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Janssen's Zytiga Shines At ASCO But Competition Looms

LUCIE ELLIS lucie.ellis@informa.com

Janssen Pharmaceutical (a **Johnson & Johnson** company) reported positive Phase III data for *Zytiga* (abiraterone acetate) in hormone-naïve metastatic prostate cancer, providing a non-chemotherapy option for patients that is expected to change the standard of care. However, the market impact of Janssen's triple therapy could be limited due to a busy late-stage drug pipeline that includes novel mechanisms of action.

Data from the Phase III LATITUDE study, the subject of the June 4 plenary session at the American Society of Clinical Oncology's annual meeting in Chicago, showed that Zytiga plus prednisone in combination with androgen deprivation therapy (ADT) reduced the risk of death by 38%. The combination has already been filed in Europe where a label extension decision for the drug is expected later this year.

Median overall survival (OS) for patients treated with Zytiga plus prednisone in combination with ADT has not been reached yet, but median OS for the placebo plus ADT arm of the Phase III trial was 34.7 months. Median radiographic progression free survival (rPFS) was 33 months in the Zytiga arm compared with 14.8 months with placebo plus ADT.

ASCO chief medical officer Richard Schilsky said the results were likely to change the standard of care for hormone-naïve patients with metastatic disease "overnight."

ADT plus docetaxel chemotherapy has been the standard of care since 2015 for metastatic prostate cancer patients, but due to the exclusion of chemotherapy in the Zytiga triple therapy regimen, its use is expected to be welcomed by doctors. ASCO panelist Sumanta Kumar Pal said Janssen's combination is an "important alternative to chemotherapy" that will "shake up treatment regimens."

Lead study author Karim Fizazi said, "The benefit from early use of abiraterone we saw in this study is at least comparable to the benefit from docetaxel chemotherapy, which was observed in prior clinical trials, but abiraterone is much easier to tolerate, with many patients reporting no side effects at all."

Still, doctors at ASCO raised concerns about the costs associated with Janssen's triplet therapy compared to ADT plus docetaxel chemotherapy. ZS Associates analyst Sharon Karlsberg noted that the tradeoff for removing chemotherapy from a treatment regimen in favor of Zytiga is 4.3 months of inexpensive chemotherapy versus three years of branded Zytiga.

Zytiga's main patent expired in the US in 2016, but according to IMSHealth the drug is protected by a combination patent family that could delay generic entry until August 2027, potentially protecting Zytiga on a global scale.

PIPELINE PROWESS

Despite LATITUDE's positive results, its relevance in high-risk metastatic hormone-naïve prostate cancer might be questioned soon as newer options move through the pipeline.

Progress in prostate cancer had been slow until recent years, but the space has changed dramatically in just a few years following the introduction of Zytiga and

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from the editor

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Oncology accounts for around a third of the pharma industry's pipeline, so ASCO is for many the most important medical conference in the calendar. Scrip was out in force in Chicago – see the first six pages of this issue for analysis of major data presentations as well as an interview with Bristol-Myers Squibb's head of early oncology development; there will be more next week and online.

The uncertainty inherent in drug development means many programs in the crowded and fast-moving cancer drug space will eventually fail to make the cut. Still, you've got to be in it to win it, and with oncology enjoying higher trial success rates than other major therapeutic areas (see p20), there will also be many winners.

The same is true of the Scrip Awards. With new categories added for 2017 you can now take up to 16 shots on goal, and you still have one more week to get your entries in. Our annual event recognizes individuals and teams from companies small and large around the world. It's free to enter, judged by an independent panel of global industry experts, and winners are announced at our ceremony in London on November 29.

You can submit your entry at www.scripawards.com, where you will also find a guide to entering and a podcast offering tips on avoiding common errors and enhancing your chances of winning, along with information about new awards categories. Good luck – and see you at the London Hilton in November.

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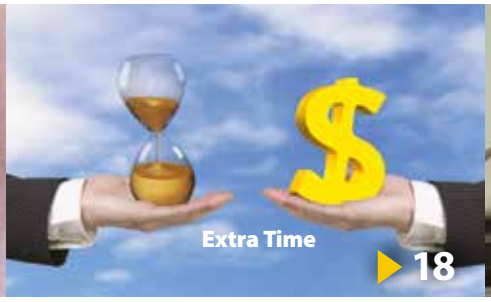

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Ticking Off Investors, Akari CEO Exits Amid Coversin Trial Controversy
http://bit.ly/2qSA6QQ
Akari, which is looking to ticks to provide a new PNH drug, has seen its CEO resign and investors launch class action suits amid controversy over a Phase II clinical trial for paroxysmal nocturnal hemoglobinuria.

Cancer Treatment Complexity And Costs Increased Substantially Over Two Decades
http://bit.ly/2rvYnyZ
A QuintilesIMS Institute study of global oncology trends illustrates the benefits and downside of therapeutic advances – more therapeutic options with better targeting, but also significantly higher complexity in setting a therapeutic course, which is complicated by rising costs.

Reducing The Pain Of Skin R&D: Almirall And Leo Collaborate
http://bit.ly/2sbsuNo
Two European companies with portfolios in skin conditions have taken their first collaborative steps, researching non-painful skin sampling.

Chronic Lymphocytic Leukemia Market To Grow Despite Biosimilar Wave
http://bit.ly/2rO0ezN
The chronic lymphocytic leukemia market is set to increase in size over the next decade despite an anticipated influx of biosimilars, new research by Datamonitor Healthcare finds.

BTG's Louise Makin On Joining IO Agents And Localized Intervention
http://bit.ly/2qWbefs
BTG's CEO says combining novel immuno-oncology therapies with image-guided, minimally invasive therapies could deliver treatments where needed while lowering overall treatment costs.

Finance Watch: Bicycle Spins Toward Clinic With $52m Round; Stock Spikes Spur Offerings
http://bit.ly/2qSeBzV
Bicycle closes a $52m Series B to test its bicyclic peptides in humans, while Decipera, Harpoon and TP Therapeutics also top a $263m list of recent venture capital deals. In public company financings, Alnylam, Aerie and others price offerings to raise cash while their stocks are on the rise.

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AZ's OlympiAD Trial Kick-Starts PARP In Breast Cancer

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AstraZeneca PLC's *Lynparza* (olaparib) has set an important, if modest, precedent for PARP inhibitors with positive progression-free survival results from the Phase III OlympiAD study opening the door for a new indication for use in women with BRCA-mutated breast cancer.

The company released results from the study of about 300 women with metastatic HER2-negative (hormone receptor-positive or triple negative) breast cancer on June 4 during a plenary session at the American Society of Clinical Oncology (ASCO) annual meeting in Chicago. Based on OlympiAD, AstraZeneca plans to seek US FDA approval for the drug in breast cancer during the second half of this year and file for approval in the EU in 2018.

OlympiAD tested Lynparza as a monotherapy against physician's choice of three kinds of chemotherapy (eribulin, capecitabine or vinorelbine) in patients who previously had up to two prior lines of chemotherapy. Platinum-based chemotherapy (e.g. carboplatin and cisplatin) is standard in this patient population and participants could have had this treatment, but were not allowed into OlympiAD if they had progressed.

Lynparza demonstrated a significant progression-free survival benefit compared to chemotherapy alone with a median of seven months versus 4.2 months for chemotherapy, a 42% reduction in risk. An overall survival benefit has not been demonstrated yet. Furthermore, the objective response rate was 60% for Lynparza versus 29% for chemotherapy. The ASCO data release followed a top-line disclosure in February of a positive outcome in the study.

The first PARP inhibitor on the market, Lynparza (olaparib) is currently approved for fourth-line ovarian cancer with germline BRCA mutations and in this indication AstraZeneca is looking to move earlier into the maintenance setting and for tumors regardless of mutation status. Lynparza had sales of $218m in 2016 and a breast cancer indication has the potential to improve its financial outlook.

While only about 8% of patients with HER2-negative breast cancer have BRCA mutations, given the prevalence of breast cancer that translates into tens of thousands of women who could be candidates for treatment, commented Erica Mayer, assistant professor of medicine at Harvard Medical School, during an interview at the conference.

Lynparza dosing for ovarian cancer is 400 mg twice daily in capsule form, but it was given at 300 mg twice daily by tablet for the OlympiAD breast cancer study. AstraZeneca explains that this new dosing regimen is more convenient for patients, because far fewer pills need to be taken, but notes that the formulations are equivalent in terms of efficacy. The new tablet formulation will be priced at parity with the capsules, execs explained during a June 4 media briefing at the ASCO meeting.

"It is not a commercial advantage – it's more a practicality advantage for the patients," said Klaus Edvardsen, head of oncology, global medicines development at AstraZeneca. In addition to demonstrating better efficacy, Lynparza was also better tolerated, with a lower rate of grade 3 or higher adverse events (36.6% versus 50.5%) and fewer discontinuations due to toxicity (4.9% versus 7.7%).

Lynparza also is being evaluated in Phase III trials testing the drug in various breast cancer settings (*see table p5*). Daniel Hayes, president of ASCO and a breast cancer specialist at the University of Michigan Health System Comprehensive Cancer Center, commented during an ASCO press briefing that the results represented a "major step forward in breast cancer."

Plenary discussant Allison Kurian concluded that the data were "practice-changing."

Kurian noted the long development history of PARP inhibitors in breast cancer and a major misstep in breast cancer in particular that shows why Lynparza's efficacy now is a step forward for the field.

Sanofi's iniparib looked promising as an add-on to platinum-based chemotherapy in a Phase II trial of triple negative breast cancer released in 2011, but went on to fail progression-free survival and overall survival endpoints in Phase III, putting a damper on development for PARP inhibitors in breast cancer.

OlympiAD represents the "end of the beginning of a long road for the development of PARP inhibitors for breast cancer therapy," said Kurian, director of the Women's Clinical Cancer Genetics Program at Stanford University Medical Center in Palo Alto, Calif.

Asked to explain the iniparib failure in contrast with the olaparib success, OlympiAD lead investigator Mark Robson, medical oncologist at **Memorial Sloan Kettering Cancer Center**, said during the press briefing that iniparib structurally is not actually a PARP inhibitor, as originally thought.

QUESTIONS ABOUT TRIAL DESIGN

The OlympiAD trial was positive and ground-breaking, but drew scrutiny. ASCO acknowledged in a press release about the data: "More research is needed to determine how well olaparib works in cancers that worsen despite platinum-based chemotherapy, a standard regimen not included in this study, and whether platinum-based chemotherapy would be useful after cancers worsen despite olaparib."

Platinum-based chemotherapy is very active in BRCA-mutated breast cancer, but has a similar mechanism of action on DNA repair as PARP inhibitors. Consequently, PARP inhibitors are less effective in women who have progressed on prior platinum-based chemotherapy and many trials for drugs with this mechanism of action are not evaluating the therapies in this population, Jennifer Keating Litton, associate professor in breast oncology at the **MD Anderson Cancer Center**, commented in an interview at the meeting.

Litton also noted, however, that there are advantages in terms of less toxicity for PARP inhibitors over platinum-based chemotherapy and PARP inhibitors also have more convenient oral administration, rather than intravenous delivery.

Harvard's Mayer noted that platinum-based chemotherapy has a variety of unpleasant side effects, including weakening of the immune system, nausea and fatigue.

"Our goals of care in treating metastatic breast cancer are not only prolonging survival, but also maintaining and preserving quality of life, and a therapy that can better allow us to help patients feel as good as possible while also prolonging survival is a wonderful step forward," Mayer commented.

