PBMs Were On Capitol Hill, But Pharma Still Took Some Heat

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Pharmacy benefit managers had their turn on Capitol Hill, called into testify on drug pricing before the Senate Finance Committee April 9, but drug makers got a lot of the blame for high drug prices.

Leaders from five PBMs testified in the third hearing held by the Senate Finance Committee on drug pricing, about six weeks after seven pharmaceutical leaders similarly testified. Among the PBM participants were United Healthcare Services Inc.’s OptumRx CEO John Prince, CVS Health Corp. Exec VP and CVS Caremark President Derica Rice, Humana Inc. Healthcare Services Segment President William Fleming, Cigna Corp. Exec VP and Chief Clinical officer Steve Miller and Prime Therapeutics Interim CEO Mike Kolar.

The hearing went off without any big surprises, with the PBMs pushing back on pharma’s main lobbying message, that high list prices are powered by PBMs, who benefit financially through rebates charged as a percent of list price.

Senators appeared to be going through the motions, pressing the pharmacy distributors on the role of rebates and fees and how they relate to drug costs, but without a lot of specificity. Perhaps congressional leaders were as befuddled by the pharmacy middleman as the general public. As Ranking Member Ron Wyden, D-OR, quipped, “I’m of the view that PBMs guard their operations with greater secrecy than HBO is guarding the ending of Game of Thrones.”

Nonetheless, pharma still took a lot of heat. As Senator Sheldon Whitehouse, D-RI, spelled out, only $23bn of the $480bn the US spends on drugs, or 5%, goes to PBMs, while $323bn goes to pharmaceutical companies.

“It has to be interesting to you all to witness how the pharmaceutical industry has been able to take pressure on their pricing and turn it into, with political jiu-jitsu of almost magical variety, pressure on their greatest adversary, the most powerful force for pushing prices down,” Whitehouse said. “I hope you at least respect what they have been able to pull off here.”

Indeed, industry has been quite successful turning attention to PBMs in the debate over drug pricing and highlighting the growing rebates drug makers pay off list prices to negotiate formulary access with payers. One of the pivotal changes being proposed by the Trump Administration to lower drug prices is a proposal to eliminate rebates or pass them on directly to consumers at the point of sale. Drug makers are broadly supportive of the plan, but payers argue that the proposal will result in higher insurance premiums.

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US drug pricing is once again to the fore in this week’s issue, with the Senate Finance Committee’s third hearing on the thorny subject, and this time it was the pharmacy benefit managers in the spotlight. It was no surprise that they pushed back on pharma’s main lobbying message, that high list prices are powered by PBMs, who benefit financially through rebates charged as a percent of list price. Jessica Merrill has the full story on p1, and also reports on how HHS, the Centers for Medicare and Medicaid Services and others who are working to eliminate rebates will try to lessen the impact on Medicare Part D insurance premiums (see p3).

M&A news was dominated by the shareholder go-ahead for Bristol-Myers Squibb’s $74bn acquisition of Celgene. The next big step will be the combination of their commercial product portfolios and drug development pipelines, with the new Bristol-Myers Squibb making a claim to have the top biopharma oncology and cardiovascular franchises. See p4 for all the details.

Other deal developments saw Alnylam team up with Regeneron in a $800m multi-disease deal on the same day the RNAi specialist and Sanofi announced that the research portion of their longstanding R&D collaboration had ended, but development work continues. Joe Haas has all the details on p6.

Meanwhile, we take a look at the upcoming catalysts for this quarter; turn to p11 to see what you can expect to happen in the next few months.
Rebate Reshuffle: Could Pharma Foot The Bill To Offset Higher Premiums?
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A big challenge facing HHS, the Centers for Medicare and Medicaid Services (CMS) and other stakeholders working to eliminate rebates from the drug distribution system is how to blunt the impact on Medicare Part D insurance premiums, which are expected to increase as a result of changes.

Some industry watchers expect pharma could be asked to step in and pick up the tab, or some of it, given that drug makers are poised to benefit financially from the proposal that’s in development.

Bernstein Research analysts Luke Wilkes and Ronny Gal speculated in an April 8 research note that one solution to the issue would be for the Administration to charge the drug industry a fee and use it to “buy down” premiums.

“The fee could be a direct payment to the plan sponsor, or it could be a reduction in prices or take some other form,” Wilkes and Gal speculated. “The intent would be to utilize some of the drug companies’ benefits from the plan to reduce net cost for the plan sponsors back toward the original net cost.”

There is still a lot to work out about how rebates will be removed from the system or given directly at point-of-sale. The industry is still awaiting a final rule from HHS. A proposed rule was issued by the HHS Office of Inspector General in January with an effective date of Jan. 1, 2020.

Published online 8 April 2019
To read the rest of this story go to: https://bit.ly/2IFOgR4
As Expected: Shareholders Back Bristol’s $74bn Celgene Buy

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The shareholders of both companies have voted in favor of Bristol-Myers Squibb Co.’s $74bn acquisition of Celgene Corp., which is on track to close in the third quarter of this year – an outcome that was expected ahead of both drug makers’ April 12 shareholder meetings, since activist investor Starboard Value LP recently dropped its campaign to sway other Bristol stock owners against the deal.

Analysts generally anticipated that shareholders would eventually support the deal and that it would close on schedule, especially when Starboard said on March 29 that it would no longer stand in the way of the transaction. The activist shareholder determined that, despite its own objections, it would be difficult to convince other Bristol investors to vote against the Celgene purchase after the independent proxy advisory firms Institutional Shareholder Services (ISS) and Glass Lewis & Co. recommended that shareholders vote in favor of the deal.

Holders of more than 75% of Bristol’s outstanding shares voted in favor of the transaction, while 98% of the votes cast by Celgene shareholders – representing more than 70% of its stock – voted for the deal.

Both companies closed slightly down, however, on April 12 with Bristol’s stock declining 1.1% to $45.57 per share and Celgene dipping 0.1% to $94.14.

With the shareholder votes behind them, Bristol and Celgene can focus on closing the transaction, after obtaining sign-offs from regulators globally. Then, they’ll have to combine their large commercial product portfolios and drug de-
development pipelines. Bristol claims that it will have the top biopharma oncology and cardiovascular franchises – topped by its own immuno-oncology blockbuster Oprodo (nivolumab) and Celgene’s multiple myeloma market leader Revlimid (levaldilomide), plus Bristol’s antiangiulant Eliquis (apixaban).

The combined immunology and inflammation franchise will rank in the top 5 globally, according to Bristol’s estimates, including Bristol’s selective T-cell co-stimulation modulator Orenica (abatacept) for rheumatoid arthritis and psoriatic arthritis (PsA), among other indications, and the Celgene phosphodiesterase-4 (PDE4) inhibitor Otezla (apremilast) for psoriasis and PsA.

“We think that the combined company has clear therapeutic area overlap in oncology and immunology and that Celgene’s strong cash flow from operations over the next few years – growing north of $10 billion a year in 2022–23 in our model – will help Bristol reduce leverage and prepare for commercialization of Celgene’s late-stage pipeline, as several launches are on tap through the end of 2020,” Morningstar analyst Karen Andersen said in an April 12 note.

However, the companies’ combined immunology and inflammation franchise could be a problem for regulators reviewing the Bristol-Celgene deal for anti-competitive concerns. Bristol informed shareholders on March 26 that the Federal Trade Commission in the US requested more information from both companies about their marketed and pipeline assets for psoriasis.

In addition to Celgene’s only approved immunology and inflammation asset, the oral drug Otezla, for which psoriasis is an important indication, Bristol has initiated a Phase III program in psoriasis for its own small molecule, the TYK2 inhibitor BMS-986165, after promising Phase II results. (Also see “Bristol Engineers An Oral TYK2 Inhibitor With Biologic-Like Efficacy That Rivals JAK Safety” - Scrip, 12 Sep., 2018.)

Otezla has been a key product for Celgene because it helped the company diversify its revenue, which comes primarily from hematological and oncology drugs; Revlimid still comprises about two-thirds of its total revenue.

Meanwhile, Bristol’s TYK2 inhibitor is one of six late-stage pipeline assets from the companies’ merged pipelines that Bristol expects to generate $15bn in combined revenue at their peak. BMS-986165 is the only drug candidate of the six that comes from Bristol.

The other five potential blockbusters include:

- The S1P receptor modulator ozanimod, which recently was resubmitted to the US FDA for approval to treat relapsing and remitting multiple sclerosis after the agency issued a refuse-to-file letter last year (Also see “More Bad News: Celgene Reveals Refuse-To-File Letter For Ozanimod In MS” - Scrip, 27 Feb., 2018.);
- The erythroid maturation agent luspatercept, for which Celgene and partner Acceleron Pharma Inc. submitted a biologic license application (BLA) to the FDA earlier this month for myelodysplastic syndrome (MDS)-associated anemia and beta-thalassemia-associated anemia (Also see “‘Totality Of Data’ Make A Case For Luspatercept In Beta-Thalassemia, MDS” - Scrip, 3 Dec., 2018.);
- The CD19-targeting chimeric antigen receptor T-cell (CAR-T) therapy JCAR017 (lisocabtagene maraleucel, or liso-cel) that is said to be on track for submission to the FDA in 2019 for third-line or greater diffuse large B-cell lymphoma (DLBCL) (Also see “CAR-T Forecast: Celgene Follows, But Also Leads As Next Batch Of T-Cell Therapies Near Market” - Scrip, 3 Jan., 2019.);
- The bluebird bio inc.-partnered bb2121, a B-cell maturation antigen (BCMA)-targeting CAR-T therapy for multiple myeloma, which also is expected to be submitted for FDA approval in 2019 (Also see “Poseida, Legend/Janssen Look To Snag Celgene/Bluebird’s BCMA Crown” - Scrip, 4 Dec., 2018.); and
- Fedratinib, a JAK2 inhibitor under priority review at the FDA for myelofibrosis that Celgene bought a year ago for more than $1bn. (Also see “Celgene’s $1.1bn Impact Buy Is First Of More Deals To Come In 2018 And Beyond” - Scrip, 9 Jan., 2018.)

