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BMS Values Celgene's Portfolio At $74bn, But Does It Price In Risk?

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Bristol-Myers Squibb Co. has agreed to buy **Celgene Corp.** in a cash and stock deal valued at $74bn that will diversify the big pharma beyond its top product *Opdivo* (nivolumab), but the deal comes with risks that will be shifted from Celgene's investors to Bristol's.

The transaction announced Jan. 3 will expand Bristol's presence in oncology and immunology, where it already has a strong presence, with the promise of near-term approvals for six of the combined company's products – including five Celgene assets. While the deal gives Bristol the blockbuster multiple myeloma drug *Revlimid* (lenalidomide), it's a product with few years of market exclusivity left and Celgene has struggled to produce suitable replacements.

As a result of those risks, the big biotech's stock has been in a freefall for the past 15 months as setbacks in Celgene's pipeline put the company's post-Revlimid revenue growth strategy into doubt. So while Bristol's buyout offer valued at $102.43 per share is a premium to Celgene's recent stock price, it's a bargain compared to the biotech's peak of $145.82 back in September 2017 – a month before the clinical trial failure that kicked off Celgene's decline.

Celgene investors will receive $50 in cash and one share of Bristol stock per Celgene share that they own, which accounts for the acquisition deal's $102.43 per share value based on Bristol's Jan. 2 closing stock price of $52.43. Bristol investors will own a majority of the merged company's shares – 69% – leaving Celgene shareholders with a 31% stake.

Celgene investors also will receive one contingent value right (CVR) per share, which will result in a payout of $9 per CVR upon US FDA approval of Celgene's ozanimod for multiple sclerosis and lisocabtagene maraleucel, or liso-cel (JCAR017) for lymphoma by Dec. 31, 2020, and bb2121 for multiple myeloma by March 31, 2021.

The upfront deal terms represent a 54% premium to Celgene's Jan. 2 closing price of $66.64, which sent the company's stock up 20.7% on Jan. 3 to $80.43. The transaction was a welcome boost to Celgene investors after several months of stock price declines that started with the failure of closely-watched inflammatory bowel disease (IBD) drug candidate mongersen (GED-0301) in October 2017. *(Also see "Celgene IBD Pipeline In Question As Mongersen Crohn's Disease Trial Ends" - Scrip, 20 Oct, 2017.)*

"For Celgene's shareholders, this cash and stock transaction recognizes and unlocks significant value by delivering immediate and substantial cash value and providing meaningful participation in the combined company's future," Celgene chairman and CEO Mark Alles said during a joint conference call with Bristol.

"The strategic vision of this transaction is obvious and compelling: it significantly enhances our strong global leadership in oncology and vaults our inflammation and immunology business into the global top tier," Alles continued. "Together with Bristol-Myers Squibb, we will have the

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from the editor

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The biopharma universe usually gets a new year off to a lively start, with many companies storing up their best fireworks for the J.P. Morgan Healthcare conference in January. This year has proved to be no exception. The 2019 meeting got off to a bang with Lilly announcing it had agreed to buy Loxo Oncology for $8bn (more on that in next week's issue, or you can read it on our website right away).

But even before the bio-hordes descended on San Francisco, Bristol-Myers Squibb had woken everybody up from their holiday hangovers by slapping $74bn on the table for Celgene (see cover story).

From a peak of more than $145 in September 2017, Celgene's share price had dropped under $60 by Christmas 2018, its lowest for more than five years. Despite a string of recent setbacks, the company still has interesting assets in its pipeline – and at least some mileage left in the mega-blockbuster *Revlimid* – but so far Bristol-Myers Squibb's investors don't appear to be viewing this as an unmistakable bargain. Still, BMS has itself fallen quite a way since it was first fêted as a PD-1 pioneer with *Opdivo* suffering trial disappointments and commercial challenges versus rivals and ceding its leading position by sales to Merck's *Keytruda*. The combination of BMS and Celgene has the potential to make for a more powerful group with a wider range of options to prioritize; but it could also just create a company with more ways to go wrong. Getting it right is now the $74bn question.

Come back next week for our J.P. Morgan insights.

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Japan 2018 Review: Takeda/Shire Dominates But Pharma Life Goes On

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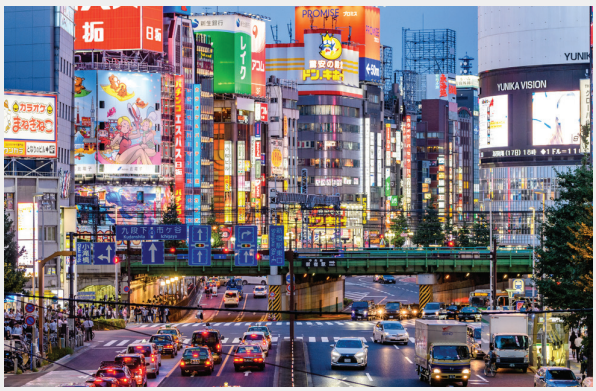

2018 will probably be looked back on as the year that Japan's largest pharma company, **Takeda Pharmaceutical Co. Ltd.**, began the process that transformed it into a truly global player.

Through the $62.4bn acquisition of larger target **Shire PLC**, due to be formally completed in early January 2019, the company will move well inside the global top 10 in pharma sales terms (around seventh), earning it a place among the worldwide industry elite.

By the end of the year, the largest-ever outbound M&A deal for any Japanese company - and around the fifth-biggest of all time in the global pharma sector - was all but done and dusted, following shareholder votes in favor at both companies in early December.

The combined entity will have around $30bn in revenues, with Shire bringing a new presence in rare diseases and plasma operations, and a stronger geographic footprint in the US, adding to Takeda's positions in Japan and in oncology, gastrointestinal and CNS disorders, plus vaccines.

A lot of the focus in Japan had been on the financing of the deal, and the roughly $30bn in debt that Takeda will take on to finance it; plus the fact that some saw the 237 year-old firm potentially taking a big step away from its Japanese roots.

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To read the rest of this story go to: https://bit.ly/2FdsG4W

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financial strength to accelerate our research and development engine for sustainable long-term growth."

The headline of Leerink analyst Geoffrey Porges' Jan. 3 note on the deal pointed out that "the best deal is sometimes the only deal" and said, "we view the proposed transaction as a fortuitous exit for Celgene investors given the low likelihood that Celgene's stock would recover to 2017 highs, at least within the next two to three years."

But while Celgene investors felt they had a lot to gain from the transaction, Bristol's stock fell 13.3% to $45.12 on Jan. 3 following the deal announcement.

"The $66bn deal value at current share prices is roughly four times Celgene's 2019 consensus sales estimates, which would be well below recent transaction multiples; however … significant questions remain regarding Celgene's long-term revenue prospects," William Blair analyst Matt Phipps said in a Jan. 3 note, pointing out that Revlimid is the biggest uncertainty going forward.

Caforio, when asked about the risk of generic competition for Revlimid, deferred to Celgene's investor presentation during the American Society of Hematology (ASH) conference in December during which Alles laid out the patented life left for Revlimid.

Alles explained then that generic market entry is not expected to occur until 2022, and under a patent settlement with **Natco Pharma Ltd.** the initial generic launch will be limited, allowing for full generic market entry in 2026. Litigation with other generics makers is ongoing, but Celgene believes that appeals court decisions in those cases aren't likely until late 2021, keeping additional Revlimid copies from hitting the market before 2022.

However, Bernstein's Ronny Gal pointed out a potential earlier risk to Revlimid's patent estate in a Jan. 3 note. "A risk is negative institution decision on the Revlimid dosing patents. These could happen in February (~2/3/2019) or March (~3/2/2019)," Gal wrote. "We thought settlement was likely ahead of those decisions. However, with the deals announced, we see odds of settlement as much lower (why would CELG sell if it was close to resolution)."

Six Near-Term Launches On The Horizon

Ozanimod: Celgene's S1P receptor modulator for multiple sclerosis. On track for re-filing in first quarter 2019 after FDA refused to file in 2018. In Phase III for ulcerative colitis and Crohn's.

Luspatercept: Celgene/**Acceleron Pharma Inc.** erythroid maturation agent for myelodysplastic syndrome and transfusion-dependent beta-thalassemia. Regulatory filing planned first half 2019.

Liso-cel (JCAR017): Celgene's CAR-T therapy acquired with **Juno Therapeutics Inc.** On track for FDA filing in 2019 for relapsed or refractory diffuse large B-cell lymphoma (DLBCL), likely the third CAR-T to market.

Bb2121: Celgene/**bluebird bio Inc.**'s CAR-T product targeting B-cell maturation antigen (BCMA), potentially first-to-market for multiple myeloma. FDA filing planned in 2019 based on results of ongoing Phase II study.

Fedratinib: Celgene's JAK2 inhibitor, acquired with Impact Biosciences, which its founders reacquired from **Sanofi**, for Jakafi-resistant myelofibrosis. US regulatory filing was on track for fourth quarter 2018.

BMS-986165: Bristol's oral tyrosine kinase 2 (TYK2) inhibitor in Phase III development for psoriasis and mid-stage studies for Crohn's disease and psoriasis.

CAFORIO MAKES THE CASE FOR MERGER'S BENEFITS

Caforio focused his comments regarding the value of the Celgene acquisition on the six product approvals the companies anticipate in the next 12 to 24 months – for Celgene's ozanimod, luspatercept, liso-cel, bb2121 and fedratinib as well as Bristol's TYK2 inhibitor BMS-986165 (*see sidebar*). *(Also see "Bristol Engineers An Oral TYK2 Inhibitor With Biologic-Like Efficacy That Rivals JAK Safety" - Scrip, 12 Sep, 2018.)*

He also emphasized the combined company's early- to late-stage research and development pipeline, which will have 10 Phase III programs and 50 Phase I and II programs across four key therapeutic areas – oncology (immuno-oncology and solid tumors), oncology (hematology), cardiovascular disease and fibrosis, and immunology and inflammation.

"We will broaden our market portfolio, augment and diversify our pipeline, and maintain the speed and agility that is central to our approach," Caforio said.

Bristol also noted that it and Celgene will achieve $2.5bn in "synergies" as the companies combine their R&D, sales and manufacturing operations, and cut duplicate functions.

Bristol expects the deal to be accretive to earnings immediately after it closes in the third quarter of 2019, pending shareholder and regulatory clearances, generating more than $45bn in free cash flow during the first three years post-closing.

That cash will be used for R&D, including business development to further grow Bristol's pipeline, and to pay down debt associated with the Celgene deal. The big pharma will use a combination of cash and debt to fund the transaction and already has a bridge loan in place, so closing the deal does not have to wait for Bristol to arrange financing.

Caforio noted that after the deal closes "we will have nine products with more than $1bn [each] in annual sales and significant potential for growth in these areas." On top of currently marketed products, he said the six drugs that may be approved in the near term add another $15bn in revenue potential.

William Blair's Phipps cast doubt on that $15bn peak sales forecast in his note, pointing out that "many of these assets are entering highly competitive markets, including ozanimod in multiple sclerosis, liso-cel in B-cell malignancies (being the third CD19 CAR-T therapy to likely gain approval), and bb2121 in multiple myeloma (although it undoubtedly has first-mover advantage). Execution will be key, but we believe Bristol-Myers commercial execution has been strong, particularly considering recent clinical setbacks."

Opdivo in particular has had some striking clinical trial disappointments, yielding ground in the PD-1 class to **Merck & Co.**

Inc.'s *Keytruda* (pembrolizumab). *(Also see "Roche, Bristol On The Defensive After Merck's Lung Cancer Wins At ASCO" - Scrip, 6 Jun, 2018.)* Bristol has been under pressure to pursue mergers and acquisitions that will help it diversify beyond its top-seller Opdivo as Keytruda continues to gain a leading share of the market. *(Also see "Amid PD-1 Uncertainty, Bristol Under Pressure For M&A Activity" - Scrip, 25 Oct, 2018.)*

Given Bristol's need to diversify beyond immuno-oncology (IO), BMO Capital Markets analyst Alex Arfaei said in a Jan. 3 note that "we agree with the strategic rationale" of the Celgene acquisition at an "opportunistic" deal value. However, he noted that based on Bristol's leadership in IO it may become a takeover target itself.

