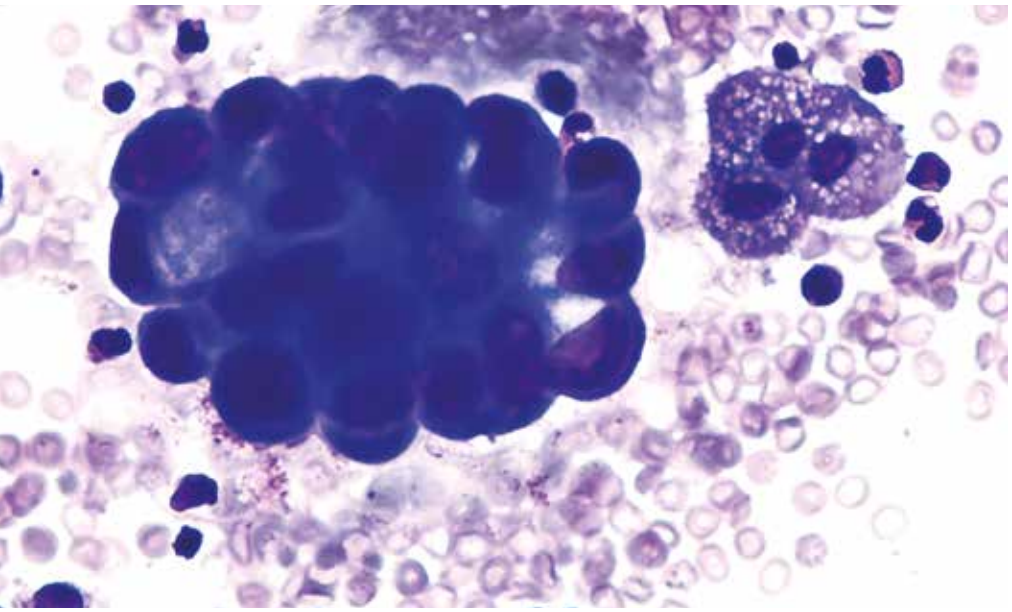
Scrip
30 June 2017
No. 3860
scrip.pharmamedtechbi.com
Pharma intelligence | informa



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Was PD-L1 Test To Blame For Failure Of Bristol's Opdivo In '026 Trial?

EMILY HAYES emily.hayes@informa.com

The type of PD-L1 test and the way it was used by **Bristol-Myers Squibb Co.** could explain the failure of *Opdivo* in the CheckMate 026 first-line lung cancer trial, according to an editorial accompanying the study publication in the *New England Journal of Medicine*,and the author advises the assay used by competitor **Merck & Co. Inc.** is the best choice for newly diagnosed patients.

Full results for the CheckMate 026 study were published by David Carbone, Ohio State University Comprehensive Cancer Center, and colleagues on June 22, following the bombshell news of its failure in August 2016 and a presentation at the European Society of Medical Oncology meeting that October. The study's primary endpoint was progression-free survival (PFS) for the PD-1 inhibitor Opdivo (nivolumab) compared to chemotherapy as a first-line treatment for metastatic non-small cell lung cancer (NSCLC) patients with at least 5% expression of the PD-L1 biomarker.

The test used to assess PD-L1 expression in the study was the PD-L1 IHC 28-8 pharmDx assay developed with Dako, part of **Agilent Technologies Inc.**

The finding that the drug also failed to show a benefit in a subgroup analysis of patients with over 50% PD-L1 expression was especially disappointing and surprising. After all, **Merck & Co. Inc.**'s competing PD-1 inhibitor *Keytruda* (pembrolizumab) demonstrated a PFS and OS benefit over chemotherapy in the first-line KEYNOTE-024 study of first-line NSCLC prospectively selected for having at least 50% expression. *(Also see "Merck Poised To Be First To Market With A PD-1 For First-Line Lung Cancer" Scrip, 16 Jun, 2016.)*

"In the exploratory subgroup analysis involving patients with a PD-L1 expression level of 50% or more, the hazard ratio for disease progression or death was 1.07 (95% CI, 0.77 to 1.49), and the hazard ratio for death was 0.90 (95% CI, 0.63 to 1.29). In this subgroup, the response rate was 34% (95% CI, 24 to 45) in the nivolumab group and 39% (95% CI, 30 to 48) in the chemotherapy group," the CheckMate 026 investigators reported in the NEJM.

Keytruda is now the first and only checkpoint inhibitor approved for first-line metastatic NSCLC. *(Also see "NSCLC Momentum Goes To Merck And Roche, Bodes Well For Combinations" Scrip, 9 Feb, 2017.)*

In an NEJM editorial accompanying the full CheckMate 026 results, Edward Garon, of the David Geffen School of Medicine at the University of California, Los Angeles, highlighted the similarities between Opdivo and Keytruda and questioned whether differences in the PD-L1 assays used by Merck and Bristol could be at the root of the different outcomes.

"Could efficacy greatly differ between these similar drugs? In many tumor types, including previously treated NSCLC in an unselected population of patients, the two agents show remarkably similar results. Strong differences in efficacy that are limited to first-line therapy for NSCLC are highly improbable," he said in the editorial.

It's possible that the use of too broad a population, "coupled with a PD-L1 assay that discriminates poorly at certain values,"

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BROUGHT TO YOU BY THE EDITORS OF **PHARMASIA NEWS**, **START-UP** AND **SCRIP INTELLIGENCE**

CANTOS's Pleasant Surprise
Stabilizing plaques prevents CV events (p11)

New Hope In MS
At last, cladribine tablets near EU market (p21)

Bio 2017
Growing the biotech ecosystem (p14–16)

from the editor

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Quis custodiet ipsos custodes? How do we know that the biomarkers used in drug development are beyond reproach? We must police the assays.

The latest speculation over the surprising contrast in performance in first-line lung cancer between Bristol-Myers Squibb's PD-1 inhibitor *Opdivo* and Merck & Co's rival PD-1 inhibitor *Keytruda* points a finger of possible blame at the assay used by BMS to determine the level of the PD-L1 biomarker expression in patients (see cover story). On the basis of the trials each company conducted, Merck's product got a first-line NSCLC indication and BMS's didn't.

In these cases, the biomarker wasn't used as a surrogate for drug efficacy, but to categorize patients. It isn't certain that the assay accounted for the differing trial outcomes, but the author of an *NEJM* editorial thought it a plausible hypothesis. In any case, the mere possibility reminds us that pharma R&D engines operating at speed in highly competitive fields are subject to intense stress. Biomarkers and their assays are the unglamorous but essential cogs in the galloping, gaudy whirl of the immuno-oncology carousel, and they need due care and attention.

The recent "tissue-agnostic" approval of Keytruda based on a biomarker rather than tumor location heralded a new dawn for biomarker-based therapeutics.

However, the US FDA is still figuring out how to validate assays to be used to support the qualification of biomarkers for use as drug development tools. Using biomarkers to develop new drugs – and ultimately to determine personalized treatment approaches – is still in its infancy.

Scrip

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Scrip is published by Informa UK Limited. ISSN 0143 7690.

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Shire CEO: Mydayis To Be Big ADHD Drug, But No Ex-US Launch Planned (Yet)
http://bit.ly/2tcpxg3
Flemming Ornskov says FDA approval of long-lasting ADHD therapy Mydayis is part of Shire's plan to dramatically increase neuroscience revenues – but it won't launch the drug outside the US for some time.

Novartis' Brolucizumab Shows Dose Advantage Over Eylea In nAMD Trials
http://bit.ly/2tMEhzA
Prospects for Novartis' nAMD eye treatment brolucizumab rose on news the novel anti VEGF treatment met primary and key secondary endpoints in two Phase III studies compared to Eylea, using less dosing.

ADA 2017: Outlook For New Longer Acting Insulins Amid US Pricing Sensitivity
http://bit.ly/2sV1bYg
The high cost of basal insulins in the US has drawn a fair amount of scrutiny recently, placing increased pressure on new longer acting insulins to demonstrate superior cost-efficacy compared to standard of care Lantus to gain preferential formulary placement.

Pfizer, Cipla Pledge Better Access To Affordable Cancer Therapies In Africa
http://bit.ly/2slq4p0
Pfizer and Cipla have separately committed to expanding access to affordable oncology drugs in sub-Saharan Africa in collaboration with the American Cancer Society and the Clinton Health Access Initiative.

Novartis' Kisqali CHMP Nod In Fast-Moving Market
http://bit.ly/2rTMtg0
The likely upcoming EU approval of Kisqali, Novartis' answer to Pfizer's Ibrance, opens a new front in a breast cancer marketing battle that is likely to get more intense.

Versant & MPM Back Synthetic Lethality Newco With $68M
http://bit.ly/2tdnuZr
Repare Therapeutics Inc., a Boston and Toronto-based cancer biotech, focusing on synthetic lethality, has hit the ground running with a $68m series A round from seasoned venture capitalists.

inside:

Is BMS The Must Have Immuno-Oncology Accessory Of The Season?

LUCIE ELLIS lucie.ellis@informa.com

Pfizer Inc. has been spouting recently about potential large scale M&A opportunities – prompting suggestions the pharma giant might have an interest in acquiring its US big pharma peer **Bristol-Myers Squibb Co.** for the latter firm's superior immuno-oncology pipeline.

BMS is a leader in the IO market with its programmed cell death protein 1 (PD-1) inhibitor *Opdivo* (nivolumab), and it has been jockeying for the number one position against closest rival, **Merck & Co. Inc.'s** *Keytruda* (pembrolizumab), since both drugs were approved in 2014 for use in melanoma.

Opdivo and Keytruda are well matched cancer therapies, with very little to differentiate the two drugs. BMS has an attractive intensive, and extensive, clinical development program for Opdivo, testing the drug in numerous cancer combination trials. BMS also has the luxury of having several novel IO mechanisms in development in-house – as monotherapies and in combination with Opdivo. BMS's early IO research includes trials for drugs with new mechanisms of action in oncology immunotherapy, such as indoleamine 2,3-dioxygenase (IDO) inhibitors and molecules targeting lymphocyte-activation gene 3 (LAG3). *(Also see "Bristol's New Chief Scientific Officer Lists Oncology Priorities, But Little New" Scrip, 6 Jun, 2017.)*

Most importantly though, the company is a bite-sized big pharma (similar to **AstraZeneca PLC**, a former Pfizer M&A target) making it digestible for a sprawling drug maker like Pfizer. *(Also see "You blew it, Pfizer tells AstraZeneca" Scrip, 26 May, 2014.)*

All of this has led some market speculators to suggest an acquisition of BMS would make Pfizer a much more relevant player in the IO space.

WE NEED TO TALK ABOUT BAVENCIO

One major roadblock for a Pfizer and BMS pairing is the former company's existing IO deal with **Merck KGAA** of Germany. Pfizer initiated this collaboration in 2014, not long after its attempted acquisition of AstraZeneca failed. From the deal, the two companies have successfully brought *Bavencio* (avelumab), an anti-PDL1 product, to market.

However, "as the fourth entrant into a field of five anti-PDx therapies that are already approved, avelumab seems like it will struggle to gain much traction. Further, initial clinical studies suggest the product might have a slightly worse side-effect profile, but Pfizer downplays the clinical implications of this," Timothy Anderson, Global Pharmaceuticals Analyst at Sanford C. Bernstein, highlighted in a June 19 note about Pfizer's large-scale M&A potential.

The fifth anti-PD-1/PD-L1 drug on the market currently is AstraZeneca's *Imfinzi* (durvalumab), which was approved earlier this year just after Pfizer and Merck's Bavencio. *(Also see "AstraZeneca's Imfinzi Debuts In Bladder Cancer With Combo Coming Soon" Scrip, 1 May, 2017.)*

With Bavencio playing catch up to the likes of Keytruda, Opdivo and Roche's *Tecentriq* (atezolizumab), Anderson highlighted that Pfizer could upgrade its PD-1 agent to keep up with the swift moving IO field. Pfizer has not disclosed the value of a potential breakup fee to get out of its deal with German Merck, but has previously noted it would be immaterial relative to the size of a large acquisition, Anderson said.

However, Pfizer has repeatedly said in analyst and investor calls that it is committed and happy with Bavencio as its backbone in IO and Anderson said a U-turn on this statement would be out of character for Pfizer – which he called a "consistently transparent company that reliably signals its intentions."

> Pfizer is 'equipped to integrate a large deal'

As recently as June 9 – during an investor call about the 2017 American Society of Clinical Oncology annual meeting, held in Chicago June 2-6 – Pfizer's VP of early development, translational and IO, Chris Boshoff said: "We are pleased with what we've achieved with Merck KGaA… in the last 24 months. We now have two approvals, 30 ongoing programs, 11 registration programs [and] nearly 5,000 patients have now been treated in clinical trials. So, we believe that this will be a meaningful checkpoint inhibitor in combinations in the future."

