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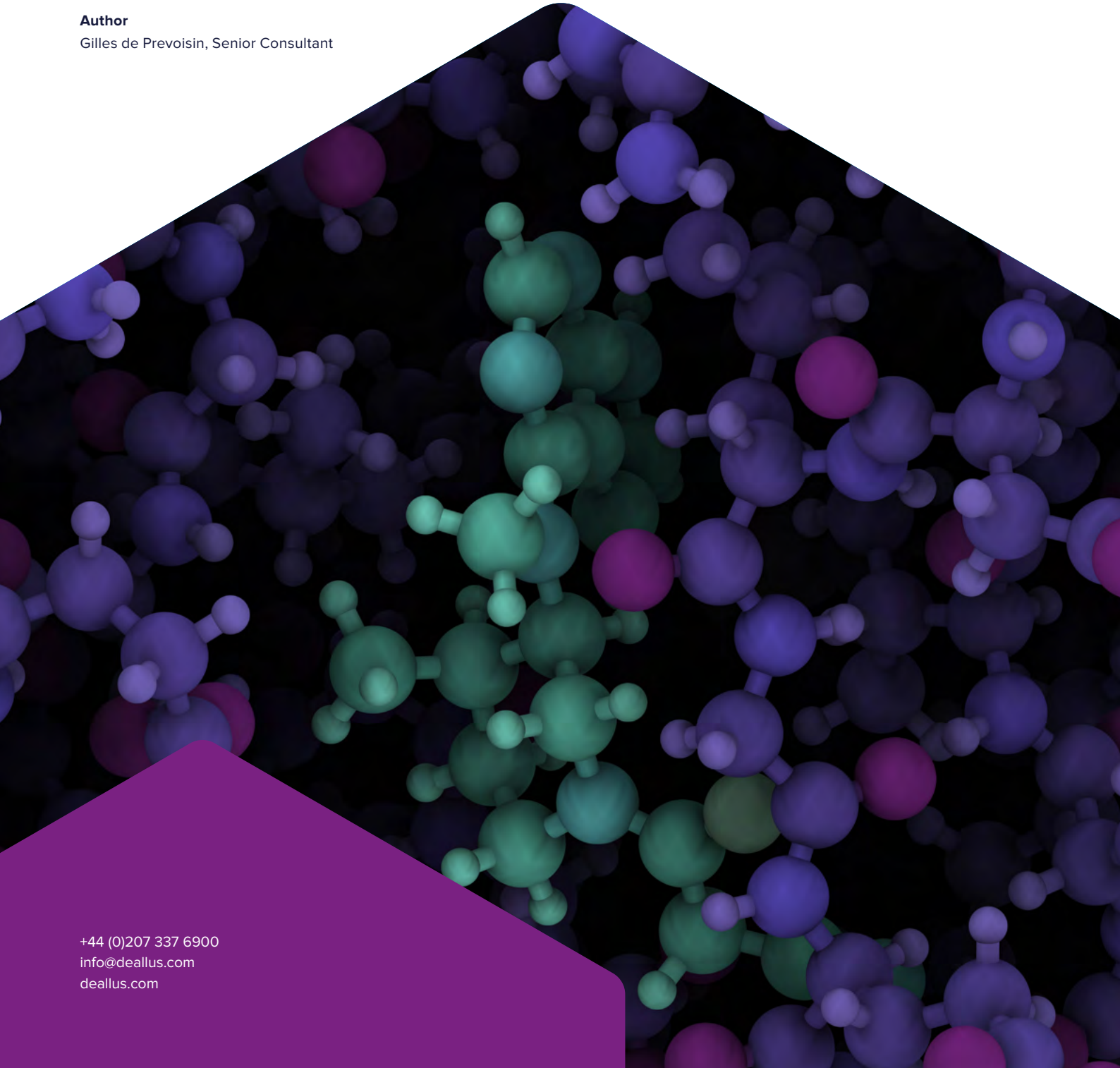
THE FUTURE OF JAK INHIBITORS

Will JAK inhibitors triumph over persisting regulatory roadblocks to offer patients a new treatment option?

