Rheumatology

Pfizer's new RA pill Xeljanz—in full launch mode since early this year—is seeing uptake in the post anti-TNF portions of the market. But is the debut strong enough to imply that the med will attract a strong following? **Noah Pines** on the roll-out, a biologic maker's response, and how the upstart, which will soon be marketed directly to patients, may prompt a move away from needle-based therapies

Pfizer's Xeljanz (tofacitinib) appears to be a solid base hit as the first new disease-modifying anti-rheumatic drug (DMARD) in more than a decade. That's because the pill, which was approved last November, inaugurates oral drugs in a market dominated by injectable TNF inhibitors.

To hit a home run, the small-molecule drug, whose $25,000-a-year price is on par with the current biologics, must erode sales of the older drugs, including anti-TNF drugs* like AbbVie's top-selling Humira (adalimumab), which brought in $4.4 billion in US sales last year; Amgen's Enbrel (etanercept); and Johnson & Johnson's Remicade (infliximab). With the market for such products in rheumatoid arthritis (RA) estimated at $23 billion worldwide, according to Credit Suisse, other would-be oral competitors like AstraZeneca and Eli Lilly are also vying to take a crack.

Some of these oral candidates offer the potential for more convenient dosing and a better safety profile than Xeljanz. The late-stage pipeline includes AZ and Rigel's fostamatinib, a Phase III SYK inhibitor; Incyte's baricitinib (INCB28050) which was licensed to Lilly; and Galapagos NV's GLPG0634, a JAK1 inhibitor that AbbVie will market. Additionally, Vertex has a JAK inhibitor in Phase IIb development in the US and Europe, dubbed VX509.

Elsewhere in the rheumatology pipeline, and another area where physicians want new options, Merck continues to develop odanacatib for osteoporosis. Odanacatib brings a new mechanism of action in hopes of meeting provider needs and addressing safety issues hampering usage of the older bisphosphonates.

But the questions Merck must address are efficacy, reimbursement and safety profile—especially now that the Phase III agent's FDA filing has, for undisclosed reasons, been pushed back to 2014.

The big story in this sector is the US launch of Pfizer's 5-mg, twice-daily Xeljanz (its EU debut was stayed by an April rejection). Analysts say the extent to which orals can impact RA treatment depends on winning over rheumatologists. So far, despite unmet need, physicians' allegiance for most patients remains in the anti-TNF camp. "We have heard from numerous physicians that they have identified patients who are appropriate for Xeljanz, and they are using it both after methotrexate and after anti-TNFs," reports a Pfizer spokeswoman commenting on the launch.

To drive momentum, Pfizer's Victoria Davis says the firm initiated an HCP-oriented campaign in March, and it's expected to roll out DTC advertising mid-year. DTC has been instrumental for the TNFs in driving patient awareness. Pfizer knows that well—Enbrel, which it will continue to co-promote in the US with Amgen until October—is a heavy user of the channel, as does AbbVie with Humira.

"Tofa' is capturing the low-hanging fruit: patients getting sub-optimal treatment who have exhausted the TNFs," says Evolution Marketing Research's John Taenzler. The uptake curve isn't steeper, says Taenzler, because rheumatologists, after prescribing Xeljanz to one or two patients, "are waiting to see some results, talking with colleagues." No doubt they're also scrutinizing the med's uncertain safety profile and lack of post-market surveillance data.

Indeed, FDA required a REMS program due to the potential risks associated with the drug, including infections, tuberculosis, cancers and lymphoma. "Several JAK-3s have been tested and could not get through the first few phases of clinical trials," says Taenzler.

