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Keytruda Approval Opens New Routes For Immuno-Oncology

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The US FDA's approval of **Merck & Co**'s *Keytruda* for patients with microsatellite instability-high or mismatch repair deficient solid tumors marks a new route into difficult markets for PD-1/L1 inhibitors.

Cancer immunotherapy has yielded poor response in many cancers that are immunologically "cold" – i.e., they aren't suited to respond to immuno-oncology drugs. PD-1/L1 sponsors have been avidly researching ways to turn "cold" tumors "hot" by priming them with different therapies or combination approaches. But small subsets with genetic mutations have also offered a way into these tumor types, which include major solid tumors like breast cancer and colorectal cancer (CRC).

The most certain biomarker so far has been microsatellite instability-high (MSI-H) CRC, which the industry has previously pegged at approximately 15% of the CRC population, although the FDA put the number of metastatic CRC patients with MSI-H or mismatch repair deficient (dMMR) tumors at 5%.

Merck's accomplishment opens the door to any solid tumor patient with MSI-H or dMMR mutations – both of which inhibit the cell's natural processes of DNA damage repair – and specifically in biomarker-positive colorectal cancer patients who have completed earlier lines of treatment. *(Also see "Biomarker-Led Claim Is Small Step For Merck's Keytruda, Giant Leap For Cancer Indications" - Pink Sheet, 23 May, 2017.)*

MARKET WILL DEPEND ON TESTING

The FDA reported the biomarkers are most commonly found in colorectal, endometrial and gastrointestinal cancers and they're less common in other tumor types, including breast, prostate, bladder and thyroid gland.

It is hard to know how many patients will be eligible for treatment, but Merck's challenge is lessened by the fact that mutations are detected through common tests and thus do not require dedicated companion diagnostics. "MSI molecular testing is already largely diffuse at the clinical level, which increases its potential as a ready-to-use approach to predict immunotherapeutic response in patients who have failed conventional therapy," according to a factsheet from the European Society for Medical Oncology (ESMO).

"In order to start seeing broader impact of this sort of genetic testing across oncology and across the industry, we'll need a more coordinated and continued interest and investment in validating biomarkers and ensuring genetic testing is accurate," Informa Pharma Intelligence consultant Markella Kordoyanni said in an interview.

Kordoyanni does see the potential for change in physician practices. "At the end of the day, physicians will have to use their judgement based on the data available; this means that physicians will need to make a call when they have a patient who might benefit from this drug based on the results of their diagnostic test and make a second call to stop treatment if that patient is not responding so as to minimize toxicities (and keep costs down). And the accuracy of testing will become increasingly important here," she told *Scrip*.

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from the editor

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Innovation in the pharma industry means a lot more than just discovering new medicines.

It's about designing new business structures; it's about introducing novel ways to assess the effectiveness of treatments; it's about advocating for new, more rational ways of defining illnesses - and recognizing differences and similarities between diseases – and it's about establishing appropriate financial and economic models to measure the costs and the value of treatment, among many other things. Of the various fine examples of innovative thinking in this issue of *Scrip*, I will note just a few.

Our cover story highlights an important new development in the registration pathway for cancer medicines. FDA's approval of *Keytruda* for solid tumor patients with particular biomarkers is the first time a cancer drug has been approved in the US for specific genetic mutations regardless of the cancer's location. In advancing the field of oncology, the pharma industry has been a driving force behind a redefinition of cancer itself.

It is also incumbent on industry to show society the value of its scientific advances, and engage thoughtfully in the pricing debate. On p7, Bayer's Dieter Weinand calls for innovation in valuation to accompany innovation in science. He has a compelling case for why calculating the cost-benefit ratio of a medicine based on its price at launch is a mistaken endeavor.

Finally, on p10, Joseph Haas explores the many advances that have been made by innovators in the rare disease therapy area, and how their examples could provide useful models for cell and gene therapy firms.

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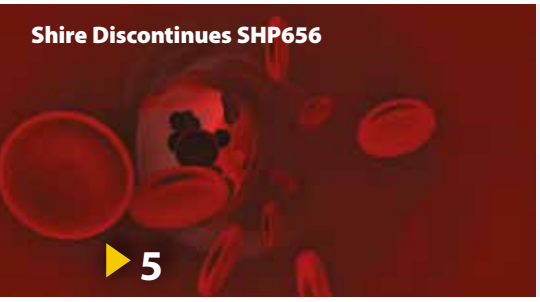

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All Change At Alexion, But Will It Boost Investor Confidence?
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The US rare diseases company Alexion appoints a new COO and is now looking for a new CFO, head of R&D, and head of human resources, as leadership changes leaves its CEO searching for a new executive team.

The Future's Bright For Microbiome Investing, Says VC
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Seventure Partners' Eric de la Fortelle explains how the venture capitalist's €160bn fund will prosper from the increased understanding of human and microbe interactions.

Producing Monoclonal Antibodies For A Tenth Of The Cost
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Dutch antibody technology company Biosana Pharma is offering to make monoclonal antibodies at between 5% and 10% the usual cost of manufacture. Video interview from BIO-Europe Spring.

Shanghai Henilus Biotech Has Blockbuster Biologics In Biosimilars Crosshairs
http://bit.ly/2r7qxA4
Dr. Cheni Kwok, a business development and strategy consultant, caught up with *Scrip*'s Mike Ward to outline how Shanghai Henilus Biotech is positioning itself to provide affordable healthcare globally.

Bone Therapeutics Looks To ALLOB Data Progress
http://bit.ly/2rAJqNw
Following its IPO in 2015, Belgium's Bone Therapeutics has been making progress on its allogeneic osteoblastic cell product, ALLOB, which recently appointed CEO Thomas Lienard pegs as the company's most valuable platform. With the product currently in Phase II trials, Lienard shares his plans for the company.

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Sanofi/Regeneron's *Kevzara* Priced To Break Into A Crowded Market

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Sanofi and **Regeneron Pharmaceuticals Inc.** are looking to break into the crowded rheumatoid arthritis market by establishing a compelling value proposition for the interleukin-6 receptor blocker *Kevzara* (sarilumab). The wholesale acquisition cost of Kevzara is set at $39,000 per year for both the 200 mg and 150 mg doses, a price that is 30% lower than the two market-leading tumor necrosis factor inhibitors, **AbbVie Inc.**'s *Humira* (adalimumab) and **Amgen Inc.**'s *Enbrel* (etanercept).

Kevzara also could undercut **Roche**'s entrenched IL-6 inhibitor *Actemra* (tocilizumab), depending on the dosing that is used, although not as substantially. Actemra may be a tough competitor because it has been on the market nearly seven years and now is approved for three other indications, including most recently, an FDA approval for giant cell arteritis on May 22.

Sanofi/Regeneron announced the FDA approval of Kevzara after market close on May 22 for the treatment of adults with moderate to severe RA who have had an inadequate response or intolerance to one or more disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate. The indication is the same as the one Actemra received for RA, and both drugs also include a black box warning on the risk of infections.

The approval follows a lengthy delay due to a manufacturing deficiencies at Sanofi's Le Trait, France, fill-and-finish facility. FDA issued a complete response letter to the application in October, although Sanofi reported early this year that the issues were resolved and thus, the approval was anticipated.

How valuable the steeply discounted WAC will be to payers still is uncertain because rheumatoid arthritis is a highly competitive category in which market access is dominated by high-volume rebates and discounts. Sanofi/Regeneron confirmed they also will offer rebates and discounts on the price of Kevzara but did not say how substantial those would be.

Barclays analyst Geoffrey Meacham, in a May 23 research note, speculated the gross-to-net discount for Kevzara could be roughly 20%.

The price of Kevzara is only more affordable than subcutaneous Actemra if a weekly dosing schedule is used for the latter product. Actemra's dosing is dependent on a patient's weight and clinical response, and patients can be dosed either weekly or every other week. Kevzara's recommended dose is 200 mg every other week, according to labeling.

The annual cost of Actemra ranges from $23,400 for bi-weekly dosing to $46,900 for weekly, according to Roche. The average real-world cost of Actemra, based on the 2014 CORRONA data, is approximately $37,500, the company said. The cost of the intravenous formulation runs even lower.

STEP THERAPY MAY AFFECT UPTAKE

Another challenge for new drugs is that in exchange for rebates, many payers impose step-therapy requirements mandating patients try Humira and/or Enbrel before moving to another biologic, according to a survey recently completed by the Institute for Clinical and Economic Review (ICER). Regeneron Senior Director for Health Economic and Outcomes Research Andreas Kuznik recently discussed the issue at an ICER council meeting. He criticized the system, claiming it creates a disincentive to compete on price in RA. *(Also see "Market Failure? Lower Drug Prices Don't Improve Access In Rheumatoid Arthritis" - Pink Sheet, 7 Apr, 2017.)*

Kevzara is expected to be a modest revenue generator for Sanofi/Regeneron, given the high level of competition in the category. Barclay's Meacham forecast peak worldwide sales of the drug at $1bn.

The bigger commercial opportunity for the partners in the near term is the launch of *Dupixent* (dupilumab), the first targeted biologic for atopic dermatitis, approved by the FDA on March 28. In the case of Dupixent, the companies also set the price conservatively, with a WAC of $37,000 a year, below the cost of many biologics for a different skin condition, psoriasis.

The careful pricing strategy and transparency is notable in the current political environment, where drug pricing has become a big issue within the bigger health care debate. Regeneron CEO Leonard Schleifer has been one of the more outspoken leaders in pharma and biotech to criticize some of the industry's pricing practices.

Despite the competitive dynamics in RA, drug makers continue to bring forward new treatments. **Johnson & Johnson** outlined plans to expand in immunology and inflammation at a recent R&D day, including plans to launch the IL-6 inhibitor sirukumab, partnered with **GlaxoSmithKline PLC**, later this year. *(Also see "J&J Forges Ahead In Immunology Despite Competitive Dynamics" - Scrip, 18 May, 2017.)* The unmet need remains high, despite existing treatment options, because patients continue to progress and cycle through treatments. Only 20% of patients with RA achieve remission, J&J said.

Eli Lilly & Co. also is preparing to launch the oral janus kinase inhibitor *Olumiant* (baricitinib), though it was delayed by FDA. *(Also see "Baricitinib Complete Response May Put Lilly/Incyte Behind IL-6 Blockers In RA" - Scrip, 14 Apr, 2017.)*

While the anti-TNFs dominate the RA category, drugs like Actemra and **Pfizer Inc.**'s *Xeljanz* (tofacitinib) have carved out substantial niches, though they have needed time to achieve blockbuster sales. Xeljanz is on track to surpass $1bn in sales for the first time in 2017. *(Also see "Pfizer's Xeljanz: The Slow Road To Blockbuster Status" - Scrip, 4 May, 2017.)* Meanwhile, sales of Actemra were CHF1.7bn ($1.74bn) in 2016, with growth of 16%, with the company attributing the uptick to increased single-agent use and a newer subcutaneous formulation, approved by FDA in 2013. US sales of Actemra were CHF647m ($664m).

Kevzara is dosed subcutaneously. The approval was based on data from two Phase III trials – MOBILITY, studying Kevzara plus methotrexate; and TARGET, studying Kevzara plus DMARD. The European Medicine Agency's CHMP recently gave sarilumab a positive opinion.

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Shire Discontinues Development Of Once-Weekly SHP656 For Hemophilia A

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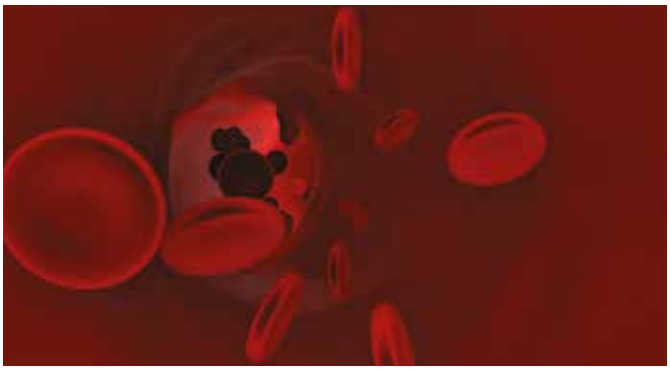
Xenetic Biosciences Inc. revealed on May 22 that its partner **Shire PLC** ended development of SHP656 for hemophilia A, because the long-acting coagulation Factor VIII could not be dosed once-weekly, which eliminates the product candidate's best chance for differentiation in the marketplace.



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Physicians, patients and especially payers are looking for hemophilia therapies that can be dosed once-weekly or less frequently to reduce the burden and cost of infusions required two to four times per week under the dosing regimens of approved Factor VIII products (*see sidebar*). With dosing required more often than once per week, SHP656 wouldn't be much different from **Bioverativ Inc.**'s *Eloctate* [antihemophilic Factor (recombinant), Fc fusion protein], which is approved for infusions every four days, or product candidates from **Bayer AG** and **Novo Nordisk AS** – BAY94-9027 and N8-GP, respectively – that may be given with up to one week between infusions.

