



China doll Upjohn ‘magic’ Mylan merger mate? Deal with Pfizer unit welcome

By Randy Osborne, Staff Writer

Calling the tie “magic,” [Pfizer Inc.](#) CEO Albert Bourla defended his firm’s decision to spin off its [Upjohn](#) unit and merge in an all-stock deal with [Mylan N.V.](#), creating a new entity to be named later with pro forma revenues as high as \$20 billion. “We have a commercial footprint that is very much focused on China, on emerging markets,” he said, which will help Mylan.

Bourla was responding on a conference call with investors to a question from Raymond James analyst

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Canadian medicine chest not big enough for both Canada and the U.S.

By Mari Serebrov, Regulatory Editor

Even as the Trump administration is committing itself to helping states implement laws that would allow drug importation from Canada as a way to combat higher U.S. prescription drug prices, Canadians are pushing back against the idea.

“We are deeply concerned by the implications of any legislation in the U.S. Congress and state legislatures that would allow for the draining of Canada’s medicine supply to the United States,” 15 Canadian patient advocacy, pharmacy and professional groups said in a letter last week to Canada Health Minister Ginette Petitpas Taylor.

Earlier in the week, U.S. Health and Human Services (HHS) Secretary Alex Azar had committed to working on importation efforts to help lower U.S. drug costs. That commitment came after

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Lexicon shares crash after Sanofi abandons diabetes alliance

By Michael Fitzhugh, News Editor

Shares of [Lexicon Pharmaceuticals Inc.](#) (NASDAQ:LXRX) fell 70.3% Monday to \$1.69 as [Sanofi SA](#) terminated a \$1.7 billion diabetes collaboration with the company. The decision followed two trials in which [Zynquista](#) ([sotagliflozin](#)), a dual SGLT inhibitor, failed to make a statistically significant dent in blood sugar control in patients with chronic kidney disease, a common result of diabetes. As a result, Sanofi will not launch the product in Europe, where its already approved as an adjunct to insulin therapy for type 1 diabetics, a spokesman told *BioWorld*.

In dispute with Sanofi, Lexicon called notice of the termination a breach of contract and held fast to optimism about Zynquista’s odds of “achieving continued success in the balance of the core phase III program,” CEO and president Lonnel Coats said.

Lexicon declined to make further comment on the termination ahead of an investor call it has scheduled for Thursday. But in a statement about the development, its chief medical officer Pablo Lapuerta pointed to the potential benefits of Zynquista for type 2 diabetics (T2D) demonstrated in other components of the phase III program, called Insynchrony. Although adults with severe CKD “narrowly missed statistical significance on A1C,” he said, “we are very encouraged by the overall results in that study and look forward to phase III data from the remainder of the core studies from the Insynchrony program later this year.”

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Entresto from Novartis fails its critical phase III in heart failure

By Lee Landenberger, Staff Writer

The failure of [Novartis AG’s Entresto](#) in a phase III clinical trial staggered the stock (NASDAQ:NVS) somewhat Monday, down just 1.14%, but the real trauma may well be the loss of roughly \$2.5 billion in anticipated sales.

While Novartis didn’t release specific numbers, the pharma giant said the Paragon-HF clinical trial “narrowly” missed its composite primary end point in reducing cardiovascular death and total heart failure hospitalizations in patients with preserved ejection fraction. The study was an

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The BioWorld Biome

Much bias, little binary

In sex differences in gene expression, ‘the whole genome is in the game’

By Anette Breindl, Senior Science Editor

Sexual dimorphism in gene expression is widespread across chromosomes, and is partially conserved across species from mice to humans, the first study to investigate such differences both across species and across tissues has found.

But though there was much sex bias, there was little sex binary. “In males and females, many sliders are being moved a little bit,” David Page told *BioWorld*.

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Regulatory front

Teva Pharmaceutical Industries Ltd. agreed to pay the state of California \$69 million in what California Attorney General Xavier Becerra Monday called the largest pay-for-delay settlement received by any state. The settlement, which includes an injunction prohibiting Teva from entering into pay-for-delay agreements for 10 years, resolved state allegations that the Jerusalem-based company delayed generic competition to narcolepsy drug Provigil (modafinil) through four pay-for-delay agreements between 2006 and 2012. Last month, California reached a \$760,000 settlement, included an eight-year injunction, with **Endo International plc**, of Dublin, over pay-for-delay agreements delaying generics of shingles drug Lidoderm (lidocaine topical patch 5 percent) for almost two years. Separate, smaller settlements were reached with Teva and **Teikoku Pharma USA**, a subsidiary of Japan's Teikoku Seiyaku Co. Ltd., over the Lidoderm agreements, Becerra said.