Pfizer will conduct an extensive post-marketing clinical program

TOP 50 RHEUMATOLOGY PRODUCTS, 2012

Category leaders, ranked by US sales, and their media spend

Rank	Product	Manufacturer	US sales $ (millions)*	Vs. prior 12 mos.	TRx (000s)	Vs. prior 12 mos.	US DTC media $ (000s)	Vs. prior 12 mos.	US journal media $ (000s)	Vs. prior 12 mos.
1	**Humira**	AbbVie	$4,377.0†	28.0%	1,545.8	3.8%	$198,045.0**	>100.0%	$3,751.4	32.0%
2	**Enbrel**	Amgen/Pfizer	$4,302.6††	14.1%	1,416.0	-2.6%	$169,857.1**	42.8%	$1,574.4	-2.2%
3	**Remicade**	Johnson & Johnson	$3,583.0†	9.4%	64.6	-4.3%	$109.0	>100.0%	$29.9	-97.7%
4	**Cymbalta**	Eli Lilly	$3,917.8†	29.4%	17,764.0	7.3%	$246,323.8**	-16.6%	$0.0	-100.0%
5	**Copaxone**	Teva	$3,581.0††	13.3%	N/A	N/A	$0.0	N/A	$682.8	>100.0%
6	**Rituxan**	Roche/Biogen	$3,499.2‡	8.3%	11.5	6.5%	$389.3**	-17.5%	$0.0	N/A
7	**Lyrica**	Pfizer	$2,025.7††	10.1%	N/A	N/A	$137,617.9**	13.3%	$6,383.9	>100.0%
8	**Celebrex**	Pfizer	$1,985.0††	6.6%	N/A	N/A	$133,497.0	15.8%	$0.0	N/A
9	**Avonex**	Biogen Idec	$1,703.2††	1.1%	N/A	N/A	$128.1	1.2%	$916.0	47.3%
10	**Meloxicam**	Generic	$1,354.6	-39.9%	22,413.0	12.5%	$0.0	N/A	$0.0	N/A
11	**Rebif**	Pfizer/EMD Serono	$1,245.8††	1.0%	N/A	N/A	$0.0	N/A	$100.9	-66.1%
12	**Evista**	Eli Lilly	$862.1	4.4%	3,237.1	-10.9%	$81.3	-99.2%	$1,511.5	-32.8%
13	**Gilenya**	Novartis	$852.2††	107.2%	N/A	N/A	$10,560.4	100.0%	$850.7	40.6%
14	**Betaseron**	Bayer	$820.4††	4.5%	N/A	N/A	$0.0	N/A	$58.8	-68.8%
15	**Orencia**	Bristol-Myers Squibb	$815.9††	27.8%	95.5	231.6%	$53,423.2	16.7%	$1,416.4	23.1%
16	**Venlafaxine HCl ER**	Generic	$770.8	-41.3%	14,050.7	17.4%	$0.0	N/A	$0.0	N/A
17	**Pristiq ER**	Pfizer	$678.1	5.8%	3,587.3	-9.8%	$30,465.5	-68.7%	$622.8	-81.8%
18	**Asacol**	Warner Chilcott	$653.8	-1.8%	1,124.8	-8.7%	$0.0	N/A	$0.0	N/A
19	**Stelara**	Johnson & Johnson	$627.0†	41.5%	49.4	1.7%	$27,185.4	-39.3%	$463.6	-44.0%
20	**Tacrolimus**	Generic	$594.6	15.6%	N/A	N/A	$0.0	N/A	$0.0	-100.0%
21	**Zometa**	Novartis	$556.5	-21.9%	7.6	-7.7%	$0.0	N/A	$1,064.7	-30.6%
22	**Actonel**	Warner Chilcott	$502.2	-25.1%	2,331.2	-36.4%	$0.0	N/A	$0.0	N/A
23	**Synvisc-One**	Sanofi/Genzyme	$496.7	15.7%	36.9	-22.8%	$141.9	-95.0%	$602.2	61.2%
24	**Budesonide**	Generic	$494.5	182.4%	403.0	150.8%	$0.0	N/A	$0.0	-100.0%
25	**Lialda**	Shire	$476.5	16.4%	695.7	6.4%	$53.7	-30.4%	$860.1	67.6%
26	**Forteo**	Eli Lilly	$423.6	11.0%	309.7	0.9%	$0.0	N/A	$2,413.4	-24.0%
27	**Cimzia**	UCB Pharma	$419.9†c	42.0%	171.3	7.8%	$5,077.2**	-85.1%	$218.4	>100.0%
28	**Diclofenac Sodium**	Generic	$402.1	18.9%	7,868.3	6.6%	$0.0	N/A	$0.0	N/A
29	**Tysabri**	Biogen/Elan	$383.1†	17.3%	9.2	1.0%	$0.0	N/A	$802.2	-4.0%
30	**Prograf**	Astellas	$370.9	-12.0%	459.9	-11.5%	$0.0	N/A	$117.5	-16.2%
31	**Reclast**	Novartis	$351.6	-10.4%	13.4	-4.2%	$17,056.3	-56.3%	$0.0	-100.0%
32	**Methotrexate**	Generic	$335.1	24.8%	5,759.5	3.9%	$0.0	N/A	$0.0	N/A
33	**Pentasa**	Shire	$334.4	11.8%	446.5	-3.3%	$0.0	N/A	$132.8	-14.1%
34	**Cellcept**	Roche/Genentech	$330.9	-10.9%	162.5	-22.0%	$0.0	N/A	$0.0	N/A
35	**Effexor XR**	Pfizer	$292.5	-49.8%	680.4	-62.4%	$0.0	N/A	$0.0	N/A
36	**Simponi**	Johnson & Johnson	$292.0†	24.3%	120.9	11.3%	$746.0	-93.5%	$34.1	-96.1%
37	**Ibandronate Sodium**	Generic	$286.8	N/A	1,454.0	N/A	$0.0	N/A	$0.0	N/A
38	**Myfortic**	Novartis	$286.2	23.3%	293.2	15.7%	$0.0	N/A	$168.5	>100.0%
39	**Euflexxa**	Ferring	$270.8	53.9%	56.4	50.9%	$0.0	N/A	$337.7	>100.0%
40	**Actemra**	Roche/Genentech	$265.8	68.0%	15.4	24.1%	$3,370.9	28.2%	$587.6	-64.7%
41	**Asacol HD**	Warner Chilcott	$255.9	33.5%	414.0	21.1%	$0.0	N/A	$0.0	N/A
42	**Venlafaxine HCl**	Generic	$246.1	-23.7%	3,013.3	-5.0%	$0.0	N/A	$0.0	N/A
43	**Mycophenolate Mofetil**	Generic	$241.4	-43.0%	1,192.2	13.8%	$0.0	N/A	$0.0	N/A
44	**Boniva**	Roche/Genentech	$235.4	-68.3%	829.5	-75.5%	$10,404.3	-80.8%	$0.0	N/A
45	**Naproxen**	Generic	$229.8	-28.5%	16,630.1	3.2%	$0.0	N/A	$0.0	N/A
46	**Alendronate Sodium**	Generic	$225.8	-53.9%	13,315.5	-15.5%	$0.0	N/A	$0.0	N/A
47	**Rapamune**	Pfizer	$206.6	2.6%	189.0	3.9%	$0.0	N/A	$0.0	N/A
48	**Nabumetone**	Generic	$201.5	-7.4%	3,024.6	-6.8%	$0.0	N/A	$0.0	N/A
49	**Canasa**	Axcan Pharma	$173.3	27.9%	243.0	1.0%	$0.0	N/A	$0.0	-100.0%
50	**Benlysta**	GlaxoSmithKline	$99.7†a	N/A	N/A	N/A	$521.4	34,940.9%	$438.5	-59.6%