“To break even, we estimate that Bristol needs only $6bn-$7bn cumulative peak sales from Celgene’s ‘Big Five’ pipeline assets,” BMO Capital Markets analyst Alex Arfaei said in an April 12 note. “In our base case, we forecast that the ‘Big Five’ can reach peak sales of ~$10bn, below Celgene/Celgene’s $12bn-$14bn guidance.”

Sticking to established timelines for the ozanimod, liso-cel and bb2121 submissions is essential for Celgene investors to realize the full value of Bristol’s purchase of the company. In addition to $50 in cash and a share of Bristol stock, Celgene investors will receive a contingent value right (CVR) worth $9 per share of Celgene stock they own if the FDA grants approval for ozanimod and liso-cel by Dec. 31, 2020, and for bb2121 by March 31, 2021.

The biggest risk of the Bristol-Celgene combination for Bristol shareholders, however, could be a drastic decline in revenue when Revlimid generics hit the market. Both companies have downplayed that risk, since the first generics in 2022 will be limited-release copies of the multiple myeloma backbone therapy. Also, Celgene continues to reduce that risk by settling outstanding patent challenges; it won a reprieve in March when the US Patent and Trademark Office (USPTO) Patent Trial and Appeal Board (PTAB) denied the last remaining request for an inter partes review (IPR). (Also see “Celgene/Bristol’s Revlimid Patent Risk Incrementally Lower After PTAB Denies Alvogen IPR” - Scrip, 14 Mar., 2019.)

The late-stage assets that Bristol is so keen to buy are essential to diversifying the Celgene portfolio, regardless of how long it takes for Revlimid to realize full generic competition (expected in 2026, under various patent litigation settlements). However, Celgene has endured several setbacks in its attempts to diversify, including the RTF for ozanimod, that have decreased its stock value and made the company a relative bargain compared to when Bristol first made a bid to merge in 2017. (Also see “Bristol Approached Celgene Nearly Two Years Ago, Got A Better Deal Later” - Scrip, 1 Feb., 2019.)

When the Bristol-Celgene transaction closes in the third quarter, it will be the third-largest mega-merger in biopharma history, behind Pfizer Inc.’s $84.1bn deal with Warner-Lambert Co. in 2000 and the $78bn combination of Glaxo Wellcome Inc. and SmithKline Beecham Corp., also in 2000. (Also see “Bristol/Celgene A Record-Setting Merger, If It Happens” - Scrip, 3 Jan., 2019.)

Published online 12 April 2019
long a partner of choice in the RNA-interference arena, Alnylam Pharmaceuticals Inc. added and subtracted R&D partners on April 8, announcing a five-year, multi-disease pact with Regen-er-on Pharmaceuticals Inc. that will bring it $800m up front, split between cash and equity. That same day, the RNAi pioneer and Sanofi announced that the research portion of their longstanding R&D collaboration has ended, but development work continues.

The new deal combines Alnylam’s tech-nological expertise with Regeneron’s clinical development and commercial heft, while offering diversification to Re-generon, which gets to pursue targets not ideally suited for its usual antibody approach. The companies will partner to discover, develop and commercialize RNAi therapies for ocular disease, central nervous system (CNS) disorders and liver indications, beyond the scope of the partnership in non-alcoholic steatohepatitis (NASH) that the pair signed in 2018. (Also see “Alnylam and Regeneron Plan 50/50 Gene R&D Pact To Find NASH RNAi Drugs” - Scrip, 22 Mar, 2018.)

That partnership is expected to enter clinical development next year, with an RNAi therapy candidate that targets the liver-expressed protein HSD17B13. The two firms also say they’ll expand their work in NASH under the new agreement.

Alnylam CEO John Maraganore predicted during a same-day investor call that the collaboration could yield “industry-leading” drug development efforts for RNA-directed therapies in eye and CNS indications.

“We believe that the scope of this new opportunity with Regeneron is substantial with a large number of diseases that could be addressed with RNAi therapeutics,” he said. “In the CNS, this opportunity includes Alzheimer’s and other forms of dementia: Huntington’s; Parkinson’s and ALS, where there are clear human genetic data that we believe create opportunities for RNAi therapeutics. In the eye, there are also a large number of opportunities, including both wet and dry forms of age-related macular degeneration (AMD), glaucoma and a number of genetic diseases.”

FIRST CANDIDATE MAY BE PNH COMBO THERAPY

The liver-focused part of the work will address complement-mediated diseases. Possibly first into the clinic from the collaboration will be a combination therapy testing Regeneron’s Phase I antibody candidate pozelimab (REGN3918) with Alnylam Phase II candidate cemdisiran in paroxysmal nocturnal hemoglobinuria (PNH). Regeneron will lead the combination work, while Alnylam will retain rights to cemdisiran monotherapy in atypical hemolytic uremic syndrome (aHUS).

“The combination product could allow more complete C5 inhibition than either approach alone and could also enable subcutaneous administration of the monoclonal antibody with infrequent dose regimens,” Alnylam President of Research and Development Akshay Vaishnav told the call. “We and our colleagues at Regeneron believe that there’ll be other sRNA-antibody combination opportuni-ties in the future, and we will explore these as they emerge from collaborative efforts.”

The deal commits Alnylam to work exclusively with Regeneron in the ocular and CNS spaces. The Cambridge, Mass.-based firm, which recently brought its first commercial product Onpattro (patisiran) to market, gets $400m in upfront cash from Regeneron along with a $400m equity investment comprising 4.44m Alnylam shares at $90 apiece.

Onpattro obtained US FDA approval to treat transthyretin-mediated amyloidosis in August, the first approval for an RNAi therapeutic. (Also see “Alnylam Offers Flexible Value-Based Deals For Breakthrough RNAi Drug Onpattro” - Scrip, 11 Aug, 2018.)

Alnylam also can earn up to $200m in near-term milestones under the agreement, pegged to early clinical development in eye and CNS indications. The companies’ goal is to advance programs against 30 targets – not all of which are pre-specified – into the clinic over the next five years. Alnylam will earn $2.5m at program initiation and $2.5m at candidate identification for each asset, which it says could generate additional revenue of up to $30m annually.

Regeneron will lead development and commercialization for eye indications, while advancement and leadership of the programs in CNS and liver diseases will alternate between the two companies. Alnylam can earn milestone fees and royalty payments for the eye disease programs. In CNS, at candidate selection, the party not leading development and commercializa-tion has the option to participate in future profits under a cost-sharing arrangement.

GOOD TERMS FOR ALNYLAM, EYE DIVERSIFICATION FOR REGENERON

Analysts generally agreed that the deal terms are advantageous for Alnylam, while offering Regeneron diversification beyond antibody therapies, but at a high price for early-stage research.

Baird Equity Research analyst Brian Skorney said in an April 8 note that “the size of the upfront and the relatively early nature of the programs is unlikely to generate investor enthusiasm, on [Regener-on’s] side of the deal.”

The partnership should benefit from Regeneron’s experience in ophthalmol-o gy with Eylea (aflibercept), which has US label indications for AMD, macular edema and diabetic retinopathy, the analyst added. “Successful candidates in this space may help diversify Regen-er-on’s highly concentrated reliance on Eylea sales, which are expected to come under fire as competitors enter the market in coming years,” he wrote.

Eylea obtained a supplemental approv-al from the FDA in August for less-frequent dosing, which Regeneron hopes will help it compete against late-stage candidates in the vascular endothelial growth factor
As clinical trials of beta-amyloid-targeting therapies continue to fail in the treatment of Alzheimer’s disease, the global biopharmaceutical industry increasingly is shifting its attention to tau pathology, which is more proportionally correlated with disease progression and severity.

South Korea’s Alzheimer’s Disease Experts Lab (ADEL) Inc. is one of those pursuing the tau hypothesis.

Its founder and CEO Seung-Yong Yoon, who is also an associate professor in the Department of Brain Science, University of Ulsan College Of Medicine, began to develop an anti-tau antibody several years ago when anti-amyloid beta antibodies were in the spotlight and very few Alzheimer’s disease (AD) drug developers focused on anti-tau antibodies.

“Based on our research, we believed tau was a better target for AD therapy, although anti-amyloid antibodies were at the center of the focus at that time,” the CEO said in an interview with Scrip.

As Amyloid Therapies Fail, Tau Antibodies Near Data Events

As most of the amyloid-targeting therapeutics, including Eisai Co. Ltd. and Biogen Inc.’s aducanumab, have failed in clinical trials, interest in AD therapies with other targets such as the tau protein has been rising. At present, there are about 20 clinical stage antibodies targeting beta amyloid and about seven clinical stage anti-tau antibodies.

Biogen and Eisai said in March that they will discontinue the Phase III trials testing aducanumab in patients with mild cognitive impairment due to AD and those with mild AD dementia. (Also see “Why Biogen/Eisai’s Aducanumab Failure Is Not The End Of Amyloid Hypothesis” - Scrip, 21 Mar, 2019.) This follows Roche’s decision in January to discontinue two Phase III studies of crenezumab after an independent interim analysis concluded the anti-beta amyloid monoclonal antibody was unlikely to meet the studies’ primary endpoints. (Also see “AC Immune/Roche Drop Crenzumab After Phase III CREAD Alzheimer’s Failure” - Scrip, 30 Jan, 2019.)

Anti-tau antibodies currently under development include RG-6100, which is being developed by AC Immune SA and Roche’s Genentech Inc., with the results of a Phase II study expected to read out in 2020. (Also see “Interview: AC Immune CEO Reflects On Alzheimer’s R&D Post-CREAD” - Scrip, 14 Feb, 2019.)