The discontinuation of SHP656 development is not a major setback for Shire, which dominates that market with $3.7bn in 2016 sales of hemophilia products across all major and several smaller indications; it markets the top-selling hemophilia A therapy *Advate* [antihemophilic Factor (recombinant)] that's dosed three to four times per week. *(Also see "Competition Coming For Hemophilia Franchises, But Will Patients And Payers Embrace New Drugs?" - Scrip, 15 Mar, 2017.)* The company's stock fell 0.9% on May 22 to $187.49.

The failure of SHP656 is a big blow, however, for Xenetic, which entered into an agreement with **Baxter International Inc.** in 2006 – when Xenetic was still known as **Lipoxen PLC** – to develop long-acting hemophilia therapies with the small biotechnology firm's *PolyXen* technology platform. *(Also see "Deals Shaping the Medical Industry (1/07)" - In Vivo, 1 Jan, 2007.)* The deal was done long before Baxter spun out its bioscience business into **Baxalta Inc.**, which Shire later acquired, and the transaction – amended in 2014 – promised Xenetic up to $100m in milestone fees plus royalties.

Xenetic had just $4.3m in cash as of March 31, including a $3m payment it received from Shire in January. The Lexington, Mass.-based company said in its first quarter earnings report filed with the US Securities and Exchange Commission (SEC) on May 15 that the money was enough to fund its operations through the first half of 2017.

Even with a second potential milestone fee from Shire based on the outcome of the Phase I/II trial for SHP656, Xenetic said in its SEC filing that it would need to raise additional capital this year – the success of which would be based in part on the hemophilia study's outcome. Without the additional milestone payment and with dampened prospects for a future fundraising event, the company's ability to begin another mid-stage study for its lead cancer drug candidate during the second quarter of this year is unknown.

DESPITE SETBACK, INVESTORS REMAIN HOPEFUL

As a result, Xenetic's stock price fell by as much as 27.7% to $2.35 on May 22, but closed the day with a 3-cent gain at $3.28. The nearly 1% rise in the company's stock may have been fueled by a comment from Shire's global head of research and development Philip Vickers indicating that all is not lost.

"While Shire is disappointed by this outcome, the company is encouraged by the knowledge gained through this research and remains committed to transforming the treatment landscape for patients with bleeding disorders. Given the potential application of polysialic acid technology, the companies will explore future collaborations," Vickers said in Xenetic's statement about SHP656, which proved to be an effective recombinant Factor VIII product in the Phase I/II trial despite the inability to achieve once-weekly dosing.

Xenetic's PolyXen platform extends the half-life of protein therapeutics by attaching the biodegradable polymer polysialic acid (PSA) to protein or peptide therapeutics. PSA increases the therapeutic's size, which reduces the rate of clearance from the body and shields the protein from other degradation pathways.

"Including our own studies with a polysialylated erythropoietin ("PSA-EPO," "ErepoXen") candidate, this is the second instance in which PolyXen has been demonstrated, in a human clinical trial setting, to confer extended half-life to a biotherapeutic, while maintaining pharmacological activity and a favorable safety and tolerability profile," Xenetic CEO Scott Maguire said in the company's statement. "Moving forward, we believe data from Shire's SHP656 program continues to support the broad utility of our proprietary PolyXen technology platform, and we remain focused on building a growing pipeline of partnerships utilizing this proven platform. We truly value our continuing relationship with Shire and look forward to exploring other potential applications of PolyXen within the Shire portfolio."

Xenetic's cancer drug candidate is XBIO-101 (sodium cridanimod), a small-molecule immunomodulator and interferon inducer that increases progesterone receptor (PrR) expression in endometrial tissue. It is being studied in a 58-patient Phase II trial in women with PrR-negative endometrial cancer under a long-time cancer clinical trial partnership with Pharmsynthez PJSC of St. Petersburg, Russia and its subsidiary AS Kevelt in Tallinn, Estonia. *(Also see "Lipoxen to test pharma candidates with Russia's Pharmsynthez" - Scrip, 19 Nov, 2009.)* Xenetic planned to also begin a study during this quarter to test XBIO-101 in conjunction with progestin therapy for the treatment of progestin-resistant endometrial cancer.

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Celgene's Positive Ozanimod Data Puts Focus On MS Commercialization

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Positive data from a second Phase III trial testing **Celgene Corp.**'s ozanimod in multiple sclerosis has positioned the drug for a US FDA regulatory filing by the end of the year, raising new questions about the commercial strategy in MS and forthcoming generics for an established drug.

The company announced on May 22 that it had the data it needed to turn its attention to a new drug application (NDA) submission. Analyst and investor scrutiny has increased in response to the news in terms of the opportunity for ozanimod in MS, Celgene's launch strategy and how the drug might compete against an existing product, **Novartis AG**'s *Gilenya* (fingolimod), especially if it becomes available generically in 2019 as anticipated.

Celgene bought ozanimod with the $7.2bn acquisition of **Receptos Inc.** in 2015 and has enormous expectations for the drug. At the time of the acquisition, the company forecast peak sales would reach $4bn to $6bn in just two indications – relapsing MS and ulcerative colitis. *(Also see "Celgene Sets Sights On Becoming Inflammation and Immunology Power Player" - Pink Sheet, 20 Jul, 2015.)* A Phase III trial is ongoing in ulcerative colitis (UC) and a Phase II trial in Crohn's disease is under way.

One uncertainty related to the commercialization of ozanimod has been whether Celgene would market the drug in the US on its own or seek a partner. The competitive dynamics in multiple sclerosis are serious, with the market long dominated by entrenched players, and Celgene has no current experience in neurology, although it has built inflammation and immunology into a cornerstone franchise since entering the field in 2010.

Management indicated it would wait to see the Phase III results before making a decision about the commercialization strategy. CEO Mark Alles said during the J.P. Morgan Healthcare conference in January that Celegne was reviewing both options and that there was interest from potential partners, but he seemed to signal a strong possibility the company will commercialize independently.

"It feels to me neurology, particularly MS, when you look at the high patient touch, specialty, high unmet medical need, it feels like something we could do very, very well on our own," he said during the investor Q&A session. "But we would take a look at the totality of the data and make a decision on that sometime this year."

In a later media briefing, Alles spoke even more enthusiastically about the potential of neuroinflammation as a new business segment under Celgene's Immunology & Inflammation umbrella. "We see ozanimod as almost a tunnel or bridge to what Celgene's future might be in the neuroinflammatory space," he said. *(Also see "Neuroscience Reaches A New Inflection Point, Big Biotechs Say" - Scrip, 24 Jan, 2017.)*

Credit Suisse analyst Alethia Young remarked in a same-day research note that after speaking to the company, "We think they are planning to market ozanimod in MS alone in core markets."

"Celgene remains very confident that they can successfully launch this product in key markets with a potential sales force of [about] 200 and already have some employees on board who have direct experience with Gilenya," she wrote.

Young forecast peak sales of ozanimod in MS at $800m in 2025. Barclays analyst Geoff Meacham has modeled ozanimod revenues at $1.5bn in 2020, including both the MS and UC indications.

SAFETY BENEFIT OVER GILENYA STILL UNCLEAR

"In our view, differentiation of ozanimod on the safety/tolerability side with generic fingolimod is key to commercial success," Meacham said.

Celgene's hope for ozanimod is that the oral selective sphingosine 1-phosphate 1 (S1P1) and 5 receptor modulator would prove to be best in class, with particular benefits on safety, since it will have to compete against Gilenya, a similar S1P modulator. Gilenya was heralded as the first oral drug for multiple sclerosis when it debuted in 2010, but it also carried safety concerns related to cardiovascular risks and liver injury. Gilenya is contraindicated in patients who have recently experienced a heart attack or stroke.

Gilenya binds with high affinity to the sphingosine 1-phosphate receptors 1, 3, 4 and 5, which is why Celgene believes ozanimod might act differently. Gilenya generated $3.1bn in 2016, but the drug is expected to face generic competition in 2019 after the US Court of Appeals for the Federal Circuit recently upheld a decision by the US Patent and Trademark Office's Patent Trial and Appeal Board that invalidated a composition patent covering Gilenya. *(Also see "PTAB Finds Favor In Court; Novartis Is Latest To Strike Out In Challenge" - Pink Sheet, 14 Apr, 2017.)*

In the second Phase III trial testing ozanimod, RADIANCE, and the initial Phase III trial, SUNBEAM, Celgene did not provide details on safety or efficacy. It only said the safety and tolerability profile was consistent with the recently completed SUNBEAM trial and previously reported Phase II results.

"This is KEY for ozanimod," Evercore ISI analyst Umer Raffat said in a May 22 email to investors. Details of both trials will be released later this year at an upcoming medical congress, according to Celgene.

RADIANCE enrolled 1,313 relapsing MS patients, who were treated with one of two doses of ozanimod (0.5mg or 1mg) or the interferon *Avonex*, sold by **Biogen**. Both doses of ozanimod demonstrated statistically significant and clinically meaningful reductions in the primary endpoint, reducing annualized relapse rate compared to Avonex. The trial also met secondary endpoints related to the number of new or enlarging T2 MRI lesions over 24 months of treatment and the number of gadolinium-enhancing MRI lesions at 24 months of treatment compared to Avonex.

SUNBEAM was a similarly designed study that measured the same two doses of ozanimod versus Avonex, using the same primary endpoint. *(Also see "Safety Is Key As Celgene's Ozanimod Succeeds In First Pivotal MS Test" - Scrip, 17 Feb, 2017.)*

In a pre-specified pooled analysis of the time to confirmed disability progression in both RADIANCE and SUNBEAM, the ozanimod arms did not show statistical significance versus Avonex, though a low rate of disability was observed across all three treatment groups.

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Bayer's Weinand On Broadening Value-Based Pricing Views

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Bayer AG's head of pharma Dieter Weinand has warned the pharma industry it should act now to help broaden thinking and remove silos related to value-based assessments for new drugs, if it wants to unlock the next scientific revolution arising from breakthroughs like CRISPR gene editing.

"We are on the cusp of the next scientific revolution and we need to figure out how, comprehensively and long-term, we look at outcomes to determine value of novel drugs to unlock this next wave," Weinand told *Scrip* in a recent interview. He highlighted CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) gene editing and cell and gene therapies as recent R&D breakthroughs that will struggle to reach the market because of value-based pricing assessments. *(Also see "US Outcomes-Based Contracts In Oncology? CAR-T Could Be Case Study" - Pink Sheet, 26 May, 2017.)*

During the FT US Healthcare and Life Sciences Summit, held in New York on May 18, Weinand cautioned that "shortsightedness or siloed approaches" by pharma and payers will prevent novel research from reaching patients. He added that in a time when drug developers are "forced to focus on demonstrating the economic benefit" of new therapies, the real benefit to society of a new treatment can be forgotten.

Weinand, who came into the pharma industry from a scientific background, said he is motivated by the impact of new treatments on patients' lives, but in his experience, discussions around the value of novel drugs "has turned into an economic battle."

He added, "We are forced to constantly talk about the economic benefits – it is an argument we are forced to make to justify use of a drug."

Bayer

Dieter Weinand, head of Bayer Pharmaceuticals

'Giving the product to only those patients who will benefit allows for money to be saved from patients that would not benefit, which is very important in the current environment'

Weinand is advocating for a system in the US market particularly that takes a more comprehensive and broader look beyond the patent life of a drug to assess its value and in turn its cost. "We need to look beyond the eight or nine years of patent exclusivity and instead [consider] the possible 50 years of benefit a drug can provide," he said.

"Looking broadly at the benefit a drug provides long beyond patent exclusivity expiration is how we calculate value to society; calculating the incremental value based only on the price during patent exclusivity is a fallacy," he added.

COMPANION DIAGNOSTICS IN CANCER

Meanwhile, Weinand believes companion diagnostics will pave the way towards better use of treatments in the right patients at the right time – cutting down on "wastefulness" and helping to secure use of costly cancer therapies.

Bayer is developing a companion diagnostic for its pipeline antibody-drug conjugate anetumab ravtansine to enable the identification of patients who significantly over-express mesothelin.

"Giving the product to only those patients who will benefit allows for money to be saved from patients that would not benefit, which is very important in the current environment," Weinand said.

Anetumab ravtansine, which is currently in Phase II trials for mesothelioma, consists of an antibody that targets mesothelin with **ImmunoGen Inc.**'s DM4 cancer-cell killing agent attached, using one of the company's engineered linkers. Mesothelin is expressed in many types of cancer cells, such as ovarian cancer and pancreatic cancer.

