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GSK's Oncology R&D Head: GSK2857916 'Proves We're Still Here'

STEN STOVALL sten.stovall@informa.com

GlaxoSmithKline PLC's first-in-class anti-BCMA antibody-drug conjugate – which now has breakthrough therapy designation in the US for relapsed and refractory multiple myeloma – “serves notice that GSK is truly back in the oncology business”, its divisional R&D head said in an interview.

GSK2857916 is an anti B-cell maturation agent (BCMA) monoclonal antibody-drug conjugate. GSK on Nov. 2 said the agent received breakthrough therapy designation from the FDA as a monotherapy in patients with multiple myeloma who have failed at least three prior lines of therapy, including an anti-CD38 antibody and are refractory to a proteasome inhibitor and an immu-

nomodulatory agent. In October, the European Medicines Agency granted PRIME designation to GSK2857916 for the treatment of relapsed and refractory multiple myeloma patients whose prior therapy included a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody. The investigational medicine has also received orphan drug designation from both EMA and FDA for multiple myeloma.

Multiple myeloma is a blood cancer that forms in plasma cells that help the body fight infections by making antibodies that recognize and attack pathogens. Multiple myeloma causes cancer cells to accumulate in the bone marrow, where they crowd out healthy blood cells.

Axel Hoos, who heads oncology R&D at GSK, said GSK2857916 was proof the UK's biggest drug maker had not exited the oncology space, a view many took in 2014 when GSK agreed to acquire **Novartis AG's** global vaccines business for \$5.25bn, divested its mature oncology business to Novartis for \$16bn, and formed a consumer health care joint venture with the Swiss firm. The transaction closed in March 2015.

“Many people mistook that transaction as us exiting oncology,” GSK's Hoos told *Scrip*. “As you can see, that's not the case. We have been quietly incubating a new portfolio of agents to rebuild our oncology presence.”

“This agent [GSK2857916] is the first potential blockbuster drug that comes from the new oncology portfolio at GSK. In a way, it's our first big 'comeback'; it proves that we're still in oncology and that we never left! And we'll soon have a lot more to show about this maturing oncology portfolio,” Hoos said.

DRUG'S SCIENCE

Phase I/II-stage GSK2857916 is an antibody-drug conjugate consisting of a humanized anti-BCMA monoclonal antibody linked to a cytotoxic drug called monomethyl auristatin-F. The linker technology was licensed from **Seattle Genetics Inc.**

“Essentially, the antibody binds to the tumor cell and gets internalized, then the cytotoxic agent blows up the malignant multiple myeloma tumor cell. It is extremely specific, as BCMA is not expressed in other cells,” Hoos explained.

“It also has a mechanism that many other drugs in this space don't have, and that's immunogenic cell death that kills the cell and the poison that's involved in that creates added responses and generates an immune response which is unique to BCMA and unique to some components in the

CONTINUED ON PAGE 7

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Stock Scan

How generics are holding back pharma (p18)

Q3 Reports

Pfizer, Takeda and Sanofi plus Scrip's analysis of the quarter (p4, 6 & 8)

NASH Pursuit

Followers look to improvements to succeed (p16)



from the editor

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News that GlaxoSmithKline is to lose its R&D head Patrick Vallance to a senior UK government role but that it has poached Roche/Genentech veteran Hal Barron to replace him sent the group's share price up 1.45% on the London Stock Exchange before the market closed (see p7).

That represented a gain of nearly £1bn for the company's market capitalization, a relatively small spike that fell more than £7bn short of the fairly stable level it enjoyed for most of October – until third-quarter results day. Taking a longer view, the share price is still lower than it has been for the vast majority of the past five years. Emma Walmsley, who has helmed the company for seven months, will be hoping this marks a turning point for GSK's declining valuation that has also seen GSK diverging

downwards from the path of the FTSE100 since the summer. The company's renewed pride in its oncology R&D portfolio (see cover story) is one sign that company is turning from portfolio pruning to focusing on its promising assets.

When it comes to investor perceptions around company announcements, our second-quarter biopharma stock analysis indicates a level of volatility in big pharma share prices that is suggestive either of a tendency among investors to over-react to news, or that communication conduits between pharma companies and their shareholders may need some attention. While major upheavals like senior executive changes can come as a genuine surprise, quarterly updates ought to come as less of a shock. Read our quarterly and monthly stock analysis on p8-9 and p18-19.

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Value creation for Pfizer

▶ 4



Sanofi feels the pressure

▶ 10



UK transformation

▶ 11



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Allergan Readies Cost Cuts As Restasis Generics Approach

<http://bit.ly/2znRnXb>

Allergan is working on a plan to reduce costs now that Restasis generics could hit the US market in 2018, but the company said sales growth for other drugs coupled with new product launches will boost revenue even if the dry eye drug loses its blockbuster status.

Mylan Insists Complex Generics Strategy Is Poised To Deliver

<http://bit.ly/2lZtpyB>

With one high-profile approval in its pocket – a version of Teva's blockbuster Copaxone – Mylan's management believes its strategy of investing in complex generics and biosimilars will help the company navigate challenges in the US generic market.

Bluebird Bio Sings Cheerily Of Its "Biggest ASH Ever"

<http://bit.ly/2zrkxqN>

Company highlights LentiGlobin sickle cell and beta thalassemia data updates in investor call about the upcoming ASH meeting, which will feature 11 presentations across its clinical and preclinical programs.

M&A Buzz In Korea: CJ HealthCare On the Block

<http://bit.ly/2lZC2t8>

CJ Group plans to sell its healthcare affiliate, in what could potentially emerge as the first major M&A deal involving a South Korean pharma firm in recent years. Although the company has not ruled out the option of an initial public offering as an alternative, the sale plan possibly reflects the changing dynamics in the Korean pharma industry.

Deal Watch: Neos Says 'Thanks, No Thanks' To Repeated PDL Offer

<http://bit.ly/2h9B87X>

Daiichi teams with Glycotope on an antibody-drug conjugate for cancer, while Alektor will partner with AbbVie to research antibody targets for Alzheimer's disease.

Tech Transfer Roundup: Busy Inspyr Collaborates With Virginia, NYU

<http://bit.ly/2ArdFI2>

University researchers will examine adenosine receptor modulator technology's potential in *C. difficile* infection and atherosclerosis. CRISPR Therapeutics is partnering with University of Alabama-Birmingham to evaluate gene-editing procedures in Friedreich's ataxia.

inside:

COVER / GSK's Oncology R&D Head: GSK2857916
'Proves We're Still Here'

- 4 Pfizer Says Big Deals Create Value & 10 Other Notable Q3 Moments
- 6 Takeda's Deal Flurry Set To Wane
- 7 GSK Bags Barron As Vallance Joins UK Government
- 8 Quarterly Reporting: Investor Reality Check Or Pharma Communication Gap?
- 9 Teva CEO Schultz's Tough Start
- 10 MS Franchise A Surprising Concern For Sanofi In Q3; Dupixent Out-Performs
- 11 UK To Offer Firms More Flexible Commercial Deals On 'Transformative' Drugs, Earlier Access To Market
- 12 Alnylam Enjoys Autumn in Paris With hATTR Win Over Ionis
- 13 CAR-T To Go: Juno Sees JCAR017 As Safer, Suited For Outpatients
- 14 End Of The Line For AstraZeneca's Tralokinumab
- 16 Behind The NASH Leaders, Pursuers Already Anticipating Second-Wave Improvements
- 18 Stock Scan October: Generics Pull Pharma Down
- 20 Influenza And Beyond: Sanofi Pasteur R&D Chief Talks Strategy
- 22 Pipeline Watch
- 23 Amgen, Novartis May Screen 30,000 Patients To Find 2,000 For Alzheimer's Trial
- 23 Appointments



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Pfizer Says Big Deals Create Value & 10 Other Notable Q3 Moments

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M&A is always a hot topic during **Pfizer Inc.**'s earnings calls, with investors eager to see the company bolster its growth prospects, particularly given recent speculation the company could be looking to make a bigger splash in immuno-oncology by buying a rival like **Bristol-Myers Squibb Co.**

Pfizer CEO Ian Read and CFO Frank D'Amelio said they aren't ruling out a mega-deal, during the company's third quarter earnings call on Oct. 31, which gave analysts an opportunity to press management on their latest thinking on M&A and other topics. And when an analyst pushed for a comment on whether or not big deals at the company have been value-enhancing, both executives agreed they have.