Amgen Inc.'s efforts in prosecuting its 8,273,707 patent, which claims methods of purifying proteins using hydrophobic interaction chromatography, doomed its infringement suit against **Coherus Biosciences Inc.**, of Redwood City, Calif., according to the **U.S. Court of Appeals for the Federal Circuit**. The appellate court Monday affirmed a decision by a lower court, which found that, in Amgen's efforts to overcome a patent examiner's rejections based on prior art, the Thousand Oaks, Calif.-based company repeatedly argued that the prior art didn't disclose the particular combinations of salts cited in the '707 patent. When Coherus developed a biosimilar to Amgen's Neupogen (pegfilgrastim), it used a different combination of salts in its process. Amgen claimed infringement based on the doctrine of equivalents. But since "Amgen clearly and unmistakably surrendered salt combinations other than the particular combinations recited in the claims," the Federal Circuit said it couldn't claim infringement under the doctrine

of equivalents. The court rejected Amgen's assertion that the arguments made in its last response prior to the patent allowance "must be the focus of any argument-based estoppel analysis." While the appellate court recognized that Amgen's last response to the U.S. Patent and Trademark Office didn't include "particular combinations," it said that didn't erase Amgen's prior statements. "There is no requirement that argument-based estoppel apply only to arguments made in the most recent submission before allowance," the Federal Circuit said in the precedential ruling.

The **FDA** revised its 2014 draft guidance on rare pediatric disease priority review vouchers. In addition to incorporating comments on the original draft, the revision reflects provisions of the 2016 Advancing Hope Act that updated the definition of a rare pediatric disease as a rare disease with serious or life-threatening manifestations that primarily affect individuals 18 years old or younger. The revisions include explanations of the eligibility requirements for the voucher and the rare pediatric disease designation process, along with examples to illustrate the agency's current thinking on review determinations. Comments on the revised draft should be submitted by Sept. 28. In related news, the FDA finalized its 2017 draft guidance on developing drugs to prevent delayed graft function in kidney transplantation.

The **FDA** approved a new boxed warning about an increased risk of blood clots and of death with the 10-mg, twice-daily dose of tofacitinib (Xeljanz, Xeljanz XR) indicated to treat ulcerative colitis. The agency also limited the drug's approved use for ulcerative colitis to patients who are not treated effectively or who experience severe side effects with certain other drugs. The labeling changes for the New York-based **Pfizer Inc.** JAK inhibitor followed a review of interim data from an ongoing safety clinical trial of tofacitinib in patients with rheumatoid arthritis (RA). The trial is examining the 10-mg, twice-daily dose and a lower dose of the medicine, the agency said. The higher dose is not approved for RA or psoriatic arthritis.

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Mylan

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Elliot Wilbur, who called Upjohn, which is New York-based Pfizer's off-patent branded and generic established medicines unit, "basically a conduit for Pfizer loss of exclusivity [LOE] assets" that "ultimately is a fixed portfolio, and these assets all have finite lives. So how do we think about your ability to generate growth from this portfolio currently being acquired over a medium to longer-term horizon? Is there any component of the transaction that would give Upjohn or the newco optionality on Pfizer products that may be going off patent in the U.S. and have similar profile to the existing product portfolio?"

As organizers formed Upjohn, "we particularly picked a portfolio of Pfizer products that have gone recently LOE, and we looked at where are the sources of growth for these products," Bourla said. Officials took into account the "expansion of the old middle class, the desire of patients in mostly emerging markets and in China to have access to better-quality, trusted brands. We saw the rise of noncommunicable diseases – 70% of patients in the world die from noncommunicable diseases and 80% of those deaths come from the emerging markets. And that's where we saw we can make a difference. That's where we saw opportunities."

Analyst Wilbur called the transaction "innovative, creative" and "a win for both companies." Cowen's Ken Cacciatore wasn't so certain, writing in a report over the weekend when news of the pact surfaced that "slamming bad things together [is] unlikely to solve" Mylan's problems. "The simple answer is that [the Upjohn combo] is indeed better than Mylan" by itself. "But we should note that we have long felt that standalone Mylan was absolutely broken."

Under the terms, Pfizer shareholders would own 57% of the combined firm, with Mylan, of Hertfordshire, U.K., taking 43%. The boards of both companies have approved the deal unanimously.

The pro forma 2020 adjusted earnings before interest, taxes, depreciation and amortization (EBITDA) is expected to range between \$7.5 billion and \$8 billion, including what the companies described as "phased synergies" of about \$1 billion annually to be realized by 2023. Pro forma free cash flow for 2020 is forecast at more than \$4 billion, and the new company, to bear a name not yet disclosed, aims to achieve a 2.5x ratio of debt to adjusted EBITDA by the end of 2021. It also plans a dividend of about 25% of free cash flow beginning the first full quarter after the deal is finalized, and the potential for share repurchases once the debt to the adjusted EBITDA target is sustained.

The combined firm will be led by Mylan's chairman Robert Coury, who will serve as executive chairman, "a real active" and non-traditional role, he said during a conference call with investors. Coury will "lead the strategic direction" with Michael Goettler, group president of Upjohn, who is taking the CEO role. Rajiv Malik, current Mylan president, will serve as president of the new company. Ken Parks, currently chief

financial officer of Mylan, will depart and Heather Bresch, Mylan's CEO, is retiring when the deal closes. The board of the created firm will include the chairman, CEO, and eight members designated by Mylan, with three chosen by Pfizer. Incorporated in Delaware, the firm will be domiciled in the U.S. and will operate global centers in Pittsburgh, Shanghai, and Hyderabad, India. Coury said Pfizer brings to the table a "welcome discipline." The new company expects to have particular leverage in China.

'Wealth-destroying mess'?