Pfizer's apparent enthusiasm and long-term commitment to Bavencio – which was approved for use in Merkel cell carcinoma and bladder cancer in March and May this year, respectively – could hamper any larger IO deal, despite the company's claims it is shopping around with oncology being the most relevant M&A area.

BROADER M&A UNCERTAINTIES LINGER

Pfizer management said during the 38th Goldman Sachs Annual Healthcare Conference that its R&D team was "equipped to integrate a large deal" and that the company continued "to look at potential deals of all sizes" – comments that could be seen as a precursor to a takeover bid.

Regardless of Pfizer's eagerness for M&A in general (with or without BMS on the cards), Goldman Sachs analysts highlighted in a June 19 note about the group's Annual Healthcare Conference that the political environment in the US was still a concern for companies attempting large-scale deals.

Analysts cited tax policy uncertainty, ongoing buyer/seller disconnects, poor performance of recent deals and concern about repercussions from the Trump administration in the event of job losses, as reasons why big M&A action might not occur in the second half of 2017. Still, they added that "investor conversations suggest hope hangs high" for more pharma deals this year.

Published online 23 June 2017

Pfizer's Xeljanz Is First JAK Positive In Psoriatic Arthritis

INES MIHEL & CHRISTINA VASILIOU

Rheumatologists suggested **Pfizer Inc.**'s *Xeljanz* (tofacitinib) will be a suitable treatment option for patients with heavy joint involvement and minimal skin disease, or patients not concerned about their skin symptoms, after Pfizer unveiled pivotal Phase III data from the OPAL BEYOND and OPAL BROADEN studies in psoriatic arthritis (PsA) at the recent European League Against Rheumatism (EULAR) meeting in Madrid, Spain.

Xeljanz is expected to be the first-in-class JAK inhibitor in PsA. Pfizer filed the lower dose tested in the studies (5 mg twice daily) with the US FDA for the expanded indication in May, and approval is likely to be granted in the first quarter of 2018. Xeljanz is already marketed in rheumatoid arthritis (RA), following FDA approval in 2012 and EU approval in 2017. Pfizer is also investigating the JAK inhibitor in other autoimmune indications, including ulcerative colitis and atopic dermatitis.

In the OPAL BEYOND trial, 5 mg and 10 mg twice daily doses of Xeljanz were tested against placebo in PsA patients who were inadequate responders to at least one anti-tumor necrosis factor (TNF) biologic either due to lack of efficacy or an adverse event. Xeljanz met the primary endpoint of American College of Rheumatology 20 (ACR20), with response rates of 50% and 47% observed in the 5 mg and 10 mg treatment groups, respectively, compared to 24% in the placebo arm. Significant improvements as measured by ACR 20 and the Health Assessment Questionnaire Disability Index (HAQ-DI) score were observed as early as week two.

In addition, improvements in other PsA domains including dactylitis (inflammation of fingers or toes) and enthesitis (where tendons or ligaments insert into the bone) were also observed in this trial, and were significant after three months of treatment with both doses. But Xeljanz's efficacy in the management of skin symptoms was less impressive, with the Psoriasis Area and Severity Index (PASI) 75 response rate in the 5 mg group not meeting statistical significance after three months of treatment.

In the OPAL BROADEN trial, 5 mg and 10 mg twice daily doses of Xeljanz were tested in patients who were naïve to TNF inhibition. The study included **AbbVie Inc.**'s *Humira* (adalimumab) as a comparable control. At month three, Xeljanz 5 mg and 10 mg showed statistically significant improvements compared to placebo as measured by the primary endpoint of ACR20. ACR20 responses were reached by 50% of patients on the 5 mg dose and 61% on the 10 mg dose vs 52% in the Humira arm and 33% in the placebo arm. Response rates for Xeljanz achieved statistical significance as early as week two, and were maintained to 12 months. Improvements in dactylitis and enthesitis were once again observed but were not significant after three months for the 5 mg dose.

Philip J. Mease, the lead author of this study, presented the non-responder imputation (NRI) analysis for PASI 75 scores, which classifies missing values as non-responders. Mease stressed that PASI 75 response rates were statistically significant after three months with both Xeljanz doses.

In both trials, no unexpected safety signals were observed, and the frequency and type of reported adverse events (AEs) were consistent with the AEs observed in the RA studies. Xeljanz's safety profile appears to be comparable to that of the leading TNF inhibitors. Although skin findings were disappointing in the two trials after three months, with the Xeljanz 5 mg twice daily dose not meeting the PASI 75 endpoint, Mease noted that "most patients who visit a rheumatologist have minimal skin involvement". Additionally, he highlighted that after 12 months in the NRI analysis, the 5 mg twice daily dose reached a PASI 75 response of 56%, which was comparable to the response rate observed in the Humira arm.

STRUGGLE

With Phase III trials in both TNF-naïve and TNF-experienced patients, Pfizer is aiming to ensure use across multiple lines of therapy. However, it may flounder in both settings.

Xeljanz will struggle to establish a place early in the psoriatic arthritis treatment algorithm, despite the convenience of its oral formulation. Branded anti-TNF biologics currently dominate the early treatment setting in PsA and are difficult to displace due to their proven efficacy and preferential formulary placement. The growing availability of anti-TNF biosimilars complicates the picture further. The reduction in the cost of anti-TNFs following the launch of biosimilars will negatively impact Xeljanz's uptake, as payers are likely to enforce step therapy requiring treatment with an anti-TNF before Xeljanz can be used.

Celgene Corp. 's oral phosphodiesterase-4 (PDE-4) inhibitor, *Otezla* (apremilast) is also expected to pose a threat to Xeljanz. Celgene reported that Otezla achieved global sales of $1.0bn in 2016. Despite its modest efficacy compared to the leading anti-TNFs, Otezla has seen strong uptake since its 2014 launch in PsA. Key opinion leaders attribute Otezla's strong uptake to its strong tolerability and safety profile, and note that this will give the PDE-4 inhibitor a competitive edge over Xeljanz. Xeljanz carries a black box warning for an increased risk of serious infections and malignancies.

One KOL interviewed previously by Datamonitor Healthcare believes that Otezla's safety profile will be its strong suit. "There may be some competition [between Xeljanz and Otezla] but I think one of the stronger points that apremilast has is its safety profile. So, there may be less efficacy but definitely better safety, so that is why it is a better drug to start with."

Aside from having a more favorable safety profile, Otezla also benefits from an attractive price tag. The annual treatment cost for Otezla is approximately 30% lower than that of the leading biologics *Enbrel* (etanercept) and Humira. Xeljanz's pricing in psoriatic arthritis will be dictated by its price in RA, which is in line or higher than that of the key anti-TNFs once discounts are factored in. Indeed, payers are currently restricting patient access to Xeljanz in RA based on its high cost.

Xeljanz will also face competition in later lines of therapy. **Novartis AG**'s interleukin 17 (IL-17) inhibitor, *Cosentyx* (secukinumab) and the Phase III IL-17 agent *Taltz* (**Eli Lilly & Co.**'s ixekizumab), which mainly target late lines of therapy, have demonstrated strong efficacy in both joint and skin manifestations. Indeed, Cosentyx is now the preferred agent in the post-TNF setting and benefits from long-term data showing high and sustained responses. Datamonitor Healthcare analysts believe Xeljanz will be a suitable option for patients with minimal skin involvement since its efficacy in joint manifestations is comparable to that of Cosentyx and Humira.

Published online 20 June 2017

Sanofi Sees Immunology Momentum Heading Toward Cures

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Whereas drug development and treatment in the past has mainly focused on one mechanism, **Sanofi** explains, research now is focused on multiple targets with growing understanding of the causes of inflammatory diseases – and potential to target the causes of diseases rather than symptoms.

Sanofi has hit some important milestones in recent months. Its interleukin-6 receptor blocker *Kevzara* (sarilumab), which is partnered with **Regeneron Pharmaceuticals Inc.**, was approved in May for moderate to severe rheumatoid arthritis. In March, the company scored a victory with the approval of *Dupixent* (dupilumab), a dual inhibiting antibody of IL-4 and IL-13 for atopic dermatitis. Dupixent now is the only biologic approved for this condition.

Following these two approvals, Sanofi is now "firmly anchored in immunology" beyond multiple sclerosis, Frank Nestle, global head of immunology therapeutic research area and chief scientific officer for North America, said during a June 21 webinar about Sanofi's R&D strategy in the space. Through its partnership with **Genzyme Corp.**, Sanofi already was established in MS with the drug *Aubagio* (teriflunomide).

But the approvals are just the beginning for the company – Sanofi has a full pipeline covering multiple mechanisms in autoimmune diseases and is taking a broad approach to development.

Autoimmune diseases are associated with enormous costs to the health care system, the company noted, accounting for $100bn in costs per year in the US, compared to $100bn for heart diseases and $57bn for cancer. According to Sanofi, there are some 80 autoimmune and chronic inflammatory diseases and the worldwide market is worth around $60bn and growing.

For diseases like rheumatoid arthritis, there are many approved options – but the company said there still is room for improvement. Combination therapies for RA typically only provide a 50% improvement in about one-third of patients and only 30% of patients with Crohn's disease and ulcerative colitis get a complete remission with therapy, company execs noted during the webinar.

Sanofi also pointed to many autoimmune diseases where therapeutic options are limited, including atopic dermatitis, idiopathic pulmonary fibrosis and scleroderma (*see box*).

While a lot has been achieved in the last 20 years, the company is "not sitting back on what we achieved so far" and is aiming for higher goals, said Christian Antoni, therapeutic area head for immunology and inflammation.

Currently, Sanofi's immunology pipeline focuses on dermatology, respiratory, rheumatology and allergies (*see table below*).

While immunology drug development traditionally was driven by serendipitous discovery and typically focused on one target per disease, there has been a fundamental change in that today researchers are really understanding the mechanisms underlying disease and investigating multi-targeted approaches, Nestle said.

Today researchers know that "a multitude of molecular events" make up a disease and are developing antibodies that recognize two or even three targets, the exec explained.

Sanofi's pipeline includes a bispecific antibody – SAR156597 – that targets IL-4 and IL-13 and is being developed for scleroderma. Dupixent also targets both IL-4 and IL-13 and in addition to its approval for severe atopic dermatitis, is in development for asthma, nasal polyposis and eosinophilic esophagitis.

"Today we are capable with our very advanced pharmaceutical pipeline to control or partly control disease activity, but what we want to do is really move to sustained remission," and prevent disease from developing in the first place, Nestle said.

It now is possible to deplete specific immune cells, for example B-cells or T-cells, with antibodies that are very specific. Ideally, the company wants to go for cell types that are known to be causal for disease and are "essential for disease pathogenesis," Nestle said.

Sanofi also is hoping to incorporate a target that has proven to be very successful in immuno-oncology – checkpoint inhibition – in its arsenal against autoimmune diseases. The company licensed rights to a drug targeting the CD40 ligand (INX-021) from **ImmuNext Inc.** in January, in a deal worth up to $500m in milestone payments plus sales royalties.

"We are going to bring this into the clinic to essentially deliver a smart therapy in terms of checkpoint inhibition for a broad variety of autoimmune disorders," Nestle said.

Published online 23 June 2017

Sanofi's Immunology And Inflammation Pipeline

DRUG DISCOVERY (SELECT EXAMPLES)	PHASE I	PHASE II	PHASE III
Anti-CD40 ligand: Autoimmunity	SAR440340, anti-IL-33: Asthma and COPD	Dupixent, dual inhibitor of IL-4 and IL-13: Eosinophilic esophagitis	Dupixent, Anti-IL-4 and IL-13: Asthma, nasal polyposis
RORγT sm: Autoimmunity	SAR439794, TLR4 agonist: Peanut allergy	SAR15659, IL-4 and IL-13 bispecific antibody: Systemic scleroderma	
		GZ389988, TrkA antagonist: Osteoarthritis	

Source: Sanofi

CONTINUED FROM COVER

could have led to a failure in patient selection in the study, the clinician said.

In the KEYNOTE-024 study, Merck had prospectively identified patients with at least 50% PD-L1 expression using the Dako 22C3 PD-L1 study.

"In light of these data, the presence of PD-L1 expression in at least 50% of tumor cells versus in less than 50% of tumor cells should be determined in patients with newly diagnosed, advanced NSCLC with the use of the assay associated with pembrolizumab efficacy until a prospectively evaluated alternative biomarker shows similar predictive value," Garon advised.

Garon reached his conclusions after considering differences in baseline characteristics of the study arms in CheckMate 026 and differences in use of prior radiotherapy relative to Merck's KEYNOTE-024 study and deciding that these factors were unlikely to be central to the CheckMate failure.

In a June 22 note, however, Evercore ISI analyst Umer Raffat cited a Project Blueprint study presented at the American Association of Cancer Research meeting in 2016 that compared assays and determined the tests of Merck and Bristol were "strikingly similar."