Also, Axon Neuroscience completed recruitment for its Phase II clinical trial of AADvac1, an active vaccine targeting Alzheimer’s tau. Top-line data from the Phase II study are expected to be available in mid-2019. Eisai’s E2814, an anti-tau monoclonal antibody jointly developed with University College London, is set to enter Phase I trials early this year.

In addition, Merck & Co. Inc. has reached a worldwide license agreement to bring in Teijin Pharma Ltd.’s preclinical antibody targeting tau protein.

ADEL Candidate’s Novel MOA, Unique Target

While beta amyloid is about 42 amino acids in length, tau protein is much longer with 441 amino acids. As a result, it is much harder to choose the right epitope in tau...
proteins for therapeutic effects. In addition, it is unclear which of the various post-translational modifications – such as phosphorylation, O-GlcNAcylation, ubiquitination, acetylation, methylation, glycation and cleavage – are related to AD and which modifications should be targeted to gain therapeutic effects.

As a result, it is crucial to select and target the right location and modification of tau to successfully develop an AD therapy, Yoon noted.

Among the several tau antibodies in clinical development, the initial group mainly target N-terminal, while second movers target mid-region. Meanwhile, ADEL’s lead asset ADEL-Y01 – a tau antibody/vaccine – targets a different location and different modifications of tau to inhibit propagation and aggregation of tau.

It targets a unique epitope different to that of competitors, and the epitope has disease-specific, post-translational modification. In this respect, the company’s anti-tau antibody has a novel mechanism of action.

“In terms of epitope, ADEL-Y01 is seen as a first-in-class tau antibody,” Yoon commented.

ADEL’s first R&D strategy was to decide the best therapeutic epitope by directly comparing the in vivo therapeutic efficacy in tau transgenic mice among the putative epitopes.

“We confirmed that our antibody had greater efficacy versus a rival antibody in inhibiting tau propagation,” said the CEO.

The company is developing cell lines and processes and selecting an overseas contract research organization to conduct non-clinical studies overseas this year. It aims to receive an investigational new drug (IND) application approval by the end of next year in an overseas market, including the US, to enable future clinical trials.

So far, ADEL is the sole company in South Korea pioneering in the tau antibody field.

“In South Korea, no one is developing tau antibodies at our level. This could be our strength. When global firms focused on researching amyloids, we started to develop a tau antibody,” he said. Some South Korean companies may be internally discussing development of tau-targeting therapies for AD, but they are likely to be substantially behind others in this area, Yoon noted.

As amyloid-targeting therapies continue to fail, global pharmas and biotechs have been keen to bring in preclinical or even earlier stage tau-targeting therapies from smaller companies.

ADEL is seeking partners that have strong manufacturing facilities for antibody therapies, but it is flexible in regard to the timing of the licensing as it is essential to find the right partner.

Going forward, the company aims to further progress its lead asset and find licensing partners to expand its pipeline into additional antibodies, proteins and peptide therapeutics in neurological diseases, including AD. Its pipeline already includes the tau vaccine/antibody ADEL-Y01, an early-stage companion diagnostic for plasma biomarkers, and novel target-based antibodies and peptides.

So far, ADEL has raised KRW2bn ($1.8m) in Series A financing and KRW800m from angel investors. The company also received financial support from the state-run Korea Drug Development Fund in 2017. It is considering raising additional funds in a Series B financing late this year or early next year to further progress its pipeline.

Published online 10 April 2019
of insulin. The program is being funded with additional manufacturer discounts. (Also see “Express Scripts Insulin Program Lowers Cost Sharing With Supplemental Manufacturer Discounts” – Pink Sheet, 3 Apr, 2019.)

Insulin costs are a big burden to patients, with news reports citing incidences of patients skipping their insulin to ration doses and triage costs – further spotlighting a potentially dangerous predicament for patients. High prices are getting specific scrutiny from legislators on Capitol Hill amid the broader outcry over the high cost of drugs.

But the new wave of savings programs may be too little too late to appease legislators. As Congresswoman Diana DeGette (D-CO) said of the savings initiatives during a Congressional hearing on insulin prices April 10, “It’s not a solution to the problem. It’s just a temporary band-aid, and it’s one that we have to stop.”

DeGette is the chair of the House Energy and Commerce Committee Subcommittee on Oversight and Investigation, which held the hearing. Representatives from the three big insulin makers, Sanofi, Eli Lilly & Co. and Novo Nordisk AS, were called into testify. Three pharmacy benefit managers (PBMs) – Express Scripts, United Healthcare Services Inc.’s OptumRx and CVS Health Corp. – also testified at the hearing.

As DeGette closed the hearing she warned that the bipartisan investigation into high insulin costs will continue. “We are prepared to talk to you now and we are prepared to bring you back in July or September to talk about the progress that has been made,” she said.

The House hearing was the second one on Capitol Hill in as many days to discuss drug prices. On April 9, the Senate Finance Committee brought in five PBMs to discuss the issue, where the PBM representatives tried to counter pharma’s lobbying push for rebate reform. (Also see “PBMs Were On Capitol Hill, But Pharma Still Took Some Heat” – Scrip, 9 Apr, 2019.)

SANOFI EXPANDS ACCESS PROGRAM
Sanofi Exec VP-External Affairs Kathleen Tregoning highlighted Sanofi’s savings program for insulins during her opening testimony at the House hearing. The Insulin Valyou Savings Program was created in 2018 to help cash-paying patients in the US who don’t qualify for other assistance programs. The program includes all of Sanofi’s insulins, including its two long-acting insulin glargine products Lantus and Toujeo. The program originally set a price of $99 for one 10mL vial or $149 for a box of SoloSTAR pens, but under the newly announced expansion, patients can get up to 10 boxes of pens and/or 10mL vials for $99 per month.

“We believe the up to 10 vials and/or boxes of pens will cast the widest net of helping the people who need it,” Sanofi said. How big of an impact the expanded program depends on how much insulin a patient needs, which is highly variable. The company noted that some people may need two vials a month and one box of pens (which is usually three pens for Toujeo and five for the other insulins).

Even that amount would represent a welcome savings of around $200 a month for patients, and the expanded program appears more aligned with a trend to cap patient out-of-pocket costs.

Sanofi estimates that about 10% of its patients pay cash and would be eligible for the program. Since it was launched a year ago, the program has resulted in approximately $10m in patient savings, Sanofi said. It is not available to patients under Medicare, Medicaid or other state or federal programs due to government regulations.

Meanwhile, Mike Mason, the senior VP overseeing Lilly’s insulin global business unit, outlined in written testimony to Congress the company’s savings program for insulins that caps costs at the pharmacy at $95 for patients in the high-deductible phase of their coverage, with Lilly picking up the remainder of the costs.

Lilly also recently announced the launch of an authorized generic version of its short-acting insulin Humalog (insulin lispro) in the US at a 50% discount to the list price of the brand. The higher-priced product is still available to patients, meaning Lilly has the same drug available in two different versions at two different prices to address some of the complexities for reimbursing drugs in the US. This strategy, which some other drug makers are also testing, can be used to assist Medicare Part D patients, who aren’t able to use many other forms of assistance programs.

Legislators and the public are confused by the growing list price of insulins, but drug makers argue the list prices do not reflect the hit they’ve absorbed on net prices as a result of growing rebates.

Sanofi, for example, in its testimony said that while the list price of its insulins has grown 125% from 2012 to 2018, the aggregate net price fell 25%. The net price of Lantus has fallen 30%, and is in fact less than it was in 2006.

One policy proposal drug makers are advocating as a longer-term fix to the patient affordability issue is to have insulin added to preventative medications lists, which would exempt insulin from deductibles.

Published online 11 April 2019
Dainippon Pursues Organ Generation In New Alliance With Japan Partners

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Why treat the symptoms of a disease when you can replace a whole organ? That appears to be the fundamental question being asked by Sumitomo Dainippon Pharma Co. Ltd. (SDP) in a new basic research alliance that goes a step further than the cell and gene therapy approaches now becoming increasingly common in the global pharma industry.

Rather than pursuing the development of treatments for renal disorders, immunosuppressants to support organ transplants, or the partial regeneration of compromised organs, the mid-sized Japanese pharma company is taking a more direct and holistic approach. It is linking with a group of partners in Japan to progress basic research into regenerative medicine techniques for renal disorders, with a focus on an induced pluripotent stem cell (iPSC)-based organogenic niche method for the generation of whole organs, in this case kidneys.

The aim of the initiative, with four other academic and venture partners, is “to achieve commercialization in the 2020s,” the company said. Under the alliance, SDP will be responsible for selling any renal regenerative medicine developed as part of the collaboration, but other detailed terms were not disclosed.

The firm will conduct the joint R&D with the Jikei University School of Medicine and Meiji University in Tokyo, along with two Japanese regenerative medicine bioventures, Tokyo-based Bios and PorMedTec based in Kawasaki City near Tokyo.

SDP’s main commercial therapeutic presence is in diabetes and hypertension, along with neurology, and most of its current pipeline is in various CNS indications and oncology. So the move appears to indicate something of a shift in both therapeutic and strategic focus, although the company is already active in the regenerative medicine research space through several pipeline projects.

At present, these include two cell-based therapies derived from iPSCs, in the non-renal areas of Parkinson’s disease and age-related macular degeneration, for which the company is again pursuing academic and corporate alliances, working respectively with Kyoto University’s CIRA (Center for iPS Cell Research and Application), and the national research institute Riken and Japanese venture Healios KK.

ORGANOCENIC NICHE APPROACH

New alliance partner Bios was established to develop and apply the technologies required for the organogenic niche method, and a differentiation-inducing technique built upon the findings of research originally conducted by Professor Takashi Yo- koo and team at Japan’s Jikei University School of Medicine.