Bourla said during the call that the arrangement combines "the best aspects of Pfizer's and Mylan's DNA." Mizuho analyst Irina Koffler agreed, calling the setup "a Goldilocks scenario for Mylan." Pfizer has predicted that Upjohn would take a hit this year and next year because of the LOE for the fibromyalgia/pain drug Lyrica (pregabalin), returning to low-single digit growth afterwards, "we conservatively assume revenue in the merged business decline 5% without additional pipeline investment or mergers and acquisitions." Lyrica pulled in 39% of first-quarter revenue this year and recently went generic, she pointed out in a report.

Cowen analyst Steve Scala, in a report Sunday, said that divesting Upjohn would leave Pfizer's biopharma business "with a number of very good components – internal medicines, oncology, hospital, vaccines, inflammation/immunology, and rare disease," noting that Pfizer earlier took biosimilars as well as sterile injectables out of Upjohn though leaving such major players as the cholesterol therapy Lipitor (atorvastatin calcium), arthritis drug Celebrex (celecoxib) and erectile dysfunction treatment Viagra (sildenafil).

BTIG's Timothy Chiang sounded cautious, saying the merger "might make sense" since it would create a leading global generics company with "well-established off-patent products from Upjohn, which still generate significant cash flow, and Mylan's global pharma platform, which we estimate to generate over \$11 billion of revenue with EBITDA of greater than \$3 billion this year," though he cited "a number of challenges" for Mylan, "especially in the U.S. where fundamentals remain weak due to price erosion and operational issues."

Mylan's Coury said during the call that he was "extremely pleased to find out what assets they put in Upjohn, because it fit us like a glove. It would have taken us, I kid you not, probably another three years to get to this place. We were moving in this direction" but the merger gives Mylan in one stroke "everything that we need" while strengthening the bottom line, which is "why we have the confidence to change the business model to return capital to shareholders immediately." He promised analysts that "we are going to sit with you and we're going to come up with the right way to profile this very unique company that's really an 'N' of one." Moody's placed the A1 senior unsecured long-term rating of Pfizer under review for downgrade while affirming the company's Prime-1 commercial paper rating. Although the

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Canada

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President Donald Trump had asked Azar to cooperate with Florida Gov. Ron DeSantis in implementing that state's new law permitting drug importation from Canada.

The Florida law is one of more than 27 different importation measures introduced in the U.S. Congress and state legislatures over the past year. Many of the measures would allow American consumers to buy Health Canada-approved drugs through "authorized" wholesalers and Canadian online pharmacies, while others would permit personal importation from Canadian pharmacies.

Under current U.S. law, importation is already permissible, but it requires HHS certification that the imported drugs are safe. That's something no HHS secretary has been willing to do – yet. (See *BioWorld*, March 2, 2017.)

In writing to Petitpas Taylor, the organizations, which include the Canadian Medical Association and Diabetes Canada, noted that Canadians are already suffering the impact of drug shortages – and that's without having to share their drugs with the U.S. The letter cited a recent report by the C.D. Howe Institute that found 250 drug shortages per month in Canada in 2017. One of the researchers involved in that report said Canada routinely experiences a shortage of 700 to 1,000 drugs at any given time.

Those shortages would be exacerbated if patients in the U.S. started relying on drug imports from Canada. "Hospital and community pharmacies in Canada are resourced to serve the Canadian public [about 36 million people]. They are not equipped to support the needs of a country 10 times its size without creating important access or quality issues," the organizations said.

The letter also raised concerns that U.S. importation would fuel a proliferation of illegal online sites claiming to be licensed Canadian pharmacies. As it is, such sites already threaten patient safety on both sides of the border, the organizations said. They pointed to estimates from the U.S. National Association of Boards of Pharmacy indicating that about 35,000 online drug sellers are operating, 96% of which are operating illegally outside of Canada's borders. In addition, 600 new illegal pharmacy sites are launching every month.

"Canadian law enforcement cannot protect patients from illegal foreign actors who blatantly disregard both Canadian and U.S. laws, and operate anonymously or hide offshore," the groups said in the letter.

In light of the importation efforts in the U.S., the organizations asked Health Canada to intervene to ensure the availability of prescription drugs for Canadians. They also asked the agency to provide clarity on the implications U.S. importation would have on the Canadian drug supply by discussing existing laws and regulations that would keep Canadian drugs from leaving the country and additional measures that could be taken to protect Canada's drug supply. ♦

Mylan

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Upjohn separation is likely to be leverage neutral, the review for downgrade is prompted by other aspects of the transaction that are credit-negative, the service said, including a reduction in Pfizer's scale and product diversity, and a significant reduction in free cash flow. The latest move also tilts Pfizer's business mix toward that of a pure-play pharma company, which Moody's views as higher risk due to factors including R&D chances taken and the volatility created by patent expirations. "Pfizer's scale and diversity is likely to further decline based on the likely exit of a consumer products venture with Glaxosmithkline plc," of London, Moody's said.