"As we've always said, we're agnostic to size," Read said, while D'Amelio highlighted Pfizer's \$68bn acquisition of Wyeth in 2009.

"I think the retrospective on that is it's been very value-enhancing," he said. "If you look at our portfolio today, much of it has come from the Wyeth acquisition. When we announced that deal, we announced what, \$4bn in synergies? We clearly exceeded that."

But Read would not provide any additional insight into the company's current thinking on a deal in the IO space as it relates to PD-1/L1. Pfizer already launched its own PD-L1 inhibitor, under a partnership with **Merck KGAA**, in March in Merkel cell carcinoma, but the partners were late to the game with *Bavencio* (avelumab), and are trying to catch up in the crowded category. (Also see "Pfizer's Avelumab Makes Its Debut, In Rare Form Of Skin Cancer" *Scrip*, 23 Mar, 2017.)

"On avelumab, we remain committed to our programs with our partner," Read said. "Regarding any rumors you may or may not have heard, I really can't speculate on them."

Beyond M&A, the execs covered a lot of ground including pipeline updates, strategic options for consumer healthcare, and industry trends like Amazon entering the pharmaceutical distribution business. Here are 10 other notable discussion points from Pfizer's third quarter call:

- **Ibrance Sales Through The Roof:** The CDK4/6 inhibitor Ibrance (palbociclib) continues to impress, despite the entry of new competition earlier this year, **Novartis AG's** *Kisqali* (ribociclib) and **Eli Lilly & Co.'s** *Verzenio* (abemaciclib). Ibrance has been a key driver of growth for Pfizer since it debuted in early 2015, and it appears poised to remain that way. Sales of Ibrance jumped 60% in the third quarter over the year-ago quarter to \$878m. Sales in the US grew 34% to \$713m.
- **Consumer Healthcare Asset Swap An Option:** Pfizer revealed Oct. 10 it is exploring strategic alternatives for its consumer healthcare business, which includes brands like *Advil* and *Nexium 24HR OTC*, but hasn't commented since. (Also see "Pfizer Déjà Vu: Is It Time To Sell The Consumer Health Business?" *Scrip*, 10 Oct, 2017.) Read said the decision came about as part of a regular business review and the company is considering everything from a full or partial separation of the business to deciding to retain it. An asset



Value-creating deals come in all shapes and sizes

"If you look at our portfolio today, much of it has come from the Wyeth acquisition. When we announced that deal, we announced what, \$4bn in synergies? We clearly exceeded that"

swap could also be an option, he said. "I think the process we're going to take in the strategic review may shake loose more alternatives in that aspect," Read said.

- **Eucrisa Will Be A \$2bn-Plus Product:** Pfizer isn't backing off early forecasts for the topical atopic dermatitis product *Eucrisa* (crisaborole) to become a blockbuster, despite a slow start. Pfizer launched *Eucrisa* in January as the first new drug for atopic dermatitis in more than a decade as part of a move into dermatology. (Also see "Pfizer's *Eucrisa* Approval By FDA Adds New Dermatology Anchor" *Scrip*, 14 Dec, 2016.) But the launch appears off to a slow start, generating just \$15m in the third quarter. Group President-Pfizer Innovative Health Albert Bourla insisted Pfizer is sticking to its early blockbuster forecasts for *Eucrisa*. "We think that it will be a \$2bn-plus product, and we are very excited with the progress," he said. He said the company used significant sampling and couponing, including a free trial voucher, to launch the drug, and only 50% of commercial lives have unrestricted access to the drug.
- **On Amazon And Pharma Distribution:** While Amazon has not publicly announced plans to enter the prescription drug arena, reports the company is pursuing pharma distribution licenses in several states has fueled speculation that major

pharmacy disruption could be on the horizon. When asked about his thoughts on Amazon entering the market, Read said: "Any system of distribution where you can cut costs and get a wide availability of products to patients is something that the whole industry will be interested in." But, he said a new model taking on pharmacy benefit management could still be a challenge, given issues over deciding differential access. "That's a whole different skillset," Read said.

- **Tanezumab Data In 2018:** The anti-nerve growth factor class could present a new option for pain relief, without the risk of addiction associated with opioids, though the class has run up against some safety issues. Nonetheless, Pfizer and partner **Eli Lilly & Co.** are continuing to develop tanezumab in six Phase III clinical trials for osteoarthritis and chronic back pain in roughly 7,000 patients. "We are very encouraged and optimistic that this could be a real, very important option for patients going forward," President Worldwide R&D Mikael Dolsten said. Data from the studies will begin to read out in mid-2018, he said.
- **Established Products Business Return To Growth Plan:** Pfizer Established Products is poised to return to growth, Group President-Pfizer Essential Health John Young insisted. The business segment, tasked with managing Pfizer's mature drugs and loss of patent exclusivities, faces challenges given the portfolio's dynamics. However, Young said the business is on track to meet its goal of returning to low- to mid-single digit growth. Excluding losses of exclusivity (accounting for about \$339m in the third quarter) and the divestiture of Hospira's infusion systems business, sales were flat, Young said. Sales declined 7% in the quarter to \$5.05bn on a reported basis. "Whilst we are still on that path to recovery, I think we remain committed to and actually very positive about the aspiration to turn around this business to the growth profile that we've outlined," Young said.
- **IO/IO Combo Data On The Horizon:** Much of Pfizer's come-from-behind strategy in immuno-oncology hinges on leapfrogging the competition by developing novel IO/IO combinations. Read said the company is on track to have combination data in hand testing the PD-L1 inhibitor Bavencio in combination with 4-1BB later this year, and ready for presentation in 2018, as well as data from a triple combination (PD-L1 plus 4-1BB and OX40) in late 2018. Pfizer and Merck are running nine pivotal trials with Bavencio, with third-line gastric data expected to read out shortly, followed in 2018 by second-line lung cancer and second-line ovarian cancer.
- **On Biosimilars, "Enough Is Enough":** *Inflectra*, the first biosimilar version of **Johnson & Johnson's** *Remicade* (infliximab), is facing a challenging launch in the US, in part because of J&J's defensive contracting strategy that has effectively blocked the drug from accessing much of the reimbursable market. Pfizer has filed a lawsuit against its rival claiming the contracts are anti-competitive. (Also see "Pfizer Sets The Stage For A Biosimilar Showdown Over Exclusive Contracts" *Scrip*, 20 Sep, 2017.) *Inflectra* generated \$34m in the US in the third quarter. When asked about the reimbursement challenges, Read said, "I think the solution to this will come from a societal view that biosimilars are there to provide access to patients once the patent has expired and that enough is enough."
- **An Xtandi recovery?:** Sales of the prostate cancer drug *Xtandi* (enzalutamide) may be stabilizing after Pfizer has faced an unexpected challenge related to increased use of patient assistance

programs to pay for treatment that has negatively impacted sales. Volume was up 15% in the third quarter, although Pfizer's alliance revenues only increased 2% over the prior-year quarter to \$150m. "We are pleased to report that we have now recorded sequential revenue growth for two consecutive quarters," Read said. "The patient assistance program proportion of total demand was comparable with that seen in the first and second quarters, and we continue to expect that the program's utilization will normalize as we move into next year." The unanticipated bump in the road for *Xtandi* made investors nervous after the company spent \$14bn to acquire **Medivation Inc.** last year, but positive Phase III data from the PROSPER study, released in September, showed benefits in non-metastatic castration-resistant prostate cancer in patients treated with *Xtandi*, which has taken some of the pressure off Pfizer to prove the value of the deal. (Also see "Pfizer Poised To PROSPER From *Xtandi* In Expanded Indication" *Scrip*, 14 Sep, 2017.)