The study found that that the overall percentage agreement on results for whether the level of PD-L1 expression was 50% or not was 97.2% between the two assays, Raffat noted.

"Values above 90% are generally considered to be very good agreement," he said.

Commenting on the NEJM editorial, Bernstein Research analyst Tim Anderson said in a June 22 note that Bristol has been "quietly working behind the scenes for some time now" on a new PD-L1 assay with **Roche**'s **Ventana** unit.

Bristol has said that this does not reflect a problem with its assay, rather it has said it is "purely for commercial reasons because some hospital systems use a Dako testing platform and some use a Ventana testing platform; BMY claims that by offering both, it will broaden Opdivo's commercial appeal," Anderson said.

EXPLORING ROLE OF TUMOR MUTATION BURDEN

Lead author Carbone and colleagues had suggested a range of factors that could help explain the '026 trial failure in contrast with the Keytruda success, in their NEJM write-up. Different PD-L1 assays were used, criteria for prior radiotherapy, and glucocorticoid use was different. In addition, "imbalances in the characteristics of the patients at baseline may have favored the chemotherapy group, including disease characteristics that are associated with a better prognosis (i.e., slightly fewer liver metastases, smaller tumor burden, and a higher proportion of women)."

> Patients with a high tumor burden did have better response to nivolumab

In CheckMate 026, patients were not prospectively stratified for PD-L1 expression of 50% or higher, and there were more of these patients in the chemotherapy arm of the trial. The analyses of PD-L1 cutpoints greater than 5% were exploratory.

Fewer people in the nivolumab arm had a high tumor mutation burden, which has since emerged as being associated with better response. *(Also see "Tumor Mutation Burden Biomarker Emerges In Bristol's '026 Lung Cancer Post Mortem" Pink Sheet, 10 Apr, 2017.)* For patients with a high tumor mutation burden taking nivolumab, the response rate was 47% vs. 28% with lower tumor mutation burden and PFS was also longer (9.7 months vs. 5.8 months). Investigators did not report a difference in overall survival but there was a fair amount of crossover from chemo to nivolumab in the study.

"Overall, the current findings are consistent with the hypothesis that immunotherapy may have enhanced activity in patients with a high tumor-mutation burden. However, because this was an exploratory analysis that was not prespecified, the data are hypothesis- generating and require further prospective validation," the article states.

Garon took a cautious view of tumor mutation burden; he deemed it "intriguing, but it is akin to an algorithm developed today that predicts last season's World Series victory by the Cubs. Although potentially meritorious, its ability to pick this season's champion is unclear."

Published online 22 June 2017

EU's CHMP OKs Samsung's Adalimumab

The European Medicines Agency's scientific committee, the CHMP, has recommended approval of **Samsung Bioepis Co. Ltd.**'s *Imraldi* (SB5), a biosimilar version of **AbbVie Inc.**'s blockbuster TNF-alpha inhibitor, *Humira* (adalimumab).

Shutterstock: Puwadol Jaturawutthichai

The product was OKd for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, psoriatic arthritis, psoriasis, pediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, pediatric Crohn's disease, ulcerative colitis and uveitis.

The Imraldi submission was accepted by the EMA just under a year ago, in July 2016. The company said at the time that the EU approval application was based on results of a 52-week Phase III study which randomized 544 patients with moderate to severe rheumatoid arthritis despite methotrexate therapy and showed SB5's comparable efficacy and safety to Humira among different treatment groups. Imraldi now goes to the European Commission for a decision on marketing authorization, which should come within two or three months. If approved, it will be the South Korean company's third anti-TNF-alpha biosimilar in Europe. Marketing and distribution of the product in Europe will be handled by Samsung Bioepis' commercialization partner, **Biogen Inc.**

Amgen Inc. was the first company to gain EU approval for biosimilar adalimumab when its products *Amgevita* and *Solymbic* were authorized for marketing by the European Commission in March this year.

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Published online 23 June 2017

Shire's Ornskov On Goals And Accomplishments One Year After Baxalta Merger

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Since taking the leadership of Dublin-based **Shire PLC** early in 2013, Flemming Ornskov has become one of the most visible and outspoken CEOs in the biopharmaceutical sector, boosting his firm as a leader, if not yet the leader, in the rare disease space, and accumulating a string of notable deals, not least last year's merger with Baxalta Inc.

A bit over one year after that transaction was finalized, Ornskov spoke at length with Scrip about his ambitions for Shire going forward, specifically in ophthalmology, hemophilia and hereditary angioedema; the challenges and opportunities in the rare disease space; how his company is paying down the debt from its spate of licensing and M&A efforts; and some recent clinical development successes and setbacks. Below is a lightly edited version of the conversation.

SCRIP: *Where do things stand one year after the Baxalta merger, in terms of the integration, the synergies and how the combined portfolio and pipeline are coming together?*

ORNSKOV: From a Shire perspective, it was 7,000 Shire employees getting together with 17,000 colleagues from Baxalta and if you just look at some of the numbers today and think about where we came from, today we're at 24,000 [people], we're in 70 countries as we speak – we sell our products in 100 but we have 70 local operating countries – we have 40 marketed products, we have 40 clinical programs in the pipeline, we have 20 that are in the late stage, and we have 180 relationships now with patient advocacy groups around the world.

Seventy-five percent of our pipeline today and 65% of our sales around the world are in rare diseases and we're now in seven therapeutic areas – hematology, immunology, genetic diseases, neuroscience, internal medicine, ophthalmology and oncology, and I would say wow, this is more than I ever thought would be possible when I started as CEO in January of 2013. *(Also see "Shire's Ornskov: The Modest Pediatrician With Fierce Corporate Ambition" - Scrip, 21 Dec, 2016.)*

I think the two teams have come together incredibly fast. We both shared an ambition to become a leader in rare diseases. It's actually more a merger than an acquisition because there's a very good split of executives on both sides of the organization, a little bit more from the Shire side than the Baxalta side. But in general, I would say today we don't talk too much anymore about legacy Shire and legacy Baxalta. When I just got home from Latin America, I couldn't remember whether someone was Shire or Baxalta and I don't think they present themselves anymore as that, and it's just a mix of good talent from both companies. *(Also see "Shire's Ornskov Maps Out Future Prospects Post-Baxalta Merger" - Scrip, 6 Jun, 2016.)*

SCRIP: *How is Shire progressing in paying down the debt from the M&A it's done in recent years? Is that an issue or is it well under control?*

ORNSKOV: When you do credit ratings on individuals, you look at their past history – and I think our past history is just phenomenal. When we have done acquisitions in the past, we have paid them down incredibly fast. At the time we paid $32.5bn for Baxalta, we would not have been in the position to do that if first we hadn't obtained the credit and second started very rapidly paying that down and getting very good rates on the debt and the bonds we had to issue.

People did not believe that we have great cash flow and great discipline in paying down our debt and as we've already stated publicly, we have a clear goal of getting down to two-to-three times the multiple of our EBITDA by the end of this year. That's from a debt that was way over $20bn, so that's a very rapid payoff of debt. It's a very top priority for me personally, first of all because that's we told people we were going to do and, secondly, I think it's the right thing to do because when we borrow money and say we're going to pay it down fast, I want to do that.

It also drives us to continually look at where we can be efficient, where we can use all the excess cash that we have to pay off excess debt. That is absolutely one of my top priorities.

SCRIP: *Will Shire be doing any new issues of stock as part of its debt-reduction strategy?*

ORNSKOV: We have no strategy currently for doing any of that. We are focused on paying down the debt with the structure we have, and what we want to do is make sure that we maximize the cash flow that we generate out of the company without jeopardizing the investments we have to make in commercialization and the pipeline but [also] that we use the excess cash that we have in a [consistent way] to pay down debt.

I think you'll see this as a very disciplined, very regulated plan. If you look at the first quarter of this year, you will see that we made very good progress and reiterated our commitment of getting down to two-to-three times EBITDA. And when I interact with investors, that's one of my top messages.

SCRIP: *On recent investor calls, you've indicated that given Baxalta was the biggest M&A transaction in Shire's history and how big a task the integration was, there is no plan right now to do other large-scale M&A. Is that still the case?*

ORNSKOV: Absolutely. The priority for me and my team has been some portfolio pruning. We exited out of biosimilars, we stopped some oncology collaborations – the other thing we absolutely have continued to do is look at smaller licensing opportunities and we did one which is very attractive in the dry eye space with **Parion Sciences Inc.** for a Phase II dry eye compound. *(Also see "Shire Exits Biosimilars, Streamlines Oncology Business" - Scrip, 1 Nov, 2016.)*

So those things we continue to look at, but major M&A for the time being is not something that we are considering or focused on. We are absolutely focused on completing the [Baxalta] integration, driving the synergies, paying down the debt and then progressing the pipeline we have. We have a very rich pipeline right now, so the need to

go out and do something significant is not there. I also want to make sure that the team is focused on making the merger with Baxalta be as successful as possible and not be distracted by anything significant.

SCRIP: *With Xiidra already in your portfolio, why did you make the Parion deal to bring in another dry eye candidate?*

ORNSKOV: I cannot say to my team I have a favorite area because if they don't work in that area, they probably will be disappointed, but I've spent a significant time during my career leading ophthalmic businesses. I led the ophthalmic business at **Novartis AG** and during that period had the opportunity to license in the compound *Lucentis* [ranibizumab], against a lot of skepticism initially but it worked out.

And then when I was at **Bayer AG**, I had the opportunity to work on Eylea [aflibercept], which was a successful competitor, you could say, to Lucentis, and when I was at **Bausch & Lomb Inc.**, I had the opportunity to be involved both in an antibiotic that we brought to market for ophthalmic infections and then also a glaucoma product [latanoprostene], we licensed that is pending to get on the US market from **Nicox Inc.**

So, I've always been incredibly focused on that area and one of the first deals I did at Shire was to acquire **SARcode Bioscience Inc.** I've been involved in some failed attempts in the past at trying to develop a breakthrough compound for dry eye, so being able to bring the first product to market in the US and hopefully globally that has indications for both signs and symptoms of dry eye disease for me is a personal highlight in my career so far. *(Also see "Shire To Launch Potential Dry Eye Blockbuster After FDA Backs Xiidra" - Scrip, 12 Jul, 2016.)*

But I think there is still a lot of unmet need. There are 16m diagnosed patients alone in the US, 30m estimated sufferers. I think the uptake of Xiidra [lifitegrast] shows the significant unmet need. If we look back at the clinical data, they were outstanding, I think, in terms of the impact it can have on patients' lives and relief of symptoms and signs, but there's still opportunity for developing drugs for the surface of the eye and treatment of dry eye disease.

When I got to know about the Parion compound, which is a so-called ENaC compound – an epithelial sodium channel potassium inhibitor – and looked at the data, I was really impressed and said to the team we need to be the one that develops the pivotal clinical trials for that drug, given the expertise we already have, and I want to have a second entrant into this market. I'm really enthused about the science, the compound and the continued ability to build our ophthalmic and front-of-the-eye dry eye franchise. *(Also see "With Parion Deal Done, Shire CEO Looks To Next Bright Ophthalmic Innovation" - Scrip, 2 May, 2017.)*

SCRIP: *Even though there was a competitor on the market, Shire focused on disease awareness with the Xiidra launch last year, including the EyeLove disease-awareness campaign with Jennifer Aniston. Has that campaign made the impact you hoped for?*

ORNSKOV: When I started to look at dry eye together with the team, there was one compound on the market with the indication of increasing tear flow – Restasis [cyclosporine ophthalmic emulsion] – and **Allergan PLC** basically built this market. They have sales of over $1bn but if you look at the number of patients still either untreated, not treated with Restasis when we came to market or only treated with artificial tears, there remained a significant opportunity.

As I mentioned, there are 16m patients that are diagnosed and 30m sufferers in the United States, so we thought that there was a significant opportunity to activate more patients and make them aware that there were now other options available. I think [that strategy] has been proven right. Before we came to market, the market was flat. After that, we saw growth in the market on a weekly basis, so I think we've contributed significantly to the growth of the overall market and, of course, to the growth of Xiidra. *(Also see "Shire Plays Up Xiidra Launch, Downplays Missed Sales Expectations" - Scrip, 1 Nov, 2016.)*

Over time as Xiidra became available in managed care and on formulary, we had to shift more focus to promotion of the actual benefits of Xiidra, as opposed to just general disease awareness. But we'll continue to run general disease awareness, and we're also getting into ex-US markets, where there's a significant opportunity, whether you talk about Europe or Japan. We plan to file later in the year in Europe, we have filed in Canada and could get approval potentially later this year, we've filed in Israel and we've started negotiations about what is needed to get approval in Japan, where we'll probably have to do an additional study.

We also have a compound in Phase III for viral conjunctivitis [SHP640], where we have both viral and bacterial studies ongoing, and we also have earlier-stage products in other indications, so ophthalmology is very important for us and this is an area where I want to build out. I have a great team, I know the area and I think there's significant unmet need for bringing innovative medicines to ophthalmic medicine.