Author
Gilles de Prevoisin, Senior Consultant



+44 (0)207 337 6900
info@deallus.com
deallus.com

THE FUTURE OF JAK INHIBITORS

From blockbuster drugs to black box warnings, Janus kinase inhibitors (JAKs) have seen dramatic highs and lows in their journey to market access across the last few years. This innovative drug class has faced dizzying twists, turns and falls within the landscape of safety acceptability. Yet despite the hurdles JAKs are facing, pharma's conviction in their potential to generate a paradigm shift in patient care means R&D activity and interest remains undaunted.

Driven by the sheer scale of the Immune-Mediated Inflammatory Diseases (IMIDs) treatment market and clear scenario of unmet patient need, the JAKs pipeline currently comprises no fewer than 45 therapeutic candidates. [1] In different stages of development, they are in a whole slew of IMID fields - and their journey is far from over.

JAK inhibitors are an oral class of therapeutics exciting to biopharma companies, investors, patients and physicians alike. Clinical results promise patients in multiple indications effective and more convenient treatment options. The first assets to enter the market, with approval for Rheumatoid Arthritis (RA), were tofacitinib (now also approved for Psoriatic Arthritis and Ulcerative Colitis) and baricitinib, followed by upadacitinib (RA).

First-generation JAKs have proven spectacularly efficacious both in clinical trials and in the clinic in treating inflammatory and autoimmune diseases - however, nearly all are facing an imbalance between safety and efficacy.

The result? JAKs' rise in market success - for now - has hit unexpected turbulence.

[1] https://www.pharmaproff.com/report/janus-kinase-inhibitors-pipeline-analysis

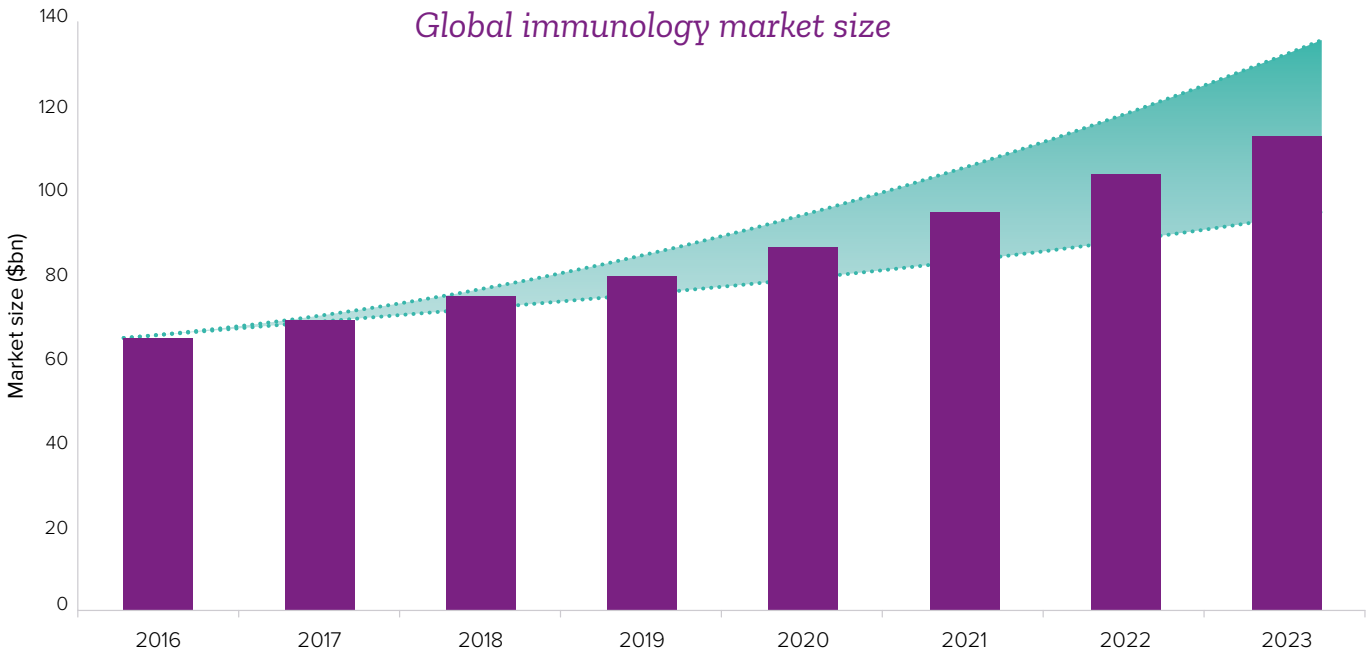
The dark shadow over the JAK inhibitor class