- **Succession Plan:** One interesting question that stood out and maybe took Read by surprise was about Pfizer's succession plan. The chief executive has led the firm for going on seven years, after being appointed to succeed Jeffrey Kindler in December 2010 in a sudden management shakeup just as the company was headed over the *Lipitor* patent cliff. (Also see "Pfizer Sets The Stage For A Biosimilar Showdown Over Exclusive Contracts" *Scrip*, 20 Sep, 2017.) Time flies, though, when it comes to leading one of the world's biggest pharmas and every leadership reign has an eventual expiration. Read didn't sound ready to pass the baton anytime soon, however. "[At] Pfizer, like all major companies, the board has a responsibility on succession planning. We have a robust succession process within Pfizer. And at due points that succession plan will become active." ▶

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Takeda's Deal Flurry Set To Wane

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Takeda Pharmaceutical Co. Ltd. has entered into numerous company and academic partnerships over the past year or so as it has strived to rebuild its R&D pipeline, but this level of feverish deal activity may soon be coming to an end.

"We don't intend to keep this pace up forever," says chief medical and scientific officer Andrew Plump. "We have a few fundamental partnerships that will be coming up, but at the same time our internal labs have now really been rejuvenated," he noted.

In the past six months, Takeda has entered 25 new external partnerships, in addition to the 50 or so signed in the previous 12 to 18 months, as the Japanese big pharma company went through a reorganization that called for a push on external research tie-ups. "We love the model of 50/50 partnerships where we share cost and reward," Plump noted.

But with Takeda raising its financial outlook, and new products starting to enter the company's research pipeline, there might be fewer opportunities for biotechs around the world to attract such a keen partner to the table.

In the first six months of fiscal 2017, ending Sept. 30, 2017, three potential new medicines have moved into Phase II, and two new projects have entered preclinical studies, Plump told analysts during the company's first-half earnings call on Nov. 1. The Takeda executive highlighted the development of an unnamed immuno-oncology agent that has just entered clinical studies and for which preclinical data have been "absolutely remarkable", plus the move of pevonedistat into Phase III studies for high-risk myelodysplastic syndrome, as examples of products now moving through the research pipeline.

Refocusing Takeda's R&D pipeline on specialty medicines including immuno-oncology agents, the setting up of external R&D collaborations, and making cultural and organizational changes are all making "terrific progress", Plump said. (Also see "Interview: Setting The Course For Takeda's R&D Future" *Scrip*, 30 Jun, 2017.) This is in marked contrast to the situa-

tion in the previous 12 months, when Takeda's internal labs did not initiate or progress any R&D projects, and when external partnerships or the billion-dollar acquisition of the US company **Ariad Pharmaceuticals Inc.** accounted for the eight programs that did enter the research pipeline. During that time, Takeda discontinued 15 research programs.

NEXT-GENERATION IMMUNO-ONCOLOGY

Takeda's CSO said the company's interest in next-generation immune-oncology agents has now solidified around six or seven platforms. These include the gamma-delta class of T-cells that it is exploring in its collaboration with **GammaDelta Therapeutics Ltd.** (Also see "Takeda Picks Next Big Thing In Immunotherapy: Gamma Delta T Cells" *Scrip*, 15 May, 2017.)

Takeda is also collaborating with the Tokyo, Japan-based biotech, **Noile-Immune Biotech Inc.**, which has technology that has the potential to direct T-cells to solid as well as hematologic tumors. Noile-Immune was founded in 2015 with next-generation CAR-T technology developed by Koji Tamada, a professor at Yamaguchi University.

Among other anticancers, the SYK inhibitor, TAK-659, that also has activity against FLT3, has shown activity in patients with diffuse large B-cell lymphoma (DLBCL) and has entered Phase II, Plump reported.

And Takeda is also working on a compound that could rival **Johnson & Johnson/Genmab AS's Darzalex** (daratumumab) – the antibody-drug conjugate, TAK-573, is a "really-interesting molecule" consisting of a CD38 monoclonal antibody conjugated to interferon-alfa, that has the potential to be a truly best-in-class CD38 agent, Plump said.

In the CNS area, Takeda is collaborating with MedImmune (**AstraZeneca PLC**) on an alpha-synuclein monoclonal antibody, MEDI 1341, which is due to enter the clinic in coming months to test the pathologic role of alpha-synuclein aggregation in Parkinson's disease and other CNS disorders. (Also see "AZ Partners Parkinson's Compound With Takeda" *Scrip*, 29 Aug, 2017.)

And in epilepsy, TAK-935 is an inhibitor of an enzyme found only in the brain, cholesterol 24-hydroxylase, that may inhibit excitatory glutamatergic NMDA receptor signaling, and has shown activity in preclinical models of seizures, and is Phase II ready in its partnership with **Ovid Therapeutics Inc.** (Also see "The New Revolutionary: Ovid's Levin On Pioneering In Neurology" *Scrip*, 7 Jun, 2017.)

FINANCIAL OUTLOOK IMPROVED

Takeda raised its financial outlook for the full year, with revenues in the 2017 fiscal-year expected to reach JYN1,720bn (\$15.1bn) instead of JYN1,680bn, and with net profit of JYN152bn instead of JYN138 bn.

Potential headwinds could include the start of generic competition in the US to *Velcade* (bortezomib). Currently Takeda is forecasting revenues of around JPY106bn for the product in fiscal year 2017, based on two or three generics entering the market in November 2017. However, the company refrained from speculating on the outcome of regulatory and legal moves – patent suits have been filed against a number of generic companies.

GROWTH DRIVERS

Takeda's growth drivers include the inflammatory bowel disease therapy *Entyvio* (vedolizumab) now approved in 62 countries; *Velcade* sales; and the growth in US sales of the antidepressant *Trintellix* (vortioxetine), whose sales grew 58.7% in the first half. The company is planning to launch the multiple myeloma drug, *Ninlaro* (ixazomib) in China next year. Important for the long-term success of *Ninlaro* is ongoing clinical studies of its use in combination with *Darzalex* for multiple myeloma, the company noted. During the first half, sales of *Alunbrig* (brigatinib) and *Iclusig* (ponatinib) from the acquired company *Ariad* showed strong performances.

Plump also highlighted the changes in the regulatory landscape in China, that has lead the company to expect seven new medicines to be approved and launched there in the next five years. ▶

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GSK Bags Barron As Vallance Joins UK Government

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GlaxoSmithKline PLC has pulled off a coup by poaching renowned cancer specialist and former research chief at Genentech Hal Barron from Google-backed **Calico Life Sciences LLC** to be its new president of R&D.

Barron will replace Patrick Vallance, who is to leave GSK to become the UK Government's chief scientific adviser. The latter's departure had been widely rumored but the appointment of Barron has taken many in the industry by surprise.

He is currently president of Calico, the Alphabet-funded company that is focused on aging and related diseases. However, Barron is best-known for being chief medical officer and head of development at **Genentech Inc.** and subsequently **Roche**, where he played a significant part in helping it become an oncology powerhouse.

