company* beat Pfizer to market in 2021 with its S1P receptor modulator Zeposia (ozanimod), which is approved for UC and in Phase III for CD with results expected in 2024. (Also see "*Zeposia's Ulcerative Colitis Approval Provides BMS's Beachhead Into GI*" - Scrip, 28 May, 2021.) BMS also has its oral TYK2 inhibitor Sotyktu (deucravacitinib) in Phase II for both CD and UC, with results expected early next year and in the second half of 2023, respectively. (Also see "*BMS Aims To Unseat Otezla In Psoriasis With US FDA-Approved Sotyktu*" - Scrip, 9 Sep, 2022.) The drug failed in an earlier mid-stage ulcerative colitis study but a higher dose is included in the ongoing Phase II trial. (Also see "*Bristol's High Profile TYK2 Inhibitor Disappoints In Ulcerative Colitis*" - Scrip, 7 Oct, 2021.)

Also in the realm of new oral options, AbbVie's JAK inhibitor Rinvoq (upadacitinib) was approved for UC in March 2022 and has been filed with the FDA for CD. The company's biologic Skyrizi (risankizumab) was the first IL-23 inhibitor approved for IBD in the US, cleared for CD in June 2022, and is in Phase III for UC. (Also see "*AbbVie Ups Its IBD Game With Latest Crohn's Data For Rinvoq*" - Scrip, 12 May, 2022.)

## New Medicines Needed, Both Oral And Biologic

Pfizer has additional oral and biologic therapies in its commercial portfolio and its R&D pipeline for IBD beyond Xeljanz and etrasimod, including the Remicade biosimilar Inflectra and the Humira biosimilar Abrilada, which is slated launch in 2023 in the US. (Also see "*Pfizer Anticipates 'Fair' Share Of Adalimumab Market In US*" - Generics Bulletin, 5 May, 2022.) The company also has PF-06480605 targeting TNF super family member 15 (TNFSF15) in Phase IIb for ulcerative colitis and the JAK3 inhibitor ritlecitinib in Phase II for Crohn's disease.

"IBD is a super crowded space, in a sense, but ... there's also a tremendous unmet need and desire for patients and health care providers for a new medicine like etrasimod," Pfizer's former global president of inflammation and immunology Michael Gladstone told *Scrip*. "These conditions, these patients, they're heterogeneous in nature, and when it comes to IBD, patients need multiple options with different mechanisms of action."

Given that patients cycle through standard-of-care TNF inhibitors and many do not achieve or maintain remission on anti-TNF therapy, and because etrasimod is an oral option, Pfizer believes it can make the case for its drug as a pre-biologic option, Gladstone said.

"There is a significant patient population that is still available that needs to transition off of conventionals and move into advanced therapies and deucravacitinib, if approved, will ultimately help fill that gap as well side-by-side with Zeposia," Carlos Dortrait, BMS senior vice president in charge of commercialization for the company's immunology and fibrosis portfolio, said in an interview.

Dortrait noted that many UC and CD patients are diagnosed in their 20s and 30s, and market research has shown that many do not want to go on to biologic therapies, despite not being served well by oral conventional therapies and being candidates for advanced medicines, because they do not want to inject themselves for the next several decades to come.

Nevertheless, biologics are entrenched therapies for moderate to severe UC and CD, and not just anti-TNF antibodies. Takeda's Entyvio is approved solely for the two diseases and J&J's Stelara has been a welcome addition to the IBD treatment armamentarium as well.

Marla Dubinsky, chief of pediatric gastroenterology at Mount Sinai Kravis Children's Hospital in New York and co-director of the Susan and Leonard Feinstein Inflammatory Bowel Disease Clinical Center at Mount Sinai, noted that TNF inhibitors were the only advanced therapies available for IBD when she was a fellow more than two decades ago. She told *Scrip* that back then it was hard to imagine having three classes of biologics – targeting TNF, integrins and IL-12/IL-23 – for patients with advanced IBD, let alone oral therapies that also could provide meaningful remission.

## IL-23 Drugs May Benefit From Stelara's Known Safety

Inhibiting IL-23 alone – the target for AbbVie's Skyrizi and *Eli Lilly and Company*'s mirikizumab, which could be the first IL-23 inhibitor approved in the US for ulcerative colitis early next year – may be an even more targeted approach than TNF inhibition. IL-23 inhibition also has a somewhat known safety profile because it is one of the two targets of Stelara, Dubinsky noted. "We have that halo of understanding the safety profile of this class," she said.