It turns out that Janus Kinase Inhibitors were aptly named. It was the two-faced Roman God 'Janus', usually depicted as looking both to the future and the past, who inspired the classification of these small molecules.

Currently JAKs are facing the challenge of overcoming their past, full of safety baggage and 'dirty' drug perceptions, in order to secure their place in the unfolding patient care landscape and their share of the burgeoning immunology drugs market. This is projected to grow to $113bn in 2023, at a compound annual growth rate (CAGR) of 8.2%.[2]

Serious concerns, however, that the drugs increase serious adverse effects - including thrombosis, infections, malignancies and embolisms - have resulted in the FDA's most severe safety warning: black box labelling.

The fallout is that groundbreaker drugs such as Pfizer's Xeljanz® and Lilly/Novartis' Olumiant® are now being pushed back to later lines of therapy. Moreover, incoming JAKs are brandishing safety warnings at launch, compounding safety concerns of established agents and fears that JAKs in the pipeline could be tarred by the same 'black box' brush, with a knock-on impact on patient and physician confidence.



[2] http://www.gbiresearch.com/report-store/market-reports/therapy-analysis/global-immunology-drugs-market-to-2023-shifting-landscape-as-uptake-of-interleukin-receptor-inhibitors-offsets-losses-for-top

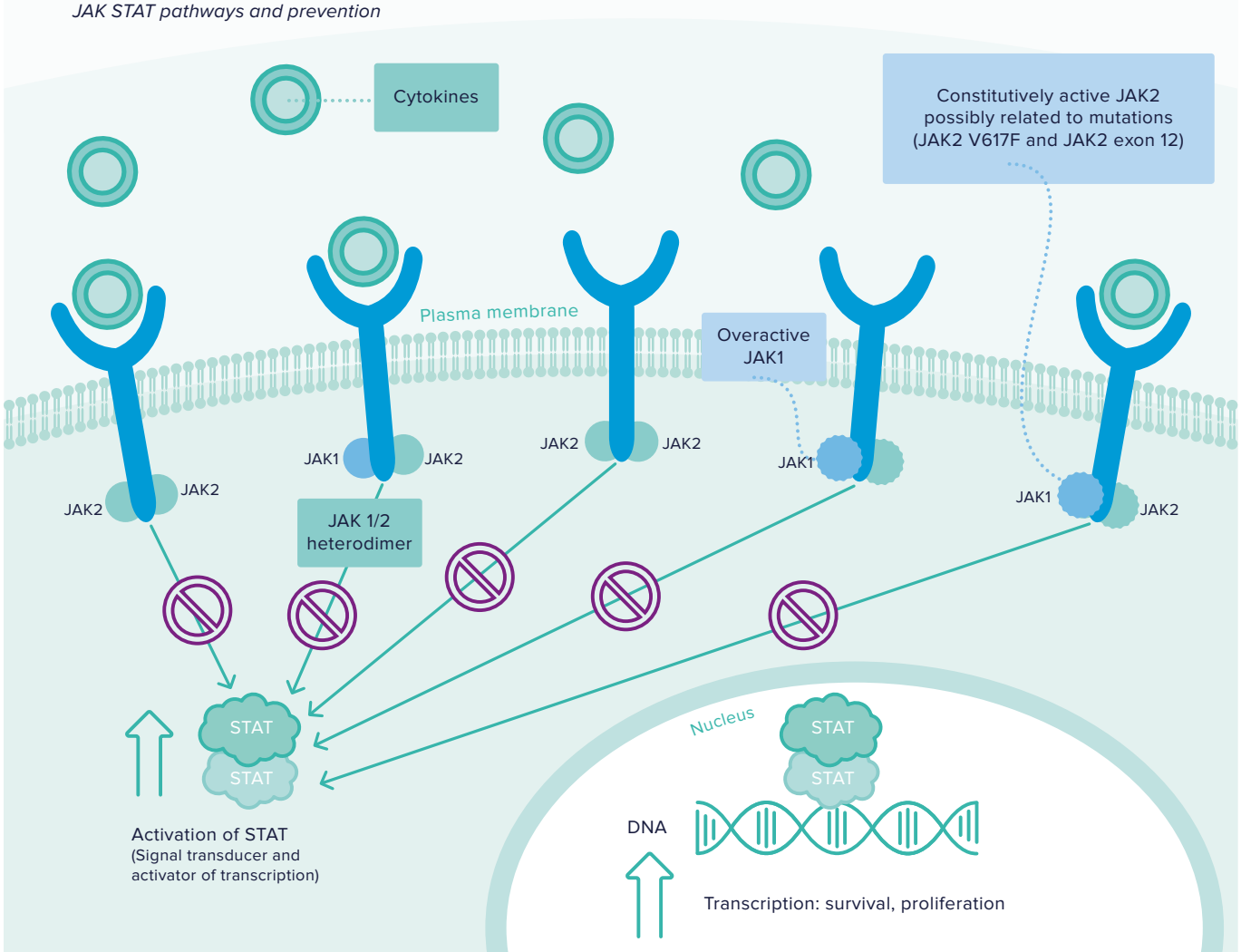
JAKs explained