*Manufacturer benchmark sales (MBS), unless noted. Note: TRx count includes retail only. List includes products FDA indicates as approved for treating rheumatoid arthritis, psoriasis, Crohn's disease, ulcerative colitis, fibromyalgia, lupus, ankylosing spondylitis, multiple sclerosis and osteoporosis.
Sources: Sales/TRx, Source Healthcare Analytics; company reports; DTC media spend, Nielsen; journals, Kantar Media
† Company reported sales. †† IMS Health ‡ >90% of sales from oncology settings [a] GSK began recording Benlysta revenue Aug. 2012 [c] includes Canada **Spend for all indications

CLINICAL CORNER

Due to the scientific and operational obstacles they face in drug development, manufacturers have been all too willing to experiment with a host of new processes and technologies, from cloud-based data management to social-media recruitment.

Some instances of new technology brought to bear for rheumatology R&D include the social network PatientsLikeMe and its use of an online registry for alkaptonuria (AKU) to help the research community understand how patients are affected by this rare disease, which can lead to arthritis and is sometimes diagnosed by rheumatologists (one existing therapy is being studied for the disease). Last year, PLM struck an accord with Merck to let the drug maker see what people are saying about the effects of psoriasis.

Richard Jones

In coming months, one big CRO says it will ask sponsors of rheumatology trials to add Big-Data-driven decision support to the list. Quintiles is launching a tool that it claims offers sponsors greater visibility into this complex process.

Combined with its centers-of-excellence, patient-focused approach to trials management, the CRO is preparing the Big Data tool for use in rheumatology and other trials as a decision-support platform. It aims to help sponsors by aiding prediction of site feasibility and the likelihood of success, while assisting with recruitment rates, issues with IRBs and country-specific investigator issues globally and in real time.