During his time at Genentech and Roche, Barron oversaw the development of the blockbusters *Avastin* (bevacizumab) and *Tarceva* (erlotinib), the skin cancer drugs *Zelboraf* (vemurafenib) and *Erivedge* (vismodegib), the HER2 breast cancer therapies *Perjeta* (pertuzumab) and *Kadcyla* (trastuzumab-emtansine) and the leukemia and lymphoma treatment *Gazyva* (obinutuzumab) (CLL). He was also responsible for developing big-sellers in other areas, such

as *Actemra* (tocilizumab) for rheumatoid arthritis, the asthma therapy *Xolair* (omalizumab) and *Lucentis* (ranibizumab) for wet macular degeneration.

Barron's credentials in cancer treatment are particularly noteworthy, given that GSK recently told *Scrip* that rumors it had left the oncology space were greatly exaggerated. In 2014, the company agreed to acquire Novartis AG's global vaccines business for \$5.25bn, divested its mature oncology business to the latter for \$16bn, and formed a consumer health care joint venture with the Swiss major.

Barron, who joins GSK Jan. 1, will be pleased to hear it. In a statement, he said he was "honored to have been chosen for this important position especially given the company's renewed focus on discovering and developing transformational new medicines. GSK is a company with a rich history of innovation, with many talented scientists."

Equally pleased is GSK's chief executive Emma Walmsley and Barron's recruitment is a sign of her making a mark on the company where she took over the top job in April 2017. She said in a statement that "scientific innovation must be at the heart of GSK and with the appointment of Hal, we are bringing one of the world's foremost R&D leaders to the company." Barron will work out of his present base in San Francisco, where GSK is

creating a new office focused on business development for R&D. The company has also published details of his financial package which includes a base salary of \$1.7m, an annual bonus also of \$1.7m and long-term incentives worth over \$4.2m.

Commenting on Barron's pending arrival, Datamonitor Healthcare analyst Ali Al-Bazergan said that "after a lukewarm quarterly earnings, this appointment sends a strong signal of intent towards GSK's future growth within pharma and a sharpened focus in oncology. Barron's wealth of experience within oncology provides GSK with the opportunity to compete again in the area as it directs investment towards its priority pipeline assets."

VALLANCE TO ADVISE

Meantime, his predecessor Vallance will leave at the end of March 2018, having joined GSK as head of discovery in 2006. The new job will see him responsible for providing scientific advice to the Prime Minister and advising the Government on aspects of policy on science and technology.

Vallance will be working again with his former boss, Sir Andrew Witty. Witty, who has just been unveiled as chair of the UK government's Accelerated Access Collaborative (see p11). ▶

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CONTINUED FROM COVER

myeloma cells and can be modulated with immunotherapy."

He said combining this with other immunotherapies, or other immune-modulating substances, "might enhance the effect, but that's something we still need to test as we only have that in a preclinical setting, but we will be testing that premise very shortly."

BEST CASE SCENARIO

If all goes to plan, GSK hopes to commercially launch GSK2857916 in 2020.

"There's a lot of dialogue that now needs to take place with the FDA, as it allows the company to work closely with the FDA to find the best and most accelerated way to make the medicine available to patients - but that dialogue is really just beginning, so we're

looking towards a 2020 launch," Hoos said.

"What we sold to Novartis were marketed products that all fit in the category of targeted therapy and what we retained was the R&D pipeline and that was mostly focused on immune oncology and immunotherapies, epigenetic compounds and cell and gene therapy," Hoos said.

During the summer GSK exercised its option on an NY-ESO-1 cell therapy from **Adaptimmune Therapeutics PLC**, the first cell therapy to show efficacy in solid tumors. GSK is meanwhile waiting to see data for the earlier stage assets like the ICOS inhibitor, which is part of the post-PD-1 checkpoint inhibitor wave of potential cancer therapies.

The EMA and FDA approaches to GSK's ADC reflect the keen interest now in developing therapies designed to target the B-cell matu-

ration antigen, which is heavily expressed on the surface of myeloma cells. At least six Phase I anti-BCMA trials are currently active, spanning from US and Canada, to Europe and China. Trial sponsors range from GSK with its ADC GSK2857916, to **Celgene Corp.** and **bluebird bio Inc.** with CAR-T therapy bb2121, and Southwest Hospital in Chongqing, China in evaluating anti-BCMA-CAR-transduced T-cell. Other early phase targeted drugs in development for multiple myeloma that target BCMA include **Amgen Inc.**'s AMG 420.

The PRIME and Breakthrough Therapy Designations from EMA and FDA, respectively, are based on results from a Phase I open-label, dose escalation and expansion study in patients with relapsed/refractory multiple myeloma, irrespective of BCMA expression. ▶

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Quarterly Reporting: Investor Reality Check Or Pharma Communication Gap?

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For this analysis, *Scrip* has taken a largely historical approach. We looked at stock price and volume movement during the third calendar quarter of 2017 (July through September) for the 50 biggest sellers of prescription pharmaceuticals in the world. However, more recently, pharma companies have continued to catch investors out: the Q3 results from **Johnson & Johnson** and **Hoffmann-La Roche Inc.** released on the October 17 and October 19, respectively, each changed their company's stock value by around 5% (Roche downward and J&J upward), equivalent to shifts in market value of \$10-12bn for each firm.

Looking more broadly across the July-September 2017 quarter for all the public companies in the top 50, *Scrip's* analysis showed that:

- For a third of companies, the appearance of a financial report caused (or coincided with) the biggest jump (or fall) in stock valuation in the quarter;
- Positive news can boost a company's value by more than \$8bn;
- Negative news can be more devastating, slashing valuations by over \$10bn in a day and escalating declines in market valuation of 40%;

Quarterly surprise syndrome affects the biggest of big pharma companies – including **Johnson & Johnson**, **Novo Nordisk AS**, **GlaxoSmithKline PLC**, **Takeda Pharmaceutical Co. Ltd.**, **Otsuka Pharmaceutical Co. Ltd.**, and **AstraZeneca PLC**.

Stock volatility might be expected from tiny or naïve companies, newly minted public minnows fresh from a fundraising or two. However, each of the companies examined sells in excess of \$2.0bn worth of drugs per year. They are, or should be, experienced in the expectations and wiles of the financial markets.

Despite this, the chasm between a company's performance and the market's earlier expectation is sometimes quite staggering.

For instance, the stock value of **Teva Pharmaceutical Industries Ltd.** fell 24% on Aug. 3, a day on which the company

announced disappointing generics sales, reduced profits and dividends and a plan to axe thousands of staff. Teva's stock fell another 13% the next day and a further 10% the day after that – wiping 40% off Teva in just three days. It is difficult to imagine just how any estimation of Teva's worth based on underlying business parameters could generate an error approaching half the company's value.

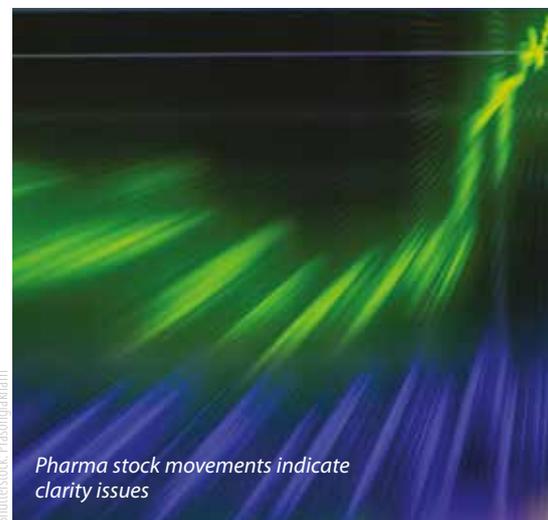
Having said that, another generics-dependent firm, **Endo Pharmaceuticals Inc.**, lost 12% of its value as its Q2 results came out, and in a 17-day period between July 24 and Aug. 10 its market cap fell 39% in total.