Bristol reported in October that Opdivo generated $1.8bn in sales for the third quarter of 2018 and $4.9bn in the first nine months of last year. The company's other blockbusters include the anticoagulant *Eliquis* (apixaban), the arthritis biologic *Orencia* (abatacept), the leukemia drug *Sprycel* (dasatinib) and the CTLA-4 inhibitor *Yervoy* (ipilimumab) – the other major piece of Bristol's immuno-oncology portfolio.

CELGENE'S STRUGGLE TO FILL REVLIMID'S BIG SHOES

Celgene reported in October that Revlimid generated $2.4bn in the third quarter and $7.1bn for the first nine months of 2018. Its other blockbusters include the PDE4 inhibitor *Otezla* (apremilast), approved for psoriasis and psoriatic arthritis; the multiple myeloma drug *Pomalyst* (pomalidomide); and the solid tumor chemotherapy drug *Abraxane* (nab-paclitaxel). *(Also see "Celgene's Focus On Execution Pays Off, But Follow-Through Is Key" - Scrip, 25 Oct, 2018.)*

Celgene has a robust early- through late-stage pipeline, but the company has struggled to bring products to market to fill the revenue void when Revlimid – which was expected to generate $9.7bn in full-year 2018 sales – faces generic competitors.

Investors had high hopes for ozanimod, which should be re-submitted to the FDA any day now, after the drug (acquired in the $7.2bn purchase of **Receptos Inc.** in 2015) posted strong Phase III results in multiple sclerosis. *(Also see "Celgene diversifies with $7.2bn Receptos buy" - Scrip, 15 Jul, 2015.)* But after the FDA issued a refuse-to-file letter for ozanimod in MS in February, investors – already troubled by the mongersen failure in Crohn's disease and lower-than-expected Otezla sales in 2017 – lost further confidence in Celgene. *(Also see "More Bad News: Celgene Reveals Refuse-To-File Letter For Ozanimod In MS" - Scrip, 27 Feb, 2018.)*

Leerink's Porges said in his note that via the Bristol deal, "Celgene's long-suffering investors are saved from their exposure to the management team at Celgene and their recent operational and executional mishaps."

The company expects the ozanimod new drug application (NDA) resubmission to the FDA to occur in the first quarter of this year. It could be approved shortly after the JAK2 inhibitor fedratinib for myelofibrosis, which Celgene bought in the early 2018 acquisition of **Impact Biomedicines Inc.** for $1.1bn up front and planned to submit to the FDA in the fourth quarter of 2018. *(Also see "Celgene's $1.1bn Impact Buy Is First Of More Deals To Come In 2018 And Beyond" - Scrip, 9 Jan, 2018.)*

FDA filings for the chimeric antigen receptor T-cell (CAR-T) therapies JCAR017 and bb2121 are expected in 2019. First half 2019 submissions in the US and EU are expected for luspatercept in myelodysplastic syndrome and beta-thalassemia. *(Also see "'Totality Of Data' Make A Case For Luspatercept In Beta-Thalassemia, MDS" - Scrip, 3 Dec, 2018.)*

SOME OVERLAP IN BRISTOL, CELGENE PORTFOLIOS

The Celgene acquisition mostly fills gaps in Bristol's commercial portfolio and R&D pipeline, though there is some overlap. In oncology, Celgene's portfolio skews towards hematologic malignancies and Bristol's skews towards solid tumors, given Opdivo's indications in multiple non-hematologic cancers.

The Revlimid revenue approaching $10bn for 2018 is a big boost for Bristol, though potentially short-lived given the pending generics, and its sales are even higher than Opdivo's $7.5bn in annualized sales as of the third quarter of last year.

Celgene's oncology pipeline also has the potential to boost Bristol's IO portfolio via the CAR-T therapies in early- to late-stage development at the big biotech; JCAR017 and bb2121 will be Bristol's first cell therapy products.

BMS Chief Scientific Officer Thomas Lynch noted during the Jan. 3 investor call that "we've said for quite some time that we've been looking at cell therapy opportunities and looking to complement our immunotherapy approach."

One IO overlap, however, is the PD-1 inhibitor tislelizumab (BGB-A317) that Celgene licensed from **BeiGene Ltd.** in 2017. *(Also see "Celgene Eyes IO Growth With BeiGene China Pact" - Scrip, 6 Jul, 2017.)* In immunology and inflammation, Bristol's Orencia is approved for rheumatoid arthritis (RA), idiopathic juvenile arthritis and psoriatic arthritis – the latter being one of the two approved indications for Celgene's Otezla. The companies' pipelines have overlapping interests in IBD, lupus and other indications across multiple products though with different mechanisms of action.

The Celgene pipeline is notable for the number of late-stage programs and impending approvals, especially since the TYK2 inhibitor BMS-986165 is the only asset from Bristol's own portfolio that it expects to win approval in the near term. That drug is in Phase III for Otezla's other indication, psoriasis, and in Phase II for Crohn's disease and lupus.

Porges was not optimistic about synergies between the two companies' portfolios outside of oncology, however. "Even though the combination of Bristol and Celgene will create one of the industry's largest companies, and a dominant one in oncology, there are relatively few obvious revenue or operational synergies (other than less overhead in New Jersey)," he said.

"The transaction is contingent on both company's shareholder votes – we expect the Celgene vote to be in favor, but it is not as clear that Bristol's shareholders will be as happy," he continued. "They are giving up 31% of their company for a principal asset that will certainly flatten in 2022, and will erode rapidly after 2025. This profile potentially compounds the risk of similar erosion for other Bristol assets in the same timeframe, and puts even more onus on Bristol to find more deals to boost revenue in that time period. Bristol does get huge additional cash flow to finance its oncology development expenses, but nothing described on the call seemed a 'deal-maker' in terms of the value created by the combination."

However, Morgan Stanley's David Risinger was more optimistic, saying in a Jan. 3 report that "product portfolios fit well, including leading franchises in oncology, immunology/inflammation, and cardiovascular disease."

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CAR-T Forecast: Celgene Follows, But Also Leads As Next Batch Of T-Cell Therapies Near Market

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With the first chimeric antigen receptor T-cell (CAR-T) therapies on the market and making headway, the next wave of development is advancing, with next-generation technologies including allogeneic therapies and CAR-T cells with an on/off switch looking to take the stage.

Celgene Corp. is likely to make up for the third-place finish for its CD19-targeting CAR-T therapy JCAR017 with a first-place win for bb2121 in the race to bring a CAR-T product to market that targets B-cell maturation antigen (BCMA) in multiple myeloma.

The company has three BCMA-targeting CAR-T assets in the clinic and presented data for its two earliest candidates at the recent American Society of Hematology (ASH) meeting, where several competitors also reported results for BCMA programs as they try to catch up with Celgene.

ASH also provided an opportunity for companies with next-generation CAR-T constructs and allogeneic T-cell therapies, including **Bellicum Pharmaceuticals Inc.** and **Allogene Therapeutics Inc.**, to present preclinical and early clinical data for technology that could overcome challenges faced by earlier generation CAR-Ts like Celgene's lead programs.

Celgene primarily is focused on autologous CAR-T therapies, which involve taking T-cells from cancer patients, reengineering them to target a specific antigen, then infusing the CAR-T cells back into the patient. Allogeneic technologies involve re-

engineered donor T-cells that companies can use to manufacture off-the-shelf, on-demand CAR-T treatments.

CELGENE: BALANCING JUNO INVESTMENT, BLUEBIRD PARTNERSHIP

Celgene's lead CAR-T product candidate is JCAR017 (lisocabtagene maraleucel, or liso-cel), the CD19-targeting asset that the company purchased in its $9bn **Juno Therapeutics Inc.** acquisition earlier this year. *(Also see "Celgene Seeks CAR-T Leadership, Hematology Diversification With Juno Buy" - Scrip, 22 Jan, 2018.)*

JCAR017 will be submitted for US FDA approval in 2019 to treat relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in the third-line or later setting based on the ongoing Phase II TRANSCEND study in that population. Celgene is waiting until it has at least nine months of follow-up from all of the DLBCL patients enrolled in TRANSCEND to submit its biologic license application (BLA), to differentiate JCAR017 from its two main competitors, whose labels reflect six-month response rates.

The FDA approved **Gilead Sciences Inc./Kite Pharma Inc.**'s *Yescarta* (axicabtagene ciloleucel) and **Novartis AG**'s *Kymriah* (tisagenlecleucel) for third-line or later treatment of relapsed or refractory DLBCL in 2017 and 2018, respectively. Biomedtracker gives JCAR017 a 45% likelihood of approval in this indication, which is 10% above average for drugs at this stage of development for this indication.

The data that Celgene presented at ASH for JCAR017 were from the Phase I TRANSCEND CLL-004 study, which enrolled patients with high-risk chronic lymphocytic leukemia (CLL) who were refractory to **AbbVie Inc.**'s and **Johnson & Johnson**'s Bruton's tyrosine kinase (BTK) inhibitor *Imbruvica* (ibrutinib).

The overall response rate (ORR) among 16 patients was 81%, including 43% who had a complete response (CR). All five patients with at least six months of follow-up as of September maintained a response and were minimal residual disease (MRD) negative.

Biomedtracker described these results as "impressive" in a Dec. 2 report and noted that the data "compare well to those reported for both Yescarta and Kymriah. For example, in 23 patients, Kymriah (CTL019) reported an ORR of 35% and a CR of 22%, which is much lower than the 81% ORR and 44% CR/CRi reported here."

In terms of side effects associated with CAR-T therapies that typically occur in the first few weeks after infusion of the cells and can be severe, 75% of CLL patients experienced cytokine release syndrome (CRS), including one patient with grade 3 CRS. There were three cases of grade 3 neurotoxicity, but no grade 4 or 5 cases of neurotoxicity or CRS. Biomedtracker noted that these side effects were in line with other CAR-T studies and said the study's investigator described the adverse events as manageable.

"We look forward to larger patient population and longer follow-up to more confidently ascertain the potential of liso-cel in CLL, including the durability of minimal residual disease-negative status and complete remission," William Blair analyst Andy Hsieh said in a Dec. 3 note.

But since JCAR017's first approved indication will be DLBCL, making it the third CD19-targeting CAR-T therapy on the market for these patients after Yescarta and Kymriah, Celgene's BCMA programs in multiple myeloma are receiving a lot of attention.

The company and partner **bluebird bio Inc.** recently completed enrollment in the pivotal Phase II KarMMa clinical trial testing their lead BCMA-targeting CAR-T bb2121 in third-line or greater relapsed or refractory multiple myeloma. The companies plan to submit bb2121 for FDA approval in 2019 based on this study.

However, Celgene and bluebird did not present any updated data for bb2121 at ASH. Instead, they presented early results for their follow-up BCMA candidate bb21217, and Celgene reported initial data for JCARH125, a Juno-developed BCMA-targeting CAR-T.

While bb2121 is in the lead relative to a slew of additional T-cell therapies engineered to recognize BCMA on multiple myeloma cells, several competitors are far ahead of bb21217 and JCARH125, including P-BCMA-101 from **Poseida Therapeutics Inc.** and LCAR-B38M from **Legend Biotech Corp.** and J&J's **Janssen Pharmaceutical Cos.**

CELGENE'S HIGH EXPECTATIONS FOR 'UNRIVALED PORTFOLIO'

Celgene CEO Mark Alles said during a Dec. 2 investor event webcast during ASH that bb2121, bb21217, JCAR017 and JCARH125 make up "a portfolio of CAR-T assets that is unrivaled by any other company in the world. We're creating a leveraged position, a strategic position, and a core competency in T-cell biology in cellular immunotherapy that really is unlike any other company in the world."