"The biggest problem in rheumatology clinical trials…has been [recruiting] the TNF inadequate-responder population," says Richard Jones, MD, therapeutic strategy head, internal medicine and immunology, Quintiles.

Therapeutic choices in the RA space range from anti-TNF biologics to IL-6 and CTLA-4 agents, along with the recently approved oral JAK inhibitor. These are a bright spot, from the perspective of patient symptoms as well as physiology and prognosis. Still, there remains a dearth of knowledge of the immune system and a frustratingly diverse array of pathologies under the umbrella of immunology. "We have been disappointed about our ability to use a single [therapeutic] mechanism across multiple diseases," says Jones.

This makes it hard to predict clinical efficacy for many of the novel biologics, he says. For example, not all patients with RA respond equally well to TNF antagonists; the TNF response rate is around 50%.

Rheumatology and the treatment of immune-mediated conditions in general is following the same trend as cancer in terms of using predictive assays and biomarkers to determine a patient's likelihood to respond to a given therapy. Quintiles, for instance, recently acquired Expression Analytics, a provider of advanced genomics testing and analysis, to help deepen its understanding of critical biomarkers to better classify patients and enable more individualized approaches.

"If we can predict what the patient will respond to, we can ultimately save money," notes Jones.

to assess the long-term safety of Xeljanz and to look at its potential in the pediatric population with polyarticular juvenile idiopathic arthritis. FDA also stipulated it wanted additional data to assess the risk/benefit profile of a 10-mg twice-daily dose.

The launch is on-track, analysts say, and could expand beyond patients with an inadequate response to TNF inhibitors. "We suggested that oral RA therapies like Xeljanz might eventually cause a paradigm shift away from injectable products," wrote Bernstein analyst Tim Anderson, MD, in a March investor note.

However, it will take time for clinicians to get comfortable, particularly given how satisfied they've been with the TNF class. "That's the group of products that everything gets measured against today," says Robert Bazemore, president, Janssen Biotech, which markets TNFs Remicade and Simponi in the US, along with biologic Stelara.

Heavyweights like Janssen are leveraging not only the data they've amassed to support their products, but also the "blue blanket" feeling of comfort that specialists have toward TNFs. "Each company's message is focused on improvement in disease activity scores, radiologic progression data, all of their long-term safety and efficacy studies," says IMS Consulting senior principal Steve Gubernick.

It's no surprise, then, that Pfizer isn't blowing away revenue forecasts. It appears to be on pace to meet the Street's estimates of $300-400 million in sales for the first full year in the US, says *in*Thought Research's Ben Weintraub, PhD. Indeed, the big question that analysts ponder is whether Pfizer can build enough steam to ramp Xeljanz into multi-billion-dollar territory.

Expanded use will be governed by formulary status as well as physicians' lingering safety concerns with the JAK-3 class, analysts say. Then there is the question of access. "We are seeing a high rejection rate for this drug compared to biologics," says *in*Thought's Weintraub. "What this means is that there is some MCO push back."

Quintiles analyst Troy Hampden notes that AbbVie and Amgen have spent years building relationships with managed care providers to keep Humira and Enbrel on formularies. "They've locked up managed care with aggressive discounts and volume-based rebates."

At least Xeljanz's efficacy could shield it from other orals. Recent topline Phase III results for fostamatinib imply that it will play second fiddle (ACR20 scores came in at 44-49% vs. 52-62% for Xeljanz). "We think that it will be hard [for fostamatinib] to dominate the oral RA market or provide major headwinds to PFE's Xeljanz and the other oral JAK inhibitors in development," wrote ISI pharma/biotech analyst Mark Schoenebaum, MD, in an April investor note.

Future indications could expand sales. Pfizer is studying the med in psoriasis, psoriatic arthritis and ulcerative colitis. Phase III psoriasis data should become available this year, and Pfizer regards this as the biggest commercial opportunity after RA, notes Anderson.

Asked whether the biologics maker worries about ceding ground to new oral competitors, a Janssen spokesperson says the firm wants to be able to give patients and HCPs all treatment options, depending on their desire. Even Janssen, one could say, sees the writing on the wall. It's developing its own oral RA therapies, one a JAK inhibitor in partnership with Astellas, as well as an internal candidate.

Adds Bazemore, "We've always considered that there may be a group of [patients] who would prefer oral therapies vs. intravenous products...but it has to be the right product." ■

**Noah Pines, an independent marketing research consultant, has done consulting work for the companies referenced in this article.*