JAK inhibitors block cytokine mediated signaling via the JAK-STAT pathway, which plays an important role in immune regulation and growth. These 'small molecule' drugs are highly specific for blocking targets identified within cells that cause chronic inflammation.

JAK consists of four intracellular non-receptor tyrosine kinases that help in cytokine mediated signaling through the JAK-STAT pathway. It contains two almost identical phosphate-transferring domains, in which one domain shows kinase activity and the other regulates the activity of the first via negative inhibition. The four receptors in the JAK family are JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). The mutation in any of these can lead to various medical conditions.

Perhaps the most exciting characteristic of the drug class is their potential responsiveness. Next-generation JAKs have a proposed selectivity varying from pan-JAKs targeting a combination of JAK1, JAK2, JAK3 and TYK2 targets. More selective JAKs may inhibit only one or two targets.

JAK STAT pathways and prevention



JAK activation is prevented → *No phosphorylation of receptor subunits* → *No receptor docking sites prevents STAT phosphorylation* → *No translocation of STAT dimer complex to nucleus* → *No transcription of pro-inflammatory genes*

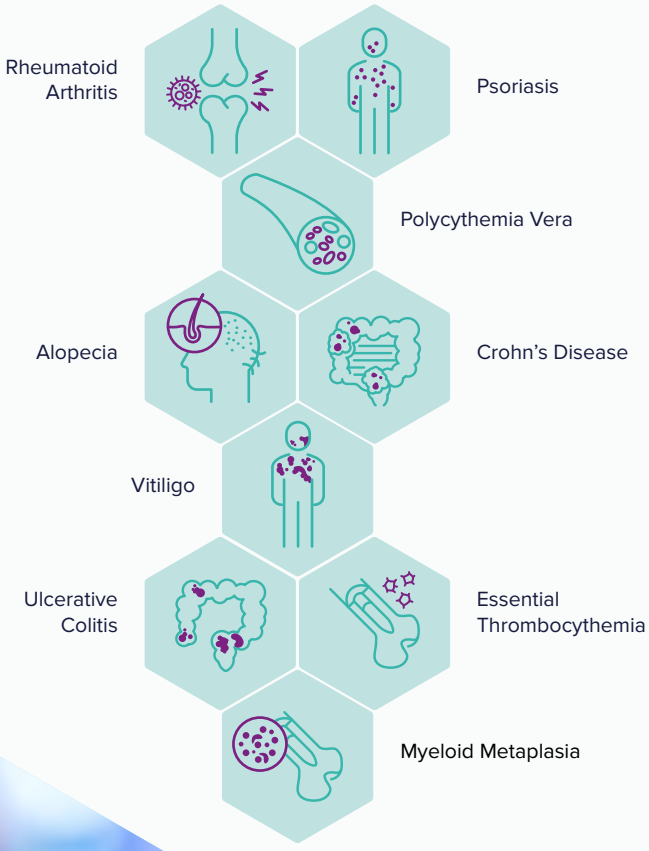
But while the general characteristics of the JAK-STAT pathway are well established, the exact molecular mechanism of JAK activation and downstream signaling in response to approximately 60 cytokines and hormones is still not exactly known.