SDP said that the renal regeneration method it is investigating is intended to regenerate a complete functional kidney by using human iPSC-derived, differentiation-induced nephron progenitor (“bud”) cells that are then injected into a renal anlagen, a fetal-stage kidney.

This will involve the early fetus of a genetically engineered pig bred specifically for application to human renal regenerative medicine, using techniques based on the research of Professor Hiroshi Nagashima at Meiji University’s International Institute for Bio-Resource Research, and provided commercially through PorMedTec.

The placing of a target organ from another animal onto a site where an embryonic organ develops in an animal’s early fetus – inducing the development of the target organ in the host animal – is known as the organogenic niche.

In the case of SDP’s renal program, the organ bud would be transplanted into the patient to initiate early organ development, and urinary tract surgery would be performed on the patient who has undergone renal anlagen transplantation to facilitate its development into a functional kidney.

OUTSTANDING NEED

While the program is still at a very early stage, SDP points out that, according to International Society of Nephrology data, the number of patients requiring kidney transplantation and similar procedures worldwide was estimated to be 5.3-10.5 million.

The figure includes around 1,750 kidney transplants conducted in Japan in 2017, although this was only a fraction of the total of around 12,500 patients applying to undergo this procedure, indicating a severe shortage of organs for transplant. The approach is therefore one way of fulfilling outstanding medical need in situations where there is no real alternative to a full transplant.

Some other companies in Japan, notably Healios, are also pursuing organ bud programs derived from iPSCs, in its case using technology licensed from Yokohama University for liver failure. The venture is hoping to begin a clinical program this year for urea cycle defects which currently require expensive enzyme replacement therapy or organ transplant.
As the FDA continues efforts to combat the opioid epidemic, Outlook Report include:

NKTR-181 FOR CHRONIC LOW BACK PAIN
As the FDA continues efforts to combat the opioid epidemic, Nektar Therapeutics’ NKTR-181 holds the potential to be a new treatment option for individuals with chronic low back pain. Although still targeting opioid receptors, NKTR-181’s small molecule-polymer conjugate technology slows entry of the drug to the central nervous system, thus preventing the euphoria often associated with common opioids. Results from a human abuse liability study confirmed that NKTR-181’s abuse potential was similar to placebo and significantly lower than oxycodone’s, thus demonstrating that NKTR-181 could be a safe, non-addictive treatment option, Biomedtracker said. It notes that in a pre-NDA meeting with the FDA, the regulator confirmed that Nektar had an adequate abuse potential assessment data package, and that together with the safety results, the data appeared to be adequate to warrant a discussion of a less restrictive scheduling than Schedule 2. The PDUFA decision for NKTR-181 should occur on May 31, 2019, the report notes.

MARIBAVIR FOR CMV
Maribavir, a key Phase III asset at Shire PLC for cytomegalovirus (CMV), is an oral benzimidazole riboside to treat CMV infection in transplant recipients. The pivotal Phase III SHP620-303 trial comparing the efficacy of maribavir to investigator-assigned treatment in transplant recipients with CMV infections resistant or refractory to prior CMV treatment was begun in December 2016. Shire expects top-line data from the Phase III SHP620-303 trial in the second quarter of 2019. Originally, maribavir was developed by GlaxoSmithKline PLC and licensed to ViroPharma Inc. worldwide, excluding Japan, in 2003. ViroPharma later merged with Shire in 2014 and was acquired by Takeda Pharmaceutical Co. Ltd. in 2019.

DENGVAXIA FOR DENGUE FEVER
Sanofi’s vaccine for dengue fever is up for FDA review. In October 2018, the FDA granted Dengvaxia priority review and set a Prescription Drug User Fee Act action date of May 1, 2019. Biomedtracker notes that while Dengvaxia’s demonstrated efficacy and safety in individuals aged over nine years is expected to be enough for it to gain US approval, an FDA advisory panel meeting in March 2019 proposed a narrower label for the vaccine – of 9-17 years – than that which Sanofi was pursuing (9-45 years), because of a lack of bridging safety data in adults. The panel also raised concerns over the lack of a commercially available test to identify patients who are seronegative at baseline and therefore should not be vaccinated. Thus there is a risk that the FDA will not approve the vaccine until such a test becomes available, which Sanofi hopes will occur in 2020.

MITOTECH’S VISOMITIN FOR DRY EYE
Mitotech SA’s Visomitin is a topical ophthalmic formulation of SkQ1, a small molecule which efficiently brings the active antioxidant plastoquinone into mitochondria to prevent damage from reactive oxygen species (ROS). Mitotech is developing Visomitin for the treatment of dry eye syndrome. Top-line results from the pivotal Phase III trial VISTA-1 are expected in the second quarter of 2019. Mitotech anticipates seeing similar positive results as with the previous Phase II trial and clinical studies in Russia, Biomedtracker says in its report. VISTA-1 was begun across the US in October 2018, with an expected enrollment of 450 patients with moderate to severe dry eye. The trial will feature three arms: high dose Visomitin, low dose of Visomitin, and a placebo. Primary endpoints include central corneal staining change and grittiness change from baseline to day 57.

HUMACYL IN END-STAGE RENAL DISEASE
Pivotal data for Humacyte Inc.’s Humacyl are expected in coming months from a Phase III trial for hemodialysis access in patients with end-stage renal disease (ESRD). In May 2016, Humacyte began a Phase III open-label, randomized, two-arm trial comparing the efficacy of Humacyl with expanded polytetrafluoroethylene (ePTFE) grafts as a conduit for hemodialysis in ESRD patients who are not candidates for an autologous AV fistula. The Phase III study’s primary objective is the time to loss of secondary patency from implantation. The rate of access-related infections will also be assessed. Humacyte expects to announce 18-month top-line results from the pivotal Phase III trial during the first half of 2019.

VYLEESI (BREMELANOTIDE) FOR FEMALE SEXUAL AROUSAL DISORDER
Biomedtracker forecasts a late June PDUFA decision for AMAG Pharmaceuticals Inc.’s hypoactive sexual desire disorder (HSDD) drug Vyleesi (bremelanotide), a novel melanocortin 4 (MC4) receptor agonist thought to impact the excitatory neural system, excluding Japan, in 2003. ViroPharma later merged with Shire in 2014 and was acquired by Takeda Pharmaceutical Co. Ltd. in 2019.
pathways in the brain to restore sexual desire. Vyleesi is being developed for the treatment of HSDD in pre-menopausal women and is given by subcutaneous injection using a single use autoinjector pen only as needed prior to anticipated sexual activity. FDA in November delayed the user fee goal date for Vyleesi with a request for data from a frequent-dosing study. The PDUFA date for completion of FDA review of the Vyleesi NDA is now June 23, but as this date falls on a Sunday, the PDUFA decision is expected the Friday before, the report says.

**PALOVAROTENE FOR TREATMENT OF FOP**

Top-line results from the pivotal Phase III MOVE study of Clementia Pharmaceuticals Inc.'s palovarotene for treating fibrodysplasia ossificans progressive (FOP) are expected in the second quarter of 2019. Overall, top-line data from the Phase III MOVE study will be instrumental in palovarotene's approvability with the FDA, Biomedtracker says. Pending these results, the company plans to submit an NDA for palovarotene in the second half of 2019. Due to the rare nature of FOP and the lack of treatment options, positive results from the MOVE study could go a long way to sealing first approved therapy for this disease, Biomedtracker's report says. Palovarotene is a retinoic acid receptor gamma selective agonist. Canada-based Clementia is being acquired by Ipsen.

**IBREXAFUNGERP FOR FUNGAL INFECTIONS**

Scynexis Inc. expects to report preliminary results at the 29th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) on April 13, 2019 from CARES, a pivotal, single-arm, Phase III trial evaluating oral ibrexafungerp as an emergency use treatment for hospitalized patients with invasive candidiasis caused by Candida auris, an emerging fungus that has been identified by the Centers for Disease Control and Prevention (CDC) as a serious global health threat. Biomedtracker says preliminary results from the CARES trial will be the first indication of ibrexafungerp efficacy against C. auris. Scynexis has indicated that positive results in the CARE and FURI studies may lead to toward a future NDA submission and potential approval through the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD), Biomedtracker notes.

**DREAMM-6 FOR GSK2857916**

GlaxoSmithKline PLC expects to have preliminary data from the DREAMM-6 study of GSK2857916 combined with standard-of-care chemotherapy in relapsed/refractory multiple myeloma in the first half of 2019, BMT notes. DREAMM-6 comprises two arms, each testing GSK2857916 in combination with different standard of care regimens in part 1 of the study. In Arm A, GSK2857916 will be evaluated in combination with lenalidomide plus dexamethasone, while in Arm B GSK2857916 is being testing in combination with bortezomib and dexamethasone. (Also see “Good DREAMM-1 Data Keeps GSK On Track For Multiple Myeloma Filing This Year” - Scrip, 25 Mar, 2019.)

Published online 8 April 2019

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**ViiV’s Dovato: Treatment-Naive HIV Is Earmarked For The “Complete Regimen”**

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A blockbuster future has been forecast for ViiV Healthcare’s Dovato, the first once-daily, single-tablet, two-drug regimen just approved in the US for patients who have never received antiretroviral treatment, which is expected to challenge widely used three-drug combination HIV therapies, particularly those marketed by key competitor, Gilead Sciences Inc.

Dovato combines the integrase inhibitor Tivicay (dolutegravir, 50 mg) and the nucleoside reverse transcriptase inhibitor (NRTI) Epivir (lamivudine, 300 mg) in a single tablet. The potential benefits of a simplified single-tablet, two-drug regimen was highlighted by the US FDA in the approval announcement on 8 April 2019, which tagged the product as a “complete regimen.”