The biggest single-day decline in dollar terms in the July-September quarter was at AstraZeneca, which lost over 15% of its market value (nearly \$13bn) on July 27, a day when its Q2 results coincided both with an announcement of a major failure in an immune-oncology program in lung cancer and the licensing of key assets to Merck & Co.

Other miserable Q2 results disclosures in the July-September quarter included companies for which bad news is becoming a habit of late: **Valeant Pharmaceuticals International Inc.** and **Allergan PLC**.

On the flip side, Novo Nordisk's quarterly announcement, together with a heavy trail of positive clinical results in type 2 diabetes, boosted the Danish company's stock nearly 8% (\$8.7bn). **Biogen Inc.** reported higher than expected sales in its Q2 announcement back in July and its stock duly rose 4.5%. Good news can be a nice surprise, but it is still a surprise.

It is unfair to focus on a few companies which did a lot better or a lot worse than investors were expecting. That is because quarterly reporting shocks are commonplace. For 17 of the 45 companies included in this analysis, the release of corporate financial reports coincided with the biggest change in the stock price (either up or down) in the entire quarter. For another nine companies, results days brought the second biggest market re-evaluation in the quarter.



Pharma stock movements indicate clarity issues

To put that another way, for over half of the largest public pharma companies, information inequality is the biggest disruptor of transparent stock valuation. The practice of revealing secrets once a quarter (but not before) appears to be widespread. Even though all the major stock markets place a fiduciary duty on companies to disclose value-altering information to their shareholders, very often pharma companies seem to want to keep information to themselves until they can unveil it with full damage control measures and due ceremony on the occasion of their quarterly presentations.

SHALL I COMPARE THEE TO A DIFFERENT RISE?

Quarterly results surprises are widespread. But how big are the re-evaluations that stem from formal reporting compared with, say, clinical results, changes of senior management, or wide-reaching political and social events?

When **Amgen Inc.** and **UCB SA**, for instance, published in *The New England Journal of Medicine* that an EVENITY (romosozumab/alendronate) combination was hugely better than alendronate alone in reducing hip fracture risk in osteoporosis, the news added \$4.5bn (3.2%) to Amgen's valuation, but did nothing much for UCB.

Novo's positive clinical result and AstraZeneca's immuno-oncology dive have already been mentioned. **Eli Lilly & Co.**'s biggest stock influencing event was also clinical, but not with respect to its own products. Rival Novo's Aug. 16 announcement of a head-to-head trial suggesting that semaglutide rather than dulaglutide might become the new standard of care in type 2 diabetes pushed Lilly's stock down over 5.6% (\$5.2bn).

Management appointments can make a difference, too. In a particularly turbulent quarter, Teva's market capitalization had halved in August, including a 24% fall on the day its second-quarter results were published showing lower-than-expected profits. That decline continued slowly but unrelentingly as the news sunk in, wiping \$15bn from the company's already severely dented market value. But then Teva announced that Kåre Schultz, who turned around **Lundbeck Inc.** in two years as CEO after leaving Novo, would become the Israeli firm's new CEO. That appointment put nearly \$4bn on Teva's market cap and wiped \$2.15bn off Lundbeck's.

The pharmaceutical industry is not immune from the influence of world events. On Aug. 10, the market values of 40 of the top 45 public pharmaceutical companies fell as the markets responded to US President Donald Trump's "fire and fury" threat to North Korea, sensitively made on the anniversary of the atomic bombing of Nagasaki.

Conversely, on Aug. 31, 40 out of 45 big pharma stocks rose together, accompanying the calming news that the US and South Korea had jointly flown military aircraft over the de-militarized zone that separates North and South Korea.

FORMING A MORE ORDERLY Q?

What does this analysis tell us? There are at least three possibilities.

One is that investors are not really paying heed to pharma companies and the environments in which they operate: that suggests that the gap between the market's estimates and the reality of given company's performance can be characterized as a phenomenon of drift between one quarter's results and the next. One possible explanation of quarterly results syndrome then is that results days prime investors, collectively, to pay more atten-

tion than usual to a company. The quarterly results give analysts, brokers and investors a chance to check their models of growth and value against reality. Any foolish observer can draw up a budget and predict future sales or spending needs but the money isn't banked until the CFO sings out the numbers at the press conference.

Another explanation may be that a 5-10% drift in the value of a large pharma company from one quarter to another represents the normal range of variation in real performance. That would suggest that selling prescription pharmaceuticals is more of a willo-the-wisp, volatile business than many had imagined, at least if not managed properly. However, big pharma revenues don't vary that much quarter to quarter or even from year to year.

A third possibility is that the mechanisms of communication between big pharma and the people who own and trade their shares is inefficient and needs attention. The onus may lie with the pharma companies who might need to do better in recognizing which aspects of their business alter perceptions of value and should, therefore, be disclosed in a timely fashion. On the other hand, perhaps investors exaggerate the impact of clinical developments or sales performance on the fundamental value of pharma stocks or depend overly much on the analyses of brokerage firms.

In an age when news, rumors and deception travel equally fast and globally, quarterly reporting looks like an anachronistic hangover from the era of ticker tape and handwritten accounts. Perhaps it is time for monthly or even daily formal reporting.

How this analysis was conducted

Scrip looked at the stock performance of 45 of the biggest pharma companies: Three of the biggest pharma companies are privately held (**Boehringer Ingelheim GMBH**, **Menarini Group** and **Servier SA**) and **Stada Arzneimittel AG** and **Actelion Pharmaceuticals Ltd.** were also excluded because both were acquired recently and subsequent events had little influence their stock value.

For each of 45 companies, *Scrip* looked at stock value changes in a five-day window around results time and compared daily value changes in that window with daily changes in the rest of the July-September 2017 quarter. ▶

Published online 1 November 2017

Teva CEO Schultz's Tough Start

Teva Pharmaceutical Industries

Ltd.'s new CEO Kare Schultz isn't exactly easing into the job. It was only his second day at the helm when Teva announced bleak third quarter financials Nov. 2 and revealed that it would miss its 2017 earnings forecasts – again.

The company is struggling to handle mounting debt challenges and is already seeing sales of its blockbuster specialty brand Copaxone (glatiramer) erode after facing new generic competition. Schultz – the former CEO of Danish neurology specialist **Lundbeck Inc.** – is the one tasked with turning around the troubled Israeli generic drug giant. His appointment was announced in September, but he only started Nov. 1. Schultz sat in on the third quarter conference call and offered some limited commentary, but he did not lead the results overview or provide any real strategic insights.

Teva's challenges have only grown in the two months since the company announced Schultz's appointment. FDA approved the first generic version of the valuable 40mg dose of Copaxone Oct. 4, which manufacturer **Mylan NV** immediately launched. The threat has been looming for some time, but Mylan had warned investors midyear not to expect an approval until 2018, so the news had an unexpected element to it.

The launch of a generic is already having an impact on sales of Copaxone, management confirmed during its Nov. 2 earnings call. "This erosion accelerated significantly last month following a competitor's approval and the launch of a generic Copaxone 40mg in the US," said Yitzhak Peterburg, who has been filling in as CEO on an interim basis since Erez Vigodman stepped down in February. ▶

jessica.merrill@informa.com, 2 Nov 2017



Click here to read the full Teva results story.
<http://bit.ly/2yjb1T1>

MS Franchise A Surprising Concern For Sanofi In Q3; Dupixent Out-Performs

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Sanofi's Q3 Results At A Glance

Net sales: €9.05bn

Pharmaceutical sales: €7.14bn

Sanofi Pasteur (vaccines unit) sales: €1.92bn

Reported EPS: €1.25

Operating income: €2.91bn

Sanofi's third quarter earnings disappointed the market, with revenues coming in below consensus expectations – still, sales of its recently approved eczema drug, *Dupixent*, were much stronger than expected.