Chief Medical Officer Jay Backstrom noted during the investor event that several trials are underway for JCAR017 alone, including the Phase III TRANSFORM study in second-line, transplant-eligible DLBCL patients; the Phase II PILOT trial in second-line, transplant-ineligible DLBCL; and the Phase II combination therapy PLATFORM study in DLBCL, in addition to TRANSCEND and TRANSCEND CLL. The CD19-targeting candidate is also being tested in a Phase II pediatric acute lymphocytic leukemia (ALL) study.

"In terms of bb2121, this remains our lead and first-in-class BCMA CAR-T asset, and we're aggressively developing across a range of KarMMa studies across lines of therapy, including, by the way, Phase II studies planned in 2019 for the front-line setting. [So, we're] very excited about the breadth and depth of bb2121 and the clinical program," Nadim Ahmed, Celgene's president of hematology and oncology, noted during the investor event.

Alles added later that "in the end, it'll be the clinical data that declares itself and bb2121 is so far ahead that we are full-steam ahead to optimize that opportunity, and then we'll see what happens with the balance of our BCMA campaign."

Celgene believes that peak sales of JCAR017 and bb2121 will be $3bn and $2bn-plus, respectively. If that's the case, the two CAR-T candidates could replace about half of the $11bn in peak sales for Celgene's multiple myeloma blockbuster *Revlimid* (lenalidomide), which is expected to face its first generic competition in 2022. JCAR017 and bb2121 are among five products that the company expects to launch in 2019 and 2020 with total peak sales of $12bn to $14bn.

However, Jefferies analyst Michael Yee is skeptical that Celgene's lead CAR-T programs will be as lucrative as the company claims. Yee said in a Dec. 3 note that he anticipates bb2121 peak sales of $1bn to more than $2bn, with revenue reaching into the higher end of the range only if the BCMA T-cell therapy is approved as a first-line multiple myeloma treatment. For JCAR017, Yee forecasts

$1bn-plus in peak sales even after the CLL results presented at ASH that he described as a "very positive surprise."

NEXT SET OF CAR-T RIVALS SET SIGHTS ON ALLOGENEIC OPTIONS

The Celgene CEO's claim that his company's CAR-T portfolio is unrivaled may be a bit of a stretch given the number of companies working on in this field, including biopharma firms run by executives at the forefront of the industry.

The original developers of Gilead's Yescarta did not take their payouts from the $11.9bn sale of Kite Pharma to Gilead just a few months before the autologous CD19-targeting CAR-T therapy's approval and walk off into the sunset. Instead, Kite CEO Arie Belldegrun and Chief Medical Officer David Chang co-founded Allogene, which came out of stealth mode in April with $300m in Series A venture capital and a portfolio of 17 allogeneic CAR-T candidates acquired from **Pfizer Inc.**

Allogene has since raised several hundred millions more, including $372.6m from its initial public offering in October. The cash will fund development of the mostly preclinical allogeneic CAR-T programs from Pfizer, which the big pharma previously licensed from **Cellectis SA** and **Servier SA**.

Allogene and Servier presented clinical data at ASH for UCART19, an allogeneic CD19-targeting CAR-T therapy that's being studied in two Phase I ALL trials – one in pediatric and one in adult patients (the PALL and CALM studies, respectively).

The partners reported that 82% of patients (14/17) who received a lymphodepleting chemotherapy regimen of fludarabine, cytarabine and an anti-CD52 monoclonal antibody prior to UCART19 treatment achieved CR or CR with incomplete blood count recovery (CRi). Overall, 67% (14/21) achieved CR or CRi.

Scrip spoke with Chang, Allogene's co-founder and CEO, at ASH and he said the data presented there show that allogeneic CAR-T therapies can drive efficacy without rejection of the re-engineered donor T-cells or severe graft-versus-host disease (GvHD).

"The biggest answer that's coming up from this presentation is that depletion of T-cells using anti-CD52 antibody is essential for the allogeneic CAR-T cells to expand and persist," he said.

Allogene's anti-CD52 antibody ALLO-647 will be part of the required lymphodepleting regimen in a Phase I study of ALLO-501 – Allogene's version of UCART19 – in non-Hodgkin's lymphoma, which is expected to begin in the first half of 2019. Servier will continue development of UCART19 in ALL.

Chang said Allogene's collaboration with Servier is going "extremely well" and noted that the company's French partner hopes to benefit from the former Kite management team's experience with bringing Yescarta rapidly through clinical development and FDA approval.

After ALLO-501 enters the clinic in 2019, Chang said Allogene will advance the BCMA CAR-T program ALLO-715 into the clinic. A third program, targeting FLT3 in acute myelogenous leukemia (AML), also has been disclosed and the next allogeneic CAR-T programs from Allogene after that will go after antigens expressed in solid tumors, such as CD70 and DLL3.

"The way I see it is cell therapy is just going to go through a couple evolutions," Chang said. "I think the first one is establishing the concept; that's autologous. And the second one is taking that from one patient at a time to a more pharmaceutical model – on-demand therapy that addresses a lot of gaps that exists in autologous; that's the allogeneic."

The next step, Chang said, will be to develop a renewable source of T-cells via induced pluripotent stem cells (iPSCs) or some other source of donor cells.

BELLICUM'S FIRST HUMAN CAR-T DATA ARRIVED AFTER ASH

Bellicum reported its first clinical trial results for its lead CAR-T candidate BPX-601 after ASH at the European Society for Medical Oncology Immuno-Oncology Congress (ESMO-IO) on Dec. 14.

BPX-601 targets prostate stem cell antigen (PSCA) for the treatment of solid tumors, including pancreatic, prostate and gastric cancers. It is designed with an activation switch – an inducible co-activation domain known as iMC (inducible MyD88/CD40) – to activate the autologous CAR-T cells in BPX-601 so that they expand and persist, and hopefully provide greater efficacy. The small molecule rimiducid is administered to flip the iMC switch.

"The premise there is if we're able to do that on an ongoing basis, we should be able to achieve efficacy in solid tumors where first- and second-generation CAR-Ts haven't been able to," Bellicum President and CEO Rick Fair said in an interview at ASH.

The company presented data at ESMO-IO on Dec. 14 from 12 patients with advanced metastatic pancreatic cancer who were enrolled in Part 1 of a Phase I/II dose-escalation study. All 12 patients received cyclophosphamide as pre-conditioning chemotherapy before BPX-601 administration, but rimiducid was given to only nine of the 12 patients to turn on the CAR-T's activation switch.

BPX-601 cells had limited expansion and did not persist in the three patients who did not receive rimiducid, but when rimiducid was administered the CAR-T cells expanded three- to 20-fold in four patients and persisted for more than three weeks in patients who got a single dose of the small molecule. Four of six evaluable patients who received BPX-601 and rimiducid had stable disease and two had tumor shrinkage of more than 20%. There was no CRS or neurotoxicity of any grade.

"This is a novel construct with a very potent activation system, it is a novel target antigen for a CAR-T, and it's in a very sick patient population, so safety is paramount," Fair said at ASH.

Bellicum will now initiate Part 2 of the study, adding patients in the second-line pancreatic and gastric cancer settings, and hormone-refractory prostate cancer with more data from the Phase I/II trial anticipated in 2019.

The company is also running a dose escalation study for BPX-701, a T-cell receptor (TCR) therapy that targets preferentially expressed antigen in melanoma (PRAME), with initial dosing in AML and myelodysplastic syndrome (MDS) and a recently added cohort in uveal melanoma. Data are anticipated from that study in 2019.

Bellicum also has two preclinical CAR-T projects directed against undisclosed targets – one in hematologic malignancies and another in solid tumors – that incorporate the company's activation switch as well as a deactivation switch. The latter is designed to allow for the elimination of CAR-T cells if they become too toxic. Both programs will move into the clinic in 2019.

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IPO Update: Returns Run Red For Most Biopharma Firms That Went Public In The US Last Year

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There were a lot of outliers in the US market for drug developer initial public offerings in 2018, including the biggest-ever biopharmaceutical IPO, but on average the returns on these investments were negative by the end of the year.

While 67 biopharma companies managed to launch IPOs in the US in 2018, 41 of these firms were trading below their offering prices as of Dec. 31, bringing the average return to -7.5%. That's a significant drop from the average of 0.3% for the 61 companies that went public last year as of Oct. 31.

However, drug developers continue to file paperwork with the US Securities and Exchange Commission (SEC) to prepare for future IPOs, despite shaky share prices within the industry and a generally unstable stock market.

The Dow Jones Industrial Average dropped 7% in 2018, while the Nasdaq – where many biopharmas trade – fell 3.9%. But while newly public drug developers sank almost twice as much as the Nasdaq with their 7.5% average loss, they did better than a broader group of their biotech peers: the Nasdaq Biotechnology Index (NBI) plunged 9.3% by the end of the year.

The IPO-tracking firm Renaissance Capital LLC noted in its year-end report across industries that the IPO market begins 2019 on "uncertain footing," due to stock performance overall in the fourth quarter of 2018, but noted that some large, highly anticipated high-tech IPOs could keep some of the past year's momentum going.

"By deal count and proceeds, 2018 was the third most active year in the past decade, behind 2013 and 2014. A surge of biotechs and foreign tech companies drove the increase over 2017; two-thirds of IPOs were either tech or health care," Renaissance reported.

The firm noted, however, that the availability of private equity could keep some companies from going public this year rather than wading into the stock market's increasingly rough waters.

> Only six companies raised $200m or more, including Moderna's largest-ever drug developer IPO in the US

BIOPHARMA STANDS OUT IN AN OUTSTANDING YEAR

"2018 went down as a good year for the IPO market, even if it ended on a sour note," the Renaissance report said. "190 companies went public, 30 more than 2017, and proceeds increased 32% to $47 billion. Biotechs raised more IPO proceeds than ever, capped with a record-setting offering from Moderna."

The messenger RNA (mRNA)-based therapeutics and vaccine developer **Moderna Inc.**, in Cambridge, Mass., launched its long-anticipated IPO on Dec. 6, bringing in $604.3m in gross proceeds before the sale of any additional shares to meet overallotments. Despite pent-up investor demand, however, the company's stock has performed poorly as of year-end, closing 33.6% below the $23 IPO price at $15.27 on Dec. 31.

Another significant IPO in December – one of 10 companies to gross $150m or more from a first-time offering in the US in 2018 – had much better results for investors.

San Diego-based synthetic biology specialist **Synthorx Inc.** priced its shares at $11 each on Dec. 6 and grossed $150.7m from the sale of 13.7m shares when the offering closed on Dec. 12. The stock gave IPO investors a 58% return as of Dec. 31 when it closed at $17.38.

Synthorx is using its Expanded Genetic Alphabet technology platform to create optimized biologics called *Synthorins* – proteins with novel amino acids encoded by a new DNA base pair to enable site-specific modifications and enhance pharmacological properties. Lead product candidate THOR-707 is a variant of interleukin-2 (IL-2) that's being developed as a single agent and in combination with an immune checkpoint inhibitor to treat multiple tumor types.

The company is one of 30 biopharma firms that grossed $100m or more in 2018. Only six companies raised $200m or more, including Moderna's largest-ever drug developer IPO in the US.

The only other company to raise more than $300m was the allogeneic chimeric antigen receptor T-cell (CAR-T) therapy developer **Allogene Therapeutics Inc.**, which grossed $372.6m in October, including overallotments, in what was the year's largest biopharma IPO, until the Moderna offering. *(Also see "Finance Watch: With The Year's Biggest IPO, CFO Says Allogene Is Ready To Go 'Full Throttle'" - Scrip, 11 Oct, 2018.)* Allogene closed at $26.93 on Dec. 31, representing a 49.6% return versus the IPO price.

Two of the six companies that grossed $200m-plus are trading under their IPO values – Moderna and **Rubius Therapeutics Inc.**, which priced at $23 per share in July and closed 30.1% below that value at $16.08 on Dec. 31.