Cowen analyst Cacciatore followed his blistering weekend report with an update Monday after the conference call and Mylan's earnings report, both of which left him even less convinced. "Many are arguing that this new entity will find itself better positioned than standalone Mylan. We are not sure that is the right question, and we are now even more unsure whether that statement is even accurate," he wrote. "Rather than fixing Mylan's problems, the Upjohn business will likely compound them." Management had guided Mylan's 2019 adjusted free cash flow to reach \$1.9-2.3 billion, "which is down dramatically vs. 2018 and essentially the same levels as 2015," he added. "With today's disclosures of their anticipated 2020 standalone revenue guidance and EBITDA expectations, it would appear that 2020 will also be another flat year of standalone cash generation. This deterioration of adjusted free cash flow over the last few years has been despite a tremendous investment (more than \$15 billion) toward both company and product acquisitions. Very rarely do we see such a systemic and wealth-destroying mess."

Mylan chalked revenues of \$2.85 billion, up 2% compared to the prior year period. Leerink analyst Ami Fadia noted that second-quarter earnings per share of \$1.03 was above the 94-cent consensus and her firm's 93-cent estimate. Shares of the company (NASDAQ:MYL) closed Monday at \$20.78, up \$2.32. Pfizer's stock (NYSE:PFE) ended the day at \$41.45, down \$1.64. ♦

Regulatory front

The U.K.'s **National Institute for Health and Care Excellence** (NICE) approved the use of **Astrazeneca plc's** Lynparza (olaparib) as a first-line maintenance treatment in advanced ovarian cancer through the Cancer Drugs Fund. The drug had previously been approved for later stage treatment. The new approval followed an undisclosed commercial arrangement with the Cambridge, U.K.-based Astrazeneca, according to NICE. Olaparib will remain on the Cancer Drugs Fund until more data are collected from an ongoing clinical trial that's comparing the PARP inhibitor with placebo. So far, trial results estimate that olaparib delays disease progression by about three years, NICE said, but patients in the trial haven't been followed long enough to determine if the drug actually delays disease progression longer.

Lexicon

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A third study, SOTA-MET, comprised the remainder of top-line results reported by Sanofi Friday. It found that a 400 mg dose of Zynquista did demonstrate a statistically significant reduction in HbA1c vs. placebo at 26 weeks in patients already on metformin.

In total, the Insynchrony program consists of 11 phase III trials to evaluate the efficacy and safety of Zynquista in adults with T2D on various therapeutic backgrounds. The trials include placebo and active comparators and are also evaluating patients with CKD, cardiovascular risk factors, and heart failure, as well as patients age 55 and older. No imbalances or new safety signals were observed in the three studies for which it disclosed results, Sanofi said.

Trouble keeping pace

The Zynquista program has struggled to catch up with Eli Lilly and Co.'s 'gliclozin, Jardiance (empagliflozin; co-marketed with Boehringer Ingelheim GmbH) and to measure up to Sanofi's apparent expectations for it following the November 2015 deal it struck with Lexicon.

Announced in the same week Sanofi struck an agreement with Seoul-based Hanmi Pharmaceutical Co. Ltd. to develop a portfolio of experimental, long-acting diabetes treatments, the Lexicon deal carried \$300 million up front up to \$1.4 billion in milestones, plus royalties. Called "significant R&D alliances" by Sanofi's then-CEO, Oliver Brandicourt, both deals were intended to bolster Sanofi's standing in diabetes at a time of "tougher-than expected market conditions," he said during the company's fourth quarter 2015 earnings call. Sanofi's collaboration with Mannkind Corp.'s inhaled insulin Afrezza

ended around the same time. (See *BioWorld*, Nov. 9, 2015 and Jan. 6, 2016.)

Despite those aspirations, Sanofi has suffered from sluggish performance relative to its big-pharma peers, with only Bayer AG, Novo Nordisk A/S and Bristol-Myers Squibb Co. posting worse returns in terms of share-price performance during a Brandicourt's tenure, according to a recent *BioWorld* analysis. Shares of Sanofi (NASDAQ:SNY) rose 67 cents Monday to close at \$43.03, up .2% from a year ago.

And despite its regulatory success in Europe, the Zynquista program has faced trouble with the FDA, drawing a complete response letter from the U.S. regulator in March. Lexicon's CEO Coats said at the time that his firm would not be making any comments about the "nature or content" of the CRL, beyond that the FDA found Zynquista not approvable. (See *BioWorld*, June 10, 2019 and March 25, 2019.)

J.P. Morgan analyst Jessica Fye said that the limited detail available on Insynchrony's outcomes suggested "Zynquista may offer limited benefit in patients with more advanced renal impairment."

"Part of our caution on the commercial opportunity for Zynquista as a late entrant in the T2D setting was that even with a label showing activity in CKD patients, it would be a challenge to gain meaningful share," she said. "The termination of the collaboration, however, represents a clear setback even relative to our low expectations as we expect it would be challenging for LXR to commercialize Zynquista for type 2 independently."

Lexicon reported having cash and cash equivalents of \$45.8 million as of March 31, the time of its first quarter earnings report. During its investor call, Thursday, it will update its financial and operating results, it said. ♦

Regulatory front

The U.S. **Health and Human Services' Office of the Assistant Secretary for Planning and Evaluation** is seeking comment on ensuring legitimate access to controlled substances, including opioids, while preventing diversion and abuse. It also is looking for ways federal, state, local and tribal governments can collaborate to address access and abuse issues. The comments will be used as the office prepares a congressional report in which it must identify obstacles to legitimate patient access, address diversion issues, advise on enhancements to state prescription drug monitoring programs and detail medical education efforts. Comments on the request for information should be submitted by Aug. 29.