There were non-significant improvements in performance for olaparib in patients who were triple-negative and naïve to platinum-based chemotherapy, Kurian noted during her presentation. It's "cer-

Phase III Studies Of PARP Inhibitors In Breast Cancer

STUDY/DESCRIPTION	PATIENT NUMBER/COMPLETION DATE
AstraZeneca's Lynparza	
OlympiAD: Efficacy and safety of olaparib monotherapy vs. physicians' choice chemotherapy in HER2-negative metastatic breast cancer with germline BRCA1/2 mutations. Prior platinum-based chemo allowed, as long as no breast cancer progression occurred on treatment or if given in adjuvant/neoadjuvant setting at least 12 months from last dose to study entry elapsed.	N=302. Primary completion date: December 2016
OlympiA: Olaparib vs. placebo as adjuvant treatment in patients with germline BRCA1/2 mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.	N=1,500. Primary completion: March 2020
PARTNER: Neoadjuvant trial for patients with triple negative breast cancer and/or gBRCA breast cancer, safety and efficacy (improvement in pathological complete response at surgery) with platinum-based chemotherapy (paclitaxel and carboplatin) vs. paclitaxel/carboplatin alone. Sponsored by Cambridge University Hospitals with AstraZeneca.	N=527. Primary completion date: January 2022.
Tesaro's Zejula	
BRAVO: Zejula vs. physician's choice of four therapies in HER2-negative gBRCA-positive breast cancer. Patients with platinum-resistant cancer excluded.	N=306. Primary completion: September 2017
AbbVie Inc.'s Veliparib	
NCT02163694: Placebo-controlled trial of carboplatin/paclitaxel with or without veliparib in HER2-negative metastatic or locally advanced unresectable BRCA-associated breast cancer.	N=500. Primary completion: May 2018
NCT02032277A: Veliparib with carboplatin vs. addition of carboplatin to standard chemotherapy vs. standard chemotherapy in early-stage triple negative breast cancer.	N=624. Primary completion: March 2016
Pfizer's Talazoparib	
EMBRACA: Talazoparib vs. protocol-specific physician's choice of chemotherapy in patients with advanced and/or metastatic gBRCA-positive breast cancer who have received zero to three prior chemotherapy regimens for advanced disease.	N=431. Primary completion: June 2017

Source: ClinicalTrials.gov

tainly plausible" that the drug would work better in these patients, but the study was underpowered to draw a conclusion on that question.

"We do need further study of subgroups to understand who really benefits from this therapy," Kurian said.

Biomedtracker analysts said in a note from the ASCO meeting that subgroup analyses showing lower efficacy in estrogen receptor-positive (ER+) and/or hormone receptor-positive (PR+) patients, or in patients who received prior platinum chemotherapy, "suggest that the trial success may have been driven primarily by triple negative breast cancer patients. Thus, regulators may want further study to better define the appropriate treatment population," the analysts commented.

AstraZeneca's Edvardsen cautioned during the company's media briefing that OlympiAD was not designed to assess performance in subgroups and advised caution in interpreting these results.

Among other questions about the trial's design, Kurian wondered why the comparator in OlympiAD was not anthracycline and taxane chemotherapy as opposed to the three types used in the study – eribulin, vinorelbine and capecitabine.

Edvardsen explained that many high-risk patients, such as the ones included in the study, would typically have already been treated with anthracycline and taxanes in the adjuvant setting and that the choices in the trial represented the standard of care.

"I disagree with that comment that the comparator in that setting should have been anthracycline and taxane," Edvardsen said.

The PFS benefit of only about three months compared to chemotherapy also raised some questions, as it was viewed as a short-lived, rather modest benefit. Researchers are exploring use of PARP inhibitors in earlier stage settings, including combination regimens, to improve efficacy and durability. "Combinations will be even more powerful," Litton said.

LYNPARZA LEADS PARPS IN BREAST CANCER

In addition to Lynparza, two other PARP inhibitors are FDA-approved and could play a role in breast cancer – **Clovis Oncology Inc.**'s *Rubraca* (rucaparib) and **Tesaro Inc.**'s *Zejula* (niraparib). All three are approved for ovarian cancer, but with differences in approved populations. Rubraca is cleared for third-line ovarian cancer with BRCA mutations and Zejula has the broadest labeling as a maintenance treatment in ovarian cancer regardless of mutation status.

Zejula and various investigational PARP inhibitors are in Phase III for breast cancer, and Rubraca is in Phase II. Clovis noted that several investigator-initiated and/or cooperative group studies are under way examining Rubraca in breast cancer, including a trial sponsored by **Roche** investigating the drug in combination with *Tecentriq* (atezolizumab).

Pfizer Inc. announced results from a Phase II study of its investigational PARP inhibitor talazoparib in heavily pretreated BRCA1/2 positive advanced breast cancer on June 3 at the ASCO meeting.

The company reported a 21% objective response rate in 49 patients who progressed after responding to platinum-based chemotherapy and a 37% ORR in a cohort of 35 patients who had progressed after at least three lines of non-platinum-based therapy. The treatment-related dropout rate was 4%. Pfizer is now testing the drug in the Phase III EMBRACA study.

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Loxo's Larotrectinib Requires Paradigm Change In Clinical Practice

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Having demonstrated a 76% response rate with deep and durable responses, **Loxo Oncology Inc.** revealed impressive pivotal data for larotrectinib, which seems poised for approval next year; the challenge now lies in awareness and adoption of testing that's required to identify the TRK fusion abnormality the drug targets.

"Testing is the key question," Loxo Chief Business Officer Jacob Van Naarden told *Scrip* June 3 in an interview at the American Society of Clinical Oncology meeting in Chicago, where the data were presented by lead investigator David Hyman of the Memorial Sloan Kettering Cancer Center.

"To really enjoy these benefits, we have to change the paradigm by which we test patients," Hyman said during a June 3 press briefing on the data, which will be submitted for US FDA approval later this year or early in 2018.

Larotrectinib is a targeted therapy that selectively inhibits the tropomyosin receptor kinase (TRK) fusion protein, but unlike traditional oncology programs that target mutations in a given tumor type, larotrectinib is not tied to the cancer location.

Loxo is aiming to have the first novel drug developed and approved for a tissue-agnostic claim, as well as the first with simultaneous approval in adults and children. **Merck & Co. Inc.**'s PD-1 inhibitor *Keytruda* recently became the first FDA approval for a molecularly defined cancer that does not specify tumor location. But the indication for microsatellite instability-high or mismatch repair deficient solid tumors was not the first approval for pembrolizumab and was based on retrospectively assessed data. *(Also see "Keytruda Approval Opens New Routes For Immuno-Oncology" - Scrip, 24 May, 2017.)*

Adoption of these histology-independent molecularly targeted therapies will be utterly dependent on testing, Van Naarden acknowledged. "Testing is the central remaining question around the program and around any rare tumor-agnostic new cancer drug, whether larotrectinib or Keytruda for MSI-H or the next five or 10 drugs that come along and look like this," he said.

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'To really enjoy these benefits, we have to change the paradigm by which we test patients'

These efforts are aided by the trend in recent years toward genetic testing in academic and community practices, facilitated by next-generation sequencing (NGS) and panels that run multiple tests at once.

TRK can be identified by standard lab-developed tests and as part of panels, which is how the clinical trials were enrolled. "Physicians were finding TRK fusion patients, not because they were looking for that, because they were looking for a whole lot of things all at once and the TRK fusion popped up. And that's fine, we love that," Van Naarden said. "Unfortunately, the problem with that approach today is that maybe one in 10 patients today gets access to a test like that."

Lack of standardization is also an issue, as is lack of insurance coverage for testing. But there are two NGS options under review at the FDA, **Foundation Medicine Inc.**'s *FoundationOne* and **Thermo Fisher Scientific Inc.**'s *Oncomine*, "and hopefully, in time, FDA approval and standardization leads to more consistent reimbursement, which then leads to more testing," Van Naarden said.

But Loxo also is partnering with **Roche**'s **Ventana Medical Systems Inc.** diagnostics business on a simple TRK immunohistochemistry test that it will submit for FDA approval as a companion diagnostic. "There's always going to be corners of the community that are going to like relying on these types of tests that are inexpensive and high throughput," Van Naarden said. "Our program is tumor-type agnostic – we're diagnostic-type agnostic. We just want more testing."

Along with testing, education and awareness are critical commercial issues for the company, Van Naarden said. That's why the company and investigators decided to present at ASCO this year – and they made it "in the nick of time" with the 55 patients that had been agreed with FDA as the pivotal dataset across three trials. "This is the biggest cancer meeting of the year," Van Naarden pointed out. "We may have an approved drug next year and the reality is that until this weekend most people had never heard of TRK and had never heard of larotrectinib. And at the end of the day, I think the drug data speak for themselves, but if you aren't looking and

Cancer types (% of trial population):

Appendix (2%); breast (2%); pancreatic (2%); infantile myofibromatosis (2%); inflammatory myofibroblastic kidney tumor (2%); peripheral nerve sheath tumor (4%); sarcoma, not otherwise specified (NOS 4%); myopericyloma (4%); cholangiocarcinoma (4%); spindle cell sarcoma (5%); GIST (5%); melanoma (7%); lung (7%); colon (7%); thyroid (9%); infantile fibrosarcoma (13%); salivary gland (22%)

don't have the awareness, you're never going to know about it."

Loxo has started hiring a commercial team and its strategy is "coming together," the exec said. "It's a very diagnostics-focused commercial plan. We're going to have to interface very tightly with oncology and pathology in the same room," which he noted was an important factor in successful clinical trial sites. "When they're integral to making the diagnosis, they have to have a seat at the table."

Patients in the clinical trial were identified with local testing; 15 different labs identified the patients. "This in a sense really represents the real-world identification of these patients," Hyman observed.

But without better testing, there's a certain amount of uncertainty about the patient population, Van Naarden admitted, adding: "Ultimately what's more important than those numbers is testing. It doesn't matter how many patients if you can't find them."

POPULATION UNKNOWN

The TRK fusion mutation occurs in dozens of cancer types across patients' lifespans. According to ASCO, the abnormality occurs in about 0.5%-1% of many common cancers, but in greater than 90% of certain rare cancers, such as salivary gland cancer, a form of juvenile breast cancer and infantile fibrosarcoma. "At this point it is hard to find a cancer type where TRK fusions have not been reported," Hyman told the press briefing.

There were 17 unique tumor types in the pivotal dataset, including common cancers as well as rare forms and pediatric cancers. The ages ranged from four months to 75 years, and patients had an average of two prior therapies.

Efficacy was seen regardless of tumor type and no one tumor type responded better than another. Of the 50 patients with confirmatory response data, there was a 76% response rate. The other five patients were too early to have their confirmatory scans, but Hyman said all five had at least a partial response and remain on study awaiting their confirmatory scans.

Twelve percent had complete responses, and most partial responses exceeded the criteria with deep tumor regression – two moved forward to curative surgery and had pathologic complete responses, Hyman reported. The median time of first response was 1.8 months, but Hyman explained that reflected the time the first scan was obtained. "In the clinic, patients report dramatic improvement of their symptoms within days of beginning therapy."

The responses have been durable, with 79% of responses ongoing 12 months after starting treatment. Of the responders, 93% remain on therapy or had surgery with curative intent.

"More than three out of every four patients responded to therapy. You'd be hard pressed to find a targeted therapy even within a single disease context that has results like this," Hyman said.

And, larotrectinib was also an "extremely well tolerated therapy," the investigator stated, with only 13% of patients requiring any dose modification and no patients discontinuing due to adverse events. The most common adverse events were fatigue (30%), dizziness (28%) and nausea (28%).

TISSUE-AGNOSTIC ADOPTION CHALLENGES

Even with "striking" and "very impressive" response data, and a likely approval smoothed by FDA's breakthrough therapy program, larotrectinib and other tissue-agnostic therapies will still face adoption challenges above and beyond biomarker testing.

"The real challenge moving ahead is for oncologists to determine whether larotrectinib would sit in existing treatment algorithms," Sumanta Kumar Pal, City of Hope, said in discussing the results. Screening and use right away makes sense in rare cancers where there's no established standard of care, but "in the case of other diseases such as colon cancer or prostate cancer, we really have to sit down and determine how larotrectinib sits against existing standards."