Rubius is developing red blood cell therapeutics and expected in 2017, after it raised $145m in Series A and B venture capital, that it would take its first program into the clinic in 2018. *(Also see "Rubius Prepares Off-The-Shelf Red Cell Therapies For First Human Trial In 2018" - Scrip, 12 Oct, 2017.)* However, the company now expects to submit its first investigational

new drug (IND) application to the US FDA in the first quarter of 2019.

Regardless of the stock market turmoil, innovative companies still are pursuing IPOs in the US, including San Diego-based autologous CAR-T developer **Poseida Therapeutics Inc.**, which said in a Jan. 4 SEC filing that it intends to raise up to $115m in a forthcoming offering. The company's move to go public was not surprising, since the company said in December when it presented data for P-BCMA-101 in multiple myeloma that it intended to rapidly progress its lead CAR-T candidate into a pivotal trial this year. *(Also see "Poseida, Legend/Janssen Look To Snag Celgene/Bluebird's BCMA Crown" - Scrip, 4 Dec, 2018.)*

Also based in San Diego, **Gossamer Bio Inc.** said in a Dec. 21 filing that it intends to raise up to $264.5m in a future IPO. The immunology-focused firm, run by executives who led **Receptos Inc.** until its $7.2bn acquisition by **Celgene Corp.** in 2015, raised $330m in venture capital last year – a $100m Series A round in January and a $230m Series B in July. *(Also see "Finance Watch: A Plethora Of Big Rounds, Led By Gossamer's $230m Series B" - Scrip, 31 Jul, 2018.)*

Harpoon Therapeutics Inc. in South San Francisco said in a Dec. 27 filing that it may raise up to $86.25m to fund its novel T-cell engagers for the treatment of cancer and other diseases, including HPN424 in Phase I for prostate cancer. The company disclosed a $70m Series C round in November and said it planned to initiate its first clinical trials for two additional candidates in 2019. *(Also see "Finance Watch: Biomatics Closes Second VC Fund; SVB Buys Leerink To Expand Life Science Services" - Scrip, 16 Nov, 2018.)*

Cambridge, Mass.-based **TCR2 Therapeutics Inc.** closed a $125m Series B round in March, but the company's expectations are not as high for its IPO, according to a Dec. 28 SEC filing saying that it will raise up to $100m in a future offering. *(Also see "TCR2 Raises $125m To Make T-Cell Therapies Available To More Cancer Patients" - Scrip, 21 Mar, 2018.)* TCR2 is developing T-cell receptor (TCR)-based therapies for cancer, including solid tumors. It filed an IND application with the FDA in December for its first therapeutic candidate and intends to submit INDs for two more programs in the second half of 2019 and in early 2020.

Stealth BioTherapeutics Inc. in Newton, Mass. also aims to raise less in its IPO than it did in its most recent venture capital financing, which brought in $100m in June. *(Also see "Finance Watch: Dementia Discovery Fund Exceeds Fundraising Goal By $150m" - Scrip, 25 Jun, 2018.)* The company, which said in a Dec. 28 filing that it is targeting an $86.25m first-time offering, is developing therapeutics to treat diseases involving mitochondrial dysfunction. Lead drug candidate elamipretide is in mid- to late-stage trials for the treatment of primary mitochondrial myopathy, Barth syndrome, Leber's hereditary optic neuropathy and dry age-related macular degeneration.

But the going isn't likely to be as easy in 2019 as it was in 2018, according to Renaissance. "The IPO market for 2019 is more difficult to predict due to increased volatility caused by domestic concerns about [US Federal Reserve] policy and the sustainability of economic growth as well as the fate of Brexit, broader European political instability and trade relations with China," the firm wrote in its year-end IPO report.

"As a result, 2019 IPO activity has a wider range of possible outcomes, from as few as 125 IPOs on the downside to 200 IPOs if the current uncertainties are resolved constructively and the broader market resumes an upward trend. Due to the negative returns for IPOs and the broader equity markets in the 4Q, 2019 IPO activity is more likely to be below 2018," Renaissance said.

The firm expects this year's IPOs to be dominated again by technology and biotech offerings, "particularly those engaged in cyber security, cloud-based data solutions, gene editing, and gene replacement."

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US Drug Pricing: What A Difference A Year Makes

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One year ago, industry insider Alex Azar had just been nominated HHS Secretary and the ink was still drying on new US corporate tax reform policies. Industry practically had a collective pep in its step heading into 2018, reassured that President Trump's threats on drug pricing would largely be limited to his Twitter bullhorn rather than notable policy changes.

Now, as drug makers head into 2019, the outlook for US drug pricing is more tenuous, particularly when it comes to those regular price increases on mature, marketed drugs that have provided a reliable way for the industry to drive growth even in a challenging drug development environment.

Democrats took over the the House of Representatives Jan. 3, which could make the target on industry's back in Washington, D.C. even bigger. Meanwhile, Azar hasn't been quite the comrade-in-power industry was hoping for. He was busy in the second half of 2018 turning ideas for lowering drug prices into written proposals.

There is still a lot of uncertainty around what policies the Trump administration will actually deliver on, but the era of unquestioned double-digit price hikes across the commercial portfolio appears to be over. More modest price increases on fewer products will put more pressure on drug makers to drive top-line growth.

One bright spot for the industry going into 2019 is the growing awareness that pharma is delivering novel groundbreaking medicines – gene therapies and cancer immunotherapies, for example – that continue to make the sector a dynamic one. Novel drugs that deliver a step change in the way diseases are treated may have more immunity when it comes to the backlash over drug pricing.

Another turn in industry's favor is that US retail drug spending across commercial and government payers was flat in 2017, largely due to decreased utilization, according to a report released by CMS in December.

Nonetheless, the political clouds appear to be building. In a recent interview with *Scrip*, **AstraZeneca PLC**'s US President Ruud Dobber predicted that the macroenvironment, including US drug pricing, will be the big headwind for the industry in 2019. "There is a lot of potential legislation coming from Washington," he said. "We need to respect that there are different views on our industry. That is the piece that is the most challenging one."

Leerink Partners analyst Geoff Porges said in a Dec. 17 note to investors, "We are very cautious about the outlook for large cap biopharma companies in 2019 based on unfavorable political forces, consumer anger and payer consolidation."

"We expect product prices to be under pressure, with market access even more challenging and product lifecycles to be shorter than ever," he added. "Looking ahead, we prefer companies with minimal reliance on price, highly differentiated products and under-valued catalysts."

> Without US price contributions from the prior five years, reported worldwide pharma revenue in 2018 year-to-date would have been $250bn, or 22% lower, Leerink's Geoff Porges concluded from an analysis

NEW YEAR, NEW PRICES

In the near-term,the industry is headed towards a reckoning of sorts in January. That's when drug makers typically take annual price increase on their products. This year, it's uncertain what type of pushback they might get from President Trump, the new Congress or the public when they do.

Indeed, on Jan. 1 many drug makers announced price increases as expected, including **Allergan PLC**, **Biogen Inc.** and **Bristol-Myers Squibb Co.**. Most of the price increases that were announced were 6% or lower, with the exception of Allergan, which raised prices by 9.5% across its commercial portfolio, according to a list of price increases provided by Evercore ISI analyst Umer Raffat.

Other drug makers are expected to follow. Pfizer already announced in November that it will raise prices on Jan. 15, but notably agreed to limit the increases to just 10% of the portfolio and to limit the amount of the price increases to 5% or less, with one exception: a 9% price increase one undisclosed drug. *(Also see "The Inevitable Is Coming: Price Increases, Starting With Pfizer" - Scrip, 19 Nov, 2018.)*

Pfizer seems to be betting that more transparency around drug prices will help to shield the company from a lot of blow back. *(Also see "The Inevitable Is Coming: Price Increases, Starting With Pfizer" - Scrip, 19 Nov, 2018.)* Last July, Pfizer agreed to roll back mid-year price increases after Trump pointed a finger at the company in a Tweet, followed by a phone conversation between CEO Ian Read and President Trump. *(Also see "Pfizer Agrees To Roll Back Prices On 40 Drugs, Yielding To Pressure From Trump" - Pink Sheet, 10 Jul, 2018.)* Many other industry players followed Pfizer's lead at the time, agreeing to hold off on mid-year price increases, amid backlash, and to give the Trump administration time to put some of the ideas in the president's drug pricing blueprint into action, but that grace period has ended.

Much of the drug pricing debate is focused on the regular price hikes on the list price of marketed drugs. Over the last couple of years, industry has tried to be more transparent about list price increases, partly to highlight how much it pays back in rebates to payers to secure formulary access and the lower increases it ends up receiving on net prices.

Allergan went public early with a pricing pledge, vowing to limit price increases to under 10%. Now, the company is walking prices right up to the ledge with 9.5% hikes, which could draw some criticism.

Open MediaRead the full article here

Even considering the difference between list and net price, those regular price increases have been a critical top-line growth driver for the industry. Curbing them puts pressure on drug makers to wring more growth from new drugs, supported by a promising late-stage pipeline.

An analysis of in-line price increases by the top 17 biopharma companies from 2013 through year-to-date 2018 by Leerink's Porges found that price growth alone contributed on average 5% a year to industry growth over the last five years.

"While total revenue growth was only 1% from 2017-2018, without the price effect, we calculate that revenue growth from 2017-2018 would have been -6%," Porges said.

Further, more than 20% of this year's total biopharma revenue of $320bn, through the third quarter, can be attributed to the cumulative effect of price increases over the last five years, he said.

In the short-term, industry can manage to hold off on price increases, but the impact is harder to digest long-term.

As Porges said, "The negative effect of these slowing price increases will have a powerful effect going forward because of the unwinding of the cumulative effect of compounding of positive price from prior year price increases." US pricing has contributed $27bn to worldwide pharma

revenue in 2014, $45bn in 2015, $59bn in 2016, $68bn in 2017 and $71bn in 2018, he concluded. But without US price contributions from the prior five years, reported worldwide pharma revenue in 2018 year-to-date would have been $250bn, or 22% lower.

HOTTER POLITICAL CLIMATE

The gloomier outlook for pharma began mid-year, even after the Trump administration released its blueprint on drug pricing, which included lots of ideas but little in the way of tangible policies to make industry insiders particularly jittery. *(Also see "'Immediate' Steps To Lower Drug Prices: The HHS Action Plan " - Scrip, 13 May, 2018.)*

But some of those ideas began to make their way into proposals – and news conferences – as the year went on. A proposal that would require drug makers to disclose list prices in direct-to-consumer TV ads is such a daunting prospect that the industry is hoping to thwart it by implementing its own voluntary proposal that would convey where consumers can go to find more nuanced information around pricing. *(Also see "Industry Makes A Drug Price Transparency Push In DTC Ads, But Is It Too Little Too Late? " - Scrip, 15 Oct, 2018.)* It's also gearing up for a First Amendment legal battle if it comes to that. *(Also see " DTC Ad Proposal: Biopharma, Advertisers Marshall Legal Arguments In Opposition" - Pink Sheet, 19 Dec, 2018.)*

A rule proposed in October, to benchmark reimbursement for some Medicare Part B drug prices against an international price index, is viewed by industry about as loathsome as opening the doors to drug importation. *(Also see "Medicare's Foreign Price Bench-marking Will Only Hurt Bad Negotiators, HHS's Azar Argues" - Pink Sheet, 25 Oct, 2018.)*

Another proposal, to reduce protections for six categories of medicines that have been protected under Medicare Part D, would pave the way for broader government negotiations on more categories of specialty drugs that have faced fewer market access restrictions. The Trump administration appears to be throwing out a whole bunch of proposals, and while it remains to be seen which ones will stick, certainly the pressure on the industry has intensified since the start of 2018.

"We are in a more interesting time than ever in my career," **Express Scripts Holding Co.** Chief Medical Officer Steve Miller said, speaking about the drug pricing environment at the Forbes Healthcare Summit in December. "Who would think my biggest advocate right now would be a Republican president named Donald Trump."