The **British Pharmacopeia** and the **U.S. Pharmacopeia** signed an agreement Friday formalizing their long-standing partnership to strengthen the quality of medicines. The agreement establishes a framework for cooperative activities, including developing drug product monographs, information sharing and expanding collaboration to new areas. The organizations said they intend to exchange scientific staff and participate in joint events.

Financings

Ziopharm Oncology Inc., of Boston, said it entered into an agreement with existing investors for the exercise of previously issued warrants to purchase common stock in a private placement, being led by existing stockholder, MSD Partners LP, that is expected to result in gross proceeds of approximately \$45 million. Concurrently, in the private placement, Ziopharm will issue new warrants to purchase up to 15 million additional shares of common stock with an exercise price of \$7. The funds help strengthen the company's balance sheet and will fund operations into 2021.

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Novartis

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investigation into the safety and efficacy of sacubitril/valsartan, a combination ACE/nephrilysin inhibitor, vs. the active comparator valsartan in patients with heart failure with preserved ejection fraction (HFpEF).

There currently is no approved treatment for these patients.

In January 2018, Novartis CEO Paul Hudson predicted wider use of Entresto had potential to rake in \$4 billion to \$5 billion a year. It's not his problem anymore though; Hudson is leaving Novartis to become CEO at Sanofi SA on Sept. 1.

Analysts at Jefferies viewed the phase III failure as a mere stumble and took a long view. The company shares can further appreciate, they noted, especially should optimistic sales figures for Novartis' Cosentyx and possible boosts from two debuts hold true.

"We still view Novartis as a quality EU Pharma growth story, with potentially exciting Mayzent and Zolgensma launches, plus ongoing Cosentyx momentum together driving consensus EPS upgrades," they wrote Monday.

Mayzent (siponimod) recently was given the nod for adults with relapsing forms of multiple sclerosis that include secondary progressive multiple sclerosis (SPMS) – where it's the first and only therapy – as well as relapsing remitting disease. Basel, Switzerland-based Novartis won Mayzent's approval based on the phase III trial called Expand, the largest-ever controlled clinical experiment of SPMS patients, which proved that the treatment significantly reduced the risk of disease progression, including impact on physical disability and cognitive decline. Jefferies analysts predict a \$1.25 billion worldwide peak in Mayzent sales. (See *BioWorld*, March 28, 2019)

Even more recent is Novartis' Zolgensma (onasemnogene neparovect), which received FDA approval for its Avexis Inc. unit. Zolgensma is a new gene therapy designed to treat all types of spinal muscular atrophy (SMA) in children under 2 with biallelic mutations in the survival motor neuron 1 gene. Jefferies weighed in again by predicting a rapid adoption of the treatment of infants with the most common and severe variant of the disease, type 1, and as much as \$2.6 billion in peak worldwide sales. After Biogen Inc.'s Spinraza (nusinersen), Zolgensma becomes the second FDA-approved therapy for SMA in an active corner of rare disease drug development. (See *BioWorld*, May 28, 2019)

The way is cleared now for Boehringer Ingelheim GmbH and Eli Lilly and Co.'s empagliflozin for the reduction of the risk of cardiovascular death and hospitalization for heart failure in people with chronic heart failure. Empagliflozin, marketed as Jardiance in the U.S., is a once-daily tablet used along with diet and exercise to lower blood sugar in adults with type 2 diabetes and to reduce the risk of cardiovascular death in adults with type 2 diabetes and known cardiovascular disease. The FDA fast tracked empagliflozin for the ongoing Emperor clinical trial, which will evaluate the effect of empagliflozin on cardiovascular death and hospitalization for heart failure in adults with chronic heart failure with reduced or preserved ejection fraction, respectively. The study is set to conclude next year.

Novartis still holds out hope for the heart of the Paragon-HF study. The company was heartened to see that safety and

tolerability were consistent with previously reported sacubitril/valsartan data.

"The totality of evidence from the trial suggests that treatment with sacubitril/valsartan may result in clinically important benefits in HFpEF. We will be discussing potential next steps with clinical experts and regulators while we prepare to present the full results at the ESC Congress 2019 in September," said John Tsai, Novartis' global drug development and chief medical officer. HFpEF is a distinct type of heart failure where the heart muscle contracts normally but the ventricles do not relax as they should during ventricular filling or when the ventricles relax. An estimated 13 million people, half of all heart failure patients, globally suffer from it.

The FDA approved Entresto a little over five years ago. The nod came less than five months after the agency granted priority review and ahead of its anticipated PDUFA date. Entresto, formerly known as LCZ-696, demonstrated an ability to reduce the rate of cardiovascular death and hospitalization related to heart failure in pivotal trials. (See *BioWorld*, July 9, 2015.) ♦

Other news to note

Algernon Pharmaceuticals Inc., of Vancouver, British Columbia, reported preclinical data on NP-120 (Ifenprodil), an N-methyl-d-aspartate receptor glutamate receptor antagonist originally developed by Paris-based Sanofi SA to treat peripheral circulatory disorders. In an animal model, NP-120 reduced fibrosis by 56%, outperforming Ofev (nintedanib, Boehringer Ingelheim GmbH) and Esbriet (pirfenidone, Roche Holding AG). Algernon plans to move the drug into a phase II study.