Dubinsky, an investigator in Lilly's Phase III program for mirikizumab in UC, noted that the biologic has shown efficacy across patient populations, including people who are new to biologics and those who have not responded or lost response to anti-TNF antibodies or other biologics.

*(Article continues beyond the infographic below.)*

*Click here to explore this interactive content online*

“One thing that was really unique about the Lilly program is related to this new outcome of urgency, and that is the bowel urgency numeric rating scale,” Dubinsky said, explaining that bowel urgency previously was only looked at in clinical trials as part of broader patient-reported outcome measures.

“And it wasn't just absence or presence of urgency, it was a severity scale in the sense of urgency, meaning how severe is it on a scale of zero to 10,” she noted. Patients treated with mirikizumab reported less frequent bowel urgency and less severe bowel urgency than placebo-treated patients.

“And the reason why I get excited about it is, it is the number one, if not the number two symptom, that patients need help with and ask about,” Dubinsky said. She suggested that if more clinical trials feature similar endpoints then doctors may ask patients more frequently about this symptom if they know there are drugs that impact the frequency and severity of bowel urgency.

Lilly also conducted a survey called CONFIDE with 200 physicians and 200 ulcerative colitis patients to assess the importance of bowel urgency and found that patients ranked it higher than doctors in terms of importance.

Patrik Jonsson, senior vice president and president of Lilly Immunology and Lilly USA, said the company expects to launch mirikizumab in the US, pending FDA approval, around the second quarter or middle of 2023 with 16 to 18 months before the next IL-23 inhibitor hits the market for UC – both AbbVie’s Skyrizi (risankizumab) and J&J’s Tremfya (guselkumab) are in late-stage clinical trials in this indication. Mirikizumab is in Phase III for Crohn’s disease with a readout expected in late 2023 or early 2024 with approval expected in late 2024 or early 2025, Jonsson said.

“If you look upon the biologic penetration, the amount of patients diagnosed with UC, but are receiving a biologic or a new oral, it's only around 15% in UC, so the biologic penetration rate is low,” he said. “It's low in Crohn's disease as well, but not as low – it's around 30% in Crohn's disease.” And with many patients not achieving or maintaining remission on advanced therapies, “that is to me a sign that there is a need for new and more efficacious treatments,” Jonsson added.

He noted that because of mirikizumab’s encouraging efficacy to date across all endpoints, including various measures of remission, maintenance of remission and improvements in bowel

urgency, Lilly is not concerned about competition from TNF inhibitors, including the coming wave of Humira biosimilars.

Jonsson added that new oral options are welcome in the UC and CD markets, but said they are in a different league in terms of efficacy and – in the case of JAK inhibitors – safety.

## J&J/Janssen Build On Remicade, Stelara, Simponi IBD Franchise

J&J and its *Janssen Pharmaceutical Cos.* are quadrupling down on biologics in IBD with the IL-23 inhibitor Tremfya for ulcerative colitis and Crohn's disease on top of its legacy products Remicade and Stelara for UC and CD plus TNF inhibitor Simponi (golimumab) for UC.

Richard Appiah, vice president and disease area commercial leader for gastroenterology and the IL-23 pathway at Janssen, noted that there is "still a significant unmet patient need in IBD, particularly for those patients that haven't achieved remission or have achieved remission but lost remission, and that occurs in Crohn's disease and ulcerative colitis."

Appiah and gastrointestinal disease/immunology medical affairs head Chris Gasink noted that Janssen continues to generate new data for both its approved and investigational drugs to serve unmet patient needs as well as to help physicians choose the right medicines to meet those needs.

In the Phase II portion of the ongoing Phase II/III GALAXI study of Tremfya in Crohn's disease, Gasink noted, 57% of patients treated with the IL-23 inhibitor at the Phase III dose achieved remission versus 16% in the placebo arm of the Phase II study. At 48 weeks, 65% of Tremfya-treated patients were in remission, including both biologic-naïve and -experienced patients.

Remo Panaccione, professor and director of the IBD unit at the University of Calgary, Alberta, Canada, said there were many interesting findings in GALAXI, including the fact that regardless of the dose level and the way in which efficacy was measured, the efficacy of Tremfya in CD grew throughout the first half of the 48-week treatment period and then hit a plateau where patients maintained whatever response they achieved.