SCRIP: *Staying on the subject of eye care, how big a setback was last year's clinical disappointment with your candidate for retinopathy of prematurity (SHP607)?*

ORNSKOV: I spent several years of my life working in a neonatology unit in Denmark, so neonatology is close to my heart. The second deal I did when I came to Shire was to acquire the rights to an insulin-like growth factor 1 which was in clinical trials for retinopathy of prematurity (ROP) but also for a pulmonary indication [severe bronchopulmonary dysplasia] and severe intraventricular hemorrhage. It is true that the Phase II study had mixed results and did not meet the primary endpoint of retinopathy of prematurity [but] it had encouraging data both on the pulmonary side and on the intraventricular hemorrhage side. We have ongoing negotiations with both European and US regulators about the path forward.

I still think that it's a very attractive compound. In neonatology, there's a significant unmet need for a compound that affects those three areas. Whether we can go straight into Phase III with a revised protocol or we have to do Phase II and then Phase III is still a discussion, but I think there's dramatic unmet need given the high mortality and the increased number of premature babies. Even though blindness is devastating to the families, there is still more morbidity and mortality associated with the pulmonary and CNS aspects, which this product may also have an impact on. We will continue this development and maybe the ophthalmic part won't be the primary part, but maybe a secondary part. I can give you many reasons why maybe we didn't hit

CONTINUED ON PAGE 10

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the primary endpoint, but that's all speculative. *(Also see "Shire Sees Future For Premature Baby Drug Despite PhII Disappointment" - Scrip, 30 Jun, 2016.)*

I said to Shire when I got here, 'I don't want slam-dunk, me-too development programs.' I like to go into areas where there is significant unmet need. When you go into respiratory distress or intraventricular hemorrhage or ROP in very premature kids, you're basically plowing a new field – there are not products for these three indications. You're going to have a higher risk profile but also potentially a higher reward profile. I don't know how many failures there have been in dry eye disease but we were the first one to get approval for the signs and symptoms of dry eye disease. So, I'm not afraid of risk because I think if you want some reward, you have to take some risk. And if you want to be a truly innovative company, you're going to have some setbacks.

SCRIP: *In the hemophilia space, Shire recently decided to terminate the Xenetic Biosciences Inc. long-acting Factor VIII program in hemophilia A, which was acquired in the Baxalta merger. How does that affect Shire's plans going forward in hemophilia?*

ORNSKOV: Again, here, the truth is a bit more mixed than talking about a failure. The predefined criteria for developing SHP656 was whether it was clearly differentiated from Adynovate [antihemophilic factor [recombinant], pegylated], which is a so-called enhanced half-life compound. And the data did not show a clear differentiation. When it did not meet that criteria, we needed to have the scientific and medical rigor to say ok, we're not continuing this program. Of course, as with other programs, you go back and see if there are other opportunities, but in this particular situation, we want to bring truly differentiated products to market versus products we already have.

You can call it a setback but we learned a lot, it's a good compound but it did not meet the criteria for what we would like to have seen to put the investment behind it. We'll continue to evaluate it. We want to continue to bring innovation to hemophilia and we have other things that we're working on that we hope will contribute to innovation. One of the areas we are very interested in investing in is the promising area of gene therapy for hemophilia A and B.

SCRIP: *One recent clinical success for Shire was the positive data for your long-acting hereditary angioedema candidate, lanadelumab. Do you view those results not only as good news for the program, but also as a validation of Shire's purchase of Dyax Corp.?*

ORNSKOV: Yes, you can imagine that when you go out and pay $5.9bn for a compound, which is in Phase I/II and you have limited clinical trial data, people may have questions about it. But I think it validated our acquisition, and also validated our ability to spot data from clinical trials and project them to what they could be in Phase III.

It was clear to me – and I was intimately involved – when I looked at the molecule, the data that the Dyax team had achieved with lanadelumab [DX2930] [showed significant promise]. The platform – remember that we get significant royalties from the companies that are developing antibodies based on the Dyax platform – along with some of the other compounds we acquired that we are developing or considering developing, [enable me to] feel extremely good about Dyax.

With lanadelumab, [the positives include] the data that we saw both in terms of the efficacy overall, the infrequent dosing, whether it was once every month or every two weeks, the small volume, subcutaneous [administration] and the length of time that people were attack-free, along with the fact that 96% of the patients continued voluntarily into the extension trial. It's one of the compounds I'm most enthused about because I think we have high unmet need in the market for a highly efficacious, convenient product and outstanding clinical data. It met all of its primary and secondary endpoints at the level of 0.0001. That's pretty impressive, I think. *(Also see "Shire CEO Says Lanadelumab Results Vindicate Dyax Buy, M&A Strategy" - Scrip, 19 May, 2017.)*

SCRIP: *If you successfully bring lanadelumab to market, what will that mean for the HAE market overall, including Shire's existing franchise?*

ORNSKOV: It will build out our global leadership in hereditary angioedema, it will bring a potential breakthrough product to patients. We will continue to expand the market. We will take market share away from other compounds in the market … it will mean some cannibalization of *Cinryze* [C1 esterase inhibitor (human)] and other C1 esterase inhibitors, but it's not one size fits all. There will always be patients that need some of these [therapeutic options]. This also will take share away from *Firazyr* [icatibant], which is going to lose patent protection in the US in 2019 anyway, so we're cannibalizing something, but it goes generic anyway.

SCRIP: *In seeking to become the leader in rare diseases, what are the challenges Shire will face? What benefit does Shire get from its relationships with 180 patient advocacy groups?*

ORNSKOV: We don't face any challenges – the word I would use is opportunity. There are so many opportunities. I'm more focused on research and development and innovation, so when I look at what's in our pipeline, when I look at other companies, when I talk to physicians, this is almost a field in explosion just in terms of applying all of the increased understanding of diseases and what the genome project has driven in terms of understanding the genetic constitution of these diseases much better.

When I recently spent time at the **Broad Institute** and heard about gene editing and what that's going to do, when I see what we and other companies are doing in gene therapy, and then when I learn about IBM Watson and application of tailored use of artificial intelligence to identify rare conditions and to apply the best treatment, I think we're at a crossroads where we can just continue to build out our leadership globally.

With Baxalta and Shire coming together, we are now in 70 countries. We have the most unique platform around the globe, so not only short-term but mid- to long-term, I think we're in an outstanding space to be the leader in driving innovation and commercial execution of these diseases. Whether we work with academic institutions, the NIH, hospitals like Children's Hospital in Boston or Pittsburgh or around the world, or have collaborations with patient associations or physician associations, I just look at this as the most unique opportunity I've experienced in my career. The biggest challenge we face is to make some choices about what to focus on because there is so much we could be doing.

Published online 20 June 2017

CANTOS Trial Brings Unexpected CVD Promise For Novartis & Regeneron

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The hypothesis of targeting inflammation to stabilize plaque and thereby prevent cardiovascular events has apparently been confirmed in top-line data from **Novartis AG**'s 10,000-patient CANTOS Phase III study of its IL-1β inhibitor antibody ACZ885 (canakinumab) in atherosclerosis.

The unexpected news – that the study measured over three years had met its primary endpoint of reducing the risk of major adverse cardiovascular events – gives the Swiss company a promising asset. Investors and the science world will need to await more details from the trial to see its precise efficacy and safety data.

TOP-LINE DATA ONLY REVEALED SO FAR

"We need to fully analyze the data, after which Novartis plans to start discussions with regulators in the US and Europe for eventual filing," a spokesperson told *Scrip*, without elaborating.

The top-line results are also promising for US-based **Regeneron Pharmaceuticals Inc.** from whom Novartis licensed the compound, and which receives royalties from its sales.

Novartis on June 22 said its Canakinumab Anti-Inflammatory Thrombosis Outcomes Study, or CANTOS, met the primary endpoint, demonstrating that when used in combination with standard of care ACZ885 reduces the risk of major adverse cardiovascular events, a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke (MACE), in patients with a prior heart attack and inflammatory atherosclerosis. Full data from the study will be unveiled at a medical congress later this year.

The medical need behind the study is clear: despite standard treatment, people with a prior heart attack live with a higher ongoing risk of having another event or dying. In about four in 10 people, this risk is directly related to increased inflammation associated with atherosclerosis, Novartis says.

"Despite current treatment, about 25% of heart attack survivors will have another cardiovascular event within five years, making the outcome of the CANTOS study a promising new development for patients," said Vas Narasimhan, Novartis' global head of drug development and chief medical officer.

He noted in a statement that ACZ885 was "the first and only investigational agent which has shown that selectively targeting inflammation reduces cardiovascular risk."

Canakinumab is an interleukin-1 beta blocker, already approved in the US as *Ilaris* for treating cryoporin-associated periodic syndrome and active systemic juvenile idiopathic arthritis.

Heart attack, the focus of CANTOS, occurs in about 580,000 people every year in Europe's five biggest economies and 750,000 people in the US. In 2015, there were an estimated 7.3 million heart attacks globally. Analysts said the unexpected CANTOS news was promising for heart patients – and for Novartis investors – given the large unmet need the drug could potentially address.

"Cantos was a high-risk study, given there were no Phase II data upon which to base expectations, and as a result, expectations for success have been low," analysts at Jefferies said, adding that "the positive headline represents a significant incremental positive for the stock."

ACZ885 is thought to work by blocking the interleukin IL-1β pro-inflammatory cytokine. CANTOS evaluated three different quarterly doses (50 mg, 150 mg or 300 mg) versus placebo.

Analysts at Berenberg pointed to studies suggesting up to 50% of heart attacks or strokes occur in healthy men and women with low cholesterol or low risk of CVD.

"This has led to the hypothesis that, in these patients at least, underlying inflammation is driving the development of atherosclerosis. However, the literature has so far failed to find evidence that inflammation causes cardiovascular death. Instead, the consensus view has been that cardiovascular disease itself causes inflammation. In this context, 'inflammation' is quantified by measuring hsCRP, a non-specific inflammatory marker." They thus raised the issue of difficulties for ACZ885 fitting into standard of care for the secondary prevention of cardiovascular disease.

"HsCRP is a notoriously difficult biochemical marker for physicians; it can be raised by thousands of different pathologies ranging from the common cold to an insect bite. The premise of selecting a therapy for secondary prevention [of cardiovascular death] based on hsCRP is alien to physicians and we question how Novartis will approach this in order to have the drug prescribed. Given Novartis failed to meet expectations with its last major CV launch (Entresto), the company has much to prove with ACZ885," they concluded.

Bernstein analyst Tim Anderson summed up by saying that "until full results are released later in the year - probably the American Heart Association congress in November), investors will likely be loath to believe that canakinumab could suddenly become a mega-blockbuster, especially because in the eyes of many, Novartis is currently a 'glass half empty' story … It will certainly be important to see the magnitude of the clinical benefit, along with the side effect profile," he concluded.

REGENERON ROYALTIES IMPACT

Novartis's CANTOS announcement prompted Regeneron Pharmaceuticals to issue a statement clarifying its royalty rights to canakinumab if approved for sale as specified in their 2009 agreement. Regeneron said it had not reviewed the CANTOS data and could not predict whether the study would result in new indications or sales in the future. Regeneron is not involved in the development and regulatory process for canakinumab. *(Also see "Novartis Ilaris Approved For Rare Autoinflammatory Disorder; Filings For More Common Diseases Planned" Pink Sheet, 18 Jun, 2009.)*

Under a 2009 agreement with Novartis, Regeneron receives a royalty on worldwide net sales of canakinumab; the royalty rate starts at 4% and reaches 15% when canakinumab annual sales exceed $1.5bn. The royalty applies to currently approved indications for Ilaris, and any potential sales for future indications, including related to the positive CANTOS top-line results. *Published online 22 June 2017*

FOLLOW THE LEADER:
Looking Across The IO Landscape

The recent **American Society of Clinical Oncology** annual meeting was a chance for oncology firms to showcase their pipelines. As the potential for cancer immunotherapy continues to grow, *Scrip* took a side-by-side look at what's coming out of the leading immuno-oncology companies.