Dovato could also be a less expensive option for the treatment of HIV/AIDS, thereby driving sales – the US price for Dovato is currently likely to be around $27,500 annually, which is 26% below the price for Gilead’s triple combination, Biktarvy, priced at around $37,000 per annum, according to Evercore ISI analysts. Biktarvy was approved for US marketing in February 2018, and in the fourth quarter had revenues of $551m in the US, becoming the “number one prescribed regimen for both treatment-naive and switch patients.”

However, a Boxed Warning in the US labeling cautions about the use of Dovato in patients co-infected with HIV and hepatitis B. “All patients with HIV-1 should be tested for the presence of HBV prior to or when initiating Dovato,” the boxed warning says. “Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported.

The HIV virus has proven difficult to eradicate completely.
If Dovato is used in patients co-infected with HIV-1 and HBV, additional treatment should be considered for appropriate treatment of chronic HBV; otherwise, consider an alternative regimen.

The benefits of Dovato are expected to include a low propensity to be associated with side effects, and good patient compliance, and DataMonitor Healthcare has forecast Dovato sales to increase gradually to $1.1bn in 2026 in the five major EU markets and the US. However, there may be residual physician concerns about the potential emergence of resistance after long-term use, particularly in non-compliant patients, and the need of the new therapy to gain recommended status in treatment guidelines, which could mute its uptake, say Biomedtracker analysts.

A two-drug regimen, Juluca (dolutegravir/rilpivirine), is already marketed in the US and EU by Viiv, but it is indicated for use in adults who are virologically suppressed on a stable antiretroviral regimen for at least six months, with no history of treatment failure and no known substitutions associated with resistance to dolutegravir or rilpivirine.

UNTREATED PATIENT OPTION

The US FDA’s director of antiviral products, Debra Birnkrant, remarked that “patients who have never been treated have the option of taking a two-drug regimen in a single tablet while eliminating additional toxicity and potential drug interactions from a third drug.” She also noted that having a “drug-sparing treatment available that uses fewer drugs is beneficial to patients who may have issues taking multiple medications over a period of time.”

Dovato has been submitted for approval in the EU, Canada, Australia, Switzerland and South Africa, and Viiv, the company owned by GlaxoSmithKline PLC, Pfizer Inc. and Shionogi & Co. Ltd., noted that additional submissions are planned during 2019.

Dovato’s approval was based on the GEMINI 1 and 2 Phase III studies, which found that HIV did not develop resistance after 48 weeks of therapy and indicated that it was non-inferior to a dolutegravir-based three-drug regimen, also containing tenofovir disoproxil fumarate and emtricitabine, in controlling HIV-1.

The US indication for Dovato states that the product is approved as a “complete regimen for the treatment of HIV-1 infection in adults with no known antiretroviral treatment history and with no known substitutions associated with resistance to either dolutegravir or lamivudine.” In a statement on the approval, the CEO of Viiv, Deborah Waterhouse, said the company was delivering what patients had been requesting: “a chance to treat their HIV-1 infection with as few drugs as possible, marking a significant step in HIV treatment.”

Published online 9 April 2019

Intercept’s OCA Data Bolster NASH Efficacy, But Pruritus Worries Worsen

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A more comprehensive look at Intercept Pharmaceuticals Inc.’s Phase III REGENERATE study of obeticholic acid (OCA) in non-alcoholic steatohepatitis (NASH) seemed to bolster the drug’s efficacy case, but investors drove the company’s stock price down April 11, perhaps due to increasing concerns about discontinuation rates seen in the study due to pruritus.

Intercept presented supportive data from REGENERATE at the European Association for the Study of the Liver (EASL) meeting April 11 in Vienna, revealing that more patients on the higher dose of OCA were showing a greater improvement in fibrosis scores.

JMP Securities analyst Liisa Bayko concluded in a same day note that the “incremental new efficacy [data] cuts support OCA’s fibrotic effects and hint at NASH improvements which may continue over time,” reiterating a “market outperform” rating for Intercept’s stock.

But investors did not respond positively, as the firm’s stock price finished the trading day down 13% at $104.75.

On Feb. 19, Intercept became the first company to report positive Phase III data in NASH, with top-line data from REGENERATE showing that 23.1% of patients who received a 25 mg daily dose of the farnesoid X receptor (FXR) agonist saw at least a one-stage improvement in their fibrosis scores at 18 months, compared to 11.9% who received placebo. (Also see “Intercept Retakes The Lead In NASH” - Scrip, 19 Feb, 2019.) However, the lower 10 mg daily dose tested in the study did not meet statistical significance for the primary endpoint – 17.6% achieved a one-stage or greater improvement in fibrosis – and the study also missed a co-primary endpoint of resolution of NASH without worsening of fibrosis.

Eight days earlier, competitor Gilead Sciences Inc. had been the first company to report Phase III NASH data, but its apoptosis-signaling kinase 1 (ASK1) inhibitor selonsertib failed to meet a primary endpoint of a one-stage or greater improvement in fibrosis score in patients with F4 fibrosis scores and cirrhosis due to NASH. (Also see “In NASH, Gilead Swung For The Fences And Struck Out Again” - Scrip, 12 Feb, 2019.) While Gilead attempted to meet a tougher endpoint than used in Intercept’s study, the trial nonetheless was not the company’s first setback in NASH – in 2016 it...
per protocol cohort data detailed

During its EASL presentation, Intercept went beyond the topline data previously released (which was based on results from 931 intent-to-treat (ITT) patients) with data from a 668-patient per protocol cohort. These patients were a subset of the ITT population who had completed 15 months of treatment or more with OCA, had an end-of-treatment or 18-month liver biopsy, had been on OCA treatment for at least 30 days prior to that biopsy, and had no major protocol deviations during their treatment.

Intercept CEO Mark Pruzanski told the EASL audience that the rationale for presenting data from a per protocol cohort is “because that as a standard is the best way to understand the true effect that the drug is having … in patients who are appropriately compliant in the context of the trial with treatment.”

In this subgroup, Intercept reported that three times as many patients who received the 25 mg dose of OCA (13.3%) achieved a two-stage or greater fibrosis score improvement compared to placebo (4.5%) (p=0.0008). For a standard of one-stage or greater fibrosis score improvement, three times as many patients receiving 25 mg of OCA improved rather than worsened (38% versus 13.1%), whereas those proportions were nearly level in the control group (23.2% vs. 20.9%).

Credit Suisse analyst Michael Morabito said in an April 11 note that the fibrosis data increase OCA’s argument for approval. “We see this two-stage improvement as very positive for OCA’s efficacy profile for regulatory approval,” he concluded. “The FDA has indicated a one-stage improvement would be necessary for approval, while the EMA has leaned toward requiring a two-stage improvement to show a benefit.”

Beyond fibrosis, the per protocol data showed benefits in key underlying aspects of NASH. For hepatocellular ballooning, 43.6% of patients getting the 25 mg dose showed an improvement of one point or greater, compared to 28.6% of placebo patients (p=0.0008). For lobular inflammation, 52.3% of patients receiving 25 mg of OCA showed a one-point or greater improvement, compared to 42% of patients receiving placebo (p=0.03).

improvements in nash’s underlying cause

OCA 25 mg also showed rapid and sustained reductions in liver biochemistry, as alanine aminotransferase (ALT) levels achieved normalization in 65.6% of patients who had elevated ALT at baseline compared to 37.3% getting placebo. For aspartate aminotransferase (AST) levels, 54.7% of patients getting the 25 mg study drug dose who had elevated levels at baseline achieved normalization, compared to 29.3% of placebo recipients.

In an interview prior to EASL, Intercept Senior VP-Medical Affairs, Safety and Pharmacovigilance Gail Cawkwell said improvement in fibrosis score offers the best correlation to positive long-term outcomes in liver disease. However, researcher Vlad Ratziu of France’s Curie University, presenting the REGENERATE report at EASL, said that the data on underlying causes of NASH suggest OCA might offer a broader benefit to NASH patients. “The effect again on inflammation and ballooning is very encouraging; there’s something going on,” he said.

Intercept also argued for OCA’s safety profile, based on findings from 1,968 randomized patients who received at least one dose of the drug, with exposure up to 37 months. It noted that serious adverse event (SAE) frequency was 14% among patients receiving 25 mg of OCA, 11% receiving the 10 mg dose and 11% in the placebo arm.

OCA, which is approved to treat primary biliary cholangitis under the brand name Ocaliva, has been troubled with safety and tolerability concerns, however, around increased levels of LDL cholesterol and pruritus. (Also see “Intercept Makes No Changes To Ocaliva NASH Study Despite PBC Safety Issues” - Scrip, 25 Sep, 2017.) The company said the LDL level findings in REGENERATE were consistent with previous OCA trials and that the drug was associated with an increase in LDL peaking at 22.6 mg/dL at four weeks, but that LDL levels typically reversed and approached baseline levels at month 18 (4 mg/dL increase from baseline).

Intercept noted that dose-related pruritus remains the most common adverse event reported in OCA studies. In REGENERATE, 51% of patients getting the 25 mg dose reported pruritus, compared to 28% getting the 10 mg dose and 19% in the placebo arm. The vast majority of pruritus incidents in the 25 mg cohort were mild to moderate, the company said, and incidence of pruritus was highest during the first three months of treatment across the full study, and then decreased. However, 9% of patients getting the 25 mg dose discontinued therapy due to pruritus – compared to less than 1% for the 10 mg OCA cohort and the placebo group.

Cawkwell indicated that the 25 mg dose was likely to be the dose recommended in the planned US and EU filings for approval later this year as it is “the dose that met the regulatory hurdle in statistical testing.”

Pruzanski said the company will have to “dig into the pruritus data to also understand the predictors of pruritus.” However, from its treatment experience with Ocaliva in PBC patients, Intercept knows how to treat patients with pruritus, he added.

