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GSK's Immunology Strategy Edges Closer To Delivering

by Jessica Merrill

GlaxoSmithKline is working to establish an immuno-inflammation portfolio and extend learnings to other therapy areas. Sirukumab could be GSK's first new product in I&I beyond Benlysta. Chief Immunology Officer Paul-Peter Tak outlined his strategy in an interview with *Scrip*.

Best known for developing respiratory drugs, HIV medicines and vaccines, *GlaxoSmithKline PLC* has ambitions to become an immuno-inflammation powerhouse. A five-year initiative to establish a pipeline of drugs in the area could deliver its first product to the commercial market next year.

GSK announced Sept. 23 that a BLA for the human anti-interleukin-6 (IL-6) antibody sirukumab was filed with FDA for the treatment of moderate to severe rheumatoid arthritis. The drug, in development under a collaboration with *Janssen Biotech Inc.*, could be the company's first new drug in immuno-inflammation beyond *Benlysta* (belimumab), which GSK acquired in 2012 with the $3.6bn acquisition of *Human Genome Sciences Inc.* (Also see "*Benlysta In GSK's Hands: A Slow-but-steady Launch, Or A Dud?*" - Pink Sheet, 23 Jul, 2012.)

> ***"You want to build a presence in the field with medicines that are very likely to work, and then after that bring very disruptive medicines [to market]," Tak said.***

GSK's Chief Immunology Officer Paul-Peter Tak has been tasked with driving immunological

research at the big pharma. The company is about to enter a new phase as Emma Walmsley, currently head of Consumer Healthcare, takes over for Sir Andrew Witty as CEO next year. The insider appointment is viewed as a commitment to the current growth strategy. (Also see "*GSK's New CEO Designate Walmsley Fortifies Volume Growth Strategy*" - Scrip, 20 Sep, 2016.)

A rheumatologist by training, Tak joined the company in 2011, transitioning from a career in academia. He worked as professor of medicine and chair of the Department of Clinical Immunology & Rheumatology at the Academic Medical Centre/University of Amsterdam prior to joining GSK as head of Immunology & Inflammation.

In January, Tak was promoted to Chief Immunology Officer, extending oversight of immunological research in other therapy areas, like immuno-oncology, dermatology and infectious diseases.

"Over the last several years, we have increasingly invested in immuno-inflammation, and I would say more generally immunology," Tak said in an interview in New York. "During the last five years, I think the immuno-inflammation portfolio has come together into a strategic and synergistic portfolio for a whole variety of diseases."

The size of the team dedicated to I&I has grown, although not substantially. Most of the focus has been on reprioritizing human resources to high-priority projects. The I&I unit – incorporating everything from early discovery to late-stage drug development – includes about 220 people.

"During the first six months after I arrived, I terminated 40% of the programs, thereby I could release the resources, including the headcount, to work on very specific and focused programs that are all consistent with the strategy," Tak said.

The budget has grown because the portfolio has matured. "There was nothing we had in the portfolio except Benlysta that was even candidate-selected five years ago and now we have quite a lot in the clinic," Tak added.

Sirukumab And Benlysta Will Anchor The Budding Pipeline

Among Tak's first priorities after joining GSK were to bring a late-stage drug into the I&I portfolio and explore new opportunities for Benlysta, approved for lupus. On the first order of business, GSK partnered with Janssen on sirukumab in December 2011, bringing in a Phase III-ready asset for RA.

Meanwhile, Benlysta, a first-in-class antibody that inhibits B-lymphocyte stimulator (BLyS), was hailed as the first new drug for lupus in 50 years when it launched in 2011 for systemic lupus erythematosus, but it failed to meet early commercial expectations. (Also see "*HGSI/GSK's*

Benlysta Gets BLySfully Clean Labeling, Escaping Feared Restrictions" - Pink Sheet, 10 Mar, 2011.) Benlysta's moderate efficacy tempered sales; it generated just £209m in 2015, leaps and bounds lower than the $5bn in sales some analysts had forecast the drug would generate in 2016 at the time it launched. The slower-than-expected launch led to the demise of HGS, when GSK took advantage of the opportunity to buy out its partner. (Also see "*Benlysta In GSK's Hands: A Slow-but-steady Launch, Or A Dud?*" - Pink Sheet, 23 Jul, 2012.)

GSK announced Sept. 23 that it filed a BLA in the US and marketing authorization application extension in Europe for a new subcutaneous formula of Benlysta in two presentations, a single-dose prefilled syringe and a single-dose autoinjector. The current formula is administered intravenously. The company is also running trials testing Benlysta in new indications.