This means that despite the improvements in next-generation JAKs, the selectivity of JAKs remains both uncharted and questioned. Skepticism is compounded by the fact that JAKs throw a wrench in the upstream pathogenesis of disease activity. This has escalated concerns of off-target effects, which plague the entire class.

Nonetheless, despite their perception as 'dirty' drugs, JAKs hold extraordinary promise in multiple treatment areas of unmet need. The prevalence populations of many indications within immunology are increasing, which is one of the major drivers of growth in the market.

It's no surprise then that the role of JAK inhibitors is also being actively investigated for the treatment of numerous conditions.

Where JAKs might help



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JAKs: the alternative to cytokines?

Historically, cytokine regulating therapies have led the revolution in the treatment of autoimmune and inflammatory disorders across recent decades.

Perhaps the most successful drug is the biologic Humira®. An arthritis medication with 11 approved indications, including Crohn's-colitis and psoriasis, it is currently the world's best-selling drug.

Cytokines have resulted in a complex landscape of approved assets and a competitive pipeline bolstered with new therapies and biosimilars. But despite their medical and commercial success, these biologics have several drawbacks:

LACK OF EFFICACY

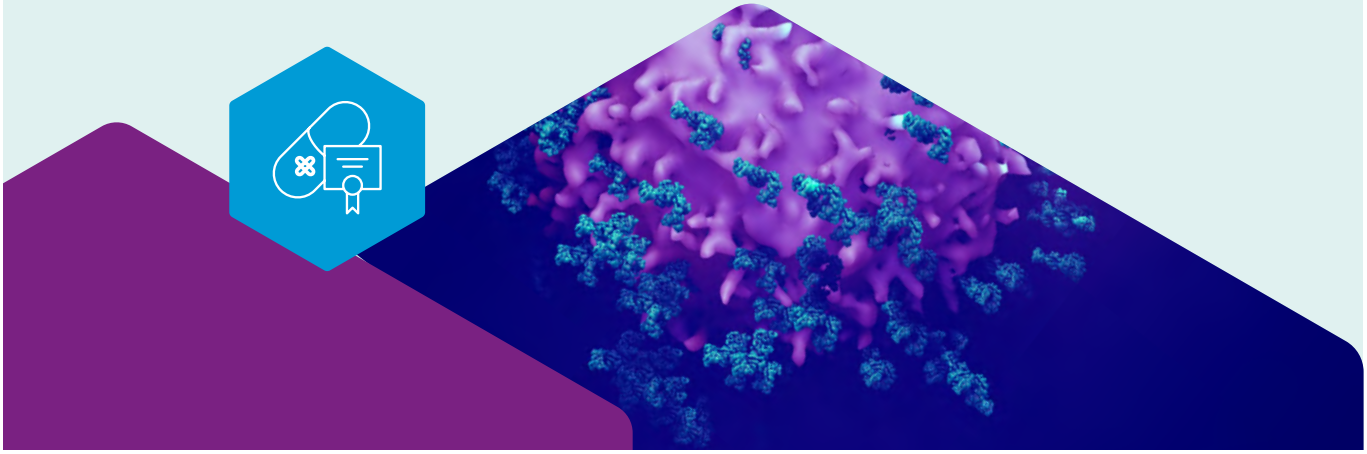
Many patients do not respond satisfactorily despite currently available cytokine therapies. For example, more than one third of patients with IBD do not respond to these treatments. In addition, blockade of such cytokines has been reported to associate with development of severe side effects and/or new immune-mediated pathologies.