“There are some patients who just won’t tolerate the drug … hopefully one day there will be other [treatment] options for them,” Pruzanski said. “But in the large majority of cases, we really do believe that we can manage this. It does seem to attenuate over time; we know that in the PBC population.”

Jefferies analyst Michael Yee said in an April 11 note on the data that OCA’s “safety continues to look good.” He added that the deeper dive into the REGENERATE data also indicated more fibrosis improvement and greater stabilization of disease in NASH patients. Published online 11 April 2019
Novartis’s NASH Chief: Our Strategy Is Combos With Tropifexor As ‘Backbone’

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Novartis AG’s NASH strategy can be summed up in one word: “combinations.”

That’s how the Swiss pharma’s NASH program head, in an interview with Scrip, described his approach to developing therapies to treat non-alcoholic steato-hepatitis (NASH).

Eric Hughes said that, although not yet a leading contender in NASH, Novartis had already built a broad, early pipeline of therapies for the condition, and would use its highly potent and selective multimodal FXR agonist tropifexor as a backbone in combination therapies.

“We had from the outset the strategy of developing monotherapies while assuming that the future is going to be driven by combination therapy,” Hughes said, speaking from Vienna where he was attending this year’s European Association for the Study of the Liver (EASL) meeting.

“NASH is very complex. It involves liver fat accumulation, inflammation and fibrosis. What we’ve seen so far in monotherapy has been encouraging, but the result are modest at best.”

He said any real transformational change for successfully treating NASH patients would need to come from combinations. “Those will require collaboration, and we’re already leaders in collaborating over combination therapies in NASH,” said Hughes, who heads global development in immunology and dermatology at Novartis.

PFIZER/ALLERGAN COLLABORATIONS

Novartis has clinical agreements with Allergan PLC and Pfizer Inc. for combination NASH trials with their respective drug candidates.

Novartis’ collaboration with Pfizer, entered in October 2018, includes research to evaluate a combination of tropifexor and up to three Pfizer compounds for the treatment of NASH.

Its program with Allergan, announced in March 2017, is for a Phase IIb clinical trial collaboration with Allergan for the treatment of NASH combining tropifexor and cenicriviroc (CVC).

“As these collaborations show, we are working to make tropifexor available in as many combinations as possible because we believe that’s a very important component for future treatments,” Hughes said.

CONATUS EMRICASAN DRAMA

Novartis’s NASH plans are also heavily banking on its commercial alliance with Conatus Pharmaceuticals Inc. for the clinical development and commercialization of the US-based small cap’s lead drug candidate, emricasan, currently in three trials for late-phase NASH.

Emricasan is a dual anti-apoptotic and anti-inflammatory hepatic drug candidate.

The duo’s partnership has had a shaky start, though. Emricasan last March posted its second Phase IIb miss in four months. (Also see “Conatus Endures Another NASH Setback With Failure To Hit Fibrosis Endpoint” - Scrip, 21 Mar, 2019.)

That setback came after emricasan in December 2017 failed to meet its primary endpoint in the ENCORE-PH trial in compensated NASH cirrhosis patients at high risk of decompensation. (Also see “In NASH Race, Bad News For Conatus, Good News For Genfit In PBC” - Scrip, 10 Dec, 2018.)

Those setbacks have fuelled speculation that the collaboration won’t be a long one.

Hughes said an overall decision would need to wait at least until the end of this year. “We’re waiting for the totality of the data. The third study, which is in very advanced patients, will be reading out towards the end of this year. So once all three of these studies have been completed, we’ll then decide where to go from there,” he told Scrip.

NLRP3 PROMISE

The other key component in Novartis’s NASH strategy is the broad portfolio of immunomodulatory medicines brought via the planned acquisition of IFM Tre targeting the NLRP3 inflammasome.

The acquisition will give Novartis full rights to IFM Tre’s portfolio of NLRP3 inhibitors. Novartis expects the deal to close this quarter. (Also see “Novartis Dives Into Inflammasome Pool With IFM Tre Purchase” - Scrip, 1 Apr, 2019.)

“The path to finding an effective treatment in NASH may take years – with incremental efficacy gains over time, but it’s our belief treating NASH will likely require combination therapy to achieve transformative outcomes for patients – we believe collaboration is key to advancement and faster development of the most effective treatments for NASH,” Hughes said.

“NASH is going to be a roller coaster ride for us all. And you’ll see continued deal making in the area. So we are willing to talk to anyone that’s interested in bringing our and their compounds together.”

Summing up, Hughes said: “This is really the beginning of a long process of developing drugs for NASH, and it is certain to be a focus of discussions at this year’s EASL conference.”

Published online 13 April 2019
Defusing US Opioid Crisis Offers Orexo “Strong Growth Potential” Says CEO

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Orexo AB’s leading product Zubsolv, for opioid dependence, will enjoy strong sales in the US as the healthcare system copes with the growing crisis of addiction there, giving the Swedish specialty pharma the solid platform to expand its pipeline while pursuing M&A possibilities, its CEO predicted in an interview with Scrip.

The Swedish-listed specialty pharma was founded 1995 to use its drug delivery technologies to develop and market products to treat addiction and pain.

Orexo’s head office is in Sweden. But its commercial base is in the US state of New Jersey from where it has built a national sales infrastructure for its opioid dependence therapy Zubsolv, which it sells there directly.

It also has three other clinical assets for treating addiction, the most advanced of which should be on the market within four years, Nikolaj Sørensen said.

“Our strategy going forward is to focus on improving and enhancing the treatment of opioid dependence ... focusing our R&D and business development activities to broaden our pipeline, both through internal R&D programs and through business development if we can find attractive assets, and thus leverage our US sales force further,” Sørensen said.

US OPIOID CRISIS SET TO WORSEN

The US market for opioid dependency treatment is growing in low double-digit figures and is currently worth about $1.5bn each year, analysts said.

Of the 47,600 deaths due to opioid overdose in the US in 2017, 60% were due to synthetic opioids. The situation is set to worsen, with annual opioid overdose deaths in the US predicted to climb to 81,700 in 2025, according to a study by the Massachusetts General Hospital Institute of Technology Assessment.

In response, states, counties and cities in the US are suing drug makers and distributors to recover billions in human and financial costs.

“The US market for treating opioid dependence is bound to increase significantly, because the number of patients who are not receiving treatment vastly outnumber those who are, and that represents a good growth opportunity for Zubsolv,” Orexo’s CEO said.

Norddea analysts in a recent report said the US opioid dependency market is concentrated, with around 5,000 physicians representing about 90% of all prescriptions. “This means it is possible to address the market with a limited sales force,” the analysts said, adding that that offered promise for Orexo’s commercial operations there.

CASH COW ZUBSOLV

Orexo’s key cash cow, Zubsolv is a mixture of buprenorphine and naloxone, which are commonly used to treat narcotic addiction. It was launched on the US market in mid-September 2013.

Zubsolv was approved in the EU in the second quarter of 2018 but the ex-US rights are being re-partnered.

Sørensen’s Zubsolv strategy was reinforced in January when the US District Court for the District of Delaware ruled that Actavis’s generic version of opioid-addiction medicine Zubsolv infringed on Orexo’s patent.

The court’s decision stops Actavis from marketing its Zubsolv generic products in all dosage strengths in the US until after 18 September 2032. Actavis was acquired by Allergan PLC in March 2015 and renamed as Allergan PLC. Actavis was then bought by Teva Pharmaceutical Industries Ltd. in August 2016.

One uncertainty clouding Zubsolv’s prospects is the extent to which it will be impacted by generic versions of Indivior PLC’s Suboxone (buprenorphine/naloxone) tablets and sublingual film in the US.

Sørensen played down any likely generic repercussions on Zubsolv sales, though. “There’s already 10 generic products out there based on an older formulations of Suboxone. And you now have three Suboxone pill generics that launched at risk in late February, but these launches have not had any impact yet on Zubsolv.

“One of the reasons for that resilience is that the price we are offering to insurance companies in the US for Zubsolv is already at 18% and sometimes better than what they can get for the generics that have been available since 2013,” he explained.

He noted that Indivior’s sales of Suboxone film had also shown strong resilience to the new generic competition.

PIPELINE PROSPECTS

With Zubsolv revenues presumed to offer stability, Orexo can focus on its pipeline’s most advanced assets: OX124 and OX125, spray formulations of either naloxone or nalmefene, respectively, which are designed to offer improvements to the existing products for opioid overdose reversal.

In January, Orexo announced encouraging results from a 20-person pharmacokinetic Phase I study of its OX124 naloxone nasal spray in which Orexo compared its drug with Narcan, the market-leading naloxone rescue medication.

All formulations of OX124 in the study were well-tolerated by trial participants and showed ‘substantially higher’ plasma concentrations of naloxone compared with Narcan. OX124 also had sustained duration of elevated plasma concentrations and equivalent or superior onset time compared to Narcan, the company said.

“So, with that we have a product that’s proven to be much more bioavailable with a higher and more extended effect than products that are currently in the market,” Sørensen said, adding: “OX124 and OX125 are both very promising. We have proven that they work in humans. That’s a major milestone, and it makes those assets the second most valuable assets for us after Zubsolv.”

The company is also developing OX382 an oral, swallowable formulation containing buprenorphine and naloxone for the treatment of opioid dependence.

Published online 11 April 2019

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Cyclerion Readies For Readouts In Sickle Cell, Other Rare, Serious Diseases This Year

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Officially spun out of Ironwood Pharmaceuticals Inc., Cyclerion Therapeutics Inc. is recruiting new management experienced in both rare diseases and large indications, and gearing up for readouts from key programs in sickle cell disease, heart failure with preserved ejection fraction (HFpEF) and diabetic nephropathy.