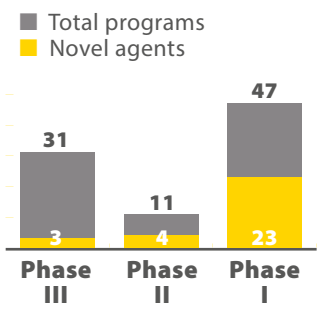
ROCHE

Oncology Pipeline:
30 Novel agents

9 Breakthrough designations

FDA approvals since 2014: **9** (5 novel)

Number of trials:



12 IO candidates in the clinic

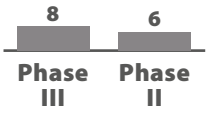
MERCK

Oncology Pipeline:
1 small molecule,
1 biologic

8 Breakthrough designations

FDA approvals since 2014: **9** (1 novel)

Number of trials:



40 potentially registrational studies for monotherapy and combinations, including **13** with **Keytruda**

13+ Internal IO candidates
All early stage/preclinical

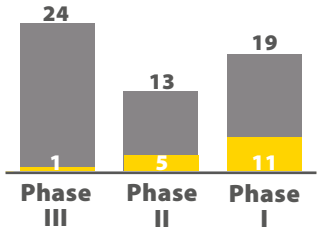
BRISTOL-MYERS SQUIBB

Oncology Pipeline:
17 Novel agents

7 Breakthrough designations

FDA approvals since 2014: **13** (2 novel)

Number of trials:



11 Internal IO candidates

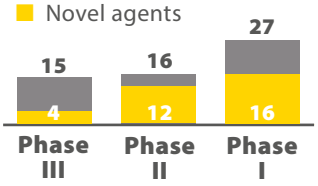
ASTRAZENECA

Oncology Pipeline:
29 novel agents

3 Breakthrough designations

FDA approvals since 2014: **5** (4 novel)

Number of trials:



10 of the Phase III programs include Imfinzi

12 IO candidates in the clinic

Winning the Race to New Markets for PD-1/L1

9	**7**	**2**	**1**
MERCK's Keytruda Indications	BMS's Opdivo Indications	ROCHE's Tecentriq Indications	ASTRAZENECA's Imfinzi Indications

Sources: FDA, the Pink Sheet's FDA Performance Tracker, company provided information , Biomedtracker, company websites/presentations

New IO mechanisms coming down the pipeline

	MERCK	ROCHE	BMS	AZ
IDO	preclinical	RG6078 in Ph I	Ph II	✓
Cancer vaccines	preclinical	Ph I	Prostvac in Ph III	✓
PD-1	Keytruda		Opdivo	✓
PD-L1		Tecentriq	✓	Imfinzi
TIGIT	MK-7684 in Ph I	RG-6058 in Ph I	Ph I	
CSF-1R		Ph I	Cabiralizumab in Ph I	✓
OX40		RG7888 in Ph I	BMS-986178 in Ph I	✓
GITR	MK-4166		BMS986156 in Ph I	✓
CTLA-4	MK-1308 (preclinical)		Ph I (NF?)	✓
LAG-3	MK-4280		BMS-986016 in Ph II	
CD73			Ph I	✓
Glypican3		T-cell bispecific in Ph I	ADC in Ph I	

ROCHE	
CEA	RG7802 T-cell bispecific in Ph I, RG7813 IL-2 variant fusion protein in Ph I
FAP	RG7461 IL-2 variant fusion protein in Ph I

MERCK	
IL-10	MK-1966 in Ph I
ERK	MK-8353
Other checkpoints	Preclinical
Other immune agonists	preclinical
Multi-specific nanobodies	preclinical

BMS	
SLAMF7	Empliciti
ICOS/CD28	BMS-931699
CD137	Urelumab in Ph II
BET	BMS-986158 in Ph I
HuMax IL-8	Ph I
CXCR4	Ulocuplumab in Ph I
Fucosyl GM1	BMS-986012 in Ph II
KIR	Lirilumab in Ph II
Mesothelin	BMS-986148, ADC in Ph I

AZ	
NKG2A	✓
A2AR	✓
CXCR2	✓
STAT3	AZD9150 in Ph I/II
TGFbetaR-1	✓
CCCR4	✓
IMCgp100	Phase I/II
TLR 7/8	✓
HPVE7	✓

✓ = compound and status not disclosed

BIO Notebook: Janssen, Boehringer And More Talk Deals, Pipeline Progress And Investment

MANDY JACKSON & JOSEPH HAAS

The BIO International Convention is under way, bringing together biopharmaceutical executives, scientists and dealmakers from June 19 to 22 in San Diego.

Scrip spoke with executives from a wide range of companies and attended various panel discussions on day one, including interviews with **Johnson & Johnson**'s Janssen Biotherapeutics division and **Boehringer Ingelheim GMBH**'s specialty care group. The first few panel discussions of the meeting on June 19 revealed insights into neuroscience dealmaking and outcomes-based contracts. **Allergan PLC** CEO Brent Saunders also gave his two cents about biopharma's declining reputation during a "fireside chat." *(Also see "Saunders: Industry Must Act Before We Lose Champions For Innovation In Congress" Scrip, 20 Jun, 2017 and on P17.)*

JANSSEN HUNTING FOR DEALS THAT DELIVER

Johnson & Johnson has built a reputation for incubating early-stage companies in the hopes of increasing the number of successes in the life science ecosystem, including technology that may be a good fit in J&J's portfolio. *(Also see "Green Shoots: Pharma Investments In Early Innovation Support Biotech Growth" Scrip, 24 Jun, 2016.)*

"We are not invested as much in building our own new platforms, but we want to partner," Barry Springer, vice president of strategy, innovation and research within the big pharma's Janssen Biotherapeutics subsidiary, said in an interview.

Springer describes himself as one of the executives from the J&J "mother ship" who interacts with the small firms and academic institutions that already are partnering with or receiving some kind of support from the multinational company. Current Janssen Biotherapeutics interests include tools that can be used to sort through big data and technologies that may deliver medicines more efficiently.

"In biotherapeutics, we're heavily focused on ways to redirect our antibodies," Springer said, noting that bi-specific antibodies may be one way to more directly delivery Janssen's biologics.

"There's no one technology that's going to solve all of our needs," Springer said. "We're always looking for better ways to deliver antibodies."

J&J is looking for better ways to manufacture antibodies as well, he said, noting that "it's another area ripe for innovation." Among the possibilities that Springer finds interesting is the idea of an "antibody gene" – a therapy that could be delivered once (or at least very infrequently) with the goal of continuously manufacturing the medicine in the body for as long as the patient needs the drug.

Any and all manufacturing options are on the table as long as they improve efficiency and reduce expenses in an environment where health care costs – especially prescription medicine costs – are coming under increased scrutiny.

But cost doesn't necessarily drive dealmaking as long as a technology platform or drug candidate fits within J&J's areas of therapeutic focus.

"At the end, it's less about cost than what are we going to be able to do with it," Springer said.

NASH GETS ANOTHER HIGH-PROFILE COMPETITOR IN BOEHRINGER

Saying it's not too late to enter the competition in non-alcoholic steatohepatitis (NASH), especially given its broad understanding of fibrosis, Boehringer Ingelheim is moving a NASH candidate into Phase II.

Ioannis Sapountzis, a 12-year Boehringer veteran recently promoted to head US business development and licensing for specialty care drugs, told *Scrip* June 19 that PX-4728A – in-licensed from **Pharmaxis Ltd.** in 2015 – will move into Phase II in the next few weeks. [See Deal] PX-4728A is an inhibitor of semicarbizide-sensitive amine oxidase (SSAO) and vascular adhesion protein 1 (VAP-1) that is thought to offer anti-inflammatory effects. *(Also see "B-Ingelheim NASH Deal Boosts Pharmaxis's Revitalization" Scrip, 19 May, 2015.) [Editor's note: This item has been updated to clarify the ongoing trials for nintedanib and mechanism of action for PX-4728A.]*

Sapountzis outlined Boehringer's ambitions for specialty care drugs, including long-term, early-stage partnerships to find novel targets and approaches to cancer immunotherapy. Boehringer might also bring special expertise to the NASH race, he said, because of its success developing *Ofev* (nintedanib), one of only two drugs approved to treat idiopathic pulmonary fibrosis (IPF), along with **Roche**'s *Esbriet* (pirfenidone). Boehringer is studying nintedanib already in Phase III in malignant pleural mesothelioma, as well as in conditions associated with fibrosis such as systemic sclerosis (scleroderma) and progressive fibrosing interstitial lung disease.

"I think the game is still really open," Sapountzis said. "There are several underlying principles for fibrotic diseases that we are trying to understand and I would say that Boehringer is actually ahead of the game there with nintedanib in IPF."

That could benefit Boehringer's efforts in NASH, he added, because the underlying principles of NASH and IPF are very similar.

"We think we very much understand the underlying principles of fibrosis and can make an impact there to the benefit of patients," he explained. "While we are not ahead of the game in the NASH field, definitely [there is] very much [still] to know about fibrosis."

NEURODEGENERATION DRIVING NEUROSCIENCE INVESTMENT

Neuroscience has a long way to go to catch up with oncology in terms of the level of investment in drug development, but dollars flowing in to the field have risen significantly in just a few years' time.

AbbVie Inc. executive vice president and chief strategy officer Henry Gosebruch shared financing and dealmaking statistics during a panel discussion titled "Breakthroughs In Neurodegenerative Diseases: Are We At The Tipping Point?"

There were 582 neuroscience licensing and collaboration deals struck between 2011 and 2013, rising to 811 between 2014 and 2016. Neurodegeneration drove a lot of the dealmaking during both periods – 225 deals during the earlier time frame and 300 during the later period.

"Neuroscience is now firmly a top three area of venture capital investing, but it's still about one third of [what's invested in] oncology," Gosebruch said, noting that neuroscience "is very much an area where you see corporate venture capital going in side-by-side" with VC firms.

Reflecting the fact that a lot of neuroscience deals are occurring at earlier stages of drug development, investment hasn't really extended into later-stage dealmaking, since 11% of biotechnology mergers and acquisitions fell into the neuroscience category in 2013 versus 13% in 2016. Gosebruch said that he expects more M&A to occur in about 24 to 36 months based on data from ongoing clinical trials.

The AbbVie executive also noted that more companies will invest together across big projects, like AbbVie did in 2016 by investing in the Google life sciences venture **Calico Life Sciences LLC**. AbbVie committed up to $750m to the collaboration focused on diseases of aging in 2014. *(Also see "AbbVie and Google's Calico strike $1.5bn age-related drug deal" Pink Sheet, 4 Sep, 2014.)*

New areas of neuroscience investment include neuro-regeneration or protective treatments as well as neuro-inflammation, both of which AbbVie is investigating.

OUTCOMES-BASED CONTRACTS: READY FOR THE NEXT LEVEL

Scrip spoke with Ernst & Young LLP Principal Susan Garfield after she moderated the panel titled "What Is The Future For Outcomes-Based Contracting? Moving From Ideas To Action" about challenges and opportunities in the negotiation of reimbursement agreements under which biopharma companies are paid for their drugs when they provide the products' promised outcomes.

"There still are opportunities or pockets of opportunities," Garfield said, noting that no companies have been able to negotiate an outcomes-based contract and then take that template to other payers and institute the same or similar agreements for that same drug. There's still a need for stakeholders to come together in one place with data on the performance of outcomes-based contracts, so that the agreements can be advanced into more complex deals.

The biggest opportunity going forward, however, is that payers and industry are starting to work together more on drug pricing concerns, including solutions like outcomes-based contracts.

"Payers and industry and beginning to see each other as partners. They're asking and answering the same questions," Garfield said. "They're working together in ways that we haven't seen until very recently."

That includes working together on issues that remain roadblocks in outcomes-based contracting and other means of negotiating reimbursement agreements, such as regulations that limit discussions between biopharma companies and payers prior to US FDA approval. *(Also see "Value-Based Contracts: Relief From Regulatory Barriers In Sight?" Scrip, 13 Feb, 2017.)*

President Donald Trump is generally expected to support outcomes-based contracts, though his administration has not come out with any specific policy proposals on that or related drug pricing issues.

"Many people feel that the Administration is open to discussing many of these topics," Garfield said, but whether that will happen in an executive order or in the ongoing health care reform bill negotiations is unclear. "There's uncertainty about the vehicle and the timing and specifics." *Published online 21 June 2017*

BIO Notebook: Deal Insights, A Payer Perspective And EMA Rumors

JOSEPH HAAS, MANDY JACKSON & MIKE WARD

The main reason that biopharmaceutical company executives travel to the annual BIO International Convention – this year in San Diego – is to seek new partners or find assets worth buying, so *Scrip* took a look at an annual survey of dealmaker intentions and spoke with executives at **Bayer AG** on June 20, among other interviews during the conference, about the focus of their transactions.

BUT SUPPLY STILL OUTSTRIPS DEMAND

In an assessment of dealmakers' preferred therapeutic areas this year, **inVentiv Health Inc.**'s Neel Patel arrived at the – perhaps expected – conclusion that cancer drug candidates and related technology remain the most in-demand biopharma licensing assets. Even so, Patel also determined that the available supply still exceeds demand.

Patel, who is managing director of commercial strategy and planning for the consulting firm, noted during a June 20 BIO presentation that 27% of buyers in the ninth annual Dealmakers Intentions Survey listed oncology as their primary therapeutic area of interest. Meanwhile, 29% of potential sellers in the survey said cancer drugs were the primary type of asset for which they were seeking buyers or partners.