The same situation applies to Merck's Keytruda and other molecularly defined treatments, he added. "It will be important to develop guidelines around testing for these expanding indications." Van Naarden admitted that more experience and data will be needed to guide the use of larotrectinib in cancer types with a well-stocked armamentarium. He noted that major tumor types were probably under-represented in the clinical database, because clinicians wanted to see patients with lung or breast or colon cancers get treated with standard of care regimens first.

That's an issue that will take time to resolve, and will be influenced by how the FDA labeling is crafted. "We'll see what it allows," Van Naarden said, but he predicts it will be flexible and allow clinicians to make treatment decisions.

Fitting in among different standards of care in different cancer settings also makes pricing an even more complicated proposition. Van Naarden thinks the efficacy and safety profile builds a strong value proposition, and while it's still early, Loxo is starting to have those conversations with payers.

Loxo may not have a long lead on the market. **Ignyta Inc.**'s entrectinib has the same breakthrough designation from FDA for treatment of NTRK fusion-positive, locally advanced or metastatic solid tumors in adult and pediatric patients. *(Also see "Oncology: Tissue-Agnostic Indications Advance Under US FDA's Breakthrough Umbrella" - Pink Sheet, 25 May, 2017.)*

Resistance is also a concern, as with many targeted therapies, but Loxo has prepared for that and has been advancing a follow-on compound, LOXO-195, in parallel. The company predicted that acquired point mutations in the TRK fusions would prevent larotractinib from binding where it had been, but that the tumor would still be addicted to the same pathway and a new TRK inhibitor that binds differently would be effective. "The idea behind LOXO-195 is this sequential therapy extension of durable disease control," Van Naarden said, akin to EGFR inhibitors in lung cancer.

LOXO-195 is being studied in patients who progress on larotrectinib, and it worked in the first two patients that developed resistance. "Eventually patients will need it – we don't know when and hope it's a long time – but we want it to be there when they do," the exec said. It was a very deliberate effort, he noted, "and frankly we think this is how modern oncology drug development ought to happen."

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BMS's Early Oncology Head On Novel IO Approaches

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Tim Reilly, head of early oncology development at **Bristol-Myers Squibb Co.**, spoke to *Scrip* on the sidelines of the 2017 ASCO meeting about the company's emerging immunotherapy compounds, how BMS fares against its peers and what will be the next big disruption in the immuno-oncology field.

Reilly leads BMS's early asset development team for oncology, developing new molecules from identification through to final preclinical testing and then into the clinic for early human trials. "Essentially, we take these interesting, fun toys and make them potential drugs," Reilly said, adding that his team usually hands the assets off to the company's late-stage development team after clinical proof-of-concept studies.

Considering BMS's broad, early stage oncology pipeline, Reilly said he is particularly interested in bringing forward new biological mechanisms that explore options for patients with resistance to available immunotherapies. "We are exploring why some patients are resistant to existing immunotherapies and why patients that initially respond subsequently relapse. We are really interested in new mechanisms that get at those questions," he told *Scrip*.

Reilly highlighted two examples of novel IO programs with new mechanisms of action that BMS is testing, indoleamine 2,3-dioxygenase (IDO) inhibitors and molecules targeting lymphocyte-activation gene 3 (LAG3).

IDO is an enzyme that produces a natural immunosuppressive metabolite that has been shown to increase when added to PD-1/PD-L1 therapy. "It's a really interesting mechanism and we believe in the potential utility of this as we currently have two discreet shots in this space," Reilly said.

In collaboration with **Incyte Corp.**, BMS is developing epacadostat, which Reilly noted has shown itself to be "a really worthwhile molecule to be combined with PD-1 pathway modulators." Epacadostat is currently being tested in combination with BMS's PD-1 inhibitor *Opdivo* (nivolumab). Efficacy data in patients with squamous cell carcinoma of the head and neck (SCCHN), melanoma, ovarian cancer, and colorectal cancer, as well as overall safety data were presented at the American Society of Clinical Oncology annual meeting in Chicago, June 2-6. *(Also see "IDO Updates At ASCO: Incyte's Combos With Merck And Bristol Take Center Stage" - Scrip, 18 May, 2017.)*

Epacadostat is also being paired with **Merck & Co. Inc.**'s PD-1 inhibitor, and Opdivo's closest rival, *Keytruda* (pembrolizumab). Epacadostat's most advanced study is the Phase III ECHO-301 study in combination with Keytruda in melanoma patients. Bristol has also moved into Phase III trials.

However, BMS also has its own IDO1 inhibitor in development that it believes has the potential to be best in class. "It is still early days but, while epacadostat has shown the power of the mechanism, we think our molecule, which we are bringing forward aggressively, has shown that it could be useful to bring the most to bear for IDO as a new mechanism for patients," Reilly said.

Reilly also highlighted LAG3 as an interesting new mechanism that BMS is pursuing. "This mechanism is really intriguing because it's sort of a secondary checkpoint pathway, I like to characterize it as an escape hatch," he said, noting that the company is also keen to explore LAG3 molecules in combination with Opdivo.

BMS hopes that its anti-LAG3 monoclonal antibody, BMS-986016, may help to overcome anti-PD-1 resistance in patients. During ASCO the company presented proof of concept data for anti-LAG3 plus Opdivo in heavily pretreated melanoma patients who had failed on prior PD-1 treatment.

In the ongoing expansion study presented for the objective response rate (ORR) was 12.5% in evaluable patients (n=48). Patients with LAG3 expression in at least 1% (n=25) of tumor-associated immune cells within the tumor margin had a nearly three-fold improvement in ORR compared to patients with less than 1% LAG3 expression (n=14; 20% and 7.1%, respectively). The early study also revealed that the safety profile of the LAG3 combination was similar to Opdivo monotherapy.

BMS now plans to expand the refractory melanoma cohort to include up to 150 patients and explore LAG3 expression as a biomarker.

COMBINATION CHAOS

Reilly said it "can be daunting" managing BMS' early oncology pipeline because there are so many IO opportunities to explore, particularly the breadth of combinations trials that are planned or ongoing. However, he said the IO space is still "rich for the picking."

"We have the opportunity to deeply interrogate the biology that exists in a patient's tumor at a particular time, to be able to hand-select the mechanisms that seem to be perturbed or over-expressed (or in some incidences under-expressed) and then to target those mechanisms to bring to life the immune system, the natural ability to detect and fight cancer," Reilly said.

He noted that the company's approach, with multiple early stage combination trials and a varied pipeline of investigational mechanisms, could seem "haphazard" but he said the group is in the midst of learning and re-learning about novel IO opportunities.

"I like to think that every patient tells us something new," Reilly noted. He said that as well as learning more about which patients are most likely to response to certain treatments, when a patient doesn't respond it is revealing too. "We learn from those patients with a lack of response or lack of sustained durable response what else can we throw in the mix."

Reilly said that one thing that was pervasive even before the onset of immunotherapy is that multi-drug combinations are necessary to be able to adapt and see maximum response in oncology. He compared cancer therapy to developments in HIV. "The HIV world is a great example and very similar in some respects [to cancer], in that you have to tackle multiple pathways for the maximal sustained benefit," he said.

"When we don't see what we want to see, which for all intents and purposes is a cure, how do we learn from that and what else do we layer on?" Reilly questioned. "Double therapies, triple therapies, quadruple therapies, at the same time or over time, that's part of what I'm so excited about in terms of the depth of our portfolio. We have lots of tools in the toolbox to fix the leaky sink," he said.

BMS's oncology pipeline includes 19 ongoing Phase I studies, 13 Phase II trials and 24 Phase III trials (22 of which include Opdivo).

PEER REVIEW

Compared to its IO peers, Reilly flagged BMS's history and background in IO as factors that should not be understated when assessing its clinical strategy. Reilly also highlighted that BMS has a "deep investment in translational science," an area he said the company had been criticized for in the past – but he maintained the firm "has been at the forefront of a lot of these developments, like PD-1." And, he added, while some drug developers follow very focused approaches with their discovery portfolios, "from a 10,000-foot view BMS wants to make treatments available for as many patients as possible."

Reilly noted that IO development is a "marathon" but that speed is still an important factor. "It's a marathon, but the time it takes to get from one block to another is still important," he said. "We are laser focused on taking on all learnings from our pipeline trials and applying these to the next opportunities, to the next mechanisms, or the next regulatory approval opportunity. We are taking learnings in discrete settings, confirming them and expanding them for patients."

Finally, Reilly highlighted biomarkers and imaging, combined, as the next big disruption to rock the IO research and development space.

"The concept of using patient biological markers is going to be the next big challenge. The question is how do we bring all these genomic factors together in real time," he said.

"Imaging technologies to detect in real time what is happening with a tumor is something we are investing in. We will get to a point where, at any moment in time, we can get a good understanding of what is going on with a patient and that patient's tumor without the need for biopsies. Then we will be able to reassess in real time and see what's working and what is not working, and maybe try a few other spices from the rack," Reilly said.

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CONTINUED FROM COVER

Pfizer Inc.'s *Xtandi* (enzalutamide). Now novel agents with newer mechanisms of action are creeping up the pipeline, such as Janssen's own apalutamide (ARN-509/JNJ-927), an androgen receptor antagonist that is in Phase III and expected to filed in the US later this year for pre-metastatic prostate cancer. Apalutamide also is being tested in several other Phase III studies for different prostate cancer populations.

Janssen also has *Zejula* (niraparib), a Poly ADP-Ribose Polymerase (PARP) inhibitor, in Phase II for prostate cancer under a partnership with **Tesaro Inc.** The companies plan to file this product with regulators before 2019.

Meanwhile, **AB Science**'s masitinib is one of a variety of Phase III compounds in development for prostate cancer. This drug, in combination with docetaxel, is being positioned by AB Science as a first-line treatment for metastatic castrate resistant prostate cancer, among other populations.

ZYTIGA BACKBONE

Craig Tendler, VP of late-stage development and global medical affairs for oncology, hematology and supportive care at Janssen, told *Scrip* that the company will continue to use Zytiga as its foundation therapy in prostate cancer as it progresses its prostate cancer pipeline. Zytiga, which is one of the biggest-selling brands in the prostate cancer market, is already approved as a treatment for patients with metastatic prostate cancer that worsened despite ADT use. The drug is a small molecule oral irreversible inhibitor of the 17 alpha-hydroxylase enzyme that catalyzes the hydroxylation of intermediates involved in testosterone synthesis

"LATITUDE validates the hypothesis that if you have active agents in the advanced prostate cancer setting and you bring them into earlier stage disease the impact can be even greater," Tendler said. He added that the Phase III data in hormone-naïve patients allows Janssen to "use Zytiga as a backbone for other investigational agents that we're trying to bring forward, such as our PARP inhibitor with Tesaro."

"We want to identify patients with the right biomarkers that will see the greatest benefit from combination treatments," he said.

Phase III Products In Development For Prostate Cancer

DRUG NAME	LEAD COMPANY	TARGET
Darolutamide	Bayer AG	Androgen Receptors
DCVAC/PCa	Sotio AS	Stem Cell
DCVax-Prostate	Northwest Biotherapeutics Inc.	Immune System
FP-001	Foresee Pharmaceuticals Co. Ltd.	Gonadotropin-Releasing Hormone Receptor
Galeterone	Novus Biologicals LLC	Androgen Receptors
Gene Mediated Cytotoxic Immunotherapy (GMCI)	Advantagene Inc.	Thymidine Kinase
JNJ-56021927	Johnson & Johnson	Androgen Receptors
Lutrate	GP Pharm, S.A.	Unknown
Masitinib	AB Science	Fibroblast Growth Factor Receptor (FGFR)
Prostvac	Bavarian Nordic AS	Immune system
Relugolix	Myovant Sciences Ltd.	Gonadotropin-Releasing Hormone Receptor
Rubraca	Clovis Oncology Inc.	Poly ADP-Ribose Polymerase (PARP)
Tecentriq	Roche	Programmed death ligands (PD-L1 and PD-L2)

Source: Biomedtracker

STAMPEDE

A second trial, the Phase II/III pilot study known as STAMPEDE, was also presented at ASCO with positive results promoting the earlier use of Zytiga in patients with prostate cancer starting long-term ADT.