Alvotech ehf, of Reykjavik, Iceland and **Cipla Gulf FZ LLC**, a wholly-owned subsidiary of Mumbai-based Cipla Ltd., said they have entered into an exclusive partnership for the commercialization of AVT-02, a MA b biosimilar to Humira (adalimumab, Abbvie Inc.), in select emerging markets. Alvotech will be responsible for development and supply of the product, while Cipla Gulf will be responsible for registration and commercialization. AVT-02 is in phase III clinical development ahead of filing with the EMA and FDA by early 2020.

Amgen Inc., of Thousand Oaks, Calif., said, following a \$167 million cash offer to the shareholders of Copenhagen-based **Nuevolution AB**, which involved its shareholders being invited to tender all their shares for SEK 32.50 each in cash, after the end of the extended acceptance period, it now controls a total of 48.54 million shares and votes in Nuevolution, corresponding to approximately 98% of the total number of issued and outstanding shares and the offer is now closed. Amgen said it has initiated compulsory acquisition proceedings for those shares that have not been tendered into the offer. (See *BioWorld*, May 23, 2019.)

Bristol-Myers Squibb Co., of New York, said the European Commission has granted unconditional approval of its pending \$74 billion acquisition of Summit, N.J.-based **Celgene Corp.** The transaction remains subject to additional customary closing conditions and other regulatory approvals. The company said it expects to close the transaction by the end of 2019 or the beginning of 2020. (See *BioWorld*, Jan. 4, 2019.)

Gene expression

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“Tremendous power and insight have been provided by the binary of testes and ovary, X and Y, egg and sperm – and all of these binaries are real,” he added.

But overall, his team’s work implies that “even biological sex in the strictest, narrowest sense is not about the XX and XY, and not just about sex hormones – the whole genome is in the game. . . I think this begins to open the door to much more nuanced ideas that can incorporate and ultimately provide some ways of thinking about, for example, gender fluidity.”

Page is professor of biology at the Massachusetts Institute of Technology, the director of the Whitehead Institute, and the corresponding author of the paper reporting those results in the July 20, 2019, issue of *Science*.

In that paper, the team looked at 12 tissues from brain to spleen in five different species – mice, rats, dogs, macaques, and humans, and found hundreds of genes with conserved sex-biased expression in each tissue.

The differences in gene expression Page and his team reported in their work were typically akin to sex differences in height. Though there is a robust and biologically determined difference in average height between males and females, it is impossible to accurately gauge someone’s sex from their height alone.

Page’s team also looked closely at genes that were tilted male or female consistently across species in their study, and showed that they could explain part of the male-female difference in average height.

Height, Page said, is “the most intensely studied trait in quantitative genetics” and a testing ground for the development of analytical methods.

But though studies have identified hundreds of minor contributors to height, “have never provided insight into why males are taller on average than females.”

One question that Page and his team have not yet addressed, though they plan to, is how autosomal chromosomes “know” they are male and female.

“We have tended to view the differences between males and females being neatly packaged on the X and Y chromosomes,” Page said. “What we’re pointing to are differences in, let’s say, chromosome 5.”

The question then becomes “How does chromosome 5 know that it’s in a male or female and why does it behave a little differently?”

“There’s a whole set of ideas that now need to be developed,” Page said.

Differences in gene expression on the sex chromosomes that then modulate the expression of genes on autosomal chromosomes are one possibility, and gene modulation by sex hormones is another.



Though average height differs between males and females, height alone cannot be used to predict sex.

In their current studies, the team observed some cases of genes with sex-biased expression “coming under control of a transcription factor that is itself sex-biased” in a domino effect. “Once you get a few, others can be recruited.”

Practice and philosophy

The work has practical implications for the biopharmaceutical industry. “A good bit of gene expression sex bias is conserved, but the great majority of it is not,” Page said. If we are looking to model in nonhuman models – as we do – then we need to understand [which] sex biases are also conserved across species.”

In pharmaceutical development, drugs can also “fall out of pipelines for any number of reasons, including untoward consequences in one sex or the other,” and better understanding of those risks could point to strategies to mitigate them. But in its demonstration that many aspects of sex are a continuum at the molecular level, Page said, “the importance of the work derives from the way it may point to the future.”

Scientifically speaking, sex and gender are everywhere and nowhere.

“We have for decades, if not centuries, been operating with a fundamentally unisex model of human biology,” he said. “It’s convenient to shunt sex to the side.”

It does make for poor science, though.

“There are profound differences in the way disease ... plays out in males and females,” he pointed out. Autism spectrum disorders affect males and females at a ratio of four to one, and “most autoimmune diseases are far more common in females than in males. And we simply do not know why that is the case ... If we knew of any other factor that increased your risk of disease by a factor of four, the whole research world would focus on it.”

It is only recently that women have routinely been included in NIH-funded clinical trials, and attempts to ensure the inclusion of female animals in preclinical studies are more nascent still.

That state of affairs is ironic given that “sex and gender is personal for everybody – there is nobody for whom this is an arm’s length question,” Page said. “There is no one whose existence is untouched or uninterested or unaffected.”

Page himself said that throughout his career, which has included sequencing the Y chromosome and mapping Y-linked genes, larger issues around sex and gender “were always in my peripheral vision.”