Overall, he said, demand and supply seem to correspond fairly well, regardless of therapeutic area, but ophthalmic care is a notable niche in which asset supply appears well shy of demand. Twelve percent of buyers in the inVentiv survey called that segment their top priority, but only 3% listed ophthalmology drug candidates as the main kind of asset they have on offer. Meanwhile, Patel said, "oncology still dominates, both in terms of the interest from the buyers as well as how many assets are available in the marketplace."

This creates both an opportunity and a challenge for companies looking to in-license new cancer assets, he added. "Despite that large demand from the buyers, there are just a whole lot more assets available to meet that demand," Patel said. "So, the challenge for the buyers … is how do they delineate, differentiate among all of those assets."

InVentiv found that treatments for central nervous system (CNS) diseases (excluding pain) were the most in-demand assets relative to supply, followed by hepatic disease, hematology and women's health. By contrast, cardiovascular disease, psychiatry, inflammation, autoimmune and oncology all show up on the buyers' market end of the scale.

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BAYER CHASING ALGETA-SIZED OPPORTUNITY

Scrip spoke with Bayer executives chasing deals at the both ends of the drug development spectrum – Chris Haskell, head of Bayer's West Coast Innovation Center, and Marc Schwabish, US head of pharma business development and licensing – about the availability of attractive biopharma assets.

> 'We will try to make something work, but we're not going to do something at a crazy valuation'

Haskell heads the company's startup incubator in San Francisco's Mission Bay, which was established to support the early-stage firms that may eventually be ideal partners for Bayer, including new ventures working in drug development or research services. Schwabish, on the other hand, seeks commercial or near-commercial assets that fit within Bayer's four main therapeutic areas – cardiovascular, women's health, oncology and rare diseases, including hemophilia.

"We saw high valuations two years or so ago and they have come down about 25%," Schwabish said, but he noted that there still is a lot of competition to buy late-stage assets, so some products or companies are still valued at more than Bayer is willing to reasonably pay.

Schwabish noted that Bayer intends to complete a deal – or a collection of deals – around the size of its $2.9bn acquisition of the cancer radiopharmaceutical developer **Algeta ASA**, which closed in 2014.

"We will try to make something work, but we're not going to do something at a crazy valuation," he said.

Haskell pointed out, however, that cardiovascular disease is an area where Bayer is getting involved with new company formation and mentoring entrepreneurs to potentially add assets to the big pharma group's pipeline.

"In cardiology-related areas, we're doing more active early partnering and setting up external innovation centers," he noted.

Bayer recently expanded its CoLaborator in San Francisco to accommodate the growing companies that already inhabit the startup incubator and to bring in new tenants. At least one of the CoLaborator inhabitants already has a lucrative relationship with Bayer – the gene-editing joint venture with **CRISPR Therapeutics AG** known as **Casebia Therapeutics**, which is focused on hemophilia, cardiovascular and other diseases.

"Cardiovascular is very difficult to do unless you're a large pharma," Schwabish said. "It's harder to do deals in that space, because there are so few small companies."

The CoLaborator is home to eight startups now, but the expanded space has room for up to 13 small companies.

A PBM COMPLIMENTED A PHARMA COMPANY? YES, REALLY

Express Scripts Holding Co. senior vice president and chief medical officer Steven Miller has been a vocal critic of drug pricing practices – a leader among payers in terms of calling out the high cost of medicines. That's why it was a surprise to hear the pharmaceutical benefit manager (PBM) executive praise a pair of biopharma companies for their strategy in pricing a new atopic dermatitis drug.

Miller, speaking during a BIO Convention super session titled "Our Common Goal: Ensuring Access And Affordability Of Innovation Medicines," complimented **Sanofi** and **Regeneron Pharmaceuticals Inc.** for proactively talking with payers about their newly approved *Dupixent* (dupilumab) for atopic dermatitis. *(Also see "Sanofi/Regeneron Choose Access Over Price With Dupixent Launch" Scrip, 28 Mar, 2017.)*

Miller noted a shift from volume-based reimbursement contracts for prescription drugs to value-based contracts under which biopharma companies are paid when drugs work as they're supposed to under US FDA-approved labels. "Value-based contracting has required people to start talking and it's not just transactional," he said, using Sanofi/Regeneron and other companies as examples.

"When Sanofi and Regeneron were bringing dupilumab to the marketplace, they went on a listening tour," Miller said. "They wanted to understand our pain points. We needed to understand their pain points."

As a result, Miller said, "they brought dupilumab out at an incredibly reasonable price" – $37,000 dollars per year versus $65,000 for biologics that treat psoriasis. Since then, Express Scripts has had similar experiences with the **Genentech Inc.** multiple sclerosis drug *Ocrevus* (ocrelizumab) and **Radius Health Inc.**'s new osteoporosis drug *Tymlos* (abaloparatide).

Of course, true to form, Miller said earlier in the discussion that "manufacturers use rebates to reward and punish PBMs. If I put a drug on my formulary, they want to give me a discount. If I don't put their drug on my formulary – I put a competitor's drug on my formulary – they want to punish me" with less of a rebate or no rebate.

EMA HEADQUARTERS RUMORS FLY AT BIO

Rumors over who will host the headquarters for the European Medicines Agency (EMA) post-Brexit were flying at BIO while at the same time hopes are falling that selection of a new location for the EMA will be based on competency alone. Members of Coreper, Europe's Committee of Permanent Representatives, are this week attempting to hammer out how the decision should be made.

Chatter during the annual industry meeting in San Diego suggest that political horse trading will determine the agency's relocation from London after the UK formally leaves the European Union.

Last month, the European Commission published its criteria for selecting a new EMA host city. These include assurance that the EMA can continue its operation from the date of Brexit, there are good international transport links, and appropriate facilities and conditions for family members. Pharma companies have called for minimal disruption.

At one point it looked like a shortlist of host nations would be created using a voting system not dissimilar to the Eurovision Song Contest, in which representatives would place their first three choices in order of preference, with those garnering the most support ending up on a shortlist for Europe's Council of Ministers to consider at a meeting to be convened in October. That option, much to the relief of stakeholders that *Scrip* has spoken to, is no longer on the table.

Nevertheless, instead of the EMA going to the nation that demonstrates the most competency to host the agency, it has been suggested that Germany and France have agreed to support relocation to one of Europe's former east bloc nations in support for splitting the London-based European Banking Authority into two new entities that would then migrate to Paris and Frankfurt. Given that each member state has a veto on any final decision, it is difficult to see

how such horse trading will work. Twenty of the 27 remaining EU states are expected to throw their hat in the ring with Stockholm, Amsterdam and Dublin being among the frontrunners if the decision is not made on purely politically expedient grounds. If one of the former east bloc nations should get the nod, it is likely that the EMA would stay in London beyond Brexit for an interim period – up to five years some say – to enable a safe handover.

While the Coreper decision is expected this week, it is unclear whether the various parties will come to a consensus. A final decision is slated for October; however, there is already talk that this might be delayed until the Council of Ministers meeting in December or even later.

WHY MIGHT PHARMA PARTICIPATE IN INTERNATIONAL PANDEMIC VACCINE EFFORT?

Merck & Co. Inc. sees its participation in an international public-private partnership that's designed to get ahead of the curve on infectious disease pandemics as – at least in part – a matter of corporate responsibility, according to Julie Gerberding, executive vice president and chief patient officer at the New Jersey big pharma. She and other biopharma executives who participated in a June 20 panel discussion outlining the plans and goals of the Coalition for Epidemic Preparedness Innovations (CEPI) were asked why they were participating in the effort. *(Also see "CEPI Global Vaccines Launch May Augur Creation Of Credible Davos Deal" Scrip, 19 Jan, 2017.)*

Gerberding noted that Merck is one of only six large companies still participating in the creation and development of vaccines.

"There is a global treasury of very limited know-how around the world and when you have the responsibility of being a custodian of that kind of capability, you have a special responsibility, which we're exercising along with **Johnson & Johnson** and **GlaxoSmithKline PLC** in the context of the recent Ebola outbreak in West Africa, to step up," she explained. "And I think that it may not be something that makes sense to shareholders today, but it certainly makes sense in terms of the traditions and ethics and values incumbent."

Nima Farzan, CEO of **PaxVax Inc.**, another private-sector partner in the CEPI effort, added that one of the goals should be to expand expertise around vaccine development. Right now, that segment of the industry is too concentrated, he said, and as a result so is the innovation in that space.

Published online 21 June 2017

Saunders: Industry Must Act Before We Lose Champions For Innovation In Congress

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San Diego – With former **Turing Pharmaceuticals AG** CEO Martin Shkreli about to face trial on charges of securities fraud, **Allergan PLC** CEO Brent Saunders said – when BIO CEO and Chairman James Greenwood asked if Shkreli is the public face of the biopharmaceutical industry – that the industry doesn't have the luxury of pretending he is not.

During a "fireside chat" to open the BIO International Convention here, Saunders – who gained wide notice upon Allergan's unilateral pledge to hold the line on annual price increases for its drugs – said the biopharmaceutical industry needs to come up with "a code of ethics or something" before its poor public image means that even its strongest defenders in Congress won't be able to vote for policies that are friendly to innovation.

"I think the political reality is the biopharmaceutical industry is so unpopular, so unpopular. And it's not just Martin Shkreli," Saunders told an overflow crowd on June 19. "If you go to Congress, to [Greenwood's] old colleagues who really understand the role of innovation and understand the role of what BIO does … they're getting 10,000 calls, 20,000 calls from constituents that are absolutely negative about this industry."

If constituents can't afford the medicines they need or continually get refusals of coverage from their insurance plans on prescription drugs, "it doesn't matter," he continued. "This industry collectively gets blamed for it. Right, wrong or indifferent, it doesn't matter, you can't argue the facts at that point. Even the people who have the greatest respect for what we all do, they are having a harder and harder time being our champions on these important issues, and it's becoming quite scary, because we are losing the champions for innovation … in Congress. They will ultimately go with populism."

The industry itself needs to set policies that will show that the value of innovation is matched with fair pricing, Saunders said, or the implications will affect all players, regardless of how they conduct their business.

"I've been a believer, I've seen this coming for two or three years that we as an industry need to do our part," he warned. "We need to do something that shows who we really are, that we are good people trying to do really good things, [but] it just gets lost. And the people who are in the news cycle aren't part of the mainstream in this industry; we know that, but that doesn't to matter to the person who's standing in line at Walgreens or CVS and can't pick up their prescription. We have to always remember how personal medicine is for patients."

ALLERGAN'S SOCIAL CONTRACT EVOLVED FROM SURPRISE QUESTION

Saunders is an ideal person to address this issue as Allergan announced last September that it would hold the line on price increases for individual products below 10% and raise such prices only once per year. *(Also see "Allergan's Price Reform Pledge: Will Others Follow?" Scrip, 6 Sep, 2016.)* He explained that the idea for Allergan's so-called "social contract" came from months of thinking after he was asked unprepared during a TV interview what he thought of the just emerging controversy around Turing's significant price increases for *Daraprim* (pyrimethamine) after it acquired the drug in 2015.

Saunders asked colleagues at Allergan to think about the social contract implicit in the biopharma industry – that pricing should re-

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flect the value its products provide while enabling drug makers to enjoy a reasonable return.

"It truly was an experiment, not knowing where the endpoint would take us," Saunders explained. "[We asked] where do you set that point of equilibrium, and I would argue today that it's not stuck in one spot. It needs to move depending on the circumstances and I that that's lost on a lot of companies in this industry that while they absolutely are doing good things, they sometimes set that point of equilibrium in the wrong spot."

Allergan's goal was to set net pricing to match annual inflation. This year, its price increases were in the 2.5% to 2.6% range after rebates and discounts to match economists' projections for inflation. Allergan followed up its price increase policy by also increasing eligibility for patient assistance for its products – to 500% of the federal poverty limit for its most expensive drugs, and to 400% of the poverty limit for its other products. Saunders estimates that roughly 200m Americans – nearly two-thirds of the US population – qualifies for patient assistance for Allergan's highest-priced drugs.

"Is this the end-all and be-all? Absolutely not," he said. "It's a starting point. We felt we needed to start somewhere … we're going to grow, we're going to figure out what does that mean to Allergan, what does that mean to our [industry] colleagues."

Published online 21 June 2017

Novo Readies For Victoza CV Benefit Claim

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Novo Nordisk AS is setting the stage for a new cardiovascular benefit claim for the GLP-1 agonist *Victoza* (liraglutide) with a CV disease awareness campaign in the US. However, Novo's requested labeling claim could be slimmed down if the FDA follows the advice of some of its external experts.

At a June 20 meeting, FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 17-2 that results from the LEADER outcomes trial provided substantial evidence to establish liraglutide reduced CV risk in patients with type 2 diabetes.

The recommendation puts liraglutide in line to become the second antidiabetic agent to add a CV benefit labeling claim, following in the footsteps of **Boehringer Ingelheim GMBH** and **Eli Lilly & Co.**'s SGLT2 inhibitor *Jardiance* (empagliflozin). Victoza will be the first GLP-1 agonist to carry the claim in a crowded category, which now includes competitors dosed weekly like Lilly's *Trulicity* (dulaglutide).