The positive results in this study were reflected on by LATITUDE panelists, who noted that the data add extra weight to the suggestion that Zytiga plus ADT should be made available to hormone-naïve prostate cancer patients.

The three-year survival rate in STAMPEDE was 76% with standard therapy alone versus 83% with standard therapy plus Zytiga.

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Novartis' CAR-T CTL019 Back On The Blockbuster Hit List

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Novartis AG reaffirmed its excitement about the commercial potential of the chimeric antigen receptor T cell (CAR-T) therapy CTL019 during a meet-the-management event at the company's research campus in Cambridge, Mass. on May 31.

CEO Joseph Jimenez pointed to the pricing potential in CAR-T as one of the reasons for optimism. Novartis has a lot riding on the success of CAR-T because the company invested early and aggressively in the field while missing out entirely on the first wave of checkpoint inhibitors, the other big area of immuno-oncology.

CTL019 was included on the company's list of potential blockbusters in development during the presentation, after being left off last year, which raised some doubts about the company's commitment to the CAR-T space. The two other oncology drugs included on the list of 12 potential blockbusters are *Kisqali* (ribociclib), the CDK4/6 inhibitor recently approved for breast cancer, and crizanlizumab (SEG101) for sickle cell pain crisis.

The intrigue grew last year, when Novartis announced a month after leaving its lead CAR-T agent off the blockbuster list that it would close its cell and gene therapy unit – the business responsible for developing CAR-Ts at Novartis – and integrate the research into the broader oncology R&D organization.

Though Novartis dismissed the speculation at the time and reaffirmed its commitment to CAR-T, there was some resetting underway. CTL019 (tisagenlecleucel-T) is one of two CAR-T therapies pending at FDA, with action anticipated in September. Novartis is seeking approval for relapsed and refractory pediatric and young adult patients with B-cell acute lymphoblastic leukemia (ALL). The other therapy is **Kite Pharma Inc.**'s axicabtagene ciloleucel, pending for aggressive non-Hodgkin lymphoma.

HIGH VALUE COULD JUSTIFY HIGH PRICE

While the class has shown impressive efficacy in some patients, the drugs also present unique safety issues. The commercial viability of the drugs, which are engineered specifically for each patient, also are uncertain, because of what is expected to be an expensive manufacturing process and the individualized, targeted nature of treatment.

But Novartis' enthusiasm for the prospects of CAR-T has grown in the last six months, Jimenez said.

"You're seeing a couple of things happen. You're seeing the data mature, which is very positive, that was a function of the early work that we did, but you're also seeing better and faster decision making on CAR-T that is leading us to believe…that this could be a potential new platform that is a very large and profitable business for the company," he said.

As another reason for optimism, the chief executive pointed to a mock assessment by the UK's National Health Service earlier this year on CAR-T therapies for ALL that indicated a cost of almost $700,000 would be cost-effective for the therapies. Drugs like CTL019 could offer value to the healthcare system even if they are priced at a premium, he said.

"You look at the huge cost of stem cell transplants and the cost of these patients on the system and you suddenly say this could be a very good business," Jimenez said. He said Novartis isn't thinking of pricing CTL019 that high, but is evaluating a premium price that would offer a strong return for the risky investment while returning value to the system.

"That's why we're excited," he said.

Novartis Institutes for Biomedical Research President James Bradner agreed, calling ALL "the tip of the iceberg" for the drug platform. Novartis expects to file CTL019 for diffuse large B-cell lymphoma in the second half of the year, a substantially larger indication than pediatric/young adult ALL. The company is also working on a next-generation CAR-T, CTL119, and will present some data on the drug at the American Society of Clinical Oncology meeting.

"What we've been missing is the commercial model that really supports that this is a sustainable business with the complexity of its manufacturing, with the uncertainty of its pricing," he said. "We now have a very strong business case."

CORRECTING MISSTEPS AND OVER-INVESTMENT

Jimenez also talked about the company's decision to integrate cell therapy R&D into the oncology research and why that improved the R&D program. After in-licensing the technology through a high-profile agreement with the University of Pennsylvania in 2012, the company felt to compete with biotechs like Kite and **Juno Therapeutics Inc.** it should establish a nimble stand-alone unit to focus on CAR-T. *(Also see "A New Industry-Academic Model: Novartis And Penn Make A Splash In Cancer Immunotherapy" - In Vivo, 26 Nov, 2012.)*

"Unfortunately, what happened is we, in great big pharma tradition, we overbuilt that business unit," Jimenez said. "When I say overbuilt, the burn rate was quite high."

"We were making the investment, but it started to crowd out some other projects, and so we made the decision about one and a half years ago to disband the unit, not just because of cost, but also because we weren't getting the full functional brunt of Novartis against CAR-T."

By bringing the research into the broader oncology R&D group, the company was able to break down some walls, he said. "We saw an exponential increase in the speed with which we were able to do things, so it was almost the opposite of what we thought was going to happen through the creation of that internal biotech," he added.

Investors have chided Novartis for missing out on the first-wave of PD-1/L1 inhibitors, while companies like **Merck & Co. Inc.**, **Bristol-Myers Squibb Co.**, **Roche**, **Pfizer Inc.** and **AstraZeneca PLC** have all launched new drugs in the category. Novartis has since added a PD-1 inhibitor to the pipeline and is accelerating development of combinations. The company has 18 immuno-oncology assets in clinical development, including 22 combination trials that will be in the clinic by the end of the year.

"My strong opinion is that Novartis is a world leader in immuno-oncology, and the CAR-T is the first of what will be many very important medicines," Bradner said.

Global Head of Immuno-Oncology Dale Granoff also pointed to the potential opportunity to combine CAR-T drugs with other therapies, for example, in chronic lymphoblastic leukemia (CLL) with a small molecule BTK inhibitor.

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AstraZeneca's 13 Outcomes-Based Contracts Show 'Proactive' Engagement On New Models

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AstraZeneca PLC has signed two new outcomes-based reimbursement contracts with Harvard Pilgrim Health Care for the blood thinner *Brilinta* (ticagrelor) and the diabetes drug *Bydureon* (exenatide extended release), bringing the total number of the company's value-based reimbursement contracts to 13.

The double-digit number represents a significant amount of contracts in what is an exploratory area for the industry, as pharma manufacturers and insurers attempt better align the cost of medicines to value.

The latest two contracts, announced May 30, are part of an initiative at AstraZeneca to be a leader in innovative reimbursement models, VP-Market Access Rick Suarez said in an interview.

"We keep proactively engaging our major national [pharmacy benefit managers] and many regional PBMs to really challenge them on how we can demonstrate the value of the products AstraZeneca brings to the market," Suarez said. "I think it just reflects the value of our medicines and also our commitment at AstraZeneca to really be a leader and a differentiated pharma company as it pertains to this type of work."

The company's 13 contracts span three therapeutic areas, oncology, respiratory disease and cardiovascular/metabolic.

"Agreements like this with Harvard Pilgrim are the perfect example of making sure we are putting patients first," Suarez said. "Let's tackle the types of disease states that are the most costly and the most endemic in the US."

That's one of the reasons why Brilinta and Bydureon are two strong candidates to serve as the basis of an outcomes-based contract, he said. Another reason these drugs have been selected is technical, because taking them can lead to a clearly defined measurable outcome to help tie reimbursement to value.

"Those medicines in my opinion are prime to demonstrate the impact AstraZeneca can have in cardiovascular disease and cardiovascular disease associated with diabetes," Suarez said.

Defining an appropriate outcome to measure, often within a relatively narrow timeline, can be one of the challenges when it comes to developing these types of contracts, despite significant interest among manufacturers and payers.

Cardiovascular disease has emerged as one of the first categories to be targeted, with several deals in place for drugs like **Novartis AG**'s heart failure medication *Entresto* (sacubitril/valsartan) and **Amgen Inc.**'s PCSK9 blocker *Repatha* (evolocumab). AstraZeneca previously had an outcomes-based contract with **Cigna Corp.** for its cholesterol drug *Crestor* (rosuvastatin) that involved using pharmacy and medical claims to assess beneficiaries' risk for atherosclerotic cardiovascular disease and giving those beneficiaries at highest risk more unrestricted access to the drug.

In the case of Brilinta, under the agreement with Harvard Pilgrim, the outcome that will be measured is reduction in hospitalizations for repeat acute coronary events versus patients on another oral antiplatelet therapy, clopidogrel. The Bydureon contract focuses on HbA1c as an outcome measure, and the ability of patients who adhere to Bydureon to get to a predetermined HbA1c goal.

If either medicine fails to meet the agreed-upon outcome criteria in patients, AstraZeneca will pay a steeper rebate.

AstraZeneca has several other outcomes-based reimbursement contracts in place for Brilinta, but the deal with Harvard Pilgrim represents the first such arrangement for Bydureon. The company is working on similar deals for Bydureon as well as for another diabetes drug, the SGLT-2 inhibitor *Farxiga* (dapagliflozin).

Harvard Pilgrim will collect the data and provide blinded patient-specific and median patient results to AstraZenca, as well as information on adherence.

"It's very important for us to understand that each and every patient were adherent to our medicines and where they got from an HbA1c perspective, and then we have different options we put into the market in how we contract with our payers in terms of their eligibility to have additional rebates if the product works," Suarez said. "Each arrangement is a little different."

Both of the Harvard Pilgrim contracts span three years, but there is an opportunity for AstraZeneca and the insurer to check in annually to evaluate progress.

WITH EXPERIENCE, LESSONS LEARNED

"What's really important about outcomes-based agreements is they are dynamic. They are not stagnant and that is something I've very proud of for AstraZeneca," Suarez said. "We know we have to morph as we glean insights from these innovative contracts and [the agreements] afford us the opportunity that possibly in the middle of the year we need to make some tweaks and changes."

This deal with Harvard Pilgrim is linked entirely to rebates and does not include any kind of formulary advantage or priority access, as is sometimes the case with outcomes-based reimbursement contracts. For example, under Amgen's outcomes-based contract with Harvard Pilgrim for Repatha, the insurer agreed to limit some access restrictions to the PCSK9 inhibitor, while Amgen agreed to pay a full refund if treatment did not live up to the expectation of reducing heart attack and strokes in patients.

The market access group at AstraZeneca keeps outcomes-based reimbursement work separate from the traditional market access group, according to Suarez. In some instances, an outcomes-based contract can provide a foot in the door for a drug that might not have a preferred formulary position.

AstraZeneca has also experimented with offering a full refund if a medicine does not work as promised in one example, for the lung cancer drug *Iressa* (gefitinib). In an arrangement with **Express Scripts Holding Co.**, AstraZeneca agreed to refund the cost of the drug if it was discontinued before the third refill for any reason, including patient non-response. Having signed so many outcomes-based reimbursement contracts over the past few years, Suarez said AstraZeneca has learned a few lessons about the challenges.

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Janssen Enriches Crohn's Portfolio In Protagonist Deal

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Johnson & Johnson's latest investment in Crohn's disease, via a partnership between its subsidiary **Janssen Biotech Inc.** and **Protagonist Therapeutics Inc.**, is a collaboration that could give the big pharma something it doesn't have for the inflammatory bowel disease: an oral drug.

Janssen committed $50m up front and up to $940m in milestone fees plus double-digit royalties for worldwide rights to Protagonist's oral peptide therapeutic PTG-200, which targets Interleukin 23 (IL-23), in all indications – including Crohn's disease and ulcerative colitis. The IL-23-focused mechanism of action is highly familiar to J&J, after its IL-12 and IL-23 inhibitor *Stelara* (ustekinumab) won US FDA approval in September 2016 for Crohn's disease.

The company's large and growing immunology portfolio also includes the TNF inhibitor *Remicade* (infliximab), which is approved for Crohn's disease and several other inflammatory diseases, as well as guselkumab, a biologic targeting IL-23 that's under FDA review for psoriasis, but in preclinical development for Crohn's.