Weinand touted that anetumab ravtansine, which German-based Bayer plans to file next year in the US, has "great prospects to make a difference for patients and has great promise economically for Bayer."

Bayer has pledged to up its R&D spend in 2017 and recently the company separated its oncology drugs into a separate, internal unit to speed up development of specific pipeline products. *(Also see "Bayer Bets On Oncology Pipeline, Vows To Increase 2017 R&D Budget" - Scrip, 22 Feb, 2017.)*

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CONTINUED FROM COVER

"It's important to recognize and appreciate … that it will impact just a small percentage of CRC patients," Kordoyanni added.

NEW TYPE OF INDICATION

The Keytruda approval is the first time the US regulatory agency has issued a cancer approval that does not specify the tumor location. "Until now, the FDA has approved cancer treatments based on where in the body the cancer started – for example, lung or breast cancers. We have now approved a drug based on a tumor's biomarker without regard to the tumor's original location," Richard Pazdur, director of FDA's Oncology Center of Excellence, said in the FDA's statement on the May 23 approval.

The research community has been interested in the tissue-agnostic (aka multi-histology, aka histology-independent) approach for several years. And while the FDA has previously signaled its openness, the Keytruda approval is the first sign of regulatory certainty.

Keytruda's new indication came through the FDA's breakthrough therapy designation process, which allows for significant collaboration during development. Two similar tissue-agnostic programs also are advancing through the breakthrough program: **Loxo Oncology Inc.**'s larotrectinib and **Ignyta Inc.**'s entrectinib, both in Phase II basket trials for NTRK fusion-positive solid tumors.

Novartis AG was an early leader in this field with its SIGNATURE program, which tested eight drugs in a histology-independent Phase II trial.

However, some of the "basket" trials driven by molecular signature have yielded results suggesting that histology does play an important role. **Roche**'s Phase II VE-BASKET trial of its BRAF inhibitor *Zelboraf* (vemurafenib) enrolled patients with any type of non-melanoma cancer who had BRAF V600 mutations, but the researchers concluded that "V600-mutated tumor types do not respond uniformly to BRAF-targeted therapy" and that "histologic context is an important determinant of response in BRAF V600-mutated cancers."

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Puma Biotechnology Inc. had a similar experience with its Phase II SUMMIT study of its irreversible pan-HER targeting tyrosine kinase inhibitor neratinib in multiple solid tumor types with HER2- and HER3- activating mutations. The results presented in April at the American Association for Cancer Research annual meeting showed that neratinib has activity in some types of cancers with HER2-activating mutations – breast, biliary tract and cervical cancers – but not others, like bladder and colorectal tumors, leading researchers to conclude that mutations may behave differently from one tumor to the next, and different mutation subtypes may be dominant, depending on the cancer type. *(Also see "Puma's Neratinib SUMMIT Study Shows Potential & Pitfalls Of Precision Medicine" - Pink Sheet, 2 Apr, 2017.)*

An important component of the basket trial design is verification in a randomized controlled trial. The Keytruda approval was not based on a prospective basket trial, but on data across five trials, both prospective and retrospective. It was an accelerated approval and Merck will have to follow up on the response rate and duration of response data with a confirmatory trial, presumably looking at overall survival.

"That could get tricky given the different standards of care across different tumor types, different levels of tumor aggressiveness and hence different progression-free survival and overall survival expectations," Informa Pharma Intelligence consultant Mark Lansdell told *Scrip*.

Going forward, the clearest application of this sort of regulatory path appears to be similarly rare mutations, but Lansdell and Kordoyanni agree it is an exciting change. "I think it will certainly encourage companies to think about this approach much more," Lansdell said, "and I'm sure we will see an uptick in trials designed to allow this kind of analysis of patients by biomarker status across a range of tumor indications." That may not translate into a boom in this type of approval, he noted. "It's certainly not an easy win."

> 'Until now, the FDA has approved cancer treatments based on where in the body the cancer started – for example, lung or breast cancers. We have now approved a drug based on a tumor's biomarker without regard to the tumor's original location'

MSI Incidence Rates

- 25% of sebaceous skin tumors
- 15% of colorectal cancer
- 15% of gastric cancer
- 10% of duodenal and ampulla of vater cancer
- 5% of Barrett's-related esophageal adenocarcinoma
- Up to 33% of endometrial cancer
- 10% of ovarian cancer
- 5% of cervical cancer
- 0-1% of breast cancer
- Exceedingly rare if not absent in glioma, hepatic, biliary tract and pancreatic cancers

Source: ESMO

Market Share

Symphony Health data for April show Opdivo is holding onto the majority share of the IO market, with 49%, followed by Keytruda with 27% (up 1 point from March), 17% for Yervoy and 7% for Tecentriq. Bristol's portion is slipping, but slower than expected, with 66% versus 72% at the end of 2016.

WHERE ARE THE OTHERS?

The most commercially significant new market for Keytruda is in CRC, and the rest of the PD-1/L1 class will be arriving soon. Datamonitor Healthcare forecasts the CRC market at $6.6bn in 2017, but just 5% of the population is a target for immunotherapy.

Bristol-Myers Squibb Co.'s rival PD-1 inhibitor *Opdivo* (nivolumab) is under FDA review for metastatic CRC in MSI-H or dMMR patients who have failed on prior therapy – the same claim as Keytruda's new indication – with an Aug. 2 user fee date. As with all oncology companies, Bristol pointed out it is evaluating a wealth of biomarker data. "In cancer, we're linking our biologic understanding of the disease and the immune system in the development of our agents to help identify the right treatment, for the right patient, at the right time and we'll be presenting numerous datasets evaluating multiple biomarkers including PDL1, MSI-H, TMB and LAG-3 at [the American Society of Clinical Oncology (ASCO) meeting in June]," the firm told *Scrip*.

Bristol has also eyed the CRC cohort as part of its ECHO-204 study of Opdivo in combination with Incyte's IDO inhibitor epacadostat; early data will be presented at ASCO. *(Also see "IDO Updates At ASCO: Incyte's Combos With Merck And Bristol Take Center Stage" - Scrip, 18 May, 2017.)*

Roche, which has a strong foothold in the CRC market with *Avastin* (bevacizumab), is counting on its PD-L1 inhibitor *Tecentriq* (atezolizumab) to keep its claim. *(Also see "Roche's Post-Avastin Strategy Stumbles As Vanucizumab Fails In Phase II" - Scrip, 21 Oct, 2016.)* It is counting on combination therapy to make CRC susceptible to immuno-oncology. Tecentriq is in a Phase III trial in combination with Roche's *Cotellic* (cobimetinib) in third-line and higher metastatic CRC, with data due in 2018, and in Phase I in combination with Cotellic and Avastin.

> 'Physicians will need to make a call when they have a patient who might benefit from this drug based on the results of their diagnostic test and make a second call to stop treatment if that patient is not responding'

The combinations should ultimately yield a broader CRC approval than Keytruda or Opdivo's monotherapy claims, as it would not be restricted to MSI-H or dMMR patients.

Still, with its in-house diagnostics capabilities, Roche more than most companies has focused on biomarker research in immunotherapy, looking at the range of patient responses and understanding the biology and immune response as a way to identify appropriate patient populations.

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Merck Under Fire For Remicade Pricing

The UK's Competition and Markets Authority is alleging that the pricing scheme that Merck Sharpe & Dohme (MSD; as **Merck & Co. Inc.** is known outside the US) has been using for *Remicade* (infliximab) broke competition law as it was likely to restrict competition from biosimilars of infliximab that were new to the market.

The scheme offered a discount to customers buying the product "in [the] same quantities, but if they were also to buy quantities of the biosimilar alternatives, the cost for Remicade would go up," a spokesperson for the CMA told *Scrip*. "So we allege that the scheme was anti-competitive by effectively penalizing customers who sought to buy alternative products as well as Remicade."

The CMA opened the investigation in December 2015 and at this stage of the investigation, the findings are still provisional. Merck told *Scrip* that is was "cooperating fully with the CMA's ongoing investigation" and "welcomes the opportunity to respond." The company is "confident that the proceedings will show that MSD has complied with competition law at all times. The discounts in question meant that infliximab was competitively priced and offered savings to the UK National Health Service, without hindering competition." Merck was "committed to the highest standards of ethics and integrity," it added.

Patient Detriment?

Warwick Smith, director general of the British Biosimilars Association (BBA), told *Scrip*: "It would be inappropriate to comment specifically on the provisional decision taken by the Competitions and Markets Authority with regard to MSD allegedly operating an anti-competitive discount scheme for its medicine Remicade. However, any activity which artificially restricts competition or impacts pricing to the detriment of patients must be examined."

Sukaina Virji Published online 23 May 2017

Is The Biosimilar Cost-Saving Theory Sustainable?

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Scrip has asked biosimilar drug developers, innovator companies and trade associations to shed light on whether the biosimilar theory of copycat drugs freeing up funds over time to pay for the next wave of novel biologics is sustainable and working in practice.

Furthermore, market commentators in Europe have offered insight on what incentives might work best to promote biosimilar use and why government involvement in biosimilar pricing brings with it problems as well as solutions.

Between 2006 and 2015, five distinct drug classes were impacted by the arrival of biosimilars:

1. human growth hormone
2. erythropoietin
3. G-CSF (granulocyte-colony stimulating factor)
4. follicle-stimulating hormone
5. tumor necrosis factor inhibitors – for example, *Remicade* (infliximab)

Meanwhile, biologics currently account for a large proportion of the top selling drugs worldwide and **AbbVie Inc.**'s *Humira* (adalimumab), a TNF inhibitor approved for inflammatory indications such as rheumatoid arthritis, has held the top spot as the world's best-selling drug for several years. In 2016, worldwide sales of Humira were $16.1bn. *(Also see "Humira's Inevitable Decline: What's Waiting In The Wings?" - Scrip, 8 Mar, 2017.)*

The consensus from market commentators is yes, the market theory for biosimilar cost-saving bringing benefits to healthcare systems, including releasing funds to afford other branded treatments, will work and have longevity… with caveats. Warwick Smith, director general of the British Biosimilars Association, said one issue that could affect the long-term success of biosimilars on the market is education. "Decision makers and clinicians and so on, they have to understand biosimilars to make sure there is the right level of uptake for these products."

Warwick Smith, British Biosimilars Association

Furthermore, until recently, one of the major barriers for competitors to biologic products losing patent protection was the lack of clear regulatory pathways for copycat versions. This situation has evolved slowly since 2000, the year the European Medicines Agency first unveiled guidelines for biosimilar drug developers seeking approval for new versions of biologics.

UNSTABLE REGULATORY PATHWAYS

Adrian van den Hoven, director general of Medicines for Europe (the European generic/biosimilar/value-added medicines association), told *Scrip* that in Europe the regulatory pathway for biosimilar drugs is stable and predictable. For example, he said that adaptations to the pathway are announced well in advance, enabling the industry to prepare for future developments. "Experience feeds back into regulatory science and the framework becomes more and more efficient," he said.

For instance, over the last few years, EU regulators have concluded that the robustness of the biosimilarity principles allow for the waiving of clinical trials for certain biologic molecules.

"We are also encouraged by the efforts of the EMA and national regulators to provide unbiased information to patients and healthcare professionals about the safety, quality and efficacy of these medicines," van den Hoven noted.

But he described regulatory developments in other jurisdictions as "moving targets."

Adrian van den Hoven, Medicines for Europe

While an approval pathway for biosimilars in the US has been established, the FDA is still issuing several important guidelines, for example: naming, labeling and interchangeability guidance. Van den Hoven pointed to the FDA's proposal for biosimilar differentiator suffixes as an unpredictable aspect for biosimilar developers in the US. *(Also see "Biologic Product Naming: US FDA Sticks With Suffixes 'Devoid Of Meaning'" - Pink Sheet, 12 Jan, 2017.)*

Generics Versus Biosimilars

GENERICS	COMPANY
Small molecules that are easy to copy	Complex biologics that are more difficult to replicate
Generic drugs take around two to three years to develop, with R&D costs falling between $2m and $5m	Biosimilars can take more than eight years to develop, with R&D costs falling between $100m and $200m
There are established regulatory pathways worldwide for generic drugs	Regulatory procedures for biosimilar products are still uncertain in many regions
Generics are interchangeable with originator products	Interchangeability is still unclear for biosimilars

FDA Biosimilar Approvals Anticipated In 2017

- Coherus BioSciences' CHS-1701: a version of Amgen's *Neulasta* (pegfilgrastim) that is expected to secure US approval in June
- Mylan and Biocon's MYL-14010: a version of Roche's *Herceptin* (trastuzumab) that is poised for a regulatory decision in September
- Amgen and Allergan's ABP 215: a biosimilar of Roche's *Avastin* (bevacizumab), also anticipated in September
- And Boehringer Ingelheim's BI 695501: a copy of Abbvie's *Humira* that should get a FDA result in the third quarter of this year

He also said the World Health Organization has been evaluating a similar biosimilar naming approach that he believes is "fraught with challenges, is incompatible with either the EU or US naming policies and which [I] hope will be dropped in favor of needed priority investments."