"It just tells us that in certain individual patients, that even transitioning from an I.V. formulation to a subcutaneous formulation, that there's still more … efficacy to be had," Panaccione said.

Also, he noted, given the known safety profile of IL-23 inhibition from Stelara's IL-12/IL-23 mechanism, there were no new safety findings in the Phase II study of Tremfya.

The QUASAR study of Tremfya in UC has a similar Phase II/III design with clinical response as the primary endpoint. At 12 weeks, 61% of patients treated with the drug had a clinical response

versus 28% in the placebo group; clinical response via the modified Mayo score was 26% versus 10%, respectively.

## Combination Therapy May Be Next Frontier

In the Phase IIa VEGA study testing Tremfya plus Simponi in biologic-naïve UC patients, 83% of those treated with the combination achieved a clinical response versus 75% for Tremfya alone and 61% for Simponi. Also, 46.5% of patients treated with the combination achieved a clinical remission via the modified Mayo score at 12 weeks versus 24% for Tremfya and 25% for Simponi.

“There's real promise that this combination approach could be more effective than just one treatment alone,” Gasink said. “That's something that is a couple more years away, but we're really excited about taking it forward and we've got now Phase IIb studies looking at this approach in both Crohn's disease and ulcerative colitis.”

Panaccione said the Simponi/Tremfya combination provides an incremental benefit, but raises several questions, such as whether the combo regimen needs to be used for the long term or short term, or whether the drugs could be given sequentially.

“Those are all unanswered questions, but certainly I think that one of the trends in the field is to explore further the value of combining advanced therapies. The question that remains is what is the best combination,” he noted. “Certainly, we want to make sure that that combination is safe for patients, and that we don't uncover any other safety concerns by combining two advanced therapies. To date, that doesn't seem to be a problem, at least over the short term. I think over the next three to five years you're going to see a big change in the way we manage inflammatory bowel disease.”

Panaccione pointed out that there is work ongoing in transcriptomics and other biomarker research to come up with companion diagnostics and other biomarker-based tools for guiding treatment decisions.

“I think it's going to come down to precision medicine,” Mount Sinai’s Dubinsky said. “When you have this many toys in your toy chest, how do you learn how to actually play with the toys so that you are giving the right therapy for the right patient at the right time?”

She said combination therapy likely will be the way forward in the next five years or so, combined with biomarkers that can predict the right therapeutic combinations. It may be that multiple pathways are addressed in combination initially to induce remission followed by use of a single mechanism of action for long-term maintenance therapy.

## Meeting Patient, Physician Goals

Gasink said both patients and physicians indicate that they are most focused on durable efficacy.

“They want a treatment that is going to make them better, and hopefully quickly, but what's most important is that it's going to really get them better for a long time,” he said. Another concern is when patients have progressed after multiple biologics, because it gets harder for them to achieve remission as they move on to other therapies.

Stelara is an option both as an early advanced treatment and for patients new to biologics and for patients whose disease has progressed on other biologics, Gasink said, “but the number of biologics that are out there to fail increases over time and that's where our future therapies really can step in. From the data we've seen, we think Tremfya is going to be perhaps an unparalleled option for those patients who failed multiple biologics before.”

Panaccione pointed out that there are patient-centric and physician-centric goals when it comes to treating Crohn’s disease, with patients typically focused on clinical remission without the need for ongoing use of steroids. From a physician’s perspective, the unmet need within the field is to achieve higher rates of endoscopic response and remission.

“The reason for that is that that's the crystal ball of looking into the future for the patients,” he said. “We know from observational studies that if we can achieve those endpoints that the patients will probably not have a progression of their disease to complications that we associate with surgery and are more likely to stay in a stable state of clinical remission not requiring steroids.”

All new agents for IBD have a place in the treatment armamentarium, Panaccione explained, whether they are biologics like the IL-23 inhibitors or oral therapies, such as the S1P modulators Zeposia and etrasimod or the JAK inhibitors Xeljanz and Rinvoq.

“I can see that, slowly, you're going to see a move away from anti-TNF therapy, more so broadly to anti-IL-23s and some of these oral medications,” he said.

*Click here to explore this interactive content online*

*[Editor’s Note: Michael Gladstone retired from Pfizer after Scrip interviewed him for the IBD Market Snapshot series.]*