For Protagonist, the deal with Janssen gives the company the resources it needs to fund its development programs for at least two more years, while keeping most of its capital focused on lead drug candidate PTG-100, an alpha-4, beta-7 integrin inhibitor that is being studied in a Phase IIb clinical trial to treat ulcerative colitis. The deal also means that PTG-200 will move into the clinic this year with a partner that's very familiar with the drug's mechanism of action and initial indication of Crohn's disease.

LOT OF INTEREST

Protagonist President and CEO Dinesh Patel noted in an interview that the company had many suitors interested in its drug discovery platform and its two oral peptides for inflammatory bowel disease (IBD).

"We have a platform with two distinct assets, two oral peptides for IBD – an area that's dominated by injectable drugs – so there was always some interest," Patel said, but he noted that Protagonist decided some time ago to keep PTG-100 for itself and find a partner for PTG-200. Janssen recently emerged as the best collaborator for the latter drug candidate. "In Janssen, we found a perfect partner for multiple reasons," Patel told *Scrip*, including the company's leading position in IBD and its experience with the IL-23 pathway in Crohn's disease via Stelara. "They have a strong interest in developing an oral targeted therapy for IBD, because that is the direction of the market."

Janssen also has been a long-term investor in Protagonist with Johnson & Johnson Development Corp. (JJDC) as the lead venture capital investor in the company's $18m Series B round in 2013. JJDC also participated in Protagonist's $40m Series C round in 2015. *(Also see "Protagonist raises $40m to test oral peptides in IBD" - Scrip, 16 Jul, 2015.)* The biopharmaceutical firm raised a total of $67m in VC cash before its initial public offering in 2016.

With the Janssen partnership in place, Protagonist has several milestones coming in the next year and a half with PTG-200 set to enter the clinic in the second half of 2017 and begin Phase II in 2018. The company also will complete an interim analysis of the Phase IIb trial for PTG-100 in ulcerative colitis during the second half of this year to determine which doses are most effective for continued clinical testing; top-line results from the completed trial are expected in the second half of 2018.

A third candidate, the injectable hepcidin mimetic PTG-300 for iron overload disorder in beta-thalassemia and other diseases, recently was moved into Phase I with results expected later this year.

Protagonist said in a filing with the US Securities and Exchange Commission (SEC) on May 30 that with Janssen's financial commitments for the company it has enough money to pursue current and planned development programs through mid-2019. Protagonist had $77.2m in cash as of the end of the first quarter of this year.

"The PTG-200 licensing deal reduces the need for future financings and increases the probability of clinical and regulatory success in Crohn's and ulcerative colitis," BMO Capital Markets analyst Ian Somaiya wrote in a May 30 report. "Janssen is an ideal partner, given the commercial success of Stelara (anti-IL-23 antibody, 2016 sales ~$3.2bn) and the company's commitment to IBD."

PTG-200 BRINGS MILESTONES

Protagonist is fully responsible for the Phase I clinical trial testing PTG-200 in healthy volunteers, while Janssen will fund 80% of the Phase II trial and 100% of Phase III studies. After the $50m upfront fee under the companies' agreement, Janssen will pay Protagonist $125m if it maintains its license for PTG-200 and stays involved in development at the end of the Phase IIa portion of the Phase II study, and $200m if Janssen remains committed to the collaboration at the end of Phase IIb.

The deal includes another $615m in regulatory and sales milestone fees plus royalties ranging from 10% of global sales to the mid-teens. Protagonist maintained a right to provide up to 30% of the commercial effort in the US, utilizing what the company hopes will be an established commercial presence in the IBD market, since PTG-100 could be on the market by the time PTG-200 is approved.

PTG-100 could be the third alpha-4, beta-7 integrin inhibitor on the market for ulcerative colitis behind **Takeda Pharmaceutical Co. Ltd.**'s *Entyvio* (vedolizumab) and **Roche**'s Phase III candidate etrolizumab, but it would be the first oral drug against that target. *(Also see "Takeda Enlists Real World Evidence To Boost Marketed Entyvio" - Scrip, 9 May, 2017.)* Entyvio also is approved for Crohn's disease and etrolizumab also is in Phase III for that indication.

Stelara is the only product targeting IL-23 that's approved for Crohn's disease, but **AstraZeneca PLC**'s IL-23 inhibitor brazikumab, **Eli Lilly & Co.**'s LY3074828 and risankizumab developed by **AbbVie Inc.** and **Boehringer Ingelheim GMBH** are in Phase II for Crohn's. IL-23 inhibitors in development for ulcerative colitis – a possible future indication for PTG-200 – include Stelara in Phase III and the Lilly and AbbVie/Boehringer candidates in Phase II, according to the Biomedtracker database. *(Also see "J&J Plots Five-Year Pharma Growth Plan Around Mega-Brands And Launches" - Scrip, 17 May, 2017.)*

All of the new market entrants for Crohn's disease and ulcerative colitis have TNF inhibitors, like J&J's mega-blockbuster Remicade, as their biggest competitors.

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Teva Clinches Third Place In CGRP Race With A Phase III Migraine Win

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Teva Pharmaceutical Industries Ltd.'s fremanezumab is the third calcitonin gene-related peptide (CGRP) inhibitor to successfully complete a Phase III clinical trial, but two candidates from competing big pharma companies are poised to take first and second place in the race to approval for a blockbuster migraine prevention therapy. That means Teva must exploit a key differentiating feature of its antibody for a potential win in the commercial market.

The company reported on May 31 that both doses of fremanezumab tested in the Phase III HALO CM trial provided about a two-day reduction versus placebo in the number of headache days experienced each month by chronic migraine patients – individuals who have 15 headaches or more per month. The results were not substantially different from Phase III data for **Amgen Inc.**'s and **Novartis AG**'s erenumab and **Eli Lilly & Co.**'s galcanezumab, but the quarterly subcutaneous injection of fremanezumab – a dosing frequency that hasn't been tested for the two most advanced CGRP inhibitors – performed about as well as the monthly dose.

"The single most important data point in [the] Teva press release this a.m. is that their quarterly arm of [the] Phase III CGRP chronic migraine trial worked," Evercore ISI analyst Umer Raffat wrote in a May 31 note to investors. "This is very important from [a] competitive positioning perspective, because Amgen and Lilly never developed their [antibodies] for quarterly dosing."

Teva will report top-line results from a second Phase III trial known as HALO EM in the treatment of episodic migraines (14 or fewer headaches per month) within the next few weeks, the company said, and it plans to submit a biologic license application (BLA) to the US FDA later this year. More detailed HALO CM results will be presented at future scientific conferences, including the American Headache Society meeting, held from June 8 to 11 in Boston.

Alder BioPharmaceuticals Inc. also has a quarterly dose of its CGRP inhibitor eptinezumab (ALD403) in late-stage development, but that antibody is administered intravenously and Phase III results aren't expected until late in the fourth quarter for episodic migraine and in the first half of 2018 for chronic migraine. Alder has a subcutaneous CGRP inhibitor in early development.

FREMANEZUMAB EFFICACY COMPARABLE AT BOTH DOSES

HALO CM enrolled 1,130 patients, including individuals taking prophylactic medicines, who were treated with 675 mg of fremanezumab followed by two monthly 225 mg injections, a single 675 mg dose of fremanezumab followed by placebo for two months, or three monthly doses of placebo. The primary endpoint was the mean change from baseline at the end of a 12-week treatment period in the monthly average number of headache days of at least moderate severity.

The number of headache days per month fell by 4.6 days in the monthly dosing group, 4.3 days in the quarterly dosing group and 2.5 days in the placebo arm ($p<0.0001$ for both fremanezumab arms). Both the monthly and quarterly doses also showed significant improvements on all secondary endpoints, including response rate, onset of efficacy, efficacy as monotherapy and disability ($p<0.0001$ across 12 of 13 hierarchical comparisons, $p=0.0004$ for the 13th). The most common adverse event was injection site pain, with similar rates in the fremanezumab and placebo groups.

"While episodic migraine is the larger market opportunity for which Teva will report data in a few weeks (~90% of migraine patients are episodic, <14 headache days per month), we believe there is a good chance today's result should translate into positive data in the episodic study given Teva's positive Phase II study in episodic migraine and the fact chronic migraine patients typically are more severe patients," Oppenheimer analyst Derek Archila wrote on May 31.

"We believe the news is a nice positive for the company given the recent management departures and turmoil within its generic business and view it as a much needed win from Teva's branded pipeline," Archila continued. "As its branded business faces the near-term threat of a Copaxone 40 mg generic, we think its emerging migraine franchise coupled with Austedo for Huntington's disease chorea and potentially tardive dyskinesia (PDUFA on August 30, 2017) will help to partially offset the lost Copaxone profits over time." *(Also see "Teva To Divest Women's Health, Some Oncology As CEO Search Proceeds" - Scrip, 11 May, 2017.)*

While Teva deals with multiple leadership and pipeline problems, fremanezumab could help that company on the latter issue if the product can achieve analyst consensus estimates of $1.7bn in annual sales, the Oppenheimer analyst noted. However, the fairly similar clinical trials results reported to date for CGRP inhibitors do not answer the question of whether Teva or any other company will be able to grab the dominant market share.

Archila conceded that "cross trial comparisons are always a challenge, and at this point we only have the top-line data" for fremanezumab in chronic migraine, but the placebo-adjusted reduction in monthly migraine days was about two days for Teva's candidate and for Lilly's galcanezumab – "the only other program with Phase III data in CM."

Amgen and Novartis reported Phase III results from two episodic migraine studies last year and Amgen anticipates a BLA submission for both chronic and episodic migraines during the second quarter of this year, using earlier Phase IIb results to support approval for the chronic indication. *(Also see "Amgen Plans 2017 Filings After Second Phase III CGRP Inhibitor Success" - Scrip, 16 Nov, 2016.)*

Lilly released top-line results from three Phase III trials for galcanezumab in episodic and chronic migraines on May 12 and said it would seek FDA approval in the second half of this year. *(Also see "Lilly Breathing Down Amgen/Novartis's Necks With Three Phase III Migraine Wins" - Scrip, 12 May, 2017.)*

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Novo Nordisk Targets 'Obesity Disease Market' Despite Commercial Doubts

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The inter-relationships shared by diabetes and obesity are compelling **Novo Nordisk AS** to trial novel new drugs for treating people who are abnormally overweight even though commercial prospects for such therapies are unclear.

"In the past, medicines for treating obesity have not had such attractive safety profiles and that has dampened the development of the market," Novo Nordisk CEO Lars Fruergaard Jørgensen said.

"So, our approach is to develop more biologically based medicines where it's based on human biology, understanding the function and then developing them, sometimes in combination with other drugs so we get dual agonists, one molecule that combines two mechanisms into one, and getting to significant weight-lowering properties than what we see today, and in a safe manner," he told *Scrip*.

He said part of the group's motivation comes from necessity.

"When you're a [insulin] market leader, there's a limit to how much more market share you can grow, so we are looking at what role we can play in helping to build infrastructure and understanding of the importance of treating obesity," said the CEO, a Dane who took over the top role at the group in January.

He noted in an interview that many physicians lack training in how to treat obesity, which was only categorized in recent years in the US as being a disease, not just a life-style related condition.

"Many didn't get training in medical school on obesity because it was simply not seen as a disease [back then] so we are looking at what roles we can play and what level of investment we should do in terms of this market in the long term," he said.

"We believe the commercial attraction is there [in obesity] and the development of the commercial opportunity is a combination of both developing the market, training physicians to make them understand that there is now the opportunity to treat obesity, and in parallel with that, develop a compound that has a very attractive profile, and combining that we believe will create a significant opportunity for Novo Nordisk."

Asked whether there will ever be a collaboration to fight obesity through alliances that involve diabetes fighters like Novo Nordisk and consumer food groups, Jørgensen replied: "That's an important issue. We are looking also as part of our strategy at what types of collaborations we could gradually enter because we believe we can do a lot. But just like diabetes is to a large degree a societal and life-style-related disease, so is obesity and we would also like to work on prevention. So, we are looking to partner with different types of stakeholders … also potentially with the food industry. We're not there yet but we're thinking about it and in discussions on what types of partnerships we could establish."