TREATMENT AND NEEDLE BURDEN

Cytokines are large molecules and must typically be injected subcutaneously (SC) by the patient or given by intravenous infusion (IV). SC doses are administered by the patient in their home, and IV doses require patients to travel to an infusion site. Both of these drawbacks are complicated by patients sensitive to or fearful of needles and injections.

So what makes JAK inhibitors a contender to these successful and entrenched biologics?

- In a treatment landscape where patients don't respond to biologics, efficacy is diminished with second- or third-line biologics. JAKs offer a new efficacious treatment option to patients who have already gone through anti-TNF and other biologic therapies.
- JAKs are given via oral route of administration (RoA), meaning that patients are more willing to participate in clinical trials and more likely to select an oral RoA over an SC or IV option. Additionally, patients don't need to be instructed on how to inject themselves, nor do they need to arrange transportation to injection sites.



JAKs and the market

JAKs have experienced some key milestones in recent years as regulatory agencies begin to tighten their outlook on both established and new JAK inhibitors.

2012

The FDA approves the first JAK, Xeljanz©, for Rheumatoid Arthritis (RA) only in patients with an inadequate response to methotrexate.

2016

Lilly/Novartis' Olumiant© was approved by the EMA for RA - the first JAK inhibitor approved to treat RA in the European Union.

2017

The EMA approves Xeljanz© for RA.

2018

The FDA issues a safety warning for Lilly/Novartis' Olumiant© for malignancies, serious infections, and thrombosis. Its sales were $133m in the first 9 months of 2018.

Revenue for Xeljanz© continues to increase with $1.774 billion in FY2018.

The FDA approves Xeljanz© for additional indications in Psoriatic Arthritis (PsA) and Ulcerative Colitis (UC).

2019

Gilead announces NDA filing in Japan for RA.

FDA imposes safety warning for AbbVie's upadacitinib, stipulating that the drug's labelling must carry prominent mention of the risk of thrombosis.

FDA imposes safety warning for a 10mg dose of Xeljanz© for US after Pfizer reports an increase in pulmonary embolism and death in a post-marketing safety trial.

AbbVie receives FDA approval of RINVOQ for RA in patients with an inadequate response to methotrexate.

https://pharmaphorum.com/news/lilly-scores-with-two-olumiant-trials-in-atopic-dermatitis/

Growing safety concerns

So, what's next for JAKs? Their potential as the next generation treatment tools has, for the moment at least, been dented by the narrowness of regulatory approvals and labeling limitations.

But pharma has not been put off. Promising results of drug candidates in pre-clinical and clinical phases is a major factor driving the development of the JAK inhibitors pipeline. And key players are still involved and investing in the global JAKs market, including Eli Lilly, Astellas, Pfizer, Baxter, Novartis, Gilead, Sierra Oncology, CTI BioPharma, and Incyte.

And, even though tofacitinib faced recent FDA warnings, Pfizer is doubling down their investment in the JAK MoA with multiple pipeline assets including those outlined here.

Other later-stage JAKs under development to note include Gilead/Galapagos' filgotinib, a late-stage candidate for rheumatoid arthritis and Astellas' peficitinib.