The company saw a weak growth rate for its leading multiple sclerosis drugs *Aubagio* (teriflunomide) and *Lemtrada* (alemtuzumab) in the quarter. Overall though revenue remained flat for the French pharma, as the company executed good cost control for the period. Analysts, Bryan, Garnier & Co., said

A significant part of the difference between actual numbers and estimates stemmed from the company's specialty care unit, Sanofi Genzyme, for the first time in a while, said analysts from investment banking group Bryan, Garnier & Co. in a November 2 note. "Sales in rare diseases grew only 2.7% in the quarter with most of the products decelerating but more notably the MS franchise reported a disappointing 15.7% growth level and sales below the previous quarter," they said. However, analysts noted this was not completely unexpected as

most companies involved in MS showed declining growth rates in Q3 2017. As an exception, **Roche's** recently approved MS drug *Ocrevus* (ocrelizumab) made rapid market share gains in the quarter.

Deutsche Bank analysts noted that "softer sales of multiple sclerosis drugs *Aubagio* and *Lemtrada* may raise concerns over competition."

Sanofi noted during its November 2 earnings call that the MS business had performed ahead of expectations for several quarters until now, making the Q3 2017 results more exaggerated. *Aubagio* saw sales of €382m in Q3 2017 and sales for *Lemtrada* (alemtuzumab) came in at €113m, this versus 2Q 2017 sales of €425m and €124m, for each product respectively. Total MS sales were lower in the third quarter than the prior period by more than €50m.

However, Bill Sibold, executive vice president of Sanofi Genzyme, said MS had always been a tough market. "The MS category continues to be competitive. It's been competitive since we entered the market five years ago, and we are now five years post-launch," he said. "We continue to see very strong growth for both *Aubagio* and the franchise overall despite new entrants."

Sibold added that *Aubagio* was the fastest growing oral MS therapy globally, and in the US, with year-over-year global patient growth greater than 25%. "We really see prescriber confidence growing in *Aubagio* still," he said.

Sanofi reiterated its full year guidance for 2017 of broadly stable EPS with a 1-2% negative foreign exchange impact. Sanofi does not give revenue guidance.

Despite conflicting financial results in Q3, Sanofi's recently approved atopic dermatitis (AD) drug, *Dupixent* (dupilumab), performed better than anticipated. Sales of *Dupixent*, the first approved biologic medication for adults with moderate to severe atopic dermatitis (eczema), were €75m for the quarter versus consensus of €63m. Sibold told the earnings call that *Dupixent's* strong performance represents "a true representation of the underlying demand" for the drug and is not because of supply stocking.

Bernstein analysts said it had been a strong quarter for *Dupixent*, which it called an "important new launch" for Sanofi. Bernstein had only forecast sales of €45m for *Dupixent* in Q3.

Sanofi confirmed that a supplemental new drug application (sNDA) for *Dupixent* in asthma would be filed with the US FDA before the end of 2017. A European regulatory application for *Dupixent* – an interleukin 4 receptor antibody, which works by modulating the effects of IL4 and IL13 in allergic conditions – is expected in the first quarter of 2018 for asthma.

Dupixent was only approved in Europe for the treatment of atopic dermatitis in September this year. Sibold highlighted that Sanofi was "on the cusp of rolling out *Dupixent* for AD in Europe." The company plans to launch the drug in Germany by the end of the year as its first European market. "Our latest market research puts the target population of patients in Europe with moderate to severe AD at between 150,000 and 200,000," Sibold noted.

In reply to queries about pricing for *Dupixent* in Europe, Sanofi said it would not announce a price until the time of the drug's launch. ▶

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Click here to read:

Voyager Cheers End Of Sanofi Partnership In Parkinson's; Investors Less Confident

UK To Offer Firms More Flexible Commercial Deals On 'Transformative' Drugs, Earlier Access To Market

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Life science companies in England will be offered “flexible and confidential commercial arrangements” when negotiating market access for certain innovative medicines, with the possibility of market access up to four years earlier than at present for genuinely “transformative” new drugs, says the UK government in its long awaited response to the Accelerated Access Review produced by Professor Sir John Bell in October 2016.

Under the plans, which basically uphold most of the proposals in the AAR, a handful of selected innovations – drugs, devices, diagnostics and digital products would each year enter a new “accelerated access pathway” (AAP) where cost-effectiveness evaluations would be conducted in tandem with the regulatory approval process.

The government expects around five innovations a year to gain a “transformative” designation and enter the new pathway, but it stresses that their use must not involve any additional costs to NHS England. Any products placed on the AAP that are “cost additive will need to be offset by products that deliver cost savings, beyond those already factored into NHS plans,” it says.

Candidate products will be selected by a new “Accelerated Access Collaborative” chaired by former GlaxoSmithKline chief executive Sir Andrew Witty and comprising representatives of national regulatory and evaluation bodies, with input from industry, patients and clinicians. The AAC will be set up by the end of the year and the first products to enter the new pathway are expected to be identified starting in April 2018.

To spur collaboration between life science companies and the NHS when negotiating commercial agreements on innovative products, the government says that a new strategic commercial unit is to be established in NHS England to give it “enhanced commercial capability” by April next year. There is “clear demand” from innovators for win-win commercial deals and the new function will be able to develop these types of arrangement, it says.

The move has been broadly welcomed by the life science industry, which has been firmly behind the proposals in the AAR, seeing them as a vital part of efforts to strengthen the sector in the run-up to the UK's departure from the EU. (*Also see “UK Life Science Strategy Urges Adoption Of Accelerated Access Review, As Govt Prepares Response” Pink Sheet, 7 Sep, 2017.*)

Steve Bates, CEO of the BioIndustry Association, said the government's response to the AAR was “a key piece in the jigsaw of UK government life science policy that will set the environment for our sector in the lead up to Brexit and beyond.” He said the plans fitted “between the publication of the Life Sciences Industrial Strategy in the summer and ahead of both an anticipated Sector Deal and the outcome of the Treasury-led Patient Capital Review later in the year.”

The fact that Sir Andrew would be chairing the AAC meant there would be “significant industrial insight into the selection process for

products able to access this new accelerated route to market,” Bates declared. “If the Review's ambition for innovation is to truly take hold then it requires both NHS buy-in and top-level government leadership.”

The Association of the British Pharmaceutical Industry said the move “should benefit thousands of NHS patients as well as delivering significant long-term savings for the health service if appropriate investment in these transformative therapies is made available.”



CRITERIA

The government's response does not go into detail on which products will be able to use the new pathway, but the AAR itself had said that the criteria for a “transformative” product were likely to include factors such as significant improvements in patient outcomes, greater affordability, unmet need, and alignment with the priorities of NHS England. New products, including “repurposed medicines where a new indication is found for an existing product,” will be eligible to enter the pathway at any point.

An important component of the plans will be the early identification of what is coming through company pipelines. The new pathway will offer horizon scanning for new technologies to identify a subset of potential breakthrough products that could benefit from the AAP, the government says, adding that this will be a “key capability required for a forward-looking NHS that can articulate its priorities to industry, and prepare to deliver against those priorities.”

The AAC, in discussion with stakeholders, will select the criteria that determine whether the scheme is a success, according to the government. “We should, however, expect that they will consider indicators such as: level of industry interest in AAP; speed of product progression through the AAP; improved health and quality outcomes; increased affordability of new technologies and products; improved value for money; increased impact of AHSNs [Academic Health Science Networks]; and SMEs getting products to patients quicker and more easily.” ▶

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Alnylam Enjoys Autumn in Paris With hATTR Win Over Ionis

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Alnylam Pharmaceuticals Inc.'s patisiran seems to be on course to become the standard of care for hereditary ATTR (hATTR) amyloidosis after the full data set from the APOLLO study on the first RNAi therapeutic to succeed in a late-stage trial were unveiled to acclaim at a conference in Paris.