Pharmacy benefit managers like Express Scripts have come under scrutiny themselves for the lack of transparency around the fees they charge and how they direct the rebates they negotiate with drug manufacturers. Another policy HHS is reviewing is around potential rebate reform, which could have consequences for PBMs as well as drug manufacturers. *(Also see "Rebate Reform: Big Changes Are Looming For The US Drug Market" - In Vivo, 12 Nov, 2018.)*

But the big question is what will happen in 2019, if anything, in terms of real policy shifts. For now, some analysts remain cautiously optimistic on the outlook for pharma on that front.

"We (cynically) believe odds are there will be less done in this Congress," Bernstein Research's Ronny Gal said in a Jan. 2 note. "The support for the drug industry crosses party lines. Many Democrats support the drug industry, notably Chairwoman Pelosi. You would need to form a cross-party coalition to carry a reform."

Nonetheless, the issue of high drug costs certainly isn't going away. For now, drug makers might try to think about navigating January price increases cautiously and wait to see if other health care topics - like insurance reform - can alleviate some of the pressure.

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Oculis Eyes Opportunities With Fresh Funding And Novartis Licensing Deal

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Oculis has bagged an injection of new cash as well as a promising mid-stage inflammatory eye disease drug from **Novartis AG** to help the Swiss biotech achieve its goal of becoming a leading player in the ophthalmic space.

On the money front, Oculis has raised a further CHF15.5m (around $15.7m) in an extension of its Series B financing round announced in January last year, bringing the total raised to CHF35.5m. The extension round was led by funds managed by Tekla Capital Management and included Nan Fung Life Sciences, both new investors, as well as its current backers such as Bay City Capital, the Novartis Venture Fund, Pivotal bioVenture Partners and the Icelandic finance house Silfurberg.

In an interview with *Scrip*, CEO Riad Sherif said the firm was very pleased to attract two new big players and expand Oculis' already supportive investor base. "It is not just about the money but also the expertise they bring," he said, noting that Tekla's Henry Skinner, formerly managing director at Novartis Venture Fund and head of strategic alliances at Novartis Institute for Biomedical Research (NIBR), would join the board.

The Lausanne-headquartered firm, which runs its research operations out of the Icelandic capital Reykjavik, has already started to spend the funds, having in-licensed LME636, a topical anti-TNF alpha antibody, from Novartis. The drug, which has been renamed OCS-02, has been evaluated in three clinical trials by NIBR, demonstrating a promising profile for treating inflammatory conditions of the anterior segment of the eye, including dry eye disease.

No financial details have been disclosed but Oculis believes OCS-02 could be potentially the first topical anti-TNF alpha therapy for ophthalmic indications. The company noted that the compound is based on a "single-chain antibody fragment technology specifically designed for topical delivery."


Riad Sherif

The Lausanne-headquartered firm, which runs its research operations out of the Icelandic capital Reykjavik, has already started to spend the funds, having in-licensed LME636, a topical anti-TNF alpha antibody, from Novartis

Sherif knows Novartis very well, having joined the giant back in 2002 and worked there until 2017 in a number of posts, including president of Europe, Middle East & Africa at its ophthalmology unit **Alcon Inc.** With regards to OCS-02, he said that "it helped that I knew the market and the product," adding that it fits with Oculis' focus on next-generation topical ophthalmic treatments and addresses unmet medical need.

CLINICAL PROGRAM

Now that Oculis has got its hands on OCS-02, Sherif said the company can start preparations for a clinical program and is looking at starting a Phase IIb or even a Phase III trial. Which route it takes will depend on discussions with advisors and regulators.

He believes that the company's portfolio of topical treatments represents "an unprecedented technical advance" for back-of-the-eye diseases that are currently managed only by intra-ocular injections or implants. These involve not particularly pleasant procedures and "I know how difficult this can be," said Sherif, who was involved in launches of Novartis' macular degeneration drug *Lucentis* (ranibizumab).

The latter and other anti-VEGF treatments such as **Bayer AG**/**Regeneron Pharmaceuticals Inc.**'s *Eylea* (aflibercept) "are all very good products," he said, "but their invasiveness is a true limitation." Topicals could also address access issues, Sherif added, saying that "there is a space for injectables but there is probably a bigger space for topicals."

POTENTIAL PARTNERING

He acknowledged that it is not easy treating the back of the eye, "which is luckily well protected," but Oculis has developed its solubilizing nanoparticle (SNP) technology that enables the formulation of a wide range of drugs as non-invasive topicals and enhances their bioavailability in the relevant eye tissues. Its lead candidate using that platform is OCS-01, which is in a 144-patient Phase IIb study for diabetic macular edema; the first readout of data is expected before the end of the second quarter this year.

As to how far Oculis can take these compounds along the development pathway, Sherif said that partnering would be an option. He stated that the company can offer deep expertise in terms of the technology and clinical development, "but commercializing a product is something else, we will see."

As for Novartis, the decision to license out fits with a strategy of reducing its research efforts in ophthalmology and focusing on innovative cancer medicines and cell and gene therapies. The company is in the process of spinning out Alcon. *(Also see "Narasimhan: Novartis' Specialized Portfolio Will Lead To Bigger Breakthroughs And Greater Value " - Scrip, 6 Nov, 2018.)*

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MyoKardia Frames End Of Sanofi Partnership As A Bet On Itself

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When an R&D collaboration between a big pharma and a smaller firm dissolves, the common view is that the larger, more established entity lost confidence in the partnership. US biotech **MyoKardia Inc.** claimed Jan. 2 that the end of its four-year tie-up with **Sanofi** around drug candidates for rare genetic heart diseases is different, and that it wanted to regain full rights to its Phase III mavacamten and Phase II MYK-491.

The French pharma notified MyoKardia earlier in the week that it would exit a partnership signed in 2014, but the reason for the termination was not doubt around efficacy or safety of the two drug candidates, MyoKardia CEO Tassos Gianakakos told a Jan. 2 investor call. Instead, Sanofi wanted to acquire part or all of the US rights to mavacamten in lead indication hypertrophic cardiomyopathy (HCM) as well as down-the-road rights in other cardiovascular indications.

Investors, however, seem less convinced about the situation than MyoKardia's management. The company's shares ended the trading day down 14% at $41.95 per share Jan. 2

"Leading up to the end of the research term [on Dec. 31], we were not interested in expanding the collaboration with Sanofi to include US commercial rights for mavacamten and additional rights in broader heart failure indications. Neither of those options makes sense for our business at this time," the exec said, adding that agreeing to share US rights to the oral, allosteric modulator of cardiac myosin "would require significant incentive."

MyoKardia received $35m in cash and a $10m equity investment from Sanofi when the deal was announced in September 2014, giving Sanofi rights to three then-preclinical programs, including mavacamten (MYK-461) for HCM and MYK-491, now in Phase Ib/IIa for dilated cardiomyopathy (DCM). *(Also see "Sanofi pays $45m for early look-in on genetic heart disease program" - Scrip, 18 Sep, 2014.)* The third candidate was MYK-224, slated to enter clinical development in HCM this year.

Besides an ongoing pivotal study of mavacamten in obstructive HCM (oHCM), MyoKardia also anticipates over the next 24 months other potential value-creating data readouts, including a Phase II study of mavacamten in non-obstructive HCM, six- and 12-month safety data from an open-label extension study of that drug in oHCM, and Phase IIa proof-of-concept data for MYK-491 in DCM.

The partnership left MyoKardia in charge of the preclinical development and early clinical development of all three programs. For later-stage development, the companies would split the costs, with Sanofi getting ex-US commercial rights for the HCM programs and full rights for the DCM candidate. Sanofi elected to continue the partnership at the end of 2016, triggering a $45m milestone payment to MyoKardia and setting the stage for another renewal decision at the end of 2018.

PARTNERSHIP TRANSFORMED MYOKARDIA, BROUGHT IN $230M

Gianakakos said his company has realized roughly $230m in funding and support from Sanofi over the life of the collaboration, considerations that enabled MyoKardia to "quickly grow into a world-class research and development enterprise with the resources, experience, expertise and funding necessary to independently pursue and achieve our mission, something we could not say in 2014." He added that when the deal was signed, MyoKardia was a privately owned company that had not yet initiated its first clinical trial.

Market analysts called the end of the collaboration a net-positive for MyoKardia, despite the fact that it will increase the company's R&D expenses near-term. Two analysts predicted blockbuster sales potential for mavacamten in notes released on Jan. 2. Gianakakos said the biotech is adequately capitalized to operate through the data readout for the pivotal Phase III EXPLORER trial for mavacamten in HCM during the second half of 2020. It had $412m in cash on hand at the end of the third quarter of 2018.

Investors, however, seem less convinced about the situation than MyoKardia's management. The company's shares ended the trading day down 14% at $41.95 per share Jan. 2.

Gianakakos stressed during the call that MyoKardia aims to become a fully integrated pharmaceutical company and that while it will consider offers to re-partner the assets returned by Sanofi, a potential deal will need to offer more than just cash to be truly compelling. "We'll really be looking at situations where one-plus-one is greater than two," he said. "You can think about that in terms of increasing the probability of getting therapy out to folks faster and potentially accessing more patients that on our own we wouldn't be able to reach."

SANOFI RETAINS 10% OWNERSHIP IN MYOKARDIA

One complication to the ended partnership is that Sanofi owns a significant stake in MyoKardia, estimated at greater than 10%. The biotech's CFO Taylor Harris said the two companies will work together to address that issue.

"It's likely that, over time, they're going to want to sell down that stake," he explained. "But look, both of us have the same incentive here. We want to maximize the value of that stake, and so I think

we're going to work together really closely to make sure we do that and that any dispositions, when they come, are done in an orderly fashion."

WedBush analyst David Nierengarten maintained a rating of "outperform" for MyoKardia's stock in a Jan. 2 note, increasing his target price from $77 per share to $84. "The economic opportunity increases, despite a higher cash burn going forward," he said. WedBush estimated that mavacamten will reach the market in 2021 and grow rapidly, falling just short of blockbuster sales in 2023 ($978m) and reaching more than $2.2bn in 2025.

"In our view, it is also likely that MyoKardia can re-partner these assets, particularly ex-US, on even more favorable terms now that the candidates are in more advanced studies compared to the original Sanofi deal," Nierengarten added.

Credit Suisse analyst Martin Auster also maintained an "outperform" rating for MyoKardia shares on Jan. 2, predicting that mavacamten offers potential as $1bn-plus product. "We believe the resulting increase in cash burn is offset by advanced economics and increased M&A opportunity around mavacamten," he wrote. Auster cautioned, however, that MyoKardia now takes on increased commercial execution risk for its pipeline outside the US.

One question the deal raises, the analyst added, is whether Sanofi's exit indicates doubt about the prospects for the DCM candidate, MK-491, whose Phase Ib data in late 2018 raised some safety concerns about potential for increasing troponin levels, a cardiovascular risk factor.

In a larger sense, Sanofi's decision may reflect an effort to do some portfolio clean-up as 2018 ends and 2019 begins. The pharma out-licensed global rights to the cannabinoid CB-1 receptor antagonist drinabant to **Opiant Pharmaceuticals Inc.** on Dec. 26 for $0.5m up front, more than $44m in potential milestone fees and sales royalties.

Then, on Jan. 2, Boston-area firm **Acer Therapeutics Inc.** announced it licensed osanetant, a selective, non-peptide tachykinin NK3 receptor antagonist for neuroendocrine-related disorders from Sanofi at undisclosed terms.

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Sanofi Takes €80M BioNTech Stake And Extends 2015 Deal

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Sean Marett

German biotech **BioNTech AG** has added **Sanofi** as a strategic investor as the French pharma giant takes an €80m equity stake and agrees to extend a 2015 research collaboration between the two companies. Concomitantly, the partners have agreed to co-develop the first cancer immunotherapy candidate from the collaboration that is entering clinical testing in multiple solid tumors.