Novo Nordisk, founded 90 years ago, already markets a version of its type 2 diabetes drug *Victoza* (liraglutide) as a treatment for chronic weight management, under the brand name *Saxenda*.

Asked by *Scrip* how liraglutide works in obesity, Novo Nordisk's chief science officer Mads Krogsgaard Thomsen replied: "It is a biological medicine that specifically tells the brain to enhance satiety and reduce the appetite, so it has this beneficial action where people will stop eating quite a bit in advance of what they normally would have done because many people with obesity feel that they don't have the normal break, it's as if they have the hunger sensation continuously and for longer than they feel they would like to and we actually see GLP-1 receptors in the part of the brain called the hypothalamus that enhances satiety and reduces appetite."

Novo Nordisk is also trialing its investigational GLP-1 agonist semaglutide in obesity, with Phase II data expected this summer.

Novo Nordisk CEO Lars Fruergaard Jørgensen

'The dream we have is creating a once-weekly, almost like a bariatric surgery injection, so instead of cutting out the stomach like you do in bariatric surgery, we will be able to take a kind of combination therapy, once a week by a simple convenient injection with a hidden needle and that would do the same job as massive surgery'

Asked whether Novo Nordisk would subsequently need to carry out a Phase III study of around 3,500 people for at least a year to gain approval for semaglutide in obesity, Thomsen replied: "That would be the bare minimum – but we are considering going way beyond. We are considering whether to take semaglutide and do a cardiovascular outcome trial with it in obese people who don't have diabetes, so that individuals who suffer from obesity and maybe had a prior event, cardiovascular event, then we can then go in and prove that if you take standard treatment versus semaglutide, that we can actually prevent the next event or even death from occurring and that would be like a landmark study, paving the way for an understanding within society that obesity is a serious, chronic condition or disease that should be treated adequately."

That Phase III semaglutide program and the cardiovascular the study would begin sometime in 2018, he said, adding: "and then it's about accruing a certain amount of cardiovascular events, and depending on how fast you recruit and how high the event rate is you can complete that in a matter of years; how many exactly I cannot say yet, it's too early."

The CSO, who is in his 26th year at the Danish group, said it has some early stage assets which look promising for study in the treatment of obesity.

"Some of them stimulate energy expenditure, so you boost metabolism, like the glucagon analog, some of them deal a 1-2-3 [knockout] blow to the body or to the obesity condition, such as the triple agonist, by working both on GLP-1, glucagon and GIP [gastric inhibitory polypeptide] receptors.

"Some of them work in the old part of the brain that we had since we were reptiles called the brain stem, and that will then change eating behavior at the most basic level, called the amylin analog, so we have, let's say, such a variety of single-acting, double-acting or triple-acting agents in the clinic that I would hesitate to choose one from the other - but they should in most cases be complementary to semaglutide so that we can add maybe up to 15% of weight loss with semaglutide, and then to that you can add whatever the others can contribute.

"So the dream we have is creating a once-weekly, almost like a bariatric surgery injection, so instead of cutting out the stomach like you do in bariatric surgery, we will be able to take a kind of combination therapy, once a week by a simple convenient injection with a hidden needle and that would do the same job as massive surgery, that's the dream we have and I think we may be on the road to ultimately proving that we can get that," Thomsen concluded.

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Pfizer's Trumenba Approval To Ignite EU Marketing Battle In Meningitis B

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Pfizer Inc.'s meningitis B vaccine *Trumenba* has been cleared by the European Commission for marketing in the EU, setting up a potential marketing battle with **GlaxoSmithKline PLC**'s well established vaccine, *Bexsero*, and completing Pfizer's portfolio of vaccines to prevent infections by the top-five meningococcal serogroups (A, B, C, W and Y).

Both two- and three-dose schedules are included in Trumenba's EU labeling.

Another Pfizer meningitis vaccine, *Nimenrix* (for A, C, W and Y serogroups) has been available in the EU since 2012, and was granted an expanded indication, use in infants as early as six weeks of age in December 2016; there is no upper age limit. *(Also see "Pipeline Watch: Phase III Success With Emicizumab, Plecanatide And Sotagliflozin" - Scrip, 28 Dec, 2016.)*

In announcing the EU approval of Trumenba, Pfizer also addressed current concerns about some vaccines being in short supply, noting that Trumenba has a 36-month shelf life. "We are also focused on consistent, reliable supply for all the vaccines we manufacture," said Susan Silbermann, president and general manager of Pfizer Vaccines.

The company said it was continuing to invest significantly in manufacturing processes and facilities to ensure a sufficient supply of Trumenba in Europe, where the majority of meningococcal disease cases (60%) in adolescents and young adults are caused by serogroup B. But the US big pharma is likely to find GSK's Bexsero an entrenched competitor: its meningitis vaccines Bexsero and *Menveo* had combined sales of almost £600m in 2016, up by 96% on 2015 sales, and contributed significantly to the company's vaccine business, which grew by 14% in 2016 to £4.6bn. *(Also see "From Witty To Walmsley – The Priorities For GSK's New CEO" - Scrip, 4 Apr, 2017.)*

The indication that Trumenba has received in the EU is the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in adolescents and young adults aged 10 years or older, a slightly different age range from that approved for the GSK vaccine – Bexsero is indicated for use in individuals from 2 months of age and older.

Pfizer points out that adolescents and young adults are a critical demographic for vaccination against meningitis B because of social and environmental factors, including close-quartered living and sharing behaviors. "Meningitis B disease is unpredictable, can progress rapidly and is associated with a significant risk of death and long-term disability," the company said.

The age range recommended for vaccination in the US, where Trumenba has been available since 2014, is narrower than in Europe, encompassing individuals aged from 10 through to 25 years of age

According to Pfizer, the reported incidence of invasive meningococcal diseases varies by region, ranging from less than 0.5 cases per 100,000 in North America and just under one case per 100,000 in Europe, and up to 10-1,000 cases per 100,000 during epidemic years in Africa. On a worldwide basis, six serogroups (A, B, C, W-135, X and Y) account for 90% of all invasive meningococcal disease.

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Gilead's Bictegravir Demonstrates Broad Non-Inferiority, But Will That Suffice?

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Gilead Sciences Inc. revealed success demonstrating non-inferiority in four Phase III trials testing its investigational integrase inhibitor bictegravir head-to-head against other HIV therapy regimens, but it remains unclear whether these findings will give the virology specialist an edge against **ViiV Healthcare**'s *Tivicay* (dolutegravir).

The Foster City, Calif.-based firm reported May 30 that bictegravir met the standard for non-inferiority in studies using comparator regimens of ViiV's *Triumeq* (dolutegravir/lamivudine/abacavir) and of dolutegravir with Gilead's emtricitabine and tenofovir alafenamide (Gilead's *Descovy*) in treatment-naïve HIV-infected patients, as well as in switch studies with treatment-experienced patients receiving either dolutegravir plus existing antiviral agents or an approved protease inhibitor/nucleoside polymerase inhibitor combination. However, Gilead did not provide full data other than that the primary endpoints had been achieved, saying it planned to present full data later this year at conferences.

Datamonitor Healthcare lead analyst Michael Haydock said the announcement might be met with relief by **GlaxoSmithKline PLC** – the primary stakeholder in ViiV, along with **Pfizer Inc.** and **Shionogi & Co. Ltd.** – because the bictegravir regimens did not demonstrate superiority to dolutegravir. In Phase II data presented this past February at the Conference on Retroviruses and Opportunistic Infections, Gilead showed that bictegravir monotherapy achieved a numerical advantage compared to dolutegravir monotherapy over 24 and 48 weeks, but the studies were not sufficiently powered for a claim of superiority.

Gilead said it planned to file the three-drug regimen of bictegravir, emtricitabine and tenofovir alafenamide (BIC/F/TAF) for US approval before the end of the second quarter. Tenofovir alafenamide (TAF), a successor to tenofovir disoproxil fumarate (TDF), has anchored successful Gilead follow-on regimens (*Genvoya, Odefsey* and Descovy) for HIV that have yielded increased sales for the franchise.

"The big danger to ViiV was that BIC/F/TAF would show superiority to the dolutegravir-based regimens," Haydock told *Scrip*. "[Triumeq and Tivicay] have been the main driving force of ViiV's HIV revenues and have helped it take market share from Gilead, so Gilead is developing BIC/F/TAF to try and recapture that market share."

In a May 30 note on the data announcement, William Blair & Co. analyst John Sonnier pointed out that Gilead held roughly a 90% market share for treatment-naïve HIV patients from 2011 to 2013, but that share dropped to 77% in 2014, the year Tivicay got approved, and 74% in 2015. Gilead rebounded a bit to 76% by the end of 2016 on the strength of the TAF-containing launches.

The investigational triple regimen that would eliminate the need for the pharmacokinetic boosting agent cobicistat, if approved, could give Gilead further help against ViiV, he said. "We believe the potential approval of [the] un-boosted triple regimen could also help the company more effectively fend off competition," Sonnier wrote.

Elvitegravir, included in existing Gilead HIV fixed-dose combo therapies Genvoya (elvitegravir/cobicistat/emtricitabine/TAF) and predecessor *Stribild* (elvitegravir/cobicistat/emtricitabine/TDF), requires a boosting agent. Even without superiority to dolutegravir, Haydock said Gilead should benefit because BIC/F/TAF would offer fewer drug/drug interaction complications than Stribild and Genvoya.

"Boosting agents are considered inconvenient (especially as the population ages) because they increase drug-drug interactions," Haydock explained. "So, if people are taking other medications (like elderly people tend to) then it means that doctors may have to consider dose reductions/swapping other medications."

The same day that Gilead unveiled the non-inferiority findings for bictegravir, Merck announced that FDA had approved a new formulation of its integrase inhibitor raltegravir, *Isentress HD*, that allows for once-daily dosing: a 1,200 mg dose comprised of two 600 mg tablets for combination therapy in treatment-naïve HIV patients or those who've achieved viral suppression with a regimen including *Isentress* dosed at 400 mg twice-daily.

GILEAD AHEAD OF SCHEDULING ON RECOUPING SHARE?

In contrast to Haydock's view that the Gilead data might be good news for ViiV, Leerink Partners analyst Geoffrey Porges issued a note May 30 saying that the initial results are in line with expectations and put Gilead on track to begin recouping additional market share more quickly than Leerink had anticipated.

Porges predicted that Gilead will use one of the two priority review vouchers it currently has on hand to ensure a six-month FDA review of BIC/F/TAF, which would mean the product could reach market before the end of the year if the company achieves its goal of filing a new drug application (NDA) this quarter.

While the bictegravir-containing regimen did not achieve superiority, he noted that it also apparently presents no liabilities for adverse events, safety signals or metabolic or hematologic safety concerns.

The full dataset, however, will need to be seen to be certain that BIC/F/TAF is "completely benign," Porges conceded, but Gilead said the regimen was well tolerated with no patient discontinuations in the four studies due to renal events. No patients randomized to bictegravir or dolutegravir-containing regimens developed treatment-emergent resistance either, the company stated.

Leerink is more bullish on BIC/F/TAF than industry consensus, Porges said, anticipating only $344m in 2018 sales based on prior expectations of a third quarter 2018 launch (compared to consensus projections of $865m that year), but it projects sales increasing to $5.9bn in 2022, compared to consensus estimates of $3.4bn. Leerink's peak sales estimate is $10.6bn, compared to consensus of $5.6bn. They forecast bictegravir will provide 20% of Gilead's total revenue and 30% of their global HIV revenue by 2022, "and this grows to 45% of Gilead's global HIV revenue at peak," Porges added.

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Sun Chief Sees 'New Normal' For First-To-File ANDAs

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India's top-ranked drug firm, **Sun Pharmaceutical Industries Ltd.**, reported a decline in earnings for the fourth quarter ended March 2017 dented, in part, by the challenging generic pricing environment in the US and management commentary indicates a tough fiscal 2018 ahead.