During a June 21 investor call to discuss results of the FDA meeting, Novo executives said the company has initiated an unbranded advertising campaign focused on awareness of CV disease in type 2 diabetics.

The HeartofType2 campaign website notes that CV disease is the number one cause of morbidity and mortality globally in type 2 diabetics. Diabetics have a two- to six-fold increased risk of CV mortality and two- to four-fold increased risk of coronary artery disease and stroke compared to nondiabetics, the site states.

BI and Lilly similarly rolled out an unbranded consumer awareness campaign ahead of FDA's December approval of empagliflozin to reduce the risk of CV death in type 2 diabetics with CV disease.

MORE SALES EFFORT BEHIND VICTOZA

Novo also is preparing to put more sales force effort behind a CV claim for liraglutide, although the drug will be sharing voice with other products in the diabetes franchise, including the fast-acting basal insulin *Tresiba* (insulin degludec) and *Xultophy*, the recently launched, fixed-dose combination of insulin degludec and liraglutide, said Jesper Brandgaard, executive vice president and chief financial officer.

If FDA approves a CV benefit claim by the Aug. 25 user fee goal date, "Victoza will compete for a share of the voice, and everything else being equal more voice attached to Victoza in second half of 2017, but not a sole dedication to Victoza," Brandgaard said. Novo also will retain a separate sales force allocated to *Saxenda*, a higher-dose version of liraglutide that is approved for treating obesity, Brandgaard said, adding that the company is hopeful there will be "positive spillover potentially for Saxenda with this positive outcome on the molecule liraglutide from the advisory panel."

Novo expects the LEADER data, and a resulting CV indication for liraglutide, will help continue to grow the overall market for GLP-1 agonists and to reinforce Novo's leadership in that space.

"This will provide further support to continued high growth level of the overall GLP-1 class, where we're currently seeing the US market expanding volume-wise in the level of 25%-30%," Brandgaard said, predicting overall market growth would continue "north of 20%."

The LEADER results give Novo an edge in a market where other GLP-1 agonists, including **AstraZeneca PLC**'s *Bydureon* (exenatide extended-release) and **Sanofi**'s *Adlyxin* (lixisenatide), failed to demonstrate a CV benefit in outcomes trials.

LEADER provides a "positive connotation for our product" given that results within the GLP-1 space are "significantly different for the individual compounds," Brandgaard said. As a result, there is a "very clear, positive recognition among the endocrinologists and the [general practitioners] for the specific merits of Victoza," which the company expects will carry over to the investigational, once-weekly GLP-1 agonist semaglutide.

Semaglutide, which was submitted to FDA in December, demonstrated a significant CV benefit in the 3,300-patient SUSTAIN-6 CV outcomes trial. However, Novo has said it will not seek CV risk reduction labeling based on those data, but instead will perform a larger, longer CV post-approval outcomes trial aimed at broadening the label.

SECONDARY VS. PRIMARY PREVENTION

The breadth of a CV labeling claim for liraglutide was one of two key efficacy issues debated by FDA's external experts at the advisory committee meeting.

Novo is seeking approval as an adjunct to standard treatment of CV risk factors to reduce the risk of major adverse CV events (MACE) in adults with type 2 diabetes and high CV risk. In LEADER, liraglutide demonstrated a statistically significant 13% reduced risk in the MACE composite endpoint and a 22% reduced risk in the CV mortality component. The other two MACE components, non-fatal myocardial infraction and non-fatal

stroke, trended in favor of liraglutide but were not statistically significant. Most of the 9,340 patients in LEADER were type 2 diabetics ages 50 years and older with established CV disease or chronic kidney disease. A lower risk group – ages 60 years and older with certain CV risk factors but not established disease – accounted for 19% of LEADER's randomized population but only 10% of first MACE events.

This lower risk subgroup had an unfavorable hazard ratio point estimate of 1.20 on the MACE primary endpoint, compared to 0.83 for the higher risk group, with an interaction p-value of 0.04.

The unfavorable point estimate "is worth noting from a clinical standpoint because the applicant seeks an indication for both primary prevention and secondary cardiovascular disease prevention," FDA Clinical Reviewer Tania Andrea Condarco said.

Committee member and Tufts University cardiologist Marvin Konstam said that while he did not think it was possible to draw any conclusions from the subgroup, "it's highly relevant to what the labeling's going to be."

"I think the evidence resides in patients who have established cardiovascular or renal disease, mostly cardiovascular disease," Konstam said. "I think that's where the relevance of those groupings come in, not drawing a definitive conclusion."

Konstam was one of several committee members who voted for approval of a new claim but suggested it should be limited to patients with established CV disease or chronic kidney disease.

"It seems completely inappropriate to me to offer an indication … to a group that is tiny and didn't demonstrate even a shred of benefit," said James de Lemos, a cardiologist at University of Texas Southwestern Medical Center.

De Lemos said there is plausibility for drugs that work differently in secondary and primary prevention. He suggested labeling liraglutide for CV risk reduction in individuals at high risk on the basis of prevalent clinical or subclinical CV disease or chronic kidney disease.

"I think it should have an indication for reduction of MACE in patients with established cardiovascular disease or with CKD," said Leslie Cho, a cardiologist at Cleveland Clinic. "I think the broader indication for high cardiovascular risk in which things like [left ventricular] dysfunction, microalbuminuria and some other things that were included … is a troubling aspect of this 'yes' vote."

DISCORDANT EFFICACY RESULTS IN US PATIENTS

The panel's struggles over what to make of discordant efficacy results in the US subgroup of patients, which represented 27% of the trial population, also carry potential labeling implications.

The US subgroup had a MACE hazard ratio point estimate of 1.03, compare to 0.81 for subjects outside the US, with an interaction p-value of 0.48.

Novo suggested the US subgroup's unfavorable point estimate resulted from a higher rate of permanent drug discontinuation, and consequently an overall lower exposure time to trial product, compared to non-US subjects. However, FDA questioned Novo's analytical methods and said it was not prepared to endorse the concept that exposure can explain the US findings.

The US subgroup results were the reason given by the two dissenting panelists on the question of whether there is substantial evidence to support a CV benefit claim.

Explaining his "no" vote, University of Florida oncologist Carmen Allegra said he was very concerned by the US subgroup analysis.

"I think the US target population is a pretty darn important population for us to consider, and we saw a significant interaction with outcomes versus the region by the FDA's analysis," Allegra said. "I was really swayed by the fact that we really didn't see evidence for superiority in the US population."

However, most panelists concluded the US subgroup findings should not override the overall positive findings from the study, although some suggested FDA include the discordant data on the US subgroup in labeling.

FDA has taken this approach before, perhaps most notably with AstraZeneca's platelet inhibitor *Brilinta* (ticagrelor). In the pivotal PLATO trial for acute coronary syndromes, ticagrelor was inferior to control in US patients. This finding has been attributed to the concomitant use of high-dose aspirin in US patients, compared to the prevalent use of low-dose aspirin in the rest of the world.

DON'T LOOK FOR A MICROVASCULAR CLAIM

FDA's update to the liraglutide label is not expected to reflect a microvascular disease benefit in LEADER, which included a composite endpoint comprising nephropathy and retinopathy. The results for the composite and the nephropathy endpoints favored liraglutide and were nominally statistically significant, while the results on the retinopathy endpoint favored placebo.

"FDA has some reservation about the microvascular definitions, method of capture, and analysis methods and does not believe that these analyses support a labeling claim of a reduction in microvascular disease," the agency said in its meeting briefing document.

RECONSIDERING THE BOXED WARNING

Advisory committee members generally found the LEADER data reassuring as to liraglutide's non-CV safety, particularly with regard to thyroid cancer, pancreatic cancer and pancreatitis.

For some panelists, the lack of a thyroid cancer signal, coupled with the significant CV benefits, seems reason enough to eliminate the drug's boxed warning on the potential risk of medullary thyroid carcinoma. The warning, which is common to all long-acting GLP-1 agonists, is based on animal carcinogenicity studies.

In LEADER, there were no cases of medullary thyroid cancer in liraglutide-treated subjects and one case in the placebo arm. There were very few thyroid cancer events of other cell types, and calcitonin assessments were unremarkable, FDA said.

"When you look at the magnitude of the effect on MACE and the number of MACE events that you see in this cohort and then you see that there were practically no cases of medullary thyroid carcinoma, I think having the black box warning really puts a lot of people off taking this drug," said Judith Fradkin, director of the division of diabetes, endocrinology and metabolic diseases at the National Institute of Diabetes and Digestive and Kidney Diseases.

However, when asked during the investor call about the potential removal of the boxed warning, Mads Krogsgaard Thomsen, Novo's executive vice president and chief science officer, said he expects the warning to remain in place across the class at least until Novo's 15-year medullary thyroid carcinoma registry study completes in 2026.

Published online 21 June 2016

Melinta To Launch First Commercial Drug Baxdela

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Melinta Therapeutics Inc. will sell its first commercial drug – the antibiotic *Baxdela* (delafloxacin) – independently through a hospital-based commercial organization that is in the process of being built, according to CEO Eugene Sun.

FDA approved the fluoroquinolone antibiotic June 19 for the treatment of acute bacterial skin and skin structure infections (ABSSI) in both an intravenous and oral formulation. The company expects to launch the drug in the fall.

While fluoroquinolones are a familiar class of antibiotics with a long history of use and are widely available generically, including ciprofloxacin, levofloxacin and moxifloxacin, Baxdela does offer advantages over existing options.

- It is active against both gram-positive and gram-negative pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) infections, while no existing fluoroquinolones are.
- It's also available in both intravenous and oral formulations, which makes it an attractive option for patients who start treatment in the hospital and are later discharged.
- And, it has fewer drug-drug interactions than other fluoroquinolones.

Nonetheless, Baxdela will face a challenging commercial market in a category dominated by generics and at a time when emphasis on cost reduction continues to grow. Baxdela will have to compete against an entrenched rival used in hospitals to treat gram-positive infections, vancomycin, as well as other generically-available drugs active against MRSA, including linezolid (**Pfizer Inc.**'s *Zyvox)* and daptomycin (**Merck & Co. Inc.**'s *Cubicin*).

Melinta sees an opportunity for Baxdela to be used as an option to treat the sickest patients, often those with an underlying condition who are on other medications, or when it's unclear if an infection is caused by a gram-positive or gram-negative bacteria.

"Skin infections tend to occur in people with some kind of underlying condition that makes them more susceptible to serious infections, like diabetes or a skin disease, cardiovascular disease, [or] obesity," Sun told *Scrip*. In addition, if a patient has a chronic condition, they are also likely to be taking chronic medications.

The drug's broad spectrum activity against both gram-positive and gram-negative infections is also an advantage. The clinical development program tested Baxdela against two drugs, not one. The two Phase III studies in patients with ABSSSI showed the I.V. and oral versions of delafloxacin as monotherapy were non-inferior to the combination of vancomycin plus aztreonam on the primary endpoint of early clinical response at 48 to 72 hours. Vancomycin is commonly used to treat gram-positive infections, while aztreonam is commonly used to treat gram-negative infections.

Like other fluoroquinolones, Baxdela carries a boxed warning on the risk of tendonitis and tendon rupture, peripheral neuropathy and central nervous system effects, but Sun pointed out that the drug was well tolerated in clinical testing and less than 1% of clinical trial patients had to discontinue due to side effects.

A 'COMPACT' COMMERCIAL TEAM

The launch of Baxdela will be the first commercial product for the 17-year old antibiotic specialist, which is privately-held and headquartered in New Haven, Conn. Melinta is building a hospital-focused commercial team to market the drug in the US and has already established partnerships for ex-US markets.

"We are going to start compact and we have targeted hospitals that we think are more likely to use the drug based on their patient demographics, and then we anticipate adding commercial strength as the product gains traction in the market," Sun said.

Earlier this year, Melinta announced a marketing alliance with the Italian pharmaceutical company **Menarini Group** to commercialize Baxdela in 68 countries in Europe, Asia, Australia and Russia. A European regulatory filing is on track for early 2018, Sun said.

The chief executive said the company has the cash runway to build the infrastructure to support the US launch while completing a Phase III trial testing Baxdela in community-acquired pneumonia and progressing its earlier-stage and highly novel pipeline into the clinic, though he would not comment on the company's cash position.

He also declined to comment on the price of Baxdela, which he said the company has not yet decided on. "Our aim is to be in a reasonable price range that is comparable to similar products, branded pharmaceuticals for serious infections," he said.

PIONEERING NEW CLASSES

Melinta operated as Rib-X Pharmaceuticals until 2013, when it was taken over by a new leadership team and completed an important $67.5m financing, led by Vatera Healthcare Partners and including Warburg Pincus Equity Partners, ABS Ventures and Vox Equity Partners. Rib-X had previously been seeking to complete an IPO but backed out.