In the original deal *(Also see "Sanofi Hopes BioNTech Pact Can Help Reboot Cancer Prospects" - Scrip, 3 Nov, 2015.)*, the partners agreed to discover and develop up to five mRNA-based cancer immunotherapies against undisclosed targets. Sanofi paid $60m in an upfront payment and near-term milestones for exclusive, worldwide rights to candidates that emerge from the deal, while BioNTech had an option to co-develop and co-commercialize two candidates in the EU and U.S.

As yet, the partners are still not providing specific details of the targets they are working on and have only disclosed that the first candidate will be developed against multiple solid tumors.

Interestingly, there was no mention in the original 2015 agreement of Sanofi taking a future equity stake in BioNTech but the biotech believes that such a move cements their long-term relationship.

"An equity stake brings a different feel to the relationship with a partner and adds a further dimension to the alignment of incentives as we drive our collaboration with the partner forward," Sean Marett, BioNTech's chief commercial officer and chief business officer, told *Scrip*.

Sanofi is not the first corporate backer in BioNTech's shareholder base. Marett revealed to *Scrip* that **Pfizer Inc.** took an equity stake in BioNTech in August 2018 as part of a collaboration to develop mRNA-based vaccines for prevention of influenza *(Also see "Interview: BioNTech And Pfizer Explore mRNA Flu Vaccines In $120m+ Deal" - Scrip, 16 Aug, 2018.)(Also see "BioNTech CBO Outlines Infectious Disease Ambitions" - Scrip, 29 Nov, 2018.)*, while the company's 2015 T-cell deal with **Lilly Research Laboratories** included an equity investment in BioNTech's cell and gene therapy subsidiary.

Marett declined to detail the size of the corporate stakes. The Strüngmann family office, a BioNTech's founding investor, remains the company's majority shareholder. Other shareholders include Redmile Group, Janus Henderson Investors, Invus, Fidelity and other undisclosed family offices, which all participated in the 2018 series A round that raised $270m *(Also see "BioNTech Raises $270M Series A Round To Pursue FIPCO Model" - Scrip, 4 Jan, 2018.)(Also see "BioNTech COO Sean Marett Reveals How To Spend $270M" - Scrip, 12 Apr, 2018.)*.

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New Takeda R&D Collabs Aim To Boost IO Pipeline

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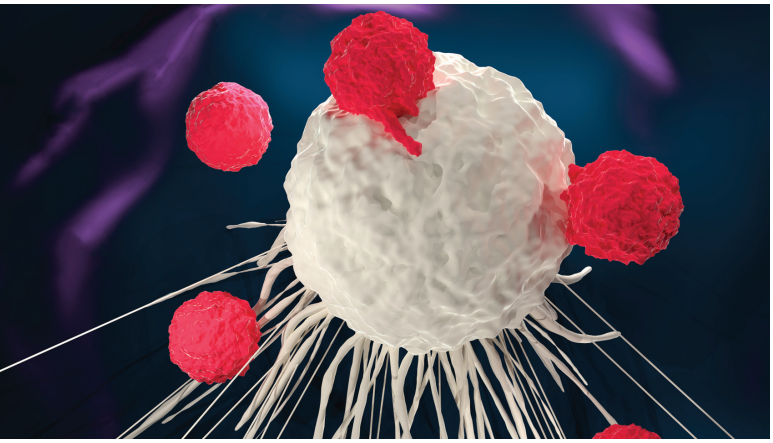
Just ahead of the formal close of its massive acquisition of **Shire PLC** - and amid news of the even larger planned $74bn merger of **Bristol-Myers Squibb Co.** and **Celgene Corp.** - **Takeda Pharmaceutical Co. Ltd.** has signaled its commitment to the immune approach in oncology, unveiling multiple research collaborations aimed at bolstering its early-stage pipeline in the area.

The new deals are aimed at the discovery of novel immunotherapies, including cell therapy approaches with "curative" potential targeting new mechanisms in the cancer immunity cycle, said the Japanese company, which is positioning immuno-oncology (IO; along with lung cancer and hematologic malignancies) as key pillars of its cancer R&D strategy.



Takeda has signaled that this strategic focus will continue post the formal close of the $64.3bn Shire deal, which is now confirmed for Jan. 8. 2019 following a Shire-related legal procedure under which a court in Jersey sanctioned a scheme of arrangement for the implementation of the plan.

But in a move that may precipitate a new global shakeout of competitive bidders with grand designs in IO, BMS and Celgene - both important players in the sector but facing challenges - said they were aiming to combine in the third quarter.

The deal, if completed, would be the third-largest ever in the biopharma sector, pushing Takeda/Shire down to sixth.

COLLABORATIONS, OPTIONS

The first of the new Takeda collaborations is a "broad, multi-faceted" deal with the Memorial Sloan Kettering (MSK) Cancer Center in the US to discover and develop novel CAR-T therapies for multiple myeloma, acute myeloid leukemia, and potential solid tumor indications.

Takeda gave little further detail except that the program would be led by Dr Michel Sadelain, director of MSK's Center for Cell Engineering and the scientific founder of **Juno Therapeutics Inc.** (which incidentally was acquired by Celgene for around $9bn last year).

The other two collaborations involve options for specific products or technology under existing research alliances. Takeda said it has now exclusively licensed from Japanese bioventure **Noile-Immune Biotech Inc.** two CAR-T therapies, NIB-102 and -103, for various solid tumors, and plans to gain approval to start clinical trials with the first of these by the end of this year.

The September 2017 alliance (routed through Takeda's wholly owned Millennium oncology arm) provided access to Tokyo-based Noile's proprietary Prime (proliferation inducing and migration enhancing) platform, and exclusive options to licensing rights to emerging assets.

Takeda has provided research funding and paid an undisclosed technology access fee and made an equity investment in Tokyo-based Noile, which licensed the Prime technology from a professor at Japan's Yamaguchi University (who co-founded the venture). The platform aims primarily to apply the CAR-T approach to solid tumors by improving related local cytokine and chemokine production at tumor sites.

The third new collaboration covers an additional component of an option to exclusively license oncology-targeted Humabody technology developed by **Crescendo Biologics Ltd.**, which was exercised in November 2017. This gave Takeda an exclusive license to Crescendo's *Humabody* therapeutics against a Takeda oncology target.

The multi-target collaboration with the UK-based venture began back in October 2016 and is related to the venture's proprietary transgenic mouse platform, which can generate 100% human VH domain molecules. Crescendo is eligible for milestones of up to $754m plus royalties under the alliance.

The new expansion will additionally allow Takeda to evaluate the Humabody VH molecules in the development of novel CAR-T therapeutics, enabling it to look at single-domain, tumor-targeted binders as an alternative to conventional single-chain, variable fragment-based approaches.

'CELL THERAPY ENGINE'

As part of this wider strategic pursuit of cell therapy and IO approaches, Takeda said that it had also newly established a "translational cell therapy engine" group, which brings together appropriate internal expertise in bioengineering, chemistry, manufacturing and control, and translational and clinical research.

The aim is to rapidly progress - with the aid of specific projects and assets from external partners - innovative differentiated cell therapies across various therapeutic areas into the clinic. The initiative is being led by Dr Stefan Wildt.

Just ahead of the Shire merger - which is aimed at part in expanding Takeda's broader late-stage pipeline - the Japanese company's main R&D oncology pipeline is in areas such as antibodies and small molecules. It has so far not had a significant CAR-T presence, although a $125m deal was signed around two years ago with **Maverick Therapeutics Inc.** to develop T-cell redirection therapies, with an option to acquire the US venture.

Takeda's current commercial oncology portfolio is led by the proteasome inhibitors *Velcade* (bortizomib) and *Ninlaro* (ixazomib) for multiple myeloma.

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From the editors of PharmAsia News.

China's Innovent Biologics Emerges As Immuno-Oncology Competitor With Sintilimab Approval

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The promise of China's biotech industry to develop innovative pharmaceuticals continued to bear fruit at the beginning of 2019, with an announcement that development of **Innovent Biologics Inc.**'s anti-PD-1 MAb, *Tyvyt* (sintilimab) was proceeding in additional indications following hot on the heels of the Dec. 27 news of the product's approval in China for classical Hodgkin's lymphoma.

The development progress justified investors who backed the seven-year-old Suzhou, China-based Innovent Biologics when it went public on the Hong Kong Stock Exchange in October 2018 – the company raised $421m in its IPO, the fourth biotech from mainland China to go public in Hong Kong.

Analysts at Morgan Stanley noted the timing of sintilimab's approval came ahead of expectations, previously being expected in early 2019, adding to another of the company's milestones being achieved ahead of expectations; the filing of an approval application for a biosimilar version of **AbbVie Inc.**'s *Humira* (adalimumab) in China has also been achieved since Oct. 2018.

Sintilimab, which is being co-developed in collaboration with the US big pharma, **Eli Lilly & Co.**, is a fully human anti-PD-1 MAb which was approved by the National Medical Products Administration of China (NMPA, formerly the China Food and Drug Administration) for the treatment of relapsed or refractory classical Hodgkin's lymphoma, after two or more lines of systemic chemotherapy. Innovent Biologics and Lilly signed an agreement in March 2015 to collaborate on the development of certain anticancer candidates, expanded in Oct. 2015 and valued at the time at close to half a billion dollars if fully exercised. *(Also see "Local Expertise, Growing Oncology Market Behind Lilly/Innovent Deal" - Scrip, 23 Mar, 2015.)*

The development of sintilimab, co-discovered by Innovent and **Adimab LLC**, has not however been smooth, with an earlier approval filing being suspended in China because of quality issues, since resolved. *(Also see "China Roundup: Innovent I/O Setback, Adagene, Hua Bag Millions, WuXi Relisting" - Scrip, 3 Apr, 2018.)*

China has a growing cancer burden, with around 2.86 million deaths expected from the condition in 2018, and 4.28 million new diagnoses, and Innovent Biologics notes that around 15-20% of cancer patients who develop classical Hodgkin's lymphoma have a relapse after first-line treatment, usually a combination of chemotherapy and radiotherapy.

ADDITIONAL INDICATIONS

The latest Phase III study with sintilimab, ORIENT-15, has just started in China in 640 patients with unresectable locally advanced, recurrent or metastatic esophageal squamous cell carcinoma who are being treated with chemotherapy as first-line treatment. Sintilimab or placebo will be added to the treatment regimen of paclitaxel and cisplatin, with the primary endpoint being overall survival, the company said on Jan. 2, 2019. Asian countries have a higher incidence of esophageal squamous cell carcinoma than western countries, being the third most common malignant tumor in China.

Sintilimab is being studied in more than 20 clinical trials, including first line non-squamous non-small cell lung cancer (NSCLC), first-line squamous NSCLC, second-line squamous NSCLC, EGFR mutant NSCLC after EGFR TKI treatment failure, first-line gastric cancer, first-line liver cancer, and second-line esophageal cancer. In all, Innovent Biologics has a pipeline of around 17 products including proprietary monoclonal antibodies and follow-on biologics, and most recently licensed three candidate oncology products from **Incyte Corp.**

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Gilead Extends Push Into Oncology With Agenus R&D Pact

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Gilead Sciences Inc. signaled its continuing push into cancer immunotherapy by inking a deal with **Agenus Inc.** to develop and commercialize up to five novel immuno-oncology treatments, an arrangement potentially worth more than $1.8bn for the Lexington, Massachusetts-based biotech.

For Gilead, the R&D pact with immunotherapy specialist Agenus is its latest effort to enter the oncology field and help offset the impact of its waning hepatitis C business.

Gilead's ambitions in the field of cancer should only be strengthened by the arrival next year of Roche pharma veteran Daniel O'Day as its new CEO. Its deal with Agenus provides Gilead with exclusive, worldwide rights to AGEN1423, a bispecific tumor microenvironment conditioning antibody, for which IND filing is planned by the end of 2018.

Gilead will also receive the exclusive option to license two additional programs: AGEN1223, a bispecific Treg depleting antibody, and AGEN2373, a CD137 targeting monoclonal antibody. Agenus has already filed the IND for AGEN1223 and plans an IND filing for AGEN2373 in the first half of 2019. The parties will also collaborate on two other treatment candidates, but they gave no details.