Van den Hoven thinks helping developing countries with regulatory capacity building, to both assess upcoming biological medicine applications and ensure quality manufacturing environments, is a critical aspect that needs addressing by groups like the WHO.

BIOSIMILAR PRICING EXPECTATIONS

Meanwhile, a spokesperson for Express Scripts, the largest US pharmacy benefit management organization, told *Scrip* the group believes that bringing biosimilars to market will help payers to afford the next breakthrough medicines that come to market despite biosimilars still being an emerging market place in the US.

"In the same way that generic utilization helped paved the way for savings in the pharmacy benefit, so too can biosimilar utilization. While there is a still a lot of work to be done to make biosimilars more readily available, we continue to advocate on behalf of our payers for greater biosimilar approval and adoption," they said.

According to 2017 primary research from Datamonitor Healthcare, US payers generally expect discounts of from 20% to 30% on biosimilars. Still, for some diseases, such as diabetes, they will be looking for higher discounts in the 40% to 50% range *(see sidebar)*.

In the US, it is expected that the focus initially for biosimilars will be driving use in treatment-naïve patients, but switching from reference products may follow. "Despite the cost-benefit that biosimilars provide, there is reluctance from some to move patients from an originator product if they are stable and responding to treatment. Some payers and physicians are therefore anticipating that biosimilars will mainly be used in biologic-naïve patients or in those who require a switch in therapy due to side effects or lack of efficacy," Datamonitor Healthcare's March 2017 report, *Biosimilars Market Access in the US*, notes.

[Editor's note: Datamonitor Healthcare's Biosimilars Market Access in the US report, available here*, includes original research with anonymized key opinion leaders.]*

Some European countries have had a more relaxed approach to switching patients from more expensive originator drugs over to biosimilars – however, many have expressly ruled out automatic switching by pharmacists and have place the decision in the hands of doctors. The Dutch agency came out in support of biosimilar switching in 2015 and others followed suit, the latest being the Italian regulator AIFA. *(Also see "Italy To Relax Biosimilar Switching Rules In Cost-Savings Effort" - Pink Sheet, 14 Dec, 2016.)*

COST SAVINGS & PATIENT ACCESS

Florian Turk, head of payor marketing, sales and relations at **Sandoz Inc.** (a **Novartis AG** company focused on generic and biosimilar drug development) breaks down the benefits of biosimilars into two categories: cost-saving benefits and patient access solutions.

Florian Turk, Sandoz

Turk believes that cumulative potential savings to healthcare systems in the EU and the US, as a result of the use of biosimilars, could reach approximately €100bn in aggregate over the next five years. But he said the success of biosimilars shouldn't be savings to healthcare systems alone. "Biosimilars allow for more patients being treated with these important medicines more cost effectively and this should be the critical measure of success," he said.

Turk noted that several barriers remain for biosimilar drugs that are disrupting the potential of these products to positively influence healthcare systems and patient access. As such, he highlighted three steps he thinks will help reimbursement bodies see the benefits of biosimilars:

- Payers must advance policies that ensure sustainability to the biosimilar market. For example, they can't impose "winner takes all tenders" and they must acknowledge that biosimilars are not generics.
- Payers and healthcare systems should also develop "gain-sharing" methods that allow physicians or hospitals to utilize part of savings from biosimilar use themselves, so they see the benefits directly.
- Finally, Turk believes quotas could be used to create competition while retaining prescriber choice.

"It is important to remember that when it comes to sustainability, we can see that biosimilars also provide the opportunity to increase efficiency of care delivery versus one-off cost savings," Turk said.

Meanwhile, van den Hoven concurred that biosimilar drugs have a crucial role to play in patient access to medicines. He noted that approximately 30%-40% of patients needing access to biological therapies face restricted access to those medicines, most of which have become standard of care treatments.

"Through competition, both in theory and over the 10 years of experience to date [with biosimilars], prices have significantly declined and healthcare systems have been able to reinvest parts of their medicines budget into the purchase of medicines for those patients currently denied access or in other much needed health services," he said.

Van den Hoven is also in favor of gain-sharing models, where part of the savings from biosimilar medicines are reinvested

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into better healthcare. He cited Norway as a region where hospital departments receive part of the savings from biosimilar usage. In the country, biosimilar medicines have reached market shares of around 90%, he noted. But in contrast biosimilar insulins in Norway – which are dispensed in a retail setting – do not use gain sharing methods for stakeholders. Van den Hoven said uptake of biosimilar insulins in Norway is close to zero percent. "The contrast is striking to say the least," he said.

Van den Hoven believes gain-sharing incentives for biosimilars are "the most successful strategy to encourage long-term competition in the biologic medicines market."

Novo Nordisk AS CEO Lars Fruergaard Jørgensen has a different take on access and biosimilars. He told *Scrip* that some cost savings from biosimilars will allow for access to future innovation. "There is a significant value allocated to biologics that are still patent protected. As biosimilars come in and drive that value down, I think there is an opportunity to release funds for future innovation," he said.

However, he added that in some markets there is still abstention when it comes to biosimilars. "In particular, in the US market there is a strong wish to get access to the best innovation, so if you have a good job, you expect your employer to provide you access … to the best. I know I'm not getting access in all cases to the latest innovation, I know it because I work in the pharmaceutical industry, but most ordinary people are not aware," he said.

He added that in the US, because of direct-to-consumer advertising, patients call for access to newer drugs. "There will be a pull and plans must have the latest innovation; with biosimilars I think there will be a balance that can help fund that pull," he said.

GOVERNMENT PRICE CUTS

In some European regions, governments have already imposed or are proposing mandatory price cuts that come into effect for originator products when a biosimilar version is approved. Ireland is one example where the country's health ministry is introducing this. *(Also see "Biosimilar Firms Say Irish Price Deal Hinders Uptake, As Govt Plans New Policy Measures" - Pink Sheet, 10 Feb, 2017.)*

Lars Fruergaard Jørgensen, Novo Nordisk

However, Smith believes this type of government intervention is not always helpful because cut-price original drugs further limit the market for biosimilars, deterring developers. "You could take lessons from the UK generics market where the government intervenes less than in other member states of the EU and we have the lowest generic prices in the EU despite this," Smith noted.

In practice, mandatory price cuts for originator products have left biosimilars redundant in markets. But without development of competitor, biosimilar versions there would be no leverage to push down prices for biologics – it is creating a scenario where biosimilar developers are not being rewarded for their R&D efforts.

As of February 2017, only three packs of **Samsung Bioepis Co. Ltd.**'s *Benepali*, a biosimilar version of Amgen's *Enbrel* (etanercept), had been sold in Ireland in the space of four months, compared with around 19,000 packs of Enbrel itself, according to the Health Enterprise Alliance, an Irish generic/biosimilar industry association that includes **Teva Pharmaceutical Industries Ltd.**, **Mylan NV** and **KrKa DD**.

Similarly, only 153 packs of *Abasaglar*, **Eli Lilly & Co./Boehringer Ingelheim GMBH**'s biosimilar version of **Sanofi**'s antidiabetic *Lantus* (insulin glargine), had been sold in the year from February 2016 to February 2017, compared with some 135,000 for the originator drug.

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NeuroVive To Move NeuroSTAT Forward

Sweden's **NeuroVive Pharmaceutical AB** has decided to take its potential traumatic brain injury therapy, *NeuroSTAT* (cyclosporine), into Phase IIb studies, after promising preclinical and Phase IIa studies suggesting it has promise in this therapeutic area of high unmet need.

There are no medicines currently available for traumatic brain injury. A violent blow to the head results in nerve damage that not only occurs immediately but also worsens over the following few days, requires hospitalization and highly expensive intensive care, and may still leave patients with functional disabilities. The initial trauma causes a release of pro-inflammatory cytokines that leads to swelling of the brain and increased intracranial pressure.

The market may be unpopulated at the moment, but a raft of companies is evaluating diverse approaches to the unmet need. **Cellvation Inc.**, for example, has been set up by **Fortress Biotech Inc.** to evaluate autologous bone marrow-derived mononuclear stem cells for brain injury that are also in Phase II clinical studies. And Stemedica Cell Technologies Inc. has a stem cell therapy in Phase II studies.

In preclinical studies conducted in collaboration with US researchers at the University of Pennsylvania, NeuroSTAT administration was associated with significantly reduced volumes of brain injury in animal studies, and improved brain energy metabolite levels, NeuroVive reported on May 23. And in a Phase IIa study conducted in Copenhagen, Denmark, cyclosporine was found to reach the CNS with dose-dependent pharmacokinetics in patients with brain injuries, with no unexpected safety signals. NeuroVive has expertise in genetic mitochondrial disorders, and believes that NeuroSTAT is inhibiting cyclophilin and protecting the function of the energy-producing cellular organelles, mitochondria, after brain injuries.

John Davis Published online 23 May 2017

Mehta Analysis: Biopharma's 10% Myth

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There's a prevailing narrative that drug spending is a relatively minor 10% of overall healthcare spending in the US. Like most narratives, this isn't completely wrong, but it ignores a relatively big portion of spending on drugs: those drugs that are administered in a hospital or clinic and get billed under a patient's medical benefit plan, rather than the drug benefit portion of their insurance. Taking those hospital administered drugs, and other such direct distribution channels into account, the biopharma share of healthcare spending jumps to an estimated 16.7% of personal healthcare spending (14.2% if you include government and insurance overhead in total spending).

We'll come back to that estimate in a bit, but first it is worth discussing where the 10% number comes from and how it became so fixed in people's minds. The where is easy: CMS (Centers for Medicare & Medicaid Services) collates and reports on national healthcare spending and has data on prescription drugs going back to 1960. It's interesting to see that in 1960, prescription drugs were right around 10% (9.8%) of the healthcare pie. But from that year on they started on a pretty steady downward trend, and were under 5% by the early 80's, when they started climbing again. By 2000 they were back to 9% and have stayed in the 9-10% range ever since.

HOSPITAL SPENDING

This seeming stability gives the impression that spending increases on pharmaceuticals have just matched overall healthcare inflation this millennium, but if we include the non-retail portion we can see this is not necessarily the case. Unfortunately, non-retail spending is not well documented. The best treatment of this comes from an Altarum Institute study based on unpublished IMS data on wholesale spending from 2008-2013. They found a remarkably consistent relationship between retail and non-retail wholesale spending, with non-retail channels coming in right around 28% of total drug spending over this six-year period.

From this data they try to extrapolate from wholesale prices, and make the assumption that markup from wholesale in each channel is the same. They acknowledge that this may not be realistic, and create a low estimate, where retail markup is 10% more than non-retail, and a high estimate where it is the reverse. However, pricing in this area is very opaque (an issue for a future column), and these adjustments may not go far enough. Studies we do have are suggestive that hospital markup is much higher than in other settings, which would lead to a significant underestimation of the non-retail share of drug spending.

More importantly, they use the fact that the share between the two channels was steady during the period they looked at, and assume it will remain relatively steady going forward. This assumption is likely not warranted, as the period from 2008-2013 was unique in recent history as a period of essentially no growth in total pharma spending with a CAGR of 1.9% vs. a 10.6% CAGR since 2013, a trend that CMS predicts will continue through the decade and into the next.

SPECIALTY DRUGS

To better understand this we need to delve a little bit into the so-called "specialty drugs" a topic that has been well covered, but not always well understood. Generally speaking, specialty drugs must have one or more of the following characteristics; expensive, difficult to administer, require special handling, a specialist to administer, or a biologic origin. For the purposes of this discussion that first one, expensive, is the most important.

Specialty drugs can be part of either the retail or non-retail channel, but they make up a much higher share of the non-retail market (58% vs. 33% according to IMS). Recently, the incredible growth in the hepatitis C market has put much of that specialty growth firmly in the retail side of the business, but this is not likely to repeat going forward with immuno-oncology, blood disorders, rare diseases, and farther in the future CRISPR therapies all making a big impact under the medical benefit, which suggests that the non-retail market will likely grow faster than the already fast pace of retail growth predicted by CMS over the next decade.

SO WHAT?

All of this raises the obvious question: So what? Drug spending is more than we thought, but it is still a small fraction of overall healthcare spending. And pharmaceuticals can lower healthcare spending in other parts of the system. So why does this overall narrative matter?

First, it matters because biopharma is approaching physician and clinical services share of around 20%.

Second, a handful of the drugs, mostly in the lesser understood 6%, account for over one-half of the healthcare inflation.

Third, this handful of drugs is much easier to target for any cost-containment efforts than the countless clinicians.