Fourth quarter sales declined by 8% to INR68.25bn ($1.05bn) compared with the same period last year, with US finished dosage sales at $381m (-34%). Net profits slid 14% to INR12.23bn.

"Sales decline in the quarter is a reflection of the pricing pressure that the generic industry is facing in the US. Also, our revenues in the previous comparable quarter were boosted due to the imatinib exclusivity in the US, which ended in July 2016," Sun's managing director Dilip Shanghvi said at a post results investor call. *(Also see "Sun Faces Price Pressures In US On Generic Gleevec" - Scrip, 18 Aug, 2016.)*

Approval delays from Sun's Halol site in India, still to receive a compliance all-clear from the US FDA, also bridled growth. Sun, being the first-to-file an ANDA for generic *Gleevec* (imatinib mesylate) with a para IV certification, was earlier eligible for 180 days' marketing exclusivity. Sun had earlier de-risked its Gleevec generic, originally filed from the Halol site, with a filing from the Cranbury site in the US.

To analysts' queries on the stage of the US generic pricing downcycle and how long the company anticipates continuing pricing pain, Shanghvi said that it's a "product-to-product situation".

"There are many products where I don't see a significant delta for price cuts. There may be a few products where there can be - depending on competitive intensity - some kind of price correction."

He, though, referred to a new normal around generics eligible for 180 days' marketing exclusivity in the US.

"For many things, there is a new normal which is getting established – like the value of the first-to-file (FTF) product, even if during exclusivity, is likely to go down. And that's a new normal," Sun's boss said.

FTF ANDAs can play a decisive role for the earnings trajectory of generic firms, since the 180-day marketing exclusivity that comes with the approval is when the product's sales and profitability typically peak.

CHALLENGING 2018

Sun also guided to a subdued FY2018, in the backdrop of the ongoing challenges in the US, including customer consolidation that was leading to pressure on pricing. Peers like **Lupin Ltd.** have also referred to the ongoing channel consolidation in the US including the recent "coming together" of Walgreens Boots Alliance Development GmbH (WBAD) and Econdisc that is expected to pile up more pricing pressure. *(Also see "US Price Pressure Clouds Lupin Outlook – Can Its Pipeline Deliver?" - Scrip, 25 May, 2017.)*

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ViiV/Janssen Forge Two-Drug Future For HIV

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ViiV Healthcare has filed for US and EU approval of a two-drug regimen for HIV consisting of its integrase inhibitor dolutegravir *(Tivicay)* and **Janssen Inc.**'s non-nucleoside reverse transcriptase inhibitor rilpivirine (*Edurant*) in a single tablet. If approved, this will be first two-drug regimen for the maintenance treatment of HIV-1 infection, and will offer patients an NRTI-free option.

In the US, ViiV is using a priority review voucher to speed the review and hopefully get the product approved within six months of the FDA's receipt of the NDA. The $130m cost of the voucher will be reported as an R&D expense in GSK's Q2 2017 Adjusted results.

The submissions are based on the SWORD 1 and 2 studies in more than 1,000 patients reported at the CROI meeting in February. The dolutegravir and rilpivirine regimen achieved non-inferior viral suppression (HIV-1 RNA <50 copies/mL) at 48 weeks compared with a three- or four-drug regimen in both pooled and individual analyses of the two trials.

The main benefits from the combination would be overall cost-savings over commonly used regimens, and for patients a simplified treatment regimen, particularly compared with commonly used second-line and beyond integrase strand transfer inhibitors (INSTIs)/protease inhibitor (PI)-based regimens which require boosting agents (e.g. *Truvada* + *Prezista* + *Norvir*; Truvada + *Reyataz* + Norvir; Truvada + *Isentress* + Norvir).

But experts have questioned whether this is enough of an incentive to rock the treatment boat. Using fewer antiretroviral agents runs a theoretical risk of resistance generation and treatment failure, even with dolutegravir's very high barrier to resistance.

Overall, the combination is not expected to prove a huge threat to ViiV's major rival in HIV **Gilead Sciences Inc.**, especially with the approach to the market of its new once-daily INSTI, bictegravir. But the fact that new data just released by Gilead showing non-inferiority but not superiority to dolutegravir will give ViiV some breathing space, as the two companies duke it out in the market.

The new data from four Phase III trials showed that bictegravir met the non-inferiority standard against ViiV's *Trumeq* (dolutegravir/lamivudine/abacavir) and of dolutegravir with Gilead's emtricitabine and tenofovir alafenamide (Gilead's *Descovy*) in treatment-naïve HIV-infected patients, as well as in switch studies with treatment-experienced patients receiving either dolutegravir plus existing antiviral agents or an approved protease inhibitor/nucleoside polymerase inhibitor combination.

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Sanofi, Debiopharm Deals Buy ImmunoGen Extra Time

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Antibody drug conjugate technology specialist **ImmunoGen Inc.** has added $60m to its balance sheet via the divestiture of one asset to **Debiopharm International SA** and the amendment of a multi-product licensing agreement with **Sanofi**.

The company had been looking to sign co-development/co-commercialization deals for development-stage candidates, monetize future royalty streams and out-license its two B-cell lymphoma programs, in order to get upfront cash, given that its current cash would only fund activities into the second quarter of 2018. ImmunoGen has several big pharma partners for its ADC technology, but not enough cash coming in to secure the future of its various in-house development programs, including a lead program in Phase III ovarian cancer trials that it is hoping to get approved by 2020.

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IMGN529 SOLD

The first of the recent deals sees one of the company's B-cell lymphoma programs disposed of. Switzerland's Debiopharm paid $25m up front for IMGN529 with a further $5m to be transferred upon the completion of the transfer of the related ImmunoGen technologies, which is scheduled to occur by the end of 2017. ImmunoGen also stands to receive a $25m milestone should this ADC, which is designed to treat patients with CD-37-positive B-cell malignancies such as non-Hodgkin's lymphoma, enter a Phase III trial.

IMGN529 has shown anticancer activity in a Phase I monotherapy trial and completed a safety run-in study in combination rituximab; it is now set to progress into a Phase II trial combination with rituximab in patients with diffuse large B-Cell lymphoma and other forms of non-Hodgkin's lymphoma.

SANOFI ROYALTIES MONETIZED

The amended arrangements with Sanofi will see the French major paying $30m up front to ImmunoGen to take exclusive development, manufacturing and commercialization rights to four named pipeline compounds and a fifth undisclosed candidate. The deal will remove ImmunoGen's future milestone and royalty rights laid out in the original agreements, signed in 2003 and 2013. It will also forego a limited US co-promotion option it had on four of the compounds.

The compounds in question are:

- Isatuximab, an unconjugated anti-CD38 antibody in Phase III development for relapsed and refractory multiple myeloma
- SAR566658, an ADC targeting CA6 in Phase II development for triple-negative breast cancer
- SAR408701, an anti-CEACAM5 ADC being studied in solid tumors
- SAR428926, an anti-LAMP1 ADC also being studied in solid tumors
- One more ADC directed to an undisclosed target

FORWARD FOCUS

ImmunoGen's lead product is mirvetuximab soravtansine, in Phase III as a single agent for folate receptor alpha-positive platinum-resistant ovarian cancer (the FORWARD 1 trial) and in Phase Ib/II in combination regimens for platinum-resistant and platinum-sensitive disease (the FORWARD II trial). The company believes it has potential to replace chemotherapy and become a preferred agent in combination regimens including with immunotherapies and PARP inhibitors. It is hoping to gain initial approval for the compound as a monotherapy in platinum-resistant ovarian cancer in 2020, and believes it has potential in other folate receptor alpha positive diseases including non-small cell lung cancer, endometrial cancer and triple-negative breast cancer.

Analysts at Leerink wrote in a May 30 research note that ImmunoGen had "other BD [business development] opportunities… to generate value in the near term, such as the divestiture of coltuximab (SAR3419) which was highlighted "best of ASCO" in 2015 [sic – it was actually 2014 – ed]." Sanofi handed back rights to coltuximab ravtansine in April 2015; the candidate had shown evidence of anticancer activity in relapsed/refractory diffuse large B-cell lymphoma in the Phase II STARLYTE trial.

The Leerink analysts also highlighted the company's other in-house clinical assets, IMGN779 and IMGN632, saying they "could represent attractive partnering assets".

ImmunoGen is scheduled to present Phase I dose-escalation data on IMGN779, an anti-CD33 ADC, in relapsed/refractory acute myeloid leukemia at EHA in June, with efficacy data expected to be ready for ASH in December. IMGN632 is an anti-CD123 ADC for hematological cancers expected to enter Phase I in the second half of 2017.

This is not the company's first monetization deal: in 2015 it notably converted a chunk of the future royalties on **Roche**'s *Kadcyla* (ado-trastuzumab emtansine), which uses ImmunoGen's toxin and linker technology, into $200m of ready money. The company was put on the back foot when Kadcyla failed to show superiority to Roche's earlier generation breast cancer best-seller *Herceptin* (trastuzumab), reducing peak sales expectations for the drug – and royalty prospects for ImmunoGen. *(Also see "ImmunoGen sucks up the cost of novelty value" - Scrip, 1 Apr, 2015.)* Kadcyla remains the only marketed drug that uses ImmunoGen's ADC technology.

Another partnered program with a future milestone and royalty stream at a relatively advanced stage is anetumab ravtansine, which **Bayer AG** testing in a Phase II trial for mesothelioma.

ImmunoGen cut 17% of its workforce in September 2016 as part of its drive to extend its cash runway.

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Clinical Trial Snapshot 2016: Novartis Leads On Volume, But Novo Nordisk Posts Highest Success Rate

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Novartis AG emerges as a standout performer in clinical development in a Trialtrove analysis of clinical trials completed in 2016. The company completed more clinical trials than anyone else, while maintaining an above-average success rate.

Few companies managed to balance a high volume of trials with a high success rate; firms that take many shots on goal tend to miss a large percentage of those shots, the Trialtrove data show. When more specialty or targeted R&D strategies pay off, sponsors see high success rates, but risk is also more concentrated. *[Editor's note: See the free report for more details on the key players in the industry by area and phase, as well as additional analysis of the 2016 clinical trial landscape.]*

Less than one-third of clinical trials met their primary outcome, Informa Pharma Intelligence Innovation Head Christine Blazynski notes in a white paper examining the clinical trials completed in 2016. The figure sets a rough benchmark, although Trialtrove points out that a majority of trials had no results released in the public domain or had a final outcome still unknown. (See Top Sponsors Of Clinical Trials - Parts I and II below and on p21.)

Novartis completed 165 trials in 2016, with **Roche** and **Glaxo SmithKline PLC** close behind. Novartis, however, posted a 35% clinical trial success rate, while 29% of Roche trials and 26% of GSK studies met the primary endpoint.

Novo Nordisk AS had many fewer trials than Novartis, with 39 completed in 2016, but Novo Nordisk posted positive results on the primary outcome for 46% of its trials. Trialtrove found only two other companies with success rates above 40%: **Otsuka Pharmaceutical Co. Ltd.** and **Amgen Inc.**

ONCOLOGY DOMINATES

The Trialtrove analysts drilled down into the clinical trial data for the three therapeutic categories with the most trials completed in 2016: oncology (826 trials), autoimmune and inflammatory (AI) disease (677 trials), and central nervous system disorders (547 trials).

Oncology stands out on most metrics. Cancer therapy had not only the most completed trials, but also the most novel agents in development. Trialtrove identified more than 200 trials of novel oncologics completed in 2016. AI had closer to 150 trials of novel agents, and the CNS count was below 100.

Oncology posted the highest success rate: 38.9% of completed oncology trials met the primary outcome.

In contrast, the overall success rate in the autoimmune and inflammation sphere was 29.2%. CNS was even lower, with 23.4% of completed trials achieving their primary outcomes. (See p21 for the top companies in oncology, AI and CNS, showing the top five firms by trials completed and success rate.)