DEAL TERMS

Under the terms of the agreement, announced Dec. 20, Agenus will receive $150m upon closing, which includes a $120m upfront cash payment and a $30m equity investment. The agreement also includes approximately $1.7bn in potential future fees and milestones.

Agenus will be responsible for developing the option programs up to trigger points at which time Gilead will decide on acquiring exclusive rights to the programs.

For one of the option programs, the biotech will have the right to opt into shared development and commercialization in the US. Gilead will also receive right of first negotiation for the two additional, undisclosed preclinical programs. "Our collaboration with Agenus gives us access to novel and differentiated immune modulating antibodies that will complement our growing oncology portfolio and cell therapy business," Gilead's R&D head John McHutchison said.

That cancer portfolio has been expanding through R&D deals and acquisitions.

In August 2017, Gilead bought **Kite Pharma Inc.** and its chimeric antigen receptor T-cell (CAR-T) pipeline for $11.9bn. *(Also see "What's Gilead Getting From Kite For Nearly $12bn?" - Scrip, 29 Aug, 2017.)*

In October 2018 Gilead joined cancer start-up **Tango Therapeutics Inc.** to develop targeted immuno-oncology treatments aimed at up to five targets emerging from Tango's functional genomics-based discovery platform, a pact worth potentially more than $1.7bn.

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Viela Adds Momentum To Burgeoning NMOSD Market With Pivotal Inebilizumab Results

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MedImmune LLC spin-off **Viela Bio** could be the third company within a year to produce encouraging pivotal study results for neuromyelitis optica spectrum disorder (NMOSD), a rare autoimmune disease affecting the CNS, with no treatment options to date.

Inebilizumab, a monoclonal antibody (MAb) that binds with high affinity to CD19, a protein expressed on a broad range of B cells, met its primary and secondary endpoints in the pivotal N-MOmentum trial. This was the largest controlled trial in NMOSD conducted to date, enrolling 231 adult patients across 128 sites in 24 countries.

The primary analysis demonstrated a 77% reduction in the risk of developing an NMOSD attack in patients treated with inebilizumab monotherapy compared with placebo. Secondary analysis demonstrated a reduction in worsening of disability in patients treated with inebilizumab compared with placebo. The safety and tolerability profiles for inebilizumab were acceptable and consistent with previous experience.

Viela's N-MOmentum trial results look to add treatment options for neuromyelitis optica patients

This Phase IIb trial was designed as a pivotal registrational study, and Viela worked closely with the US FDA and other regulatory agencies to ensure that endpoints were approvable, Viela Bio CEO Bing Yao told *Scrip*.

NMOSD is a life-threatening autoimmune disease of the central nervous system in which the body's immune system attacks healthy cells, most commonly in the optic nerves and spinal cord, resulting in severe damage. NMOSD may cause severe muscle weakness and paralysis, loss of vision, respiratory failure, problems with bowel and bladder function and neuropathic pain. It is thought to affect five in 100,000 people.

The FDA granted orphan drug designation for inebilizumab for the treatment of patients with NMOSD in March 2016, while the European Medicines Agency followed suit in March 2017.

THREE HORSE RACE

With no approved treatment in neuromyelitis optica, this year could be life changing for patients suffering from the autoimmune disease, as a potential three choices could hit the market. "Improved understanding of the pathophysiology of NMOSD, particularly the role of autoantibodies against aquaporin-4 produced by plasmablasts and plasma cells has facilitated the development of new treatments," explained Yao. "In addition, substantial progress has been made on the development of approvable endpoints and definitions of relapse, thus enabling rigorous clinical trials."

The next few months should be very interesting as three companies; Viela Bio, **Chugai Pharmaceutical Co. Ltd.** and **Alexion Pharmaceuticals Inc.** prepare to present competing data from Phase III trials at medical meetings, with all three companies planning to file regulatory submissions within the next 12 months.

In September, Alexion published results from its PREVENT study of complement inhibitor *Soliris* (eculizumab) in patients with anti-aquaporin-4 (AQP4) auto antibody-positive NMOSD. Patients who have anti-AQP4 auto-antibodies represent approximately three quarters of all patients with the condition.

The study met its primary endpoint of time to first adjudicated on-trial relapse, demonstrating that treatment with Soliris reduced the risk of NMOSD relapse by 94.2% compared to placebo. At 48 weeks, 97.9% of patients receiving Soliris were free from relapse compared to 63.2% of patients receiving placebo.

Only a month later, the Phase III SAkuraSky study of Chugai's anti-IL-6 receptor MAb satralizumab showed that, on top of immunosuppressive therapy, it significantly reduced the risk of relapse by 62%, and by 79% in AQP4-positive patients.

While satralizumab's data are not as compelling as those produced by Soliris, it may beat still beat Soliris on ease of use with a regimen of subcutaneous application once a month versus Soliris' fortnightly IV. Viela's inebilizumab could change the treatment landscape further, as it is administered intravenously every six months.

"As there is currently no approved treatment for this severe and disabling disease, it is encouraging to see multiple emerging therapies for patients with NMOSD," Yao said. "We believe inebilizumab directly addresses a key pathogenic mechanism in NMOSD, namely secretion of autoantibodies by plasmablasts and plasma cells. In our trial, we included a broad NMOSD patient population including moderate and severe disease. N-MOmentum was a true monotherapy trial."

Viela Bio is planning to present full data from the study at an undisclosed medical meeting in 2019, when the market and patients will be able to assess the full range of treatment options possible.

Chugai plans to file an approval application for satralizumab in Japan sometime in 2019, but could not confirm timings. Alexion will apply for approval in the US, EU and Japan in 2019. Viela Bio confirmed to *Scrip* that it was currently in the process of preparing a BLA filing for submission to the FDA, it anticipates filing in the first half of 2019.While the US is the first territory for regulatory filing, "global regulatory submissions will follow quickly", Yao confirmed.

Morgan Stanley analysts forecast the market for neuromyelitis optica to peak at around $500m per year.

AstraZeneca's biologics arm MedImmune spun out Viela Bio in February with six early-stage biologics all focused on inflammation and auto-immunity disorders. Backed by a group of Chinese private equity funds, a Series A financing round made the company $250m from a consortium of funds co-led by Boyu Capital, 6 Dimensions Capital, and Hillhouse Capital. AstraZeneca is the largest minority shareholder in the new company. *(Also see "AstraZeneca Keeps R&D Focus, Spins Out Phase II Neuromyelitis Optica MAb Into New Biotech" - Scrip, 28 Feb, 2018.)*

Yao stressed to *Scrip* that Viela Bio was an independent company, and as such it preparing to launch inebilizumab itself, while evaluating commercialization options.

The company has a further three candidates in Phase I studies. VIB4920 is a fusion protein targeting CD40L that Viela has completed a Phase Ib study with positive read out in rheumatoid arthritis and will be announcing new Phase II studies in early 2019.

VIB7734 is its first-in-class ILT7 candidate, which is designed to target plasmacytoid dendritic cells. This has completed a Phase Ia study and Viela has initiated a Phase Ib study in patients with autoimmune diseases. VIB9600 is an antibody designed to block FcγRIIA engagement. It has now progressed into the clinic and the company is currently recruiting healthy volunteers into an ongoing Phase I study.

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Oncology Leader Liz Barrett Joins UroGen As CEO As It Heads Towards Commercial Stage

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Former **Novartis AG** Oncology CEO Liz Barrett will be the new CEO of the urology cancer specialist **UroGen Pharma Ltd.**, the company announced Jan. 3, where she will be responsible for overseeing the FDA approval and launch of the company's first drug, now in late-stage development for low-grade upper tract urothelial cancer.

The news comes just about two weeks after Novartis announced Barrett's surprising departure after less than a year at the high-profile post. Novartis insider Susanne Schaffert, most recently the president of Novartis' newly acquired Advanced Accelerator Applications, was appointed to succeed her. *(Also see "AAA President Takes Novartis Oncology Top Job, As Barrett Leaves For Biotech" - Scrip, 20 Dec, 2018.)*

In an interview, Barrett told *Scrip* that the decision to leave Novartis after such a short time was a hard one to make and driven partly by the fact that her family remained in the US while the job


Liz Barrett

really required being in Basel, Switzerland. She also said she had long aspired to be a CEO of a biopharma company.

"Novartis could not have been more gracious. They were willing to accommodate, but at the end of the day I had to make the decision that this is what I want to do. I want to run a company."

Before joining Novartis in February 2018, Barrett was global president of oncology at **Pfizer Inc.**, where she was credited with helping to build *Ibrance* (palociclib) into a blockbuster, and she also previously worked in oncology at **Johnson & Johnson**. The transition from one of big pharma's rising stars to the CEO of a small biotech seemed sudden.

Barrett found that UroGen fell into a sweet spot for her after conversations with the company's chairman, Arie Belldegrun, the founder of **Kite Pharma Inc.** UroGen is on the cusp of launching its first drug, a product built on a unique gel technology aimed at targeting hard-to-reach cancers. But beyond the near-term commercial launch, Barrett said there is also a lot of opportunity at UroGen to plot a longer-term strategy.

The company has initiated a rolling NDA at FDA for its first drug, UGN-101 (mitomycin gel), for low-grade upper tract urothelial cancer, and expects to complete the submission in the second quarter. The product was granted fast track designation and breakthrough therapy designation by FDA and the company believes it could hit the market in about a year.

The product essentially combines the chemotherapy mitomycin with UroGen's proprietary RTGel technology platform to create a sustained-release hydrogel-based formula. The aim is to enable longer exposure of mitomycin directly to the urinary tract tissue, enabling treatment by non-surgical means.

"Hopefully by injecting it directly to the tumor, you are going to get better efficacy and you are going to get better safety," Barrett said.

The NDA submission is supported by data from the Phase III OLYMPUS trial; top-line results will be presented later in January. In an interim analysis of the trial released last year, 59% of 34 patients evaluated showed a complete response.

The company is also developing a second similar product, UGN-102, for low-grade non-muscle invasive bladder cancer. Barrett's near-term priority will be building out a commercial team targeting urologists, but she will also be focused on business development and establishing a longer-term strategy for UroGen. The company believes its RTGel platform could have utility with other molecules owned by potential partners.

"There is still a lot of work to be done," she said. "We have to figure out where we are going next, how can we maximize the opportunity of this gel technology for collaborations and partnerships, and then what's beyond this."

UroGen went public in May 2017 through an initial public offering bringing in $66.9m in proceeds. The company had cash and equivalents of $109.5m at the end of the third quarter. Barrett said the company has the cash on hand "to do what we need to get done" and will take steps to raise more cash depending on how the business strategy develops.

The emphasis on raising cash is one part of the job that will be new to Barrett, even though she has had a lot of experience managing cash investment. "I've been managing a P&L for a long time, but this is different," she said. "Every dollar counts."

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Jallal To Lead Immunocore, Building On Partnership She Forged At MedImmune

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AstraZeneca PLC Vice President Bahija Jallal, the head of its **MedImmune LLC** subsidiary, is leaving her corporate home of more than 12 years to take on the role of CEO at **Immunocore Ltd.**, a clinical-stage firm focused on bispecific antibody candidates for cancer and other diseases – which has been partnered with AstraZeneca since 2014.

The Jan. 4 announcement came the same day as another AstraZeneca exec, Executive VP Mark Mallon, departed to take the reins at **Ironwood Pharmaceuticals Inc.**

Jallal joined MedImmune from **Chiron** in 2006, a year ahead of the biotech's acquisition by AstraZeneca, and is credited with expanding the company's pipeline from about 40 candidates to 130 during her tenure, including the PD-L1 inhibitor *Imfinzi* (durvalumab), approved in the US to treat urothelial carcinoma and unresectable, stage 3 non-small cell lung cancer (NSCLC). *(Also see "Bahija Jallal: MedImmune's Modern Innovator" - Scrip, 14 Dec, 2015.)* Although the $15.6bn acquisition of MedImmune once was viewed as something of a bust for AstraZeneca, its R&D engine since has propelled the pharma into a leadership position in immuno-oncology.