Above all, the recent script has turned pointedly against the biopharma industry, and globally so. Even the FDA uncharacteristically is being recruited in this cost focus under the new commissioner Gottlieb. Add the Trump unpredictability, and the cocktail is brewing for a volatile discourse that the biopharma managers can ignore only at their peril.

The industry can begin to address the undesirable focus on the cost of specialty drugs by appreciating the implications of their fast-growing share of the healthcare pie. Both innovators and payers will have to address the value these drugs offer to patients by scrutinizing the clinical benefit to patients vs the cumulative costs over their duration of use, and how this equation translates to potential savings to the society to assess the true benefit of the circa 15% of the healthcare pie that biopharma commands.

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Reid Hamilton, a partner at Mehta Partners, contributed to this column.

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Scrip's Rough Guide To IDO

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In the highly competitive field of immuno-oncology, one new target in particular has been capturing the attention of industry, investors and clinicians alike as a potential combination partner for PD-1/L1 checkpoint inhibitors: IDO.

Immune checkpoint inhibitors – including PD-1 and CTLA-4 – have emerged in force in oncology, sweeping aside old standards of care in a range of tumor types. Many questions remain, however, including how to identify responders and improve response rates. Combination therapy is expected to be the solution to improve responses and broaden immunotherapy's reach to more patients.

As Massachusetts General Hospital developmental therapeutics expert Keith Flaherty recently said at the American Association for Clinical Research (AACR) meeting: "We are still waiting for the big wave to break in terms of novel combinations." *(Also see "IDO Emerges As Clean Combo Partner, Rising Star At AACR" - Scrip, 4 Apr, 2017.)*

Enter IDO inhibitors, seemingly a safe new combination partner for PD-1/L1 inhibitors. To date FDA has approved members of the PD-1/L1 family from five big pharma sponsors – **Bristol-Myers Squibb Co.**, **Merck & Co. Inc.**, **Roche**, **Merck KGAA**/**Pfizer Inc.** and **AstraZeneca PLC**.

Indoleamine 2,3-dioxygenase (IDO1) is an enzyme that plays an important part in immune response.

The most advanced drug in the pipeline aimed at IDO is **Incyte Corp.**'s epacadostat, which is in Phase III for melanoma in a combination study with Merck's PD-1 inhibitor *Keytruda* (pembrolizumab), having jumped straight from Phase I to a registrational trial. *(Also see "J.P. Morgan Notebook Day 1: PCSK9 Face-Off, Teva's Slowed Growth, Merck's Keytruda Wins, Lilly's CDK4/6 Hopes And More" - Scrip, 10 Jan, 2017.)* Available data suggest epacadostat may enhance efficacy but not at the cost of severe toxicity seen with the combination of Bristol's PD-1 inhibitor *Opdivo* (nivolumab) and its CTLA-4 inhibitor *Yervoy* (ipilimumab).

"The ability to provide an additional systemic therapy with improved response and really, very little penalty that we can see in terms of toxicity, is extremely attractive," Roger Perlmutter, president of Merck Research Laboratories, said during the company's first-quarter earnings call on May 2.

A PROMISING PARTNER

Incyte notes that drugs aimed at IDO were inspired by research done in pregnant women in the 1990s. At that time, scientists discovered that IDO helps a fetus evade the body's immune system, escaping rejection that would be expected considering the presence of foreign genetic material from the father.

By expressing IDO, tumors can also escape detection by immune cells.

IDO sponsor **NewLink Genetics Corp.** explains that the enzyme breaks down tryptophan into kynurenine and other molecules.

"Low tryptophan levels and increased kynurenine levels are sensed by immune cells and result in suppressed or inhibited immune responses. We refer to this whole process from IDO enzyme expression to sensing tryptophan levels and the resulting immune reactions as the 'IDO pathway,'" NewLink said.

Furthermore, several different interferons, which are signaling proteins for immune response, stimulate immune responses and induce IDO expression, NewLink said.

CEO Chuck Link commented in an interview that like PD-1 and CTLA-4 inhibitors, IDO has a similar biological effect of taking away immunosuppression. Drugs that work on IDO are synergistic with PD-1 inhibitors and the two mechanisms are being tested together initially in "hot" tumor types, i.e., those that are known to respond to immunotherapy.

Multiple mechanisms can suppress immune response but "mechanistically IDO is pretty high on most peoples' list," according to Stuart Lutzker, vice president of bio-oncology exploratory clinical development at **Genentech Inc.**, which is partnered on an IDO program with NewLink. Interferon is an important part of the antitumor immune response due to the upregulation of IDO, so the mechanism is tightly linked to biology, the companies say.

HOW THEY WORK

Incyte's epacadostat and NewLink's Phase I navoximod (GDC-0919), which is partnered with Roche, bind directly to the IDO enzyme whereas NewLink says that its Phase II indoximod interacts with multiple places along the IDO pathway to elicit immune responses.

At a high level, indoximod "mimics tryptophan, so the immune cells sense a normal level of tryptophan and stay active, not suppressed. Indoximod counteracts the consequences of IDO being expressed," NewLink explained.

The candidates have fundamentally different mechanisms action – they are not the same drug, Link said.

It's possible that the two mechanisms – a more full pathway inhibitor and a specific IDO enzymatic inhibitor – are complementary, Link said.

LITTLE DATA, BIG BETS

Oncology players have been quick to jump in on IDO, even with relatively little data publicly available. Keytruda and epacadostat were tested together in the Phase I/II ECHO-202 study of about 400 patients, but so far Phase I data for only 19 melanoma patients have been released. In that cohort, the objective response rate was 58% and the complete response rate was 26%. A Phase IIII study of the combination started about a year ago.

Investors assume the results for other tumor types in the ECHO-202 study are strong; full data will be presented at the American Society of Clinical Oncology (ASCO) annual meeting, which is being held June 2-6 in Chicago.

At the AACR meeting, NewLink presented results for Phase II NLG2103 study of 60 melanoma patients, where indoximod demonstrated an ORR for non-ocular disease of 59% with CR in 12%. The company plans to test indoximod in one large Phase III study of metastatic melanoma that it intends to start by the end of the year. *(Also see "Incyte Eyes Big Phase III IDO Expansion, NewLink Plans First Pivotal Trial" - Scrip, 4 May, 2017.)*

Despite the limited data, investors are enthusiastic about the space, partly due to the big buy-in of big pharma.

In late March, Incyte and Merck clarified that beyond melanoma, they would run six additional pivotal trials in a range of tumor types, including non-small cell lung cancer.

Incyte is also collaborating with Merck's immuno-oncology rival Bristol – and shortly after Merck and Incyte announced their expanded trial plans, Incyte and Bristol said that they were expanding their collaboration to start two Phase III studies in first-line NSCLC and head and neck cancer.

All of these pivotal studies will hopefully start by the end of this year, Incyte said during its May 4 first-quarter earnings call.

Commenting in an April 4 note on the IDO class, Bernstein Research analyst Tim Anderson referred to Incyte as a "promiscuous company."

It has maintained the freedom to work with a range of partners, and though its deal with Merck is exclusive in terms of the clinical question that can be asked, there seems to be some wiggle room. "We are told that these two competing sets of studies have differences of some ill-defined sort, and that they ask a 'different clinical question.' What these subtle differences are at the moment remain unclear, but essentially the main question has to be the same: Could IDO+PD-1 become the 'next big thing'?" Anderson said.

Incyte's arrangement with Bristol is wide open and the company is currently running studies combining epacadostat with two PD-L1 inhibitors – Roche's *Tecentriq* (atezolizumab) and AstraZeneca's *Imfinzi* (durvalumab).

Although few financial details have been disclosed on IDO-related deals, the value big pharmas are placing on the class is clear based on the fast move to pivotal studies by Bristol and Merck with Incyte and on how early and often alliances have been inked.

- Bristol has BMY-986205 in Phase I in advanced cancers, an asset it acquired through its $800m buyout of Flexus Biosciences Inc. in February 2015. The company presented Phase I safety data at the AACR meeting showing that BMY-986205 combines well with Opdivo. Whereas epacadostat and indoximod are given twice daily, BMY-986205 is given once daily and Bristol hopes to position the candidate as highly potent and best-in-class.
- Merck gained a preclinical IDO inhibitor through the acquisition of Scottish start-up IOmet Pharma Ltd. in January 2016 for an undisclosed amount. *(Also see "Flexus flips IDO inhibitors to Bristol-Myers for up to $1.25bn" - Scrip, 24 Feb, 2015.)* Through the IOmet deal, Merck also gained TDO inhibitors.

Drugs Aimed At IDO In Development

SPONSOR/DRUG	DEVELOPMENT ACTIVITY
PHASE III	
Incyte's epacadostat. Direct inhibitor of IDO enzyme, blocks tryptophan metabolism. Partnerships with Merck and Bristol-Myers Squibb.	**Phase III:** Melanoma trial with Merck, combination with Keytruda. Registrational combination studies planned in NSCLC, RCC, bladder cancer, SCCHN. **Phase II or I/II:** Ovarian cancer, advanced solid tumors with PD-1/L1 inhibitors. **Phase I:** Bladder, head and neck cancer, NSCLC, kidney cancer.
PHASE II	
NewLink Genetics' indoximod. Acts on immune cells to reverse IDO pathway mediated suppression, tryptophan mimetic. Unpartnered.	**Phase II:** Melanoma, CRPC, breast cancer, brain cancer. **Phase I:** Acute myeloid leukemia, pancreatic cancer, NSCLC. **Phase I:** Solid tumors
NewLink's navoximod (GDC-0919). Direct inhibitor of IDO enzyme. Partnered with Roche	**Phase I:** Solid tumors, in combination with Roche's Tecentriq
Bristol's BMS-986205 (F001287). Selective IDO1 inhibitor. Acquired from Flexus.	**Phase I:** Advanced cancers, in combination with Bristol's Opdivo
iTeos Therapeutics' EOS200271 (PF-06840003). Direct inhibitor of IDO1. Partnered with Pfizer.	**Phase I:** Malignant gliomas
IND or Preclinical	
NewLink Genetics' NGL802. Prodrug of indoximod. Inhibits IDO pathway, tryptophan mimetic.	**IND:** Cancer
Regen Biopharma's dCellVax. Therapy uses cells harvested from patients and modified by gene-silencing technology so as to lose expression of the immune checkpoint gene IDO.	**IND:** Breast cancer
Nektar's NKTR-218. IDO pathway inhibitor.	**Preclinical:** Cancer
IOmet's IDO inhibitor. Subsidiary of Merck.	**Preclinical:** Cancer

Source: Biomedtracker, clinicaltrials.gov, company websites

- Pfizer has also bought in, signing on for iTeos Therapeutics SA's preclinical program, led by EOS200271, in December 2014 for €24m. *(Also see "iTeos: Developing IO Therapeutics For Hot And Cold Tumors" - Scrip, 15 Mar, 2017.)*
- Roche paid $150m upfront in October 2014 for NewLink's NLG919 and additional IDO and TDO compounds. *(Also see "NewLink-Genentech deal could be worth more than $1bn " - Scrip, 21 Oct, 2014.)*

The expansion of collaborations with Incyte raised questions about whether Bristol and Merck were not that confident about their own earlier-stage internal assets.

Merck's Perlmutter acknowledged during the first-quarter call that the Keytruda/epacadostat program was "quite broad," but that it feels there are opportunities for both IDO1 and TDO1 inhibitors, and perhaps dual inhibitors. "We actually have a whole family of such compounds which have different properties. They're just beginning to come out of the preclinical space, soon into the clinic. So fairly soon we'll have an opportunity to see how those actually behave," the exec said.

Asked about IDO during Bristol's first-quarter earnings call on April 27, CEO Giovanni Caforio said that collaborations give the company the ability to be competitive from a timing perspective, while advancing potentially the best-in-class agent. (*See table below for IDO candidates in development.*)

MARKET PLAYS FAVORITES

The partnership deals and the market are showing a clear preference for Incyte and direct IDO inhibitors over NewLink's IDO pathway approach. Some investors describe indoximod as "not a real IDO inhibitor."

Biomedtracker analyst Robert Jeng noted that the mechanism of action with indoximod has been unclear and that starting out

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of the gate this has been a disadvantage. Brad Loncar, CEO of Loncar Investments, commented that there has long been skepticism about the mechanism of action for indoximod and noted the huge and perhaps unfair difference in market capitalization between Incyte and NewLink.

Upon the release of indoximod data at the AACR meeting, NewLink stock dropped by 10% to $20.79. On May 8, the company had a stock price of $16.37 and overall the company had a market capitalization of about $500m. In comparison, investors are currently valuing Incyte's IDO program alone at somewhere between $10bn and $15bn, Loncar noted.