In September, the top-line results from the APOLLO study led to a 52% leap in Alnylam's share price and the full results prompted a 20% jump just during the 20-minute presentation at the European ATTR Amyloidosis meeting in the French capital. The results from the 225-patient trial showed that for the primary endpoint of modified Neuropathy Impairment Score+7 (mNIS+7), treatment with patisiran resulted in a negative 6.0 point change (i.e. improvement) at 18 months compared to a 28.0 mNIS+7 increase (worsening) for those on placebo.

The intravenous drug, which is designed to target and silence specific messenger RNAi, potentially blocking the production of transthyretin (TTR) protein before it is made and restore function in tissues, also showed a negative 6.7 point change (improvement) using the Norfolk-Quality of Life-Diabetic Neuropathy measure at 18 months as compared with a 14.4 point increase (worsening) for the placebo group.

Saying that the data represented the first time a treatment could actually reverse as well as improve hATTR amyloidosis, David Adams of Bicetre Hospital in Paris and principal investigator for APOLLO, told *Scrip* that he was particularly impressed by the effects seen with patisiran in the cardiac subpopulation, as favorable changes were seen in several measurements, including left ventricular wall thickness and ten meter-walk. He added that he was very pleasantly surprised to see patients who had been struggling to walk unaided returning to clinic with a much-improved gait and feeling better. "The Improvements can be seen not just on a graph."

The disease affects approximately 50,000 people worldwide and hATTR amyloidosis patients have a life expectancy of 2.5 to 15 years from symptom onset. It is often misdi-

agnosed due to its variety of symptoms that overlap with other more common diseases, Adams noted, and multiple specialists are often seen prior to diagnosis and can lead to ineffective or possibly detrimental treatment. The only approved treatment options for early-stage disease are liver transplantation and **Pfizer Inc.'s Vyndaqel** (tafamidis), which is available in Europe but is not on the market in the US, and Adams said that both come with considerable limitations.

Now after a 15-year journey, it looks as though a new class of therapy with strong efficacy and safety data (13 deaths were reported but none were the result of patisiran use) may soon be available. Alnylam will start filing with regulatory authorities in late 2017, with the goal of achieving approval in mid-2018.

Adams told *Scrip* that he expected patisiran to be standard of care very quickly, not least because "at the moment there is no standard of care." He noted that an open-label extension study, in which at least 99% of patients who completed the APOLLO study took part, should hopefully produce more long-term data on the drug's effectiveness.

IONIS' INOTERSEN STILL IN THE BATTLE

The Paris conference was billed in some quarters as a head-to-head battle between patisiran and **Ionis Pharmaceuticals Inc.'s** antisense hATTR therapy inotersen. Full data from the Phase III NEURO-TTR study were presented at the meeting and the study also used the primary endpoints of Norfolk QoL-DN and mNIS+7.

The Ionis study was successful but the data were not as stellar as those from Alnylam's APOLLO trial. In terms of mNIS+7, a 19.73 point benefit was seen from inotersen at 15 months, compared with 34.0 for patisiran, while the Norfolk QoL-DN score was an 11.68-point mean improvement, compared to 21.1 for the Alnylam drug.

There is also some concern about the safety data with the inotersen trial as there were five deaths in the study, all in the inotersen arm. Four were associated with dis-

ease progression and considered unrelated to treatment but there was one fatal intracranial hemorrhage in conjunction with serious thrombocytopenia.

Participants at the Paris conference looked more favorably on the patisiran data but when it comes to filings, Ionis is first out of the blocks. The day after the meeting, Nov. 3, the company submitted a marketing authorization application to the European Medicines Agency, which will be reviewed under the latter's Accelerated Assessment program.

Chief business officer Sarah Boyce said in a statement, "We are pleased that we met the last deadline for accelerated assessment in the EU for 2017 [and] next week, we also plan to submit the New Drug Application to the US Food and Drug Administration." She added that "combined with significant efficacy and superior convenience (the Ionis drug is a weekly injection and patisiran is infused every three weeks), we believe inotersen will be the treatment of choice for this patient population."

GlaxoSmithKline PLC recently pulled out of its collaboration with Ionis on inotersen as it moves away from rare diseases but Boyce said that "we are in advanced discussions with potential co-commercialization partners. We believe the right partner can maximize the commercial success of inotersen." Alnylam will market on its own in the US and Europe and has Sanofi on board for the rest of the world. (*Also see "Deal Watch: GSK Declines Option As Ionis' Inotersen Nears Finish Line" Scrip, 11 Aug, 2017.*)

Both companies believe they will ultimately be the hATTR winner and pricing as well as safety and efficacy is likely to be a major factor. Obviously, neither company is showing their hand yet but some participants at the Paris meeting told *Scrip* that they expect inotersen to come in considerably lower. ▶

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Click here to read:
**Interview: Alnylam President
On Patisiran Lift-Off Plans**

CAR-T To Go: Juno Sees JCAR017 As Safer, Suited For Outpatients

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Juno Therapeutics Inc. is highlighting the potential of its CAR T-cell therapy JCAR017 to be used in earlier lines of therapy and perhaps in the outpatient setting, based on the strong safety and efficacy profile demonstrated in updated diffuse large B-cell lymphoma data from the Phase I TRANSCEND study.

JCAR017 is a CD19-directed, autologous chimeric antigen receptor T-cell (CAR-T) product that uses a 4-1BB costimulatory domain.

The company turned its attention to JCAR017 after its lead CAR-T program, JCAR015, was discontinued in late 2016 over major safety problems, including deaths, that emerged in acute lymphoblastic leukemia (ALL) research. (Also see *"Juno Ends JCAR015 Development In ALL, Cementing Third Place CAR-T Position"* *Scrip*, 1 Mar, 2017.)

In the process, Juno lost the CAR-T lead to competitors **Novartis AG** and **Kite Pharma Inc.** (now owned by **Gilead Sciences Inc.**). The US FDA approved Novartis's *Kymriah* (tisagenlecleucel, or CTL019) for relapsed/refractory ALL in August and Gilead's *Yescarta* (axicabtagene ciloleucel) for adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy in October. (Also see *"Novartis Beats CAR-T Competitors To The Pricing Punch With Kymriah Approval"* *Scrip*, 31 Aug, 2017.) and (Also see *"Gilead/Kite Pricing For Yescarta Undercuts Novartis's CAR-T Kymriah"* *Scrip*, 18 Oct, 2017.)

But Juno may yet get the upper hand.

The company believes that JCAR017 is best-in-class, with a safety profile that supports use in earlier lines of therapy and in the outpatient setting.

On Nov. 1, Juno released updated data from the Phase I TRANSCEND study in association with the release of abstracts for the American Society of Hematology (ASH) annual meeting. The data support the company's ambitions, though it's still early days yet in terms of follow-up. The ASH abstract data reflects results up to July 7; updated and longer term figures will be released at the meeting, to be held Dec. 9-12 in Atlanta.

The TRANSCEND study tested JCAR017 in 69 patients with relapsed/refractory DLBCL, a type of non-Hodgkin lymphoma (NHL), including de novo cases and disease that transformed from indolent lymphoma. The company highlighted results for two cohorts taking the dose of 50 million cells and the higher dose of 100 million cells that was taken forward for pivotal research and for future filings.

At the dose of 100 million cells, JCAR017 was associated with an 80% objective response rate (12/15), including a 73% complete response rate (11/15) three months after treatment. In patients who had a dose of 50 million cells, the ORR was 52% (11/21) and the CR was 33% (7/21) after three months. The safety profile looked similar across doses, the company reported. Across the study population of 69 patients, treatment-related adverse events included neutropenia (41%), fatigue (30%), thrombocytopenia (30%) and anemia (26%). There was only one case (1%) of severe cytokine-release syndrome (CRS), a feared adverse event with CAR-T therapy, and 30% with any grade of CRS. As for neurotoxicity, investigators reported a 14% rate of severe events and 20% at any grade.