What doctors and patients really need – and what could be a more lucrative commercial opportunity – are novel classes of antibiotics that can address the growing crisis of antibiotic resistance.

Melinta has developed three new classes of antibiotics that inhibit the bacterial ribosome using its discovery platform, which could present an opportunity to treat multi-drug resistant pathogens known collectively as ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* species and *Escherichia coli*.)

The company says the new classes are chemically novel and do not share cross-resistance to currently marketed therapies, including extended beta lactamases, carbapenemases and colistin. Melinta hopes to bring pyrrolocytosines into the clinic first.

"The advantage of these drugs is that it is a completely novel class," Sun said. "We think 2018 is likely when we will introduce a compound to begin clinical trials."

Many big pharmas have backed out of antibiotic discovery research, leaving a big gap in an area of high unmet need. The lack of novel antibiotics in the pipeline presents an opportunity for a company like Melinta if it can fill the gap. Success remains elusive given the challenges to developing novel antibiotics, but reevaluating the way society thinks about the value of antibiotics will be important to reenergize research in the space.

Published online 22 June 2017

CHMP OK Puts Merck KGaA's Cladribine Pill On EU Home Stretch After Long Trek

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Merck KGAA's cladribine tablets - the oral multiple sclerosis medicine it suspended in late-stage trials six years ago but then resuscitated in September 2015 – has won backing from the European Medicines' Agency's top advisory panel and thus is set to win marketing approval in Europe.

But the competitive field in that therapy area has altered significantly in the meantime. That, along with residual doubts about the medicine's safety profile, could dampen its commercial chances, analysts say.

The oral therapy, which has the brand name *Mavenclad*, selectively and periodically targets lymphocytes thought to be integral to the pathological process of MS.

EMA said "the benefits of Mavenclad are its ability to reduce the frequency of relapses and to delay disease progression." The EU's drug regulator in a statement added that "the most important side effects are lymphopenia, which can be severe and long-lasting, and infections, including herpes zoster."

Germany-based Merck – which hasn't launched a new drug in a decade – showed clear relief at the decision by EMA's Committee for Medicinal Products for Human Use (CHMP) at its June 19-22 meeting to recommend the therapy as a treatment for adults with highly active relapsing forms of multiple sclerosis.

"We strongly believe in the therapeutic value of cladribine tablets and the significant impact this investigational therapy may have on the future of MS care," said Luciano Rossetti, the German group's global head of R&D.

But Datamonitor Healthcare doubts cladribine tablets will have a significant impact in MS treatment practices, assuming its approval in the EU over coming months.

"At the time of its initial filing, cladribine's key competitive advantage was its oral formulation - coupled with the drug's low dosing frequency," Datamonitor Healthcare noted in an evaluation of the drug.

But cladribine was refused approval back in 2010 and 2011, due to malignancy concerns. In 2016, Merck presented data at that year's ECTRIMS (European Committee for Treatment and Research in Multiple Sclerosis) congress which appeared to clear these safety concerns, making an EU approval more likely. It resubmitted an application to EMA for its approval in July 2016.

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Belén Garijo, the chief executive officer of Merck's healthcare business, told *Scrip* at the time that "we believe this drug's risk-benefit is very competitive with what already exists in the MS space today. Convenience is a very big feature of cladribine which is administered for just two weeks every year and the efficacy lasts four years. The course involves 20 tablets, administered five days a week for two weeks."

"As far as the regulatory pathway, we have submitted cladribine for approval in Europe and expect a normal process, giving us a likely launch in the initial countries - the UK and Germany - sometime between July and September 2017," Garijo said in an exclusive interview last July, a forecast that seems largely on track.

But Datamonitor Healthcare warns that "the MS treatment landscape has changed dramatically since 2011, and several oral therapies are now available. There are now three oral disease-modifying therapies available in **Novartis AG**'s *Gilenya* (fingolimod), **Biogen Inc.**'s *Tecfidera* (dimethyl fumarate), and **Sanofi**'s *Aubagio* (teriflunomide), diminishing any novelty around cladribine's oral formulation," Datamonitor Healthcare told *Scrip*.

> 'We strongly believe in the therapeutic value of cladribine tablets and the significant impact this investigational therapy may have on the future of MS'

"The approval of Lemtrada means there is already an effective induction therapy on the market, and **Roche**'s *Ocrevus* (ocrelizumab) could further revolutionize the treatment landscape in 2017 as a high-efficacy, well-tolerated drug that is effective across a range of MS subtypes."

"Also, key opinion leaders interviewed by Datamonitor Healthcare highlighted that cladribine's malignancy risks are still of concern, and will need to be monitored."

"Altogether, this suggests cladribine will experience limited uptake," Datamonitor Healthcare concluded.

Published online 23 June 2017

Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

CLICK
Visit scrip intelligence.com for the entire pipeline with added commentary.

Selected clinical trial developments for the week 16–22 June 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Pfizer Inc.	*Xeljanz* (tofacitinib)	rheumatoid arthritis	ORAL STRATEGY; *The Lancet* online, June 16, 2017.
Updated Phase III Results			
Indivior PLC	RBP-6000 (buprenorphine) once monthly injection	opioid use disorder	RB-US-13-0001; improved abstinence.
Aimmune Therapeutics Inc.	AR101	peanut allergy	PALISADE; patient screening data.
Celgene Corp.	*Revlimid* (lenalidomide) plus rituximab	marginal zone lymphoma	MAGNIFY; favorable clinical responses.
Eli Lilly & Co.	*Taltz* (ixekizumab)	psoriatic arthritis	SPIRIT-2; minimal progression.
TG Therapeutics Inc.	ublituximab plus ibrutinib	chronic lymphocytic leukemia	GENUINE; good response rates.
Sanofi/Regeneron Pharmaceuticals Inc.	*Kevzara* (sarilumab)	active rheumatoid arthritis	MONARCH; better clinical improvement versus adalimumab.
Phase III Interim/Top-line Results			
Novartis AG	*Ilaris* (canakinumab)	inflammatory atherosclerosis	CANTOS; reduced CV outcomes.
GlaxoSmithKline PLC	*Shingrix* vaccine	shingles and chickenpox prophylaxis	ZOSTER-048; strong immune responses when revaccinated after *Zostavax*.
Novartis AG	brolucizumab (RTH258)	wet age-related macular degeneration	HARRIER; HAWK; met primary endpoints, visual gains with 12-week injections .
Clovis Oncology Inc.	*Rubraca* (rucaparib)	ovarian cancer	ARIEL3; improved PFS, the primary endpoint .
Lipocine Inc.	LPCN (testosterone)	hypogonadism	Positive efficacy results without titrating the dose.
ASIT biotech	Gp-ASIT+	grass pollen allergy	Encouraging results .
Phase III Announced			
Bristol-Myers Squibb Co.	Orencia (abatacept)	giant cell arteritis	Combined with glucocorticoids.
Updated Phase II Results			
BioPharmX Corp.	BPX-01 (minocycline) topical gel	acne	Reduced lesions.
Anergis SA	*AllerT* (birch pollen allergens)	allergic rhinitis	T-cell responses seen.
DBV Technologies SA	*Viaskin* peanut (peanut allergens)	peanut allergy	VIPES; induces IgG4 responses.
VBL Therapeutics	ofranergene obadenovec (VB-111)	glioblastoma, ovarian cancer, thyroid cancer	Improved survival.
Samumed	SM04690	osteoarthritis	Clinical improvements seen.
Ablynx NV	vobralizumab	rheumatoid arthritis	Impacted disease, no unexpected safety issues.
Bristol-Myers Squibb Co.	*Opdivo* (nivolumab)	Hodgkin's lymphoma	CheckMate 205; high level of responses.
Aurinia Pharmaceuticals Inc.	*Luveniq* (voclosporin)	lupus nephritis	AURA-LV; fast remission rates.
Xencor Inc.	XmAb 5871	IgG4-related disease, fibro-inflammatory auto-immune disorder	Encouraging initial responses.

Source: Biomedtracker

Lupin's founder Desh Bandhu Gupta And His People Mantra

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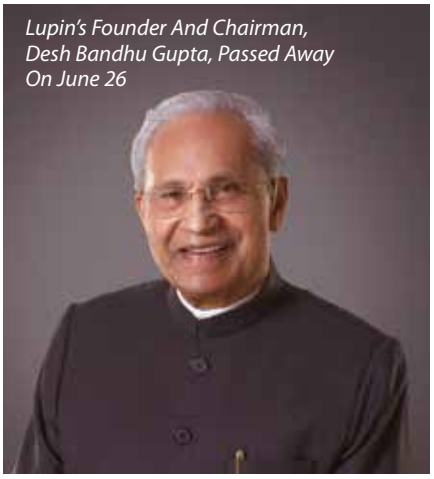

Lupin's Founder And Chairman, Desh Bandhu Gupta, Passed Away On June 26

Most senior pharmaceutical industry executives who've worked at **Lupin Ltd.** at some point in their career remember the company's founder and chair, Desh Bandhu Gupta, as someone who empowered employees to take decisions, even some tough ones, and had a generally inclusive style of management.

While his children have been steering the Indian firm for some years now, Gupta (DBG to those close to him and industry bigwigs), once noted how Lupin had created a "business democracy" where entrepreneurship could flourish within a corporate environment.

Gupta, who died aged 79 on June 26, was also known for his special touch when it came to people issues – he apparently unfailingly sent personally signed birthday cards to many employees, alongside some goodies.

This is not to say that Lupin's current management style is not people-oriented. But DBG, as even his children Vinita Gupta (Lupin's CEO) and her brother Nilesh (Lupin's managing director) emphasize, had a unique ability to "align people around a purpose, without trying too hard."

His general philosophy, they said, was that in Lupin, he liked professionals to feel like family and family to work like professionals. "DBG gives people flexibility and allows them to grow. People have gone from executive assistant to president of a division in Lupin," Vinita Gupta told Scrip in an interview in 2015.

At times, DBG may have perhaps even given people too much rope; the Lupin group's diversifications into finance and real estate in the early 1990s, along with several other Indian corporates at that time, were seen, in part, to be well-intentioned but clearly beyond the firm's core expertise.

EARLY DAYS

Founded in 1968, Lupin has clearly come a long way since its early days focused on the Indian market and tuberculosis drugs. Today DBG, whose early years included a stint as associate professor at the Birla Institute of Science and Technology in Pilani, Rajasthan, leaves behind a $2.5bn pharma company with a presence in over 100 countries. In 2016-17, the US accounted for close to 50% of Lupin's sales. The company is currently the fifth largest pharmaceutical player in the US by prescriptions and the second largest Indian drug firm by global revenues; it has also become the sixth-largest generic pharmaceutical player in Japan.

However, like many of its Indian peers, Lupin anticipates a challenging 2018 amid US price pressure, though the top brass has underscored the strength of the firm's ANDA pipeline and enhanced investments in the biosimilars, inhalation and injectables spaces.

DBG's people focus may perhaps be just as relevant in such challenging times.

Published online 27 June 2017

APPOINTMENTS

GlaxoSmithKline PLC has announced ***Luke Miels*** will start work as president, global pharmaceuticals on Sept. 4, 2017, after his start date was delayed by a disagreement with his former employer, AstraZeneca PLC. The appointment of Miels, who was executive vice president of AZ's European business and previously AZ's EVP global product and portfolio strategy, global medical affairs and corporate affairs, was announced by GSK in January, 2017. Miels will be responsible for GSK's £15bn medicines and vaccines businesses, and will report to CEO Emma Walmsley.

Chris Posner is to join **Leo Pharma AS** as executive vice president region US and president and CEO of Leo Pharma Inc., effective from July 15, 2017, when he will be responsible for all Leo's US business. Posner was previously head of worldwide commercial operations at R-Pharm US LLC, a specialty pharm start-up, and has also worked at Bristol-Myers Squibb, Pfizer, Wyeth, Endo and Merck & Co.

Valeant Pharmaceuticals International Inc. has appointed ***Arthur Shannon*** as senior vice president, head of investor relations and communications. Shannon was most recently vice president of global corporate affairs and European investor relations at Perrigo Co. PLC.

Desiree Luthman has joined UK biotech **Verona Pharma PLC** as vice president of regulatory affairs. Luthman has previously worked in regulatory affairs at Sanofi, where she led the regulatory team for the US FDA approval of dupilumab for atopic dermatitis. She has also worked at Bristol-Myers Squibb, Celgene and AstraZeneca.

Ocugen Inc., a US biotech developing treatments for sight-threatening diseases, has appointed ***Daniel Jorgensen*** chief medical officer and ***Rasappa Arumugham*** vice-president, research and development. Jorgensen has 20 years' experience in the biopharma industry, including 10 at Pfizer Inc., while Arumugham was head of microbial analytics at Merck's manufacturing division. ***Charlie Kang***, who is currently on Ocugen's executive management team, has been named chief financial officer, effective immediately.

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