"Incyte certainly deserves to be valued significantly higher because they are years ahead of NewLink, but that still doesn't necessarily add up to such a jaw-dropping valuation," Loncar commented. In his opinion, "either Incyte is grossly overvalued or NewLink is grossly undervalued." The results of Incyte's first Phase III trial in melanoma next year will be a significant determining event.

ASCO AHEAD

Investors are counting on data at the upcoming ASCO meeting to help show why Merck and Bristol have put so much faith in the IDO class. Incyte's Stein commented that the companies will "show the world" why they progressed to Phase III with certain indications.

Releases include data from the ECHO-202 study of epacadostat with Keytruda and ECHO-204 of epacadostat with Opdivo. The abstracts demonstrate that these combinations are well-tolerated and the preliminary efficacy for both demonstrate encouraging clinical activity, both within and across tumor types, commented Incyte CEO Hervé Hoppenot.

"These results compare favorably to contemporary data in the second-line setting," the exec told *Scrip*.

The ASCO meeting will also feature Phase I/II data for Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab) with NewLink/Roche's navoximod.

Barclays analyst Geoff Meacham said in a May 17 note that the Incyte's safety and efficacy data for epacadostat were in line with expectations and that Bristol's combination data were as expected.

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ASCO IDO Updates: Incyte's Merck/ Bristol Combos Take Center Stage

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IDO inhibitors are sure to be a hot topic at the American Society of Clinical Oncology annual meeting, with **Incyte Corp.** at the lead, in partnership with **Merck & Co.** and **Bristol-Myers Squibb Co.**

PD-1/L1 inhibitors can go only so far in immunotherapy, which is why there is so much focus on potential combinations. Inhibitors of indoleamine 2,3-dioxygenase (IDO1), an enzyme that plays an important part in immune response, are shaping up to be the most promising partners for the programmed-death class.

The lead IDO inhibitor is Incyte's epacadostat, which went straight from Phase I combination studies to rival Phase III trials. Early data on combination use with Merck's PD-1 inhibitor *Keytruda* (pembrolizumab) suggest epacadostat may boost efficacy without the severe toxicity seen with the combination of Bristol's PD-1 inhibitor *Opdivo* (nivolumab) and its CTLA-4 inhibitor *Yervoy* (ipilimumab).

Merck and Incyte have a Phase III pivotal study of epacadostat plus Keytruda in melanoma under way, with six other tumor types in the works. By the end of the year, Incyte and Bristol expect to have started two registrational studies of epacadostat and Opdivo.

There are some differences within the IDO category. Incyte's epacadostat and **NewLink Genetics Corp.**'s Phase I navoximod (GDC-0919), which is partnered with **Roche**, bind directly to the IDO enzyme, whereas NewLink's Phase II indoximod affects multiple places along the IDO pathway.

In a preview of the ASCO meeting, to be held June 2-6 in Chicago, Biomedtracker analysts noted that after "several years lingering on the radar" with relatively little clinical data to examine, IDO inhibitors are ready to make their mark.

The ASCO meeting features data from the Phase I/II ECHO-202 study evaluating epacadostat in combination with Keytruda.

"Data from the study have been presented previously, but the ASCO abstracts [released May 17] feature quantitative details from each tumor type that laid the foundation for the Phase III expansions," they noted.

> 'These data are more focused on the safety profile of the combination but do include early response rates'

"Overall, the data are quite positive with response rates of 35% [non-small cell lung cancer (NSCLC)], 35% (bladder), 31% [head and neck cancer (SCCHN)], and 30% [renal cell carcinoma (RCC)], which are generally higher than PD-1 monotherapy suggesting additive efficacy. The promise of a potential combination therapy with Keytruda for NSCLC is particularly noteworthy as Keytruda has been competing strongly in the large lung cancer market," the analysts added.

Top-line data were also released for epacadostat with Bristol's Opdivo in the ECHO-204 study.

"These data are more focused on the safety profile of the combination but do include early response rates for melanoma (75%), ovarian (11-18%), and [colorectal cancer (CRC)] (4%)," the analysts said.

Another highlight at ASCO this year is the release of Phase Ib data for NewLink/Roche's IDO inhibitor navoximod with Roche's PD-L1 inhibitor *Tecentriq* (atezolizumab).

"The abstract reveals a relatively low 9% ORR which appears to be all partial responses (no CRs). No details were provided on the individual dose responses, though, so the response rate could improve in the disease-specific expansion cohorts if an appropriate dose is identified," Biomedtracker analysts concluded.

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IDO At ASCO 2017: Highlights of Clinical Presentations

The American Society of Clinical Oncology meeting, being held June 2-6 in Chicago, will be an important meeting for the IDO class, particularly Incyte's epacadostat, which is being developed in combination with all of the leading PD-1/L1 inhibitors. Key presentations and abstract data are below.

PRESENTATION	ABSTRACT NUMBER	HIGHLIGHTS OF EARLY ABSTRACT DATA
INCYTE/MERCK		
Epacadostat plus Keytruda in SCCHN: Phase I/II results from ECHO-202/KEYNOTE-037	Abstract #6010	N=38, 81% had 1-2 prior lines of treatment and 19% ≥3 prior lines of treatment. ORR (CR+PR) and DCR (CR+PR+SD) for patients with 1-2 prior treatment were 34% (2 CR, 8 PR) and 62% (8 SD), respectively. For ≥3 prior treatment, ORR and DCR were 14% (1 PR) and 43% (2 SD). Grade ≥3 TRAEs: 11%. One dropout due to TRAEs (increased amylase, lipase).
Epacadostat plus Keytruda in patients with advanced urothelial carcinoma: Phase I/II data from ECHO-202/KEYNOTE-037	Abstract #4503	N=40. Preliminary ORR and DCR for evaluable patients were 35% (13/37; all PR) and 57% (21/37; 13 PR, 8 SD), respectively. For patients with 0-1 prior line of treatment, ORR and DCR were 37% (10/27) and 63% (17/27). Grade ≥3 TRAEs in 20% of patients. Three dropouts due to TRAEs (rash, COPD and diarrhea).
Efficacy/safety of epacadostat plus Keytruda in NSCLC. Phase I/II results from ECHO 202/KEYNOTE-037	Abstract #9014	N=43, ≤2 prior lines of treatment (84%), and no prior tyrosine kinase inhibitor treatment (93%). For 40 efficacy-evaluable patients, ORR and DCR were 35% (14/40; 14 PR) and 60% (24/40; 10 SD), respectively. N with PD-L1 testing: 28/40. ORR and DCR for patients with PD-L1 ≥50% and ≤2 prior treatment were 43% (3/7; all PR) and 57% (4/7; 1 SD), respectively. For patients with TPS <50% and ≤2 prior treatment, ORR and DCR were 35% (6/17; all PR) and 53% (9/17; 3 SD). Grade ≥3 TRAEs in 16%. Two TRAE dropouts (increased AST and ALT, brain edema).
Efficacy/safety of epacadostat plus Keytruda in triple-negative breast cancer and ovarian cancer: Phase I/II ECHO-202 study.	Abstract #1103	N=39 with TNBC and 37 OVC. Most had ≥3 prior lines of treatment. For TNBC patients, ORR was 10% (4; all PR) and DCR was 36% (14; 10 SD). ORR and DCR for patients with ≤2 prior treatment were 12% (2) and 29% (5), respectively, and for ≥3 prior treatment were 9% (2) and 41% (9). For OVC patients, ORR was 8% (3; all PR) and DCR was 35% (13; 10 SD); ORR and DCR for patients with ≤2 prior treatment were 13% (1) and 25% (2), and for ≥3 prior treatment were 7% (2) and 38% (11). Grade ≥3 TRAEs in 13% of TNBC,19% OVC patients. TRAE-related dropouts: one TNBC (ascites) and 1 OVC (arthralgia).
Epacadostat plus Keytruda pembrolizumab in advanced renal cell carcinoma: Phase I/II results from ECHO-202/KEYNOTE-037.	Abstract #4515	N=33. Of 30 efficacy-evaluable patients, 63% (19) had 0-1 prior treatment and 37% (11) had ≥2 prior treatment for advanced disease. ORR and DCR for patients with 0-1 prior treatment was 47% (9/19; 1 CR, 8 PR) and 58% (11/19; 1 CR, 8 PR, 2 SD respectively; for patients with ≥2 prior treatment, ORR and DCR were 0% and 36% (4/11; all SD). Grade ≥3 TRAEs in 15%. Two TRAE dropouts (autoimmune hepatitis and aseptic meningitis/headache/nausea/vomiting/anxiety).
INCYTE/BRISTOL		
Epacadostat plus Opdivo in advanced solid tumors: Phase I/II results from ECHO-204, with dose escalation	Abstract #3003	N=241. For 23 SCCHN patients on E 300 mg, DCR was 70%. Of 30 MEL patients, eight treated with E 100 mg and 22 on E 300 mg. ORR. ORR and DCR in MEL patients treated with E 100 mg were 75% (all PR) and 100% (8; 2 SD), respectively. DCR in MEL patients treated with E 300 mg was 64%. Of 29 OVC patients, 18 had E 100 mg and 11 had E 300 mg. ORR and DCR for OVC patients on E 100 mg were 11% (2; 2 PR) and 28% (5; 3 SD). For 11 OVC patients treated with E 300 mg, ORR and DCR were 18% (2; 2 PR) and 36% (4; 2 SD). For 25 CRC patients (all E 100 mg), ORR and DCR were 4% (1; PR) and 24% (6; 5 SD). TRAE dropout rate: 7%.
NEWLINK/GENENTECH		
Phase Ib dose escalation study of combined inhibition of navoximod (GDC-0919) and Tecentriq in locally advanced or metastatic solid tumors	Abstract #105	N=52, six cohorts. Median 3 prior treatments. 1 DLT: Grade 3 sepsis syndrome at GDC-0919 200 mg dose. Treatment-related ≥ Grade 3 AEs in seven (13%) patients (incl. nausea, rash, sepsis syndrome, fatigue, and pneumonitis. No treatment-related G4/5 AEs. Two TRAE dropouts (one due to pneumonitis). In 45 efficacy-evaluable patients, four (9%) PR and 11 (24%) SD.
NEWLINK/VALEANT		
Phase II randomized, double-blind study of Provenge followed by indoximod, or placebo in metastatic castration resistant prostate cancer	Abstract #3066	N=46. No difference in PSA progression or primary endpoint of immune response to Provenge for 35 patients who completed study. Median OS not reached. Median radiographic PFS: 10.3 months for treatment arm vs 4.1 months in placebo arm (p=0.011). PFS of 4.1 months similar to PFS in pivotal IMPACT study of Provenge.

Source: ASCO

Disappointing Bydureon EXSCEL Outcomes Data May Raise Stakes For Victoza

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The failure of **AstraZeneca PLC**'s GLP-1 receptor agonist *Bydureon* to prove superior efficacy over placebo in the largest outcomes study of a diabetes drug completed to date may make physicians question the robustness of the cardiovascular benefit for **Novo Nordisk AS**'s *Victoza*, some analysts say.

The Phase IIIb/IV EXSCEL study tested the once-weekly injectable Bydureon (exenatide extended release) against placebo, both on top of standard of-care therapy in more than 14,000 patients. AstraZeneca announced on May 23 that Bydureon met the primary safety endpoint of non-inferiority in terms of the risk of major adverse cardiovascular events (MACE) – a composite endpoint that includes cardiovascular (CV) death, nonfatal myocardial infarction (MI) and nonfatal stroke. The drug failed to show superior efficacy on this endpoint, though it did show a numerical improvement.

Leerink Swann analyst Seamus Fernandez noted in a May 23 report that if EXSCEL had showed a CV risk reduction benefit, it would have helped to "provide strong supporting evidence for the cardio-protective effect for the GLP-1 class," bolstering growth overall.

AstraZeneca noted in a statement that the study was "the largest and most inclusive patient population of any CV outcomes trial of the glucagon-like peptide-1 (GLP-1) receptor agonist class conducted to date, having included more than 14,000 patients from 35 countries."

Full data will be presented at the European Association for the Study of Diabetes (EASD) meeting in mid-September. Analysts will be looking for more information about the trial, including the magnitude of the numerical benefit, subgroup data and analysis about the effects on blood sugar-lowering, and blood pressure in the trial relative to other GLP-1 receptor agonists.

The FDA requires outcomes studies of diabetes drugs to rule out greater risk for cardiovascular events, so non-inferiority is a positive result from the regulatory point of view, but superiority is the upside that sponsors have been hoping for, because it promises commercial advantages in terms of increasing physician buy-in.

Bydureon is the second GLP-1 agonist to fail to show superior efficacy in a cardiovascular outcomes trial, after **Sanofi**'s Adlyxin/Lyxumia (lixisenatide), which also did not meet this mark in the ELIXA study, though it did succeed in terms of safety.