In each of the top therapy areas, Trialtrove found discordance between trial count and success rate; the companies with the most trials were not the companies with the highest percentage of trials achieving primary outcomes.

Amgen is the only company to appear near the top of both lists in oncology. Otsuka and **H. Lundbeck AS**, which have a major CNS partnership, achieve that feat for the CNS pipeline.

Published online 30 May 2017

Click here for the full Informa Pharma Intelligence white paper, "2016 Complete Clinical Trials: Industry Strategies Revealed And Graded"

Top Sponsors Of Clinical Trials – Part I

	MOST TRIALS TERMINATED				
	TRIALS TERMINATED	BUSINESS DECISION	EFFICACY	ENROLLMENT	SAFETY
Novartis	49	10	9	11	11
Pfizer	35	16	5	4	4
Roche	26	6	3	8	–
AstraZeneca	24	10	3	3	2
Merck	22	5	4	4	1

Source: Informa Pharma Intelligence white paper, "2016 Completed Clinical Trials: Industry Strategies Revealed and Graded"

Top Sponsors Of Clinical Trials – Part II

MOST TRIALS COMPLETED		
	TRIALS COMPLETED	SUCCESS RATE
Novartis	165	35%
Roche	160	29%
GSK	158	26%
Pfizer	140	25%
Merck	134	26%
HIGHEST SUCCESS RATE		
	SUCCESS RATE (% TRIALS ATTAINING PRIMARY OUTCOME)	TRIALS COMPLETED
Novo Nordisk	46%	39
Otsuka	43%	47
Amgen	41%	71
Novartis	35%	165
AbbVie	34%	82

Source: Informa Pharma Intelligence white paper, "2016 Completed Clinical Trials: Industry Strategies Revealed and Graded"

Oncology's Top Sponsors

MOST TRIALS COMPLETED		
SPONSOR	ONCOLOGY TRIALS COMPLETED	SUCCESS RATE
Roche	91	30.8%
Novartis	76	38.2%
Pfizer	42	33.3%
Amgen	40	45.0%
Eli Lilly	38	23.7%
HIGHEST SUCCESS RATE		
SPONSOR	SUCCESS RATE	ONCOLOGY TRIALS COMPLETED
Johnson & Johnson	65.0%	20
Otsuka	61.1%	18
Amgen	45.0%	40
Boehringer Ingelheim	42.1%	19
Celgene	41.9%	31

Source: Informa Pharma Intelligence white paper, "2016 Completed Clinical Trials: Industry Strategies Revealed And Graded"

CNS Top Sponsors

MOST TRIALS COMPLETED		
	CENTRAL NERVOUS SYSTEM TRIALS COMPLETED	SUCCESS RATE
Pfizer	28	10.7%
Johnson & Johnson	19	21.1%
Lundbeck	18	27.8%
Biogen	18	11.1%
Otsuka	18	33.3%
HIGHEST SUCCESS RATE		
	SUCCESS RATE	CNS TRIALS COMPLETED
Teva	71.4%	7
Lundbeck + Otsuka	55.6%	9
Novartis	54.5%	11
Roche	37.5%	8
Sumitomo Dainippon	37.5%	8

Source: Informa Pharma Intelligence white paper, "2016 Completed Clinical Trials: Industry Strategies Revealed And Graded"

Autoimmune & Inflammation's Top Sponsors

MOST TRIALS COMPLETED		
SPONSOR	AUTOIMMUNE & INFLAMMATION TRIALS COMPLETED	SUCCESS RATE
GSK	49	26.5%
AstraZeneca	45	28.9%
Roche	36	13.9%
Chiesi	28	32.1%
Pfizer	28	32.1%
HIGHEST SUCCESS RATE		
	SUCCESS RATE	AUTOIMMUNE & INFLAMMATION TRIALS COMPLETED
AbbVie	58.8%	17
Johnson & Johnson	42.9%	21
Regeneron + Sanofi	38.5%	13
Teva	36.4%	11
Vertex	36.4%	11

Source: Informa Pharma Intelligence white paper, "2016 Completed Clinical Trials: Industry Strategies Revealed And Graded"

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.

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Selected clinical trial developments for the week 26 May –1 June 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Gilead Sciences Inc.	sofosbuvir/velpatasvir/ voxilaprevir	chronic hepatitis C infection	POLARIS-1 and POLARIS-4 studies in *The New England Journal of Medicine*.
Merck & Co. Inc.	elbasvir plus grazoprevir	hepatitis C virus infection and chronic kidney disease	Clinical, virological, and health-related quality-of-life outcomes from the Phase II/III SURFER trial in *The Lancet*.
Novartis AG	buparlisib	breast cancer	BELLE-2 study in *The Lancet: Oncology.*
Shionogi & Co. Ltd. / Purdue Pharma LP	naldemedine	opioid-induced constipation	COMPOSE-1 and COMPOSE-2 in *The Lancet Gastroenterology and Hepatology.*
Phase III Interim/Top-line Results			
Gilead Sciences Inc.	bictegravir, emtricitabine, tenofovir alafenamide, fixed-dose tablet	HIV-1 infection	GS-US-380-1489, -1490, -1844, 1878; met primary objective.
Teva Pharmaceutical Industries Ltd.	fremanezumab	chronic migraine prevention	HALO; met all primary and secondary endpoints.
Eli Lilly & Co.	Cyramza (ramucirumab)	bladder cancer	RANGE; met primary endpoint of PFS improvement.
Phase III Initiated			
Sylentis SA	SYL1001	dry eye syndrome	HELIX; an RNA interference approach.
JDP Therapeutics Inc.	JDP-205 (iv cetirizine)	acute urticaria	ETTAU-03; unmet need for well-tolerated agent.
Updated Phase II Results			
NLS Pharma Group	NLS-1 (mazindol) controlled release	attention deficit hyperactivity disorder	Positive data, thought to regulate orexin system in hypothalamus.
BioPharmX Corp.	BPX-01 2%	acne	Reduces the number of inflammatory lesions with no serious drug-related adverse side effects.
XBiotech Inc.	Hutruo (MABp1)	colorectal cancer	European Phase III Study improved clinical outcomes of symptomatic refractory metastatic colorectal cancer.
Phase II Interim/Top-line Results			
Oncoceutics Inc.	ONC201	malignant glioma	Well tolerated, evidence of efficacy.
Reata Pharmaceuticals Inc. / AbbVie Inc.	omaveloxolone	Friedreich's ataxia	The MOXIe Part 1 dose-escalation trial identified 160 mg as the optimal dose.
Phase II Initiation			
Intensity Therapeutics Inc.	INT230-6	solid tumors	Administered into the tumor.
Molecular Partners AG	MP0250	multiple myeloma	With other therapies.
Oncology Ventures Sweden AB	APO 010	multiple myeloma	A FAS ligand that leads to apoptosis.
Adocia SAS	BioChaperone Lispro	type 1 diabetes	An "ultra-rapid" formulation of insulin lispro, compared to Fiasp (faster-acting insulin aspart, Novo Nordisk).

Source: Biomedtracker

Asia Executives To Watch: Changes At MSD China, CFDA

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Merck & Co, known as MSD outside the US and Canada, is reported to have appointed a new country general manager for China. **Shi Wang**, previously a senior vice president for **AstraZenecaPLC** in China, appears set to lead the regional operations for the US drug firm.

Among other responsibilities, Shi has been tasked to lead MSD's alliance management, women's health, and retail sales in China, noted local Chinese media *E-Pharma Manager*.

Mu Yanping has also been appointed as the head of MSD China's oncology business unit, moving on from **Johnson & Johnson** China, where she was a VP in charge of Joints and Sports medicine at Johnson Medical.

Meanwhile, **Xu Penglai** has been appointed the general manager of Merck's Vaccines business in China. Xu has worked in MSD for nine years and before that spent seven years at **Sanofi Pasteur**. The China FDA recently granted a long-awaited approval to Merck's human papillomavirus vaccine *Gardasil 9*. In other changes in China, **Wenkai Vicent Xiang** has become a partner at 6 Dimensions Capital following the merger of Frontline BioVentures and Wuxi Healthcare Ventures. **Yi Gloria Wang** is now Clinical Development Consultant at Gloria Clinical & Medical Solutions. She was previously Clinical Science Expert at the **Novartis Institutes for Biomedical Research**.

TAISHO TOYAMA

Across in Japan, **Taisho Toyama Pharma** has appointed **Junji Okada** as its new president. Okada is currently the president of **Toyama Chemical** and will assume the presidency of both companies. Toyama Chemical owns a 45% stake in its joint venture with **Taisho Pharmaceutical.**

The outgoing president of Taisho Toyama, **Takatoshi Ishikawa**, has resigned from the position but remains an executive director of **FujiFilm Holdings**, which owns Toyama Chemical. Now aged 60, Okada entered Fujifilm in 1979 and has held several leadership positions including president of Fujifilm Europe. He became the president of Toyama Chemical in 2016.

CHINA FDA OFFICIALS

The China FDA has appointed a number of new officials to key positions, as follows:

- **Chen Yan** deputy director, Quality Management Bureau;
- **Gao Zhengyu**, deputy director, Quality Management Bureau;
- **Zang Kecheng**, director, Administrative Office;
- **Zhang Zhen**, deputy director, Administrative Office;
- **Qian Xue**, director, Research and Inspection Bureau;
- **Wang Jianan**, deputy director, Research and Inspection Bureau; and
- **Cao Yi**, deputy director, Drug and Chemical Inspection Bureau.

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APPOINTMENTS

Eli Lilly & Co.'s chief financial officer (CFO) ***Derica Rice*** will be retiring at the end of this year after being at the company for 27 years. Rice was previously Lilly's executive vice president global services and on the company's executive committee. Lilly has said that it is considering external and internal candidates for the CFO position.

Alexion Pharmaceuticals Inc. has appointed ***John Orloff*** executive vice president, head of research & development; ***Anne-Marie Law***, executive vice president, chief human resources officer, and ***Indrani Lall Franchini*** executive vice president, chief compliance officer. Orloff has more than 20 years of experience in the biopharmaceutical industry and joins the company from Novelion Therapeutics Inc. where he was executive vice president, head of research and development. Before this, he was global head of R&D and chief scientific officer at Baxalta Inc. and has held executive R&D roles with Baxter International Inc., Merck Serono SA, Novartis AG and Merck Research Laboratories. Law joins Alexion from Hyatt Hotels Corporation, where she was chief human resources officer; before that she was executive vice president and head of human resources for Baxalta. Previously, Franchini was chief compliance officer at Hess Corporation and prior to that she spent almost ten years at Pfizer Inc., most recently as chief compliance counsel for its pharmaceutical business.

Actelion Pharmaceuticals Ltd. has announced changes to its executive team that will take effect once the transaction with Johnson & Johnson has closed at the end of Q2 2017. J&J has appointed ***Jane Griffiths***, currently company group chair, Janssen EMEA, as the global head of Actelion. Previously Griffiths was responsible for the EMEA Market Access unit and before that was international vice president for Janssen-Cilag GMBH, Northern Europe; vice president, EMEA Biopharmaceuticals; and managing director, Ortho Biotech UK & Ireland. Chief operating officer ***Otto Schwarz*** will retire but will work closely with Griffiths as senior advisor for 12 months.

Summit Therapeutics PLC. has appointed ***Anne Heatherington*** head of clinical development and quantitative sciences and ***Dave Powell*** head of research. Recently appointed chief operating officer and president of R&D, David Roblin will expand his role to become chief medical officer. He carries experience from holding various roles in the life science industry at companies including Pfizer and Bayer AG. At Pfizer, he was head of research, site director and chief medical officer for Europe R&D and at Bayer, he was head of therapy for anti-infectives. Roblin will succeed Dr Ralf Rosskamp, who has resigned. Heatherington joins the company from Pfizer, where she was vice president and head of quantitative clinical sciences in Cambridge and previously worked at Amgen Inc. Powell will join Summit from GlaxoSmithKline PLC where he is director and head of the Crick-GSK Biomedical LinkLabs, based in Stevenage, UK.

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