Cambridge, Mass.-based Cyclerion officially launched operations April 1 when its tax-exempt spinout from Ironwood – to develop a pipeline of soluble guanylate cyclase (sGC) stimulators – was finalized. The firm also named former Bayer AG and Shire PLC exec Andreas Busch as its Chief Innovation Officer on April 9.

Cyclerion CEO Peter Hecht explained that the time was right to separate the sGC stimulator pipeline from Ironwood, which had more than enough to focus on with its commercial drug Linzess (linaclotide) for irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) plus its own late-stage pipeline in the gastrointestinal (GI) space.

Hecht didn’t say whether the split into two companies was related to the motivations of activist investor Alex Denner and his Saprissa Capital Management, which acquired more than 1.6m shares in Ironwood in late 2017 and was expected to try to drive a new direction for the company.

Hecht said the spinout occurred because the sGC stimulator candidates needed to be in a research and development company focused specifically on these specific assets, while allowing Ironwood to be a commercial, GI-focused entity.

“It’s sort of trite to say, but companies when they do these spinouts always talk about unlocking shareholder value and sometimes that’s just a code for something,” he told Scrip. “But in this case, I think it was very clear that the R&D programs we have were, at best, being sort of ignored. [Ironwood] was too big and complicated a story.”

Whereas the sGC pipeline assets were perhaps viewed by some shareholders as a drag on Ironwood’s core focus, those candidates now are part of a biotech “focused on fewer priorities with smaller, tighter teams and where there’s no choice but to focus and succeed to drive success,” Hecht said.

That’s not to say that Cyclerion is a typical start-up. Hecht refers to Cyclerion as a “turbo-charged” new company with about 140 employees, $175m in financing that is expected to provide two years-plus of runway, and a pipeline comprised of three clinical candidates being investigated in four indications, with a pair of preclinical programs right behind.

The financing was a private placement backed by existing Ironwood shareholders, new investors and some of the Cyclerion management team. Ironwood, however, will not hold a stake in the new company, and the split was orchestrated so that it could be a tax-exempt transaction. Hecht and President and Chief Scientific Officer Mark Currie both moved over to Cyclerion from Ironwood in the spinout.

The hiring of Busch seems like an ideal fit for Cyclerion, as the new addition led R&D at Bayer for 13 years and then moved to Shire as its chief scientific officer and R&D head in early 2018. At Bayer, Busch directed the pharma’s efforts in sGC stimulator compounds through proof-of-concept, work that eventually led to the approval of Adempas (riociguat) for pulmonary hypertension.

“It’s not [merely] fortuitous,” Hecht said of Busch’s arrival. “Andy is one the world leaders in this area; we tend to identify awesome talent and go after it, sometimes for months or years.”

He noted that Cyclerion benefitted from good timing, since Busch was looking for another opportunity in the wake of the rare disease-focused specialty pharma’s acquisition by Takeda Pharmaceutical Co. Ltd., which closed earlier this year.

Busch’s title is Chief Innovation Officer, Hecht explained, because calling him the R&D chief would understate all of the responsibilities he will have.

“We’re trying to innovate not only in medicines, but in organization, and bring together from the very earliest stages of R&D not only discovery and development, which I think biotech does pretty well now, but the voice of the patient and the partners, so we’ve got what we call the innovation center,” Hecht explained.

“It’s the nucleus where we’ll do nearly all the decision-making in the company. Calling Busch head of R&D would be selling him short, frankly; he’s got R&D experience, but he’s also got commercial strategy and consumer insights, corporate development – the voice of the partner, the patient, the payer – and the idea is to have that involved every step of the way from the very beginning.”

One of the key differences between Ironwood and Cyclerion, the CEO noted, is that while his former company has a global focus on primary care indications, the new firm will focus on serious, life-threatening conditions, often in orphan populations. Cyclerion will try to offer a clear advancement in the standard of care.

SEVERAL DATA MILESTONES AHEAD

Sickle cell disease historically is underserved and the current primary therapy, hydroxyurea, has drug-drug interaction issues and offers a lot of room for improvement, Hecht said. Cyclerion will pursue sickle cell therapy by targeting the nitric oxide receptor, which he called a “very important, fundamental mechanism” in sickle cell disease and other disorders.

“What’s exciting about our drug olinciguat, it’s being developed as a once-daily therapy that really targets the critical element of the mechanism in the disease,” Hecht said. “The disease is caused by a genetic mutation and leads to hemolysis, to red blood cells popping open, and when they pop open, they expose the vascular region both to an enzyme called arginase, which chews up the key factory for making nitric oxide, and it also exposes heme, the iron-containing piece of hemoglobin. … Our approach is to restore normal nitric oxide signaling, to restore homeostasis of that pathway.”

Published online 9 April 2019

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Positive Phase III Data Set Stage For Japan Imeglimin Filing

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French metabolic disorders company Poxel SA and Asia partner Sumitomo Dainippon Pharma Co. Ltd. (SDP) say they remain on track for a planned Japanese approval submission sometime in 2020 for imeglimin, following new top-line Phase III results for the novel antidiabetic.

The plan could potentially lead to a 2021 launch for the oral glimin class molecule in what may become the first market worldwide for the Merck Serono spin-out’s lead asset.

In a conference call on the new data, Poxel’s chief medical officer Christophe Arbet-Engels described the results as a “significant milestone” and major step towards the submission, saying the company was “extremely pleased”.

Poxel and SDP noted forecasts that the total Japanese diabetes sector is expected to reach around $6bn by 2020, making it the second-largest single market globally for type 2 disease. “Japan is a key focus and an integral part of our business strategy,” Poxel CEO Thomas Kuhn said on the call.

‘ROBUST EFFICACY’
The Phase III TIMES 1 placebo-controlled monotherapy study in 213 Japanese patients with type 2 diabetes met both its primary and main secondary endpoints, with other secondary endpoints still being evaluated.

At 1,000mg twice daily, imeglimin showed what the companies said was “robust efficacy”, achieving statistical significance (p<0.0001) in terms of change in glycated hemoglobin A1c versus placebo at week 24.

The placebo-corrected HbA1c mean change from baseline was -0.87%, from what Arbet-Engels noted was a baseline of 7.93 in the placebo group and 7.99 in the imeglimin group.

The trial also reached significance against the main secondary endpoint of decrease from baseline in fasting plasma glucose (p<0.0001), with a placebo-corrected mean change of -19mg/dL. Overall safety and tolerability was comparable to placebo, and the adverse event profile was similar to that seen in earlier clinical studies.

The TIMES Japanese Phase III program, being run jointly with SDP, started in late 2017 and comprises three pivotal trials in over 1,100 patients. The TIMES 3 study, looking at a 36-week open label extension in combination with insulin in patients with inadequate glycemic control on insulin alone, is expected to report around the middle of this year, including a randomized, 16-week placebo-controlled component.

Data from TIMES 2, a 52-week, 714-patient open label trial assessing monotherapy or combinations with various other agents, and full results from TIMES 3, are both expected at the end of 2019.

IMPORTANCE, POSITIONING
Under the October 2017 deal in which SDP picked up rights in Japan and most of the rest of Asia, Poxel and the Japanese firm are conducting joint development, although the latter is responsible for costs and commercialization. In its other Asian markets, SDP will be solely responsible for all development and commercialization activities.

Diabetes is already positioned as a major commercial and pipeline pillar for the company, with Drug Development Division senior executive officer Nobuhiko Tamura saying that imeglimin “will be a very important addition to our existing diabetes franchise.”

Kuhn told the call that future potential milestones and sales-based payments from SDP could total up to around $257m, with escalating royalties in the double-digit range.

As to likely market positioning in Japan, Arbet-Engels said that the Japanese development program is being designed to support multiple options, including potential immediate use as first-line monotherapy (which would be allowable under Japanese diabetes guidelines). However, a more likely scenario is combination use with other standard agents of choice, including DPP4 inhibitors, which the chief medical officer noted are prescribed in more than 50% of diabetes patients in the country.

COMBINATION THERAPY
“We expect imeglimin will be first prescribed mostly in combination therapy until physicians get used to the new drug, and then gradually gain first-line share, he said.

Another setting might be in elderly and immuno-compromised patients. 15-20% of those enrolled in the TIMES 1 study have Stage IIIa chronic kidney disease, which should help build the package of data in this population.

Poxel also noted that SDP may use the Japanese TIMES results to support activities elsewhere in Asia, including China. “China could represent a very significant opportunity for us,” the CEO said, Arbet-Engels adding that “we are very seriously looking at it in great detail”.

SDP is currently in discussions to clarify the best regulatory pathway for the drug in this market.

NEW NOVEL CLASS
Imeglimin is a pioneer in the glimin class, and is thought to act on mitochondrial bioenergetics to activate AMP-activated protein kinase, increase insulin secretion, reverse insulin resistance and preserve pancreatic beta-cell function. The molecule might also work to improve diastolic dysfunction.

It was licensed last year to Roivant Sciences GmbH globally outside Asia, including in the US and Europe.

With major licensing deals for imeglimin in the bag, Lyon-based Poxel is turning more attention to its mid-stage pipeline, which includes several candidates for non-alcoholic steatohepatitis.
large drug firms are pursuing structured efforts to engage with retail channels in emerging markets in recognition of their growing influence over actual prescription outcomes.

GlaxoSmithKline Pharmaceuticals Ltd. has put in place a 250-plus strong commercial trade channel team to engage with pharmacists in India as part of efforts to gear its commercial model to deal in a systematized manner with this key partner group.

GSK’s commercial trade channel team is expected to ensure that there are no gaps in availability and inventory of core brands at the retail level and also improve engagement with pharmacists. Over 100,000 retailers are expected to be covered as the British multinational also aims to limit prescription switches, especially for a group of core brands in India. According to some industry estimates, around a quarter of prescription switches occur at the trade channel level in markets like India.