Even prior to the EXSCEL report, Bydureon did not have a strong position in the diabetes drug market and was expected to decline further in coming years. AstraZeneca reported sales of $578m in 2016 and Datamonitor Healthcare projects the drug will bring in just $238m worldwide in 2025.

COMPETITORS SHOW STRENGTH IN CV OUTCOMES

Bydureon has had a hard time competing with **Novo Nordisk AS**'s once-daily *Victoza* (liraglutide), which demonstrated modestly better blood sugar reduction and weight loss effects in a head-to-head trial, Biomedtracker and Datamonitor noted in a joint analysis issued on May 23. Bydureon also has always struggled with a more "cumbersome injection device," they commented.

Boehringer Ingelheim GMBH/Eli Lilly & Co.'s SGLT-2 inhibitor *Jardiance* (empagliflozin) became the first diabetes drug to secure a cardiovascular benefit claim from FDA in December 2016. In that case, labeling recognizes a benefit for a reduction in risk for cardiovascular death in particular. The new claim was supported by data from the EMPA-REG outcomes study, in which Jardiance demonstrated a 14% reduction in risk for MACE, driven by a 38% risk reduction for CV death. *(Also see "Jardiance's Cardiovascular Benefit Claim Bodes Well For Other Products Too" - Pink Sheet, 5 Dec, 2016.)*

Victoza demonstrated outcomes benefits in the LEADER study of 9,340 patients, with a 13% reduction in MACE and a 22% reduction in risk for CV death (*see table*). Novo Nordisk is pursuing a broad claim with FDA for Victoza in MACE reduction.

Novo Nordisk's investigational once-weekly GLP-1 agonist semaglutide demonstrated a significant 26% reduction in MACE, including a significant 39% reduction in non-fatal events in the SUSTAIN 6 outcomes study of 3,297 patients. Novo Nordisk filed the drug with regulators in December 2016,

GLP-1 Outcomes Data And Sales Data*

SPONSOR/DRUG	RESULTS, TYPE 2 DIABETES OUTCOMES TRIALS	2016 SALES
AstraZeneca's once-weekly Bydureon	**EXSCEL**: n=14,000. Exenatide met primary safety endpoint against placebo, non-inferiority for major adverse cardiovascular events (MACE). Fewer CV events were observed in Bydureon arm of, but efficacy objective of superior reduction in MACE was not statistically significant.	$578m
Novo Nordisk's once-daily Victoza	**LEADER:** n=9,340. Liraglutide significantly reduced MACE risk by 13%. Results driven by 22% reduction in CV death. Reductions in non-fatal MI and non-fatal stroke not statistically significant.	$3bn
Novo Nordisk's once-weekly semaglutide, filed in December 2016	**SUSTAIN 6:** n=3,297. Semaglutide demonstrated 26% reduced risk of MACE, mainly driven by 39% significant reduction in non-fatal stroke. Non-significant 26% reduction in non-fatal MI and neutral outcome on CV death.	NA
Sanofi's once-daily Adlyxin/Lyxumia	**ELIXA:** n=6,000. Lixisenatide neither increased nor decreased risk of MACE.	$36m
Eli Lilly's once-weekly Trulicity	**REWIND:** Results expected in 2019.	$925m

**Figures converted to $US and rounded.*

but will not pursue broad labeling for CV risk reduction based on the SUSTAIN 6 data. Rather, the company will perform a larger, longer CV post-approval outcomes trial that has the potential to broaden labeling later.

Datamonitor and Biomedtracker analysts conclude that EXSCEL results may hasten Bydureon's rate of decline, but that the major implication is the potential to change physicians' perception of the LEADER study for Victoza. "While physicians had not necessarily been expecting a GLP-1 agonist class effect given differences between drugs in the class, having a good explanation for the difference in outcomes could help NVO prevent questions about the robustness of the CV effects of Victoza," the analysts noted.

The analysts added that Bydureon's failure also increases the importance of **Eli Lilly & Co.**'s GLP-1 agonist *Trulicity* (dulaglutide) to demonstrate CV outcomes benefits, if physicians are to keep faith in the LEADER data. Data from the REWIND outcomes study of Trulicity are expected in 2019.

There are a number of noteworthy differences in the designs of the various outcomes trials. AstraZeneca's study was obviously much larger than LEADER and SUSTAIN 6.

SUSTAIN 6 was a small study and could have been "more impacted by fluctuations in the magnitude of endpoints just due to chance," the Datamonitor and Biomedtracker analysts noted.

AstraZeneca noted to *Scrip* that compared to other outcomes studies, the EXSCEL enrollment criteria had a broader age inclusion (down to age 18 with no cutoff point), very low baseline A1C levels (as low as 5.5%), and did not require patients to have pre-existing CV risk factors or existing cardiovascular disease.

An AstraZeneca-funded study comparing trial designs will be presented on June 11 at the American Diabetes Association meeting in San Diego (abstract no. 1515-P).

Evercore ISI analyst Umer Raffat questioned in a May 23 note whether Novo Nordisk had enriched its outcomes trials more than competitors. Raffat noted that in the LEADER study Novo Nordisk defined "prior cardiovascular disease" as including renal impairment or chronic heart failure, whereas AstraZeneca defined CVD using coronary artery disease, peripheral arterial disease (PAD) or ischemic cerebrovascular disease.

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PML Case With Roche's Ocrevus, Link Unlikely

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Swiss big pharma **Roche** has confirmed that it is investigating a German report of progressive multifocal leukoencephalopathy (PML) in a patient treated with its new multiple sclerosis therapy, *Ocrevus* (ocrelizumab), although in circumstances that suggest the case may not become the first to link the adverse event with the company's new blockbuster hope.

For one thing, the treating physician believes the infection may have been due to previous therapy with **Biogen**'s MS therapy, *Tysabri* (natilizumab), a drug known to be associated with the development of PML. The patient was John Cunningham (JC) virus-positive and was previously treated with natalizumab for three years, with the last infusion in February 2017, Roche noted in a statement on the case. The patient then received one dose of ocrelizumab in April 2017 in a compassionate-use program in Germany.

Further, PML has not been associated with ocrelizumab during the clinical development of the drug, although there are good reasons to believe there might be a risk of finding such an association. That's because ocrelizumab depletes CD20-expressing B lymphocytes, a similar mode of action to Roche's anticancer drug *Rituxan* (rituximab) that has in the past been associated with a handful of cases of PML. Tysabri has a different mode of action, acting as an integrin receptor antagonist.

Roche said it was gathering further details about the case. Ocrevus was first launched in the US in March 2017, for both relapsing-remitting MS and for primary progressive MS. Marketing approval in Europe is expected later this year, with analysts suggesting it will have a disruptive effect on the MS market and garner peak sales of $5bn. The most common adverse reactions to Ocrevus, according to US labeling, are infusion reactions that can be serious, and infections including upper respiratory tract infections, skin infections, and herpes.

Although no cases of PML were seen during Ocrevus's clinical studies, and there are no black box warnings about PML on its US label, the condition, which usually leads to severe disability, or death, is discussed in the US labeling, because of its anti-CD20 directed cytolytic mode of action

The US-headquartered Biogen is also assessing the information on the PML case, that company said. Natalizumab has been associated with a number of cases of PML, and the association is included in its labeling in the US and Europe. *(Also see "EMA Recommendations To Minimize Risks With SGLT2 And Tysabri " - Scrip, 29 Feb, 2016.)*

GOOD NEWS FOR FAMPYRA

Elsewhere in the MS field, Biogen had some good news to report on May 24 with its later-generation multiple sclerosis therapy, *Fampyra* (fampridine) prolonged-release tablets, getting full approval from the European Commission for improving the walking distance of MS patients.

Fampyra is licensed from **Acorda Therapeutics Inc.** to develop and market outside the US and was granted a conditional approval for the indication in 2011. *(Also see "Conditional European approval for Fampyra for MS walking disability" - Scrip, 26 Jul, 2011.)*

Biogen reports that a third Phase III study, ENHANCE, has confirmed the benefits and safety of Fampyra over the long term in patients with either relapsing or progressive forms of MS, leading to the granting of a full approval. Around 80% of patients with MS have problems with their walking, and fampridine can be used alone or in combination with disease-modifying MS therapies, Biogen noted.

In ENHANCE, results from which were first reported in 2016, significantly more Fampyra-treated patients achieved a clinically meaningful improvement in walking ability compared with placebo-treated patients (43.2% vs. 33.6%, respectively; p=0.006), as measured by the self-reported 12-item MS Walking Scale (MSWS-12), the primary endpoint.

Significantly more Fampyra-treated patients experienced improved mobility compared with placebo-treated patients, measured by the clinician-reported timed up and go (TUG) speed from baseline (43.4% vs. 34.7%, P = 0.03).

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Patient Group Collaboration In Rare Diseases Offers Model For Cell/Gene Therapy Firms

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Companies trying to bring cell and gene therapy products to market might do well to model their R&D and commercial planning efforts on drug makers working in the rare disease space, where partnerships with disease-specific foundations and patient advocacy groups have provided access to some financing as well as expertise in clinical trial design and help with trial enrollment while laying the groundwork for pricing acceptance by patients and clinicians.

Rare disease drug development has provided a model for what patient and disease advocacy groups can bring to the table, **Fibrocell Science Inc.** CEO John Maslowski said during a May 22 panel at the Alliance for Regenerative Medicine/EBD Group's Cell & Gene Exchange partnering conference in Washington, D.C. Fibrocell develops autologous cell and gene therapy applications for skin and connective-tissue disorders, with a lead candidate, FCX-007, in Phase I/II for recessive dystrophic epidermolysis bullosa. *(Also see "Fibrocell acquires rights from UCLA; seeks a lead on adult mesenchymal stem cells from dermal skin cells" - Scrip, 17 May, 2012.)*

"A lot of these diseases, there aren't models, there aren't validated clinical endpoints as there are for large, higher-prevalence diseases," Maslowski said. "You need to learn a lot about that and there's ways to do that. One of the ways is through natural history studies and through other analyses, and how you do that is you really need to know the patients and where to access them." The typical patient identification strategies used for larger indications usually won't prove very useful, he added.

"It is really important to partner early on with these organizations and then when you go to FDA and they start asking questions like 'How are you going to prove efficacy and potency?' you need to have learned a lot about the disease to answer those questions," he continued. "If you go in without anything, they're going to send you back to start collecting this data. And the first place to go, I think, is advocacy groups that are designed to be sophisticated and have these data, have control over them, and also know the patients, know what their needs are, what endpoints are really important to them."

Working with larger, umbrella organizations like the Alliance for Regenerative Medicine and Global Genes – a genetic-disease focused patient advocacy group with a mission to "eliminate the challenges of rare disease" – is one way to find models for successfully developing cell and gene therapies, **Abeona Therapeutics Inc.** CEO Tim Miller noted.

But disease-specific groups are the best source to learn about the biomarkers and biophysical changes that will matter most to that patient population, he added. "This is how these therapies are going to be measured for success and it's by engaging these rare disease communities that you are able to do that," Miller said. Abeona's two lead programs (ABO-101 and ABO-102) are adeno-associated virus (AAV)-based gene therapies for two types of Sanfilippo syndrome. *(Also see "Video Interview: Abeona Breaking Into Rare Diseases " - Scrip, 12 Feb, 2016.)*

Shutterstock: Pressmaster

"The individual disease foundations are the ones where you're going to get the endpoints and learn about the disease and what qualitative outcomes are going to be important, because again there's little [data] out there to be judged against."

PROVIDING THE 'LOW-HANGING FRUIT' BIG PHARMA SEEKS

Ron Bartek, president and co-founder of the Friedreich's Ataxia Research Alliance and a National Organization for Rare Disorders board member, explained that as larger companies began facing patent cliffs and other headwinds during the past decade or so in more common disease areas, they would tell groups like NORD that they were looking to move into rare disease drug development. But these companies also stressed that their initial focus would be on "low-hanging fruit."

"So, a lot of our foundation leaders ran back to our boards of directors and staffs and said, 'What we've got to do now is grow low-hanging fruit,'" he said. "And we have defined low-hanging fruit … as doing the things that our pharmaceutical partners – of which we had none at the beginning – need to develop rare disease therapies. Things like funding the basic discovery science ourselves – a lot of our foundations have done just that."

Doing that has helped characterize the diseases and identify the most viable targets for therapy, Bartek added. "We've established patient registries, natural history databases, and supported clinical networks consisting of clinicians and coordinators that know our patients, know our disease. We've done a lot of match-making between our discovery scientists and the

A Network Of Alliance Partners

Both Abeona's and Fibrocell's websites include sections titled "Patients & Families" that list the advocacy groups each works with and provides links and further information on those organizations.