Abrocitinib

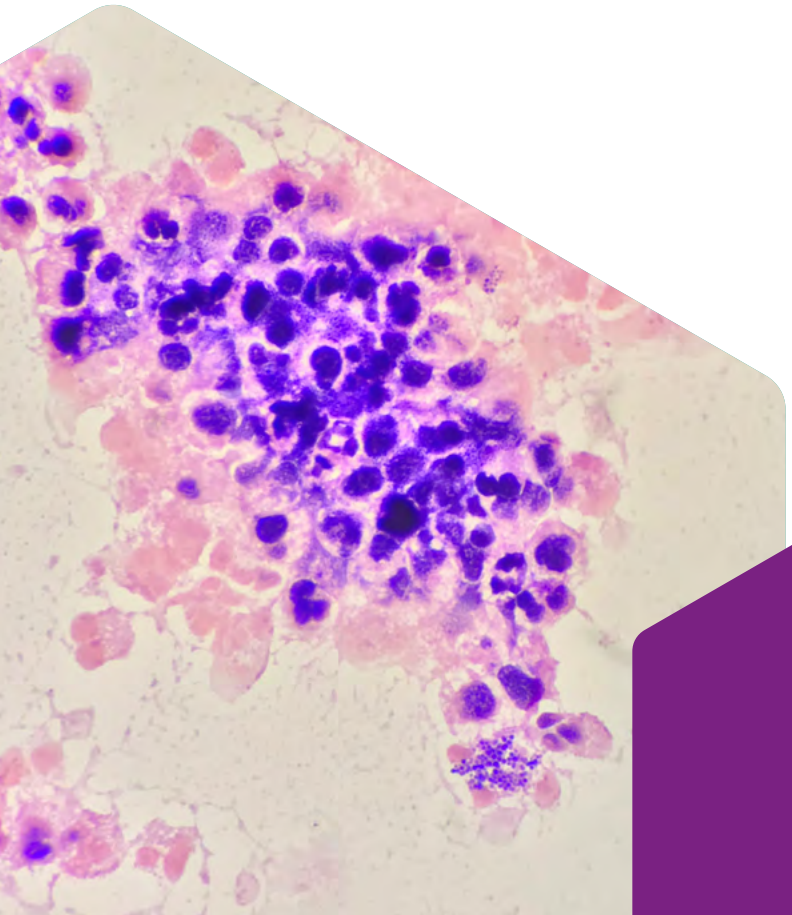
A selective JAK1 inhibitor being studied in Atopic Dermatitis

PF-06651600

A selective JAK3 inhibitor being studied in RA, UC, CD, AA, and Vitiligo

PF-06700841

A JAK1/TYK2 inhibitor being studied in PsO, UC, CD, AA, and Vitiligo



Are brighter horizons ahead?

While the future for JAKs may be unclear right now, what is clear is this: JAKs still have the potential to be blockbuster drugs for chronic diseases that countless patients need.

In the US, reports The Arthritis Foundation, the number of adults with doctor-diagnosed arthritis is projected to increase 49% to 78.4 million (25.9% of all adults) by 2040, while a study published by the National Psoriasis Foundation shows that globally more than 125 million people suffer from psoriasis.

The growth in demand for medications is expected to continue to fuel the JAK inhibitors pipeline in the coming years.

The evolving treatment paradigm can certainly find a place for them, as either high-dose induction, low-dose maintenance or combination therapies.

The question for pharma is not if, but how. While JAKs' efficacy is not in question, dosage and safety is. The challenge now is just how to set the thermostat to achieve optimum therapeutic effect.

So, while JAKs may not have gotten it right this time around, we believe that more selective JAKs will soon hit the market and begin to establish their own share of voice.

Our conclusion? JAKs are one to watch - closely.

About the Author

Gilles de Prevoisin is a Senior Consultant at Deallus based in the Los Angeles office. His expertise range across different therapeutic areas, particularly rare diseases, gene therapy, respiratory diseases, inflammation and immunology, and diagnostics. Striving to establish his teams as valuable thought partners for clients, he brings a novel approach to delivering insights and analysis.

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***Deallus** / di æ lus / (adj): intelligent, bright, astute, insightful, perceptive*

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Deallus London
1 Poultry,
London,
EC2R 8EJ

+44 207 337 6900
london@deallus.com

Deallus Tokyo
3F Kabuto-cho Daiichi
Heiwa Bl, 5-1 Kabuto-cho,
Nihonbashi, Chuo-ku, Tokyo,
103-0026, Japan

+81 3 5847 7946
tokyo@deallus.com

Deallus New York
483 Tenth Avenue,
Suite 400,
New York City,
New York, 10018

+1 646 553 4280
newyork@deallus.com

Deallus Los Angeles
11500 W Olympic
Boulevard, Suite 417,
Los Angeles,
CA 90064

+1 310 775 8910
losangeles@deallus.com

Deallus Sydney
161 Castlereagh St,
Sydney,
NSW 2000,
Australia

+61 (0) 40 699 1308
sydney@deallus.com

deallus.com