Partly because those larger issues are personal for everyone, partly because they can be a third rail, and partly for other reasons, “the scientific discourse there gets quite muddy,” he said. Currently, there is “not even much curious inquiry.”

The work now published in *Science*, he said, was undertaken in part out of “the desire to take a first step towards understanding male-female differences ... I’m excited about the possibility of a way forward.”

And, he predicted, “the future will, unless we keep it from happening, be a much more synthesized, integrated view of binary and nonbinary.” ♦

Clinical data for July 29, 2019

Company	Product	Description	Indication	Status
Phase I				
Alterity Therapeutics Ltd., of Melbourne, Australia	PBT-434	Inhibitor of alpha-synuclein aggregation	Healthy adult and elderly volunteers (eventually Parkinson's disease)	Drug was safe and well-tolerated in elderly volunteers; systemic exposure to the drug was comparable between elderly and healthy volunteers; plans to move drug into phase II development
Kodiak Sciences Inc., of Palo Alto, Calif.	KSI-301	Anti-VEGF antibody biopolymer conjugate	Anti-VEGF treatment-naïve neovascular age-related macular degeneration (wet AMD), diabetic macular edema (DME), and macular edema due to retinal vein occlusion	After 12 weeks, median best corrected visual acuity improved by 8 letters for 17 wet AMD patients, by 9.5 letters for 8 DME patients and by 26.5 letters for 10 RVO patients; median change in retinal central subfield thickness using optical coherence tomography imaging was -96 microns, -197 microns and -209 microns for wet AMD, DME and RVO, respectively; phase II Dazzle study expected to begin enrollment in the third quarter of 2019
VBI Vaccines Inc., of Cambridge, Mass.	VBI-1901	Enveloped virus-like particle therapeutic vaccine	Recurrent glioblastoma multiforme	First of 10 patients dosed in part B of study testing the optimal dose level of 10 ug defined by part A
Phase II				
Alkahest Inc., of San Carlos, Calif.	AKST-4290	CCR3 inhibitor	Neovascular age-related macular degeneration	In patients who are no longer responding to treatment with anti-VEGF injections treated for 6 weeks, 72% of patients maintained or improved their best corrected visual acuity; mean improvement was 2.0 letters; 8% of patients gained 10 or more letters
Cidara Therapeutics Inc., of San Diego	Rezafungin	Echinocandin antifungal	Candidemia and/or invasive candidiasis	In part B of the Strive study, rezafungin 400 mg for the first week followed by 200 mg once weekly for up to four weeks in total produced an all-cause mortality of 6.7% for the 15 patients treated with the 400/200 dose compared to 15.2% for the 33 patients treated with caspofungin; clinical cure and overall success at day 14 were both 86.7% for rezafungin and 69.7% for caspofungin
Intervexion Therapeutics LLC, of Little Rock, Ark.	IXT-m200	Anti-methamphetamine antibody	Methamphetamine use disorder	In an interim review of data from the Stampout study, there were dose-dependent changes in methamphetamine pharmacokinetic parameters, including area under the curve, Cmax and volume of distribution, after the first dosing challenge with methamphetamine, which were maintained through the 22- to 29-day inpatient study; company plans to continue study
Oryzon Genomics SA, of Madrid, Spain	Vafidemstat	Inhibits LSD1 and MAOB	Borderline personality disorder (BPD), attention deficit and hyperactivity disorder (ADHD) and autism spectrum disorder (ASD)	Completed enrollment of the Reimagine study with 12 ADHD patients, 11 BPD patients and 7 ASD patients; data from first 6 ASD patients to be presented at the European College of Neuropsychopharmacology in September
Oryzon Genomics SA, of Madrid, Spain	Vafidemstat	Inhibits LSD1 and MAOB	Alzheimer's disease	Completed enrollment of 12 patients in the Reimagine-AD study; data expected to be presented at the 12th Clinical Trials on Alzheimer's Disease meeting in December
Relmada Therapeutics Inc., of New York	REL-1017 (dextro-methadone)	NMDA receptor antagonist	Treatment-resistant depression	Completed dosing of all 62 patients; top-line data expected in the third quarter of 2019
Theralase Technologies Inc., of Toronto	TLD-1433	Light-activated ruthenium-based photodynamic compound	Non-muscle invasive bladder cancer	Enrolled first patient in study measuring the complete response rate as the primary endpoint; secondary endpoint is duration of CR 360 days after initial treatment