Non-availability of products at the retailer’s end could translate into sales loss, with a study by the Organization of Pharmaceutical Producers of India (OPPI) and Ernst & Young some years ago noting that the extent of sales loss could vary from up to 1% in metros (across product categories) to up to 5% in Tier 2 and rural geographies and even as high as 20% in the case of small OTX brands. OTX are mature, late life cycle, acute therapy brands that are essentially prescription-based but have a bulk of non-prescription sales.

“The variation in loss of sales across geographies and product categories can be attributed to supply chain aspects such as the reach and service levels, working capital constraints, awareness amongst customers and net margins to stakeholders,” the OPPI-EY study said.

Besides, with the high rate of self-medication in markets like India – an IQVIA report highlighted a study in rural Bengaluru that found that 40% of people self-medicate – trade channels are seen as pivotal influencers and hence a key partner for pharma.

GSK INCREASING INDIA FIELD FORCE

GSK did not respond to specific queries on the commercial trade channel team or its current activities but underscored that India is a very important market for the company where it has a “strong heritage and ambitious plans” for patient access to its world leading medicines and vaccines.

“We are focusing on key brands to drive growth in identified therapy areas where there is significant unmet patient need. We are also increasing our field force by a third, and are committed to India and its patients for the long term,” GSK India told Scrip.

GSK’s Indian arm, GlaxoSmithKline Pharmaceuticals Limited, which has been “evolving” its commercial operating model in India, expects to focus on around 20 key brands in identified therapy areas, down from around 70 brands previously. Much of the streamlining in India has generally been geared towards accelerating sustained profitable growth to create “enduring value” for shareholders. GSK’s CEO Emma Walmsley has previously emphasized the need to be more competitive in emerging markets, where returns in some cases have been hit by competition and evolving regulations.

Industry experts noted that that the push towards generic name prescriptions in India may have also necessitated a greater focus on trade channels, though dispensing (and bargaining) power is already very high with pharmacy chains that are consolidated in other countries.

“One also sees that these countries already have well-established INN [international nonproprietary name] prescribing rules applicable for generic drugs. In a fragmented retail market like India, any opportunity to develop better relationships with pharmacies is welcome and companies would be happy to pursue them,” the expert said, adding that this becomes only more applicable with the “possible advent of INN prescribing coming up.”

PHARMACISTS CONTROL SCRIPT OUTCOMES

GSK’s new targeted plans to engage retail channels is also interesting in the backdrop of the significant influence and control pharmacists tend to have over script outcomes in largely self-pay markets like India and Brazil.

“In India, for example, some two-thirds of drugs are sold by a recommending pharmacist or bought by a self-prescribing patient with little input from a physician. In Brazil, on the other hand, pharmacists often prompt switching,” a McKinsey paper, “Unlocking pharma growth - Navigating the intricacies of emerging markets”, has noted.

Among the early steps to kick-start the retail journey, the McKinsey paper suggests that by profiling the needs, capabilities and economics of target retail segments, pharmaceutical firms can identify the value propositions and products that will resonate most with their priority customers. “Value-added services such as marketing support, logistics, and account management are powerful tools for developing long-lasting retail relationships,” the management consultancy said.

IQVIA also notes how ‘hub-chemists’ in India are emerging as key influencers of physicians, patients and smaller chemists in driving purchase decisions in smaller towns and rural areas. Large hub-chemists – based in towns and with limited access to stockists – could service 20-25 rural medical practitioners for drug purchases.

“Typically, given the size and legacy of the chemist, they become key influencers and purchase points for smaller chemists, dispensing doctors as well as patients in the town. For some legacy brands, hub-chemist driven Rx sales contribute up to 20% of value,” IQVIA noted in a 2018 report.

HELPING PHARMACIES BECOME MORE THAN “MERE PILL DISPENSARIES”

But commercial trade channel teams are not uncommon. The industry expert quoted previously explained that such commercial trade channel rep teams have generally been used by multinational firms in several international markets like the UK, US and Italy, where pharmacies and distributors are consolidated and therefore are large organizations with much higher bargaining power as compared to markets with a more fragmented distribution pattern such as India, Egypt, and Turkey.
Cipla COO On Joining The Revolution In Manufacturing

ANJU GHANGURDE anju.ghangurde@informa.com

Pharma manufacturing is no longer just about large capacities and efficient supplies. It’s all about the “agility, security and assurance” of supplies and operational excellence, says Cipla Ltd.’s new global chief operating officer Dr R Ananthanarayanan.

“We’ll always be one among a few [competitors] so you need to have some differentiation. It’s all about supply – agility, security and assurance of supplies. These are dimensions that make a differentiation even if there are multiple players out there,” the executive, who has also held leadership positions in companies like Galpharm International and Dr. Reddy’s Laboratories Ltd., said.

OPERATIONAL EXCELLENCE

Cipla, he said, was prioritizing several initiatives to ensure that its manufacturing keeps pace with the changing environment in the sector. This includes addressing product turnaround times – cycle times, lead times, right level of inventory (balance between right inventory and the ability to respond to the market) and a continued focus on security and assurance of supply including controls on raw materials, finished product and packing material and therefore “how much of material can be made available as close to the customer as possible.”

“Another dimension is all about operational excellence. Can we squeeze out waste/non-value-added activity from the system so that they are not a drain on the manufacturing and supply chain continuum?” Ananthanarayanan noted.

Providing an example of a product that goes from API to finished dose, he explained how Cipla is looking at “unit operations” all through that chain.

“If there are, say for example, 15 unit operations involved, which are the ones that go in sequence or in parallel or which are the ones where you have time gaps between one unit operation to the other that are needed or can be eliminated? Can you look at 5S in the manufacturing shop floor?” he said.

The initiatives, Ananthanarayanan said, had helped unlock “huge amounts of waste reduction” and there are products where we have been able to cut down cycle time for conversion by 30%.

“And that means I have 30% excess capacity available and can manufacture more number of batches at the same time. If I can manufacture more number of batches at the same time, agility and ability to supply significantly goes up,” said the executive, who took charge as Cipla’s COO in August 2018.

The 5S management approach, where 5S essentially denotes ‘sort, set in order, shine, standardize, and sustain,’ is said to have been originally implemented by manufacturing firms in Japan. It is a systematic method for workplace organization, so that processes run efficiently.

AI, PREDICTIVE ANALYSIS AND DIGITIZATION EFFORTS

Cipla also appears to be laying the building blocks to deploy digitization and artificial intelligence on the operations side to drive efficiencies, though Ananthanarayanan emphasized that these new approaches need to be used for the “right reason and used in the right way.”

The much talked about transformation of Bayer’s site in Italy into a digital plant, he noted, was seemingly driven by an urgent need to create capacity in a very short time without investing capex, which therefore became the nucleus for driving the change.

Cipla, he explained, was taking a more measured, broader view, with the aim to ensure that its manufacturing is a “backbone” for creating an agile, flexible, secure and assured supply network.

“That is the first fundamental. What we are doing first is to create that capability very strongly. The next dimension is using the data that we have and have generated in manufacturing over the last several years,” he said.

Internally, the company has a data pool and significant data access that it expects to exploit. It will “use the Data Historian [a software program] first” to assess itself in terms of “where have we been performing and do we have predictive indicators based on our past performance to say that if we were to run a product

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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.

### PIPELINE WATCH, 5–11 APRIL 2019

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Source: Biomedtracker | Informa, 2019
of this nature then what is the predictive analysis based on past performance telling me”.

“Based on that can I leverage my manufacturing equipment and unit processes to the right optimum level of efficiency. That’s the step we are working towards. At some point along that journey curve, we will certainly bring in dimensions of digitalization and some AI elements,” Ananthanarayanan said.

Cipla, he added, was in the early days of that journey but was excited about it.

“We will work to move along that path, but the core basis will be first to eliminate waste, to bring in efficiency, use our past data to bring in more predictive analytics, bring in PAT [Process Analytical Technology] tools and then get to the digital part,” he said.

Cipla is also looking at how to integrate AI, predictive analysis and some amount of digitization in the manufacturing space. “This is something that we want to experiment with. With the kind of work that Google does including elements around Google Glass, how do I create augmented reality for training personnel on complex machines, where they can get to the heart of the machine and understand it much better, which can then bring my down time to minimal?” Ananthanarayanan added.

**PLANT COMPLIANCE**

But alongside operational excellence and incorporating new technologies, firms also need to align with evolving regulatory expectations. And while Cipla’s manufacturing sites – it has over 40 facilities - have generally had a manufacturing record free of major blemishes, the firm’s Kurkumbh plant recently did not make the compliance cut following a US FDA inspection there in March.

The FDA had conducted a product-specific pre-approval (PAI) and Good Manufacturing Practices (GMP) inspection which covered three units at the Kurkumbh plant. The company received eight GMP observations and 10 observations pertaining to the PAI for a novel technology product slated for approval beyond 2024.

Ananthanarayanan clarified with reference to the PAI that it was the first time ever that Cipla had put the new technology for the product into the filing.

“It’s a new technology and Cipla is doing it for the first time. Maybe we are among the first generic companies to have filed this technology for a product. Though it is for a potential 2024/25 launch because it’s a new technology we would want to do it early enough because we anticipate that there are learnings in that process and we’ll keep having interactions with the FDA,” he explained.

While quite a few of the observations during the PAI were related to the specific product and technology and marks a learning for Cipla, the COO said that it was “not something that puts a question mark on our system or facility”.

“It’s just that FDA wants some more details/information on that technology. And this could form the basis for us to use the technology for many other products because we are far more well understood in terms of applying that technology now,” he said.

The general GMP observations are procedural in nature and the company is working to respond to the FDA within the stipulated time period, he said, also underscored that there were no data integrity concerns. **Published online 9 April 2019**

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**APPOINTMENTS**

Click here for all appointments: https://bit.ly/2oHWRyN

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