Tak believes sirukumab and Benlysta will be anchors for an emerging pipeline of drugs to follow, some discovered internally at GSK and others by partners. The goal is to launch sirukumab as a complement to Benlysta, targeting rheumatology practices to firmly establish the I&I commercial organization and then follow up with newer novel medicines.

> ***The decision to partner on a known mechanism like sirukumab was by design, Tak said.***

Sirukumab is not a first-in-class agent and will likely be the third IL-6 inhibitor to reach the market, behind *Roche*'s marketed *Actemra* (tocilizumab) and *Regeneron Pharmaceuticals Inc./Sanofi*'s sarilumab, pending at FDA with an Oct. 30 action date. The launch could be a challenging one given the competitive dynamics in the RA market and the fact that Phase III data for sirukumab suggest the product might have inferior efficacy to Actemra and sarilumab when it comes to ACR20 responses, a standard measure used in trials. (Also see "*Too Little, Too Late For GSK/Janssen's Sirukumab in RA?*" - Scrip, 13 Jun, 2016.)

But Tak insists the decision to partner on a known mechanism like sirukumab was by design. "You want to build a presence in the field with medicines that are very likely to work, and then after that bring very disruptive medicines [to market]," he said. "Not all of them are going to make it. Some of them will fall over, but some of them will be completely transformative, we believe, and they will be blockbusters as well," he added.

Tak believes sirukumab may have some advantages over the competition because the drugs are

slightly different. Sirukumab targets the IL-6 cytokine, while Actemra and sarilumab target the IL-6 receptor. Sirukumab has demonstrated benefits to patients when dosed every four weeks via subcutaneous injection, while labeling for Actemra recommends weekly dosing and sarilumab was dosed every other week in the pivotal trials supporting the regulatory filing.

With Benlysta, GSK is looking to expand the drug to new indications, building off the knowledge the drug works in lupus, an autoantibody-dependent autoimmune disease. SLE is characterized by high circulating autoantibodies, which are produced by B-cells and can trigger inflammatory damage.

"If Benlysta works in autoantibody-dependent disease that manifests itself as the signs and symptoms of SLE, then it is quite likely that it may also work in other diseases driven by autoantibodies," Tak said. "In the first year, I started a strategic plan to go into other diseases that are dependent on autoantibodies."

One indication GSK is exploring now is Sjögren's syndrome, an immune disorder driven by autoantibodies that results in dry eyes and dry mouth.

"If you look at the official epidemiology, it is relatively rare, but I am absolutely convinced it is not rare," said Tak. "Patients are complaining about dry mouth and dry eyes and many of them are depressed and have fatigue and it is easy to miss, so it is underdiagnosed."

GSK is testing Benlysta in a Phase II trial in patients with Sjögren's syndrome, testing both belimumab as a monotherapy and in combination with Roche's anti-CD20 antibody *Rituxan* (rituximab).

"There is a very strong theoretical rationale that you might optimize the use of Benlysta by just one single course, consisting of two infusions in two weeks of Rituxan," Tak said. The company is also exploring the regimen for the treatment of SLE.

Novel Mechanisms In The Clinic

GSK has several novel drugs in earlier stages of development in I&I. In Phase II, GSK is studying the granulocyte-macrophage colony-stimulating factor (GM-CSF) cytokine GSK3196165 in patients with inflammatory hand osteoarthritis (HOA). The drug is one that GSK in-licensed in from *MorphoSys AG* in 2013. Tak described OA as a big unmet medical need and commercial opportunity because the disease impacts about 10% of the general population and no disease-modifying drugs are approved for the condition.

Another drug Tak is energized about is GSK2982772, a RIP1 kinase inhibitor that was developed internally and recently entered the clinic. RIP1 plays a key role in a variety of diseases, including TNF-mediated diseases like RA and inflammatory bowel disease, as well as diseases

characterized by apoptosis, he said. GSK is moving development forward aggressively, opting to initiate three Phase II studies testing the drug in parallel in patients with RA, psoriasis and ulcerative colitis. The studies initiated in September.

"I will know at the end of next year probably what the best indications are," Tak said.

The executive is also aiming to keep GSK involved in early and novel research by fostering relationships with biotech startups and academia, relying on a variety of mechanisms. One is the European venture firm Medicxi Ventures that GSK backs and on which Tak sits on the scientific advisory board. Another is DPAc (Discovery Partnerships with Academia), through which GSK collaborates with academics.

Tak has also established something called the Immunology Network, which has two components: a board of external immunology academics from different backgrounds that advise GSK and a catalyst sabbatical program to embed academic scientists in GSK's labs.

GSK's immuno-inflammation research has come a long way in five years, but the true test will be getting new drugs to market and establishing them as commercially successful franchises.