Company	Product	Description	Indication	Status
Meduni Vienna Division of Gastroenterology and Hepatology	Nor-urso	Nor-ursodeoxycholic acid	Primary sclerosing cholangitis	Data from the 198-patient study published in <i>The Lancet Gastroenterology & Hepatology</i> showed the drug produced a dose-dependent reduction in serum ALT compared to placebo; highest dose of 1500 mg produced a mean change -27.8% (p<0.0001)
Phase III				
Lexicon Pharmaceuticals Inc., of The Woodlands, Texas, and Sanofi SA, of Paris	Zynquista (sotagliflozin)	Inhibits sodium-glucose co-transporter types 1 and 2	Type 2 diabetes	In Sota-Met study, Zynquista (400 mg) produced a statistically significant reduction in HbA1c compared to placebo at 26 weeks in patients on metformin; in Sota-CKD3 study, Zynquista (400 mg) produced a statistically significant reduction in HbA1c in the entire population of patients with moderate (stage 3) chronic kidney disease (CKD) and in patients with a glomerular filtration rate of 45-<60 mL/min/1.73m2 (stage 3A CKD) compared to placebo at 26 weeks; HbA1c wasn't statistically significant in patients with a glomerular filtration rate of 30-<45 mL/min/1.73m2 (stage 3B CKD); in Sota-CKD4 study, Zynquista (200 mg and 400 mg) didn't produce a statistically significant reduction in HbA1c compared to placebo at 26 weeks in patients with CKD4; Sanofi terminated collaboration with Lexicon, which plans to conduct its own review of the data and believes Sanofi is in breach of contract
Merck & Co. Inc., of Kenilworth, N.J.	Keytruda (pembrolizumab)	Monoclonal antibody targeting PD-1	Triple-negative breast cancer	In an interim analysis of the 1,174-patient Keystone-522 study, Keytruda plus chemotherapy as a neoadjuvant produced a statistically significant improvement in pathological complete response rates compared to chemotherapy alone, regardless of PD-L1 status; trial will continue without changes to evaluate the other dual-primary endpoint of event-free survival
Novartis AG, of Basel, Switzerland	Entresto (sacubitril/valsartan)	Neprilysin inhibitor and angiotensin II receptor blocker	Heart failure patients with preserved ejection fraction	The Paragon-HF study narrowly missed statistical significance for its composite primary endpoint of reducing cardiovascular death and total heart failure hospitalizations for Entresto compared to valsartan alone; plans to discuss data with regulators and present it at ESC Congress 2019 in September

Notes

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Regulatory actions for July 29, 2019

Company	Product	Description	Indication	Status
Anavex Life Sciences Corp., of New York	ANAVEX-2-73	Sigma-1 receptor (S1R) agonist	Rett syndrome	EMA's Committee for Orphan Medicinal Products issued positive opinion on application for orphan designation in the indication
Canbridge Pharmaceuticals Inc., a unit of Canbridge Life Sciences Ltd., of Beijing	Hunterase (idursulfase beta)	Recombinant human iduronate-2-sulfatase	Hunter syndrome	Filed NDA with the NMPA to treat the indication, also known as mucopolysaccharidosis type II, in China
Cerecor Inc., of Rockville, Md.	CERC-802	D-mannose	Mannose phosphate isomerase deficiency	FDA accepted NDA filing
Genfit SA, of Lille, France	Elafibranor	PPAR alpha/delta agonist	Primary biliary cholangitis	FDA and EMA granted orphan drug designation in the indication
Janssen Pharmaceutical Cos., unit of Johnson & Johnson, of New Brunswick, N.J.	Stelara (ustekinumab)	IL-12/23 receptor antagonist	Ulcerative colitis	EMA's Committee for Medicinal Products for Human Use recommended marketing authorization in EU to treat adults with moderately to severely active disease and inadequate or lost response or intolerance to other therapy
Janssen Pharmaceutical Cos., unit of Johnson & Johnson, of New Brunswick, N.J., and Viiv Healthcare Ltd., of London	Rilpivirine long-acting (LA, Janssen) + cabotegravir LA (Viiv)	HIV-1 reverse transcriptase inhibitor; HIV integrase inhibitor	HIV-1 infection	Companies submitted marketing authorization application to EMA for once-monthly injectable 2-drug regimen
Merck & Co. Inc., of Kenilworth, N.J.	Keytruda (pembrolizumab)	PD-1 inhibitor	Renal cell carcinoma	EMA's Committee for Medicinal Products for Human Use recommended approval, in combination with tyrosine kinase inhibitor Inlyta (axitinib, Pfizer Inc.) for first-line treatment in individuals with advanced disease
Neuren Pharmaceuticals Ltd., of Melbourne, Australia	NNZ-2591	Diketopiperazine compound	Phelan-McDermid, Angelman and Pitt Hopkins syndromes	Submitted applications for orphan drug designation in the indications to the FDA
Neurovive Pharmaceutical AB, of Lund, Sweden	Neurostat	Cyclosporine A lipid emulsion	Traumatic brain injury	Candidate received FDA fast track designation
Orchard Therapeutics Ltd., of London	OTL-103	Ex vivo autologous hematopoietic stem cell-based gene therapy	Wiskott-Aldrich Syndrome	FDA issued Regenerative Medicine Advanced Therapy designation
Proqr Therapeutics NV, of Leiden, the Netherlands	Sepofarsen (QR-110)	CEP290 gene stimulator	Leber's congenital amaurosis 10	EMA granted Priority Medicines designation
Rhythm Pharmaceuticals Inc., of Boston	Setmelanotide	Melanocortin MC4 receptor agonist	Bardet-Biedl syndrome	EMA's Committee for Orphan Medicinal Products issued positive opinion on application for orphan designation in the indication
Spring Bank Pharmaceuticals Inc., of Hopkinton, Mass.	SB-11285	Stimulator of interferon gene (STING) agonist	Advanced solid tumors	FDA accepted IND application for phase I trial to evaluate safety, tolerability and initial antitumor activity
Notes				
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