Not much is known yet about why Jallal is leaving AstraZeneca/MedImmune for a privately held, clinical-stage biotech, but upon being named the Healthcare Businesswomen's Association's Woman of the Year in 2017, she cited greater gender balance in biopharmaceutical industry upper management positions as a goal. *(Also see "MedImmune's Bahija Jallal On Changing The Diversity Narrative" - Scrip, 15 May, 2017.)* "We are data-driven people and the data is still telling us that we are not where we should be when it comes to gender parity in this industry," Jallal said upon receiving the award.

And while Emma Walmsley took on the top post at **GlaxoSmithKline PLC** in 2017, as an internal advancement, she remains the first and only female CEO of a big pharma. The more likely pattern for women in the executive tiers at large pharma companies is to leave for a higher position at a smaller firm, where they can

build their leadership skills and perhaps have more flexibility. *(Also see "J.P. Morgan Executive Roundtable, Part 1: How To Help Women Move Into The Biopharma C-Suite" - Scrip, 24 Jan, 2017.)*

Former **Novartis AG** Oncology CEO Liz Barrett was named CEO on Jan. 3 for **UroGen Pharma Ltd.**, where she will lead the effort toward approval of lead candidate UGN-101 in low-grade, upper tract urothelial cancer. *(Also see "Oncology Leader Liz Barrett Joins UroGen As CEO As It Heads Towards Commercial Stage" - Scrip, 3 Jan, 2019.)*

ALREADY A FAMILIAR FACE, JALLAL STEPS IN AT CRUCIAL JUNCTURE

Jallal will not be unfamiliar upon arriving at Immunocore's Oxfordshire, UK, headquarters. The private firm inked a partnership with MedImmune in 2014 to study the combination of Immunocore's lead asset, IMCgp100, in Phase II for uveal melanoma with AstraZeneca's Imfinzi and experimental CTLA-4 inhibitor tremelimumab. Jallal praised Immunocore's *ImmTAC* (immune mobilizing monoclonal T-cell receptors Against Cancer) technology at the time of the deal, saying it would help advance MedImmune's IO ambitions. *(Also see "AZ third big pharma to strike deal for Immunocore's T-Cell technology" - Scrip, 8 Jan, 2014.)*

Jallal called Immunocore "the leader in cutting-edge TCR bispecifics" in an announcement about her selection to lead the company and said the biotech has succeeding in translating breakthrough science into promising clinical candidates.

On the strength of the ImmTAC platform – which creates bispecific biologic candidates that combine high-affinity T-cell receptors with anti-CD3 antibody fragments that activate the immune system to recognize and kill cancer cells – Immunocore also has signed potentially lucrative collaborations with GSK, **Genentech Inc.** and **Eli Lilly & Co.***(Also see "Interview: Immunocore Gets Ready To Go To Market" - Scrip, 20 Aug, 2018.)* The first candidate partnered with GSK – IMCnyeso – entered clinical development in August in solid tumors including NSCLC, melanoma, bladder cancer and synovial sarcoma.

Immunocore is considered a "biotech unicorn," because it is a clinical-stage firm valued at greater than $1bn. It raised a then-record $320m Series A round in 2015 and seems in no hurry to go public, thanks to investors with long-term vision and several potentially remunerative alliances.

Jallal will succeed interim CEO Andrew Hotchkiss and join Immunocore at a time when it is moving IMCgp100, which combines a TCR specific to a peptide sequence from the cancer antigen gp100 with a single-chain anti-CD3 antibody fragment, towards potential registration in uveal melanoma.

Immunocore signed onto the European Medicines Agency's adaptive pathways initiative in 2015 in the hopes of obtaining a conditional approval of the drug in a cancer setting with poor prognosis and no standard of care. The company has said it hopes to file IMCgp100 for approval as soon as 2020. A US regulatory strategy is still being worked out.

Jallal will be busy on other fronts at Immunocore as well; the biotech expanded its 2013 partnership with Genentech on Nov. 19 to evaluate the safety and efficacy of the preclinical ImmTAC IMC-C103C both as monotherapy and in combination with the marketed PD-L1 inhibitor *Tecentriq* (atezolizumab). *(Also see "Immunocore Expands IO Pact With Genentech To Target MAGE-A Antigens " - Scrip, 19 Nov, 2018.)*

And in an agreement that may broaden its scope beyond cancer, Immunocore has a $40m investment from the Bill and Melinda Gates Foundation to back its preclinical work in HIV and tuberculosis.

MALLON TAKES GI THERAPY EXPERTISE TO IRONWOOD

In a same-day announcement, it was reported that Mallon will leave AstraZeneca after a 24-year tenure to become the incoming CEO of Ironwood, as the gastrointestinal therapy specialist prepares to split into two companies during the first half of 2019. *(Also see "Ironwood Being Split In Two: Is Move To Thwart Activist Investor Sarissa? " - Scrip, 1 May, 2018.)* He will start out as a senior executive advisor to outgoing CEO Peter Hecht, who will move into a new role as CEO of the soluble guanylate cyclase (sGC) therapeutic company Cyclerion Therapeutics when the corporate split is finalized.

Most recently, Mallon was executive VP of global product and portfolio strategy at AstraZeneca. In the past, he headed up US gastrointestinal business for the pharma, with purview over products such as *Prilosec* (omeprazole) and *Nexium* (esomeprazole).

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Patients And Payers, Not Products, Are Kings In The New Pharma Model

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The biopharmaceutical industry, if it is to thrive in a world where technology providers are increasingly leaving their footprints on consumer expectation, must realize that the pharmaceutical product is no longer king, that the crown has now passed to the patient, and the payer.

A new report by Datamonitor Healthcare, *New Pharma Models for a New Healthcare Era*, suggests that, in a world where technology providers are more frequently providing valuable add-ons for patients, drugs now offer only part of a solution to a patient's needs, and that the "end goal is outcomes, not sales". And while pharma companies have been slowly reaching that realization, investors still need to be convinced by the C-Suite.

There are a good handful of examples of pharma and biotech embracing new technology partners to fit this new expectation. **Novo Nordisk AS**, **Amgen Inc.** and

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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.

Click here for the entire pipeline with added commentary: http://bit.ly/2mx4jY3

PIPELINE WATCH, 21 DECEMBER 2018 – 3 JANUARY 2019

Event	Lead Company	Drug	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Mallinckrodt plc	H.P. Acthar Gel (corticotrophin)	Focal Segmental Glomerulosclerosis	In Transplantation; Jan. 1, 2019	0	0
Phase III Updated Results	Sesen Bio, Inc.	Vicinium	Bladder Cancer	VISTA; Positive Data	0	35
Phase III Top-Line Results	Verrica Pharmaceuticals, Inc.	VP-102 (0.7% cantharidin)	Molluscum Contagiosum	CAMP-1,2; Positive Results	0	62
Phase II/III Top-Line Results	Viela Bio	inebilizumab	Neuromyelitis Optica Spectrum Disorder	N-Momentum; Achieved Endpoints	0	59
Phase III Trial Suspension	Merck KGaA/Pfizer	Bavencio (avelumab)	Ovarian Cancer, Previously Untreated	JAVELIN Ovarian 100; Would Not Show Superiority on PFS	-4	25
Phase III Trial Initiation	Retrophin, Inc.	sparsentan	IgA Nephropathy (Berger's Disease)	PROTECT; Global Double Blind Study	46	62
Phase III Trial Initiation	Allena Pharmaceuticals, Inc.	reloxaliase	Hyperoxaluria, Enteric	URRIROX-2; Second Pivotal Study	0	62
Phase III Trial Initiation	Mallinckrodt plc/NeuroproteXeon	Xenex (xenon gas)	Post Cardiac Arrest Syndrome	XePOHCAS; In 1,400 Patients	34	47
Phase III Trial Initiation	Innovent Biologics/Eli Lilly	Tyvyt (sintilimab)	Esophageal Cancer	ORIENT-15; In China, With paclitaxel, cisplatin	0	0
Phase III Trial Initiation	Novartis AG	Ilaris (canakinumab)	Non-Small Cell Lung Cancer	CANOPY-2; Alone Or With docetaxel	0	35
Phase III Trial Initiation	Flexion Therapeutics, Inc.	Zilretta (triamcinolone acetonide) Extended Release Inj	Osteoarthritis, Hip	In 440 Patients	0	100
Phase III Trial Initiation	PledPharma AB/Solasia	PledOx (calmangafodipir)	Chemotherapy Induced Peripheral Neuropathy	POLAR-A; In Japan	0	53
Phase III Trial Initiation	JHL Biotech/Sanofi	rituximab, biosimilar (JHL1101)	Diffuse Large B-Cell Lymphoma	In China	0	0

Source: Biomedtracker | Informa, 2019

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Sanofi are just three companies willing to embrace would-be competitors. Time will tell if these new partners bring with them a deeper foothold in the market, be it geographical or therapeutic.

WHY DO WE NEED NEW PHARMA MODELS?

The traditional pharmaceutical model is teetering on shifting sands. Technology entrants, the same ones that have created new dialogues, and as such expectations, with customers online are now bringing a new competitive challenge to the pharmaceutical world. "The end product is no longer a pharmaceutical; it is a health outcome. The customer is no longer a physician; they are a payer, provider or patient. R&D tools are no longer just biological and chemical; they are also digital," report author Melanie Senior summarizes.

Tech firms are bringing apps, wearables, ingestible sensors and digital pharmaceuticals to patients. And while they have not yet produced any proprietary drugs yet, they are certainly creating efficient and

In the new healthcare system the patient is king, and holds all the cards

effective ways to build relationships with, and gather data from, patients and healthcare providers.

FDA Commissioner Scott Gottlieb said in September 2018 that the industry was experiencing a "reimagining of healthcare delivery". For its part, the FDA has just approved an Apple watch with a built in built-in electrocardiogram measuring device. Together with the app, it detects irregular heart rhythms, helping millions of people to diagnose health issues much earlier. While this is progress for an empowered patient, the pharmaceutical industry will lose revenue due to patients addressing healthcare issue earlier, and therefore less expensively than before.

With companies such as Google and Apple bringing the kind of game-changing competition to pharma that it brought to the high street, the report suggests that in the digital healthcare future, some pharma firms may be relegated to suppliers rather than innovators.

Partnerships between pharma and would-be rivals embrace creative approaches to issues such as pricing, but with no single type of partner or partnership dominating, there are multiple examples of collaborations that could lead to pharma's stronger relationships with patients and payers. What is clear in this opaque collection of deals, however, is that pharma is investing into areas that are not directly correlated to financial return. For example, Amgen's value-based partnership team is signing deals that are not all explicitly about selling more drugs.

Published online 31 December 2018

To read the whole story go to:
https://bit.ly/2QytKm5

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Marie Kosco Vilbois	AC Immune SA	Chief Scientific Officer	Novimmune	Chief Scientific Officer	3-Jan-19
Daniel Schneiderman	Biophytis	Chief Financial Officer	MetaStat Inc	Vice President, Finance and Corporate Secretary	17-Dec-18
Darlene Horton	Coherus BioSciences	Chief Medical and Regulatory Affairs Officer	TulangCo Inc	Chief Executive Officer	1-Jan-19
Philip M. Brown	Dermavant Sciences	Chief Medical Officer	Lexicon Pharmaceuticals	Senior Vice President, Clinical Development	2-Jan-19
Ivan Plavec	ImaginAb Inc	Chief Business Officer and Independent Non-Executive Director		Consultant	2-Jan-19
Thomas A. Shea	ImmusanT Inc	Chief Financial Officer	Albireo Pharma	Chief Financial Officer	3-Jan-19
Lyn Baranowski	Roivant Sciences Inc	Chief Operating Officer, Altavant Sciences	Melinta Therapeutics	Senior Vice President, Corporate Development and Strategy	2-Jan-19

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

Source: Medtrack | Informa, 2019

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