For its lead indication, recessive dystrophic epidermolysis bullosa (RDEB), Fibrocell lists DebRA (the Dystrophic Epidermolysis Bullosa Research Foundation of America) and is supporting that group's 19th annual benefit in October as well as its fundraising golf event in November, and the EB Research Partnership, as well as NORD and Global Genes. In 2014, Fibrocell announced that it would present on the potential of its genetically modified autologous fibroblast technology at DebRA's Patient Care Conference to demonstrate its "commitment to engage and support advocacy groups for patients with rare diseases."

Abeona's site lists and links to an exhaustive list of research advocacy and patient-support groups for Sanfilippo syndrome and related conditions such as Batten disease. It outlines 12 US organizations – including The Children's Medical Research Foundation, Cure Sanfilippo Foundation, Team Sanfilippo Foundation and Batten Disease Support & Research Association. In addition, it links to similar groups in Australia, Canada, Ireland, Mexico, Spain and Switzerland.

biopharmaceutical industry. We've created translational tools, the assays, the cell and animal models, the biomarkers, the biorepositories that [industry] uses to advance its research. We've assembled and supported the field; we've grown the field."

As cell and gene therapy technology matures, drug developers are able to take advantage of this more mature patient and disease organizational landscape. For a field that has exploded in recent years, and as the first few products near the market, alliances with advocacy organizations can go a long way toward understanding the disease, how to study it and preparing the market for advanced therapeutics.

> 'For our patients, it's about access, but access can't be sustained if pricing goes past reimbursement and our healthcare system can't be sustained unless pricing-plus-reimbursement is feasible'

Bartek noted that when his Friedreich's ataxia group held its first scientific conference in 1999, it had 80 participating scientists and no biopharmaceutical industry partners. When the group's sixth scientific meeting convenes later this year in Italy, there will be roughly 400 participating scientists and representatives from about a dozen biopharma companies in attendance. The group works with roughly 35 companies, he said, with nine sponsoring clinical trials.

Patient advocacy groups are also working with the National Institutes of Health and the FDA, "another aspect that our pharma partners find very attractive," Bartek said. "The net result is that we go from clinical trials that are poorly organized, in which the endpoints don't match with what's important to the patients, to clinical trials that are well organized, very well matched to the patients' needs, procedures that are tolerable, and the endpoints are recognized by the FDA as validated. You do a clinical trial very quickly; you can recruit it in hours, not months or years, so you have a clinical trial that has a much better shot on goal and very few amendments, if any; very few dropouts, if any."

A key lesson learned in the past five to 10 years, said Wendy White, board chair of Global Genes, is that for companies trying to address a rare disease without consulting with advocacy groups "if they don't have the natural history, if they haven't done ethnographic research and really talked to patients, they can end up three or four years down the road and come up with something that's not going to be accepted at the FDA. Sometimes, what they find out are things they could have learned had they talked to patients at the very beginning."

Fibrocell's Maslowski noted that the rare disease community has provided a model for working with advocacy and patient groups on cell and gene therapy approaches to rare skin disorders. Abeona's Miller, however, warned that when such groups participate in a financing round, that can create potential conflicts of interest, such as a small family-run foundation wanting some guarantee that their kid will get enrolled in a clinical trial.

"Up front, when you're getting involved with a foundation, you have to have very clear lines of expectations," he said. "A very simple thing to think about is to make sure that they're involved with the enrollment criteria. For many of the gene therapies, especially AAV gene therapy, there are some exclusion criteria, particularly if you have neutralizing antibodies against that particular [therapeutic candidate]. It's very easy to come up with a line that says we're going to consider all comers, but within this realm of criteria, we can't sign over any one child or any one family, but here's what we're going to be looking at."

PARTNERING ON THE RATIONALE FOR PRICING

In an era of widespread concern about drug pricing, communicating with advocacy groups early on also can build understanding and even buy-in about how a drug for rare, unmet medical need must be priced for its development to be economically viable, the speakers said. Just as ultra-orphan drugs can carry extremely high costs, personalized therapies or gene therapies that represent a cure are likely to have high prices.

Bartek recommended talking to advocacy groups early on about a formula for making the process workable for the entire health care system, with White adding that "the earlier, the better" for such discussions.

"I would begin with what I call an algebraic formula. It's pricing-plus-reimbursement equals access-plus-sustainability," Bartek explained. "For patient groups like ours, it's really all about access, but access can't be sustained if pricing goes way past reimbursement and our health care system can't be sustained unless pricing-plus-reimbursement is feasible for the whole health care system."

A related consideration, White said, is communicating about the possibility of compassionate use protocols for high-priced medicines. Again, she stressed talking to advocates as early as possible if a company is not planning to do compassionate use.

"If you're going to decide that you're not going to do compassionate use, then you better say that really early and give a really good reason," she said. "It can't be 'Oh, we don't have enough,' because nobody really believes you."

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

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Selected clinical trial developments for the week 19–25 May 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
AstraZeneca PLC	benralizumab	severe eosinophilic asthma	ZONDA; NEJM online, May 22, 2017. BISE; The Lancet Respiratory Medicine, May 22, 2017.
Amgen Inc.	*Prolia* (denosumab)	osteoporosis	FREEDOM; The Lancet Diabetes & Endocrinology, May 22, 2017.
Eli Lilly & Co.	*Taltz* (ixekizumab)	psoriatic arthritis	SPIRIT-P2; The Lancet, May 24, 2017.
GW Pharmaceuticals PLC	*Epidiolex* (cannabidiol)	Dravet syndrome	NEJM, May 25, 2017.
La Jolla Pharmaceutical Co.	LJPC-501	hypotension/shock	NEJM online, May 21, 2017 .
AbbVie Inc./ Neurocrine Biosciences Inc.	elagolix	endometriosis	Solstice, Violet PETAL; NEJM online, May 19, 2017.
Updated Phase III Results			
Amgen Inc.	*Repatha* (evolocumab)	dyslipidemia	FOURIER; reduced CV events.
Alkermes PLC	ALKS 5461	major depressive disorder	FORWARD-4, 5; continued benefits.
Radius Health Inc.	*Tymlos* (abaloparatide)	osteoporosis	ACTIVEextend; reduced fractures through 3.5 years.
Shire PLC	SHP465	attention deficit hyperactivity disorder	Effective in adult patients.
Sunovion Pharmaceuticals Inc.	dasotraline	binge eating disorder	Reduced binge eating frequency.
Sunovion Pharmaceuticals Inc.	SUN-101/eFlow (glycopyrrolate)	COPD	GOLDEN-3, -4, -5; well tolerated and effective.
Theravance Biopharma Inc./ Mylan NV	revefenacin	COPD	Additional safety and efficacy data.
Intra-Cellular Therapies Inc./ Bristol-Myers Squibb Co.	lumateperone	schizophrenia	Well tolerated in further data.
Merck KGAA	oral cladribine	multiple sclerosis	ORACLE MS; benefit in early disease.
Phase III Interim/Top-line Results			
Amgen Inc./UCB SA	*Evenity* (romosozumab)	osteoporosis	ARCH; met primary endpoint, CV safety signal observed .
Celgene Corp.	ozanimod	relapsing multiple sclerosis	RADIANCE; met primary endpoint.
Gedeon Richter PLC	*Vraylar* (cariprazine)	major depressive disorder	Safe combined with adjunctive therapy.
AstraZeneca PLC	*Bydureon* (exenatide)	type 2 diabetes	EXSCEL; did not increase CV risk.
Shire PLC	*Natpara* (rhPTH 1-84)	hypothyroidism	RACE; maintained efficacy over three years.
Aerie Pharmaceuticals Inc.	*Roclatan* (netarsudil/ latanoprost) eyedrops	glaucoma	MERCURY2; primary endpoint achieved.
Teva Pharmaceutical Industries Ltd.	*Austedo* (deutetrabenazine)	tardive dyskinesia	RIM-TD; well tolerated over 52 weeks.
Merck & Co. Inc.	*Dulera* (mometasone/ formoterol)	asthma	Well tolerated in long-term LABA safety study.
Otsuka Holdings Co. Ltd.	tolvaptan	autosomal dominant polycystic kidney disease	Positive primary and secondary endpoints.

Source: Biomedtracker

Three CHMP Negative Opinions – But Who Got A Boon?

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The EMA's CHMP issued three negative opinions on new medicines at its May meeting. This was particularly noteworthy as there were no negative opinions issued by the CHMP in all of 2016.

The subjects of the CHMP thumbs down were:

Helsinn Group's *Adlumiz* (anamorelin hydrochloride), for anorexia, cachexia or unintended weight loss in patients with non-small cell lung cancer.

AB Science's *Masipro* (masitinib), for systemic mastocytosis.

XBiotech Inc.'s human IgG1 monoclonal antibody specific for human interleukin-1 alpha, for debilitating symptoms of advanced colorectal cancer.

"For these three products, data provided by the companies did not allow the CHMP to conclude that the benefits of the medicines were greater than their risks. In terms of timing, this is a coincidence and should be seen as such," the EMA told *Scrip*.

So bad news for patients, but what does this mean for other companies working in these areas?

Helsinn's Adlumiz (licensed from **Chugai Pharmaceutical Co. Ltd.**) is a first-in-class ghrelin receptor agonist. Of the three companies that received bad news from the CHMP on May 19, it alone has indicated it will not be seeking a re-examination of the decision. "Helsinn is in discussion with the EMA on next steps for an additional Phase III trial and will provide an update when possible," the company told *Scrip's* sister publication, *Pink Sheet*. Helsinn was already in discussions with the FDA regarding a trial design for a Phase III study of anamorelin in a bid to pursue approval of the product in the US.

AEterna Zentaris Inc. is testing a ghrelin agonist, *Macrilen* (macimorelin), in Phase II for cachexia, but the product received a complete response letter (CRL) from the FDA in November 2014 for its lead indication, adult growth hormone deficiency. Discussions with the FDA on what happens next are ongoing.

AB Science has issued a three-page statement explaining its grounds for requesting a re-examination. With Novartis in late-stage clinical testing of midostaurin in systemic mastocytosis and promising pivotal Phase II data published in the *New England Journal of Medicine* last year, the setback is significant for AB Science. *(Also see "Novartis Takes Aim At Systemic Mastocytosis With Midostaurin" - Scrip, 1 Jul, 2016.)*

XBiotech said in a filing with the US Securities and Exchange Commission that it would ask for a re-examination "promptly" of its colorectal cancer antibody and "firmly believes" it has a strong case.

This is somewhat surprising as last month the company acknowledged that the product was "unlikely" to garner a positive CHMP opinion, and that "additional steps would need to be taken to potentially gain marketing approval."

But with new immuno-oncology drugs impressing regulators on a frequent basis, nothing less than stellar clinical data is likely to get through the approval process these days. *(Also see "Keytruda Approval Opens New Routes For Immuno-Oncology" - Scrip, 24 May, 2017.)*

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APPOINTMENTS

Jigar Raythatha rejoins **Constellation Pharmaceuticals** as president and CEO from Jounce Therapeutics Inc., where he was chief business officer since December, 2012. Raythatha was the first employee at Jounce and helped build the company and previously, he was head of corporate development at Constellation. Constellation has also named ***Padmanee Sharma***, and ***Robert Schreiber***, to its scientific advisory board (SAB). Sharma is a scientific director and professor in the departments of genitourinary medical oncology and immunology at The University of Texas MD Anderson Cancer Center and is a medical oncologist and immunologist. She is the principal investigator of several immunotherapy clinical trials. Schreiber is the alumni-endowed professor of pathology and immunology, professor of molecular microbiology, and co-leader of the Tumor Immunology Program (TIP) of the Siteman Cancer Center (SCC) at Washington University. He is also founding director of the newly formed Washington University Center for Human Immunology and Immunotherapy Programs. ***James E. Audia***, Constellation's chief scientific officer since 2011, will be named independent member of the board of directors and scientific advisor of the company – effective July, 2017.

Allied Minds, a holding company focused on venture creation with the life science and technology industries, has appointed ***Jill Smith*** president and CEO. Smith is a non-executive director of Endo International plc and Gemalto and previously held the same position at SoundBite Communications, Elster Group and Hexagon.

Bone Therapeutics has named ***Steve Swinson*** and ***Damian Marron*** to its board of directors as non-executive directors replacing ***Jacques Reymann*** and ***Jean-Jacques Verdickt***. Swinson has held various senior roles in orthopedic medical technology and electronics companies, including Medtronic International, where he was vice president and general manager for the international spine division. Most recently, Marron was CEO of Agalimmune and previously he was CEO of France based companies, TxCell and Trophos.

Rita Jain has joined **Akebia Therapeutics**, Inc., a company focused on kidney diseases, as chief medical officer and senior vice president. With 20 years of experience in drug development, Jain joins the company from AbbVie, where most recently she was vice president of men's and women's health and metabolic development. She has previously held leadership roles at Pharmacia Corp. and at the North Shore University Hospital, where she was the director of the program in novel therapeutics.

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