Execs highlighted the safety profile in Juno's quarterly earnings call on Nov. 1.

Across the entire dataset, there were no Grade 5 CRS or neurotoxicity events, R&D President Sunil Agarwal noted during the call. And notably, the company said, 64% had no evidence of cytokine-release syndrome or neurotoxicity.

Juno is continuing with the higher dose in the TRANSCEND study and plans to file a BLA in the second half of 2018, with possible approval for JCAR17 the same year.

Agarwal stressed that the tolerability data were achieved without the need for prophylactic use of tocilizumab (**Roche's Actemra**) or the steroid dexamethasone.

There has been a relationship between dose response and efficacy in favor of the higher dose, but there have not been any increasing tolerability issues with the higher

dose, the exec said. Based on these tolerability data, the company has started dosing JCAR017 in the outpatient setting and will present data on a cohort of these patients at the ASH meeting.

"Our goal is to protect patients. And if you think about it from that perspective, these patients post-lymphodepletion are highly immunocompromised. And if you ask any physician, the last place you want to be if you are immunocompromised is in the hospital, unless you must be there," Agarwal explained.

Chief Commercial Officer Robert Azelby commented that the therapy promises to "democratize" access to CAR-T treatment beyond large academic transplant centers that many patients do not have access to, like those living in rural settings.

"I think that will be a true testament to the differentiation of these products," Azelby said.

Juno believes that the safety and efficacy profile means that the therapy may get broader labeling for earlier lines of therapy compared with other CAR-T therapies. Gilead's *Yescarta* is approved for patients with at least two prior therapies and it is likely that JCAR017 would initially be approved for a similar population based on current data. But over time the best-in-class profile will move JCAR017 into additional populations, Chief Medical Officer Mark Gilbert maintained.

"We're looking at both the transplant-eligible population and the non-transplant eligible population for second-line therapy or first salvage. And I think those are going to be the main areas where there'll be label expansion, particularly for our drug," Gilbert said.

DATA WELL RECEIVED

Juno's presentation was well-received by the market and analysts. The company's stock price closed up by about 24% to \$59.91 on Nov. 2.

In a Nov. 1 note, Leerink Swann analyst Michael Schmidt said that while it is still

CONTINUED ON PAGE 14

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early and difficult to compare across trials, the data for the higher dose being used in the ongoing pivotal DLBCL trial support the thesis that that the product could “potentially emerge as best-in-class CD19 CAR-T therapy.”

The updated data look “comparable (or better) in most efficacy and tolerability endpoints compared to Gilead’s Yescarta or [Novartis] CTL019,” Schmidt concluded.

In a Nov. 2 note, BTIG Equity Research analyst Dane Leone said that overall the data are very encouraging, but added that it is “definitely early for making decisive claims regarding superiority.”

A key focus at the ASH meeting will be the response rate in patients who had the higher dose after six months, Leone commented.

However, Leone also pointed out that while the low 1% CRS rate with no need for prophylactic tocilizumab is impressive, the 14% rate of serious neurotoxicity is actual higher than the 13% rate seen in the JULIET study of Novartis’ Kymriah. “We do not downplay CRS, but discussions re-

garding the safety profile of CD19+ CAR T are generally more tuned towards concern over neurotox, as CRS is viewed as [a] less rapid and more manageable toxicity,” Leone said.

The idea of outpatient treatment has hit a nerve, the analyst added. “Bringing CAR T access to beyond the major cancer centers is a great effort, so we hope that the Juno team is successful,” Leone said.

BRANCHING OUT FROM DLBCL

While the market is focused on the therapy’s first indication in third-line DLBCL, the company is investing in a broad clinical development program to support moving to earlier lines of DLBCL and also to move into new diseases like chronic lymphocytic leukemia, CEO Hans Bishop said.

The TRANSCEND data “underscore the broader value of the technology platform we are building at Juno.”

“We believe the positive data we’re reporting are in no small part a consequence of the degree of control we have over the total cell dose and composition of the cells that make up that dose,” Bishop said.

The platform technology underpinning the product “will be a source of competitive advantage, both as we move forward in earlier lines of NHL and the new indications, for example, multiple myeloma,” Bishop said.

Just a few years ago, to many, it was unclear whether CAR-T cells could be applied broadly or would be limited to a relatively small group of patients, but it’s “increasingly clear that we have the potential to impact a broad range of tumors that afflict a large number of patients, including lymphoma, leukemia and multiple myeloma,” the exec said.

The company estimates that there are about 50,000 patients in the US and a similar number in the five major European Union markets and Japan with these tumor types who have failed first-line therapy and need better treatments.

Juno’s pipeline covers all of these indications and the company is already in potential registrational studies or will be in them by 2018 for almost all of the indications that make up these markets, Bishop said. ▶

Published online 3 November 2017

End Of The Line For AstraZeneca’s Tralokinumab

ALEX SHIMMINGS alex.shimmings@informa.com

AstraZeneca PLC’s anti-interleukin-13 (IL-13) human monoclonal antibody tralokinumab has failed in two further Phase III studies (STRATOS 2 and TROPOS), leaving the company now banking on benralizumab to help offset generic pressure to its asthma franchise.

AstraZeneca has yet to call time on tralokinumab; it said it was still analysing the results but would provide an update on the product’s fate as part of a future pipeline summary. Top-line results show that neither study met its primary endpoint. STRATOS 2 did not see a significant reduction in the annual asthma exacerbation rate (AAER) for tralokinumab compared with placebo in patients with severe, uncontrolled asthma and elevated levels of a biomarker, fractional exhaled nitric oxide (FeNO).

And, in TROPOS, tralokinumab did not significantly reduce oral corticosteroid (OCS) use when added to the standard of care, in patients dependent on OCS.

Tralokinumab had already failed in the

STRATOS-1 trial in May. The drug yielded no improvement in the AAER over placebo in the overall population of severe asthma patients inadequately controlled despite receiving inhaled corticosteroids (ICS) plus a long-acting beta2-agonist (LABA).

At that time, AstraZeneca put its hope in a pre-planned subpopulation analysis in STRATOS 1 in which tralokinumab showed a clinically relevant reduction in AAER in patients with elevated FeNO. The expectation was that this would translate into success in STRATOS 2.

Analysts at Biomedtracker said it was not clear if there were other biomarkers where the drug showed signs of efficacy in both the STRATOS trials. “However, then they would need to do another confirmatory study, and coming substantially later to the market would be a commercial handicap, with the drug potentially relegated to patients that others do not work in.”

Datamonitor Healthcare analyst Chris Mulligan said: “While this is obviously disap-

pointing for AstraZeneca, it is not surprising as tralokinumab has been struggling for some time, as such, Datamonitor expect this latest data release to signal the end of tralokinumab’s development in asthma.”

Overall, targeting IL-13 in asthma has been a bit of a disappointment for drug developers. **Roche/Genentech Inc.**’s IL-13 inhibiting product lebrikizumab failed in one of its two pivotal trials, LAVOLTA II, in early 2016, and was dropped for this indication later that year. **Novartis AG**’s anti-IL 13 monoclonal antibody QBX-258 is in Phase II, but **AbbVie Inc.**’s similar product ABT-308 has been dropped.

Sanofi/Regeneron Pharmaceuticals Inc.’s dupilumab, which targets both IL-13 and IL-4, is in Phase III for asthma.

“These results are in contrast with the more consistently positive ones in drugs targeting the IL-5 pathway, as well as dupilumab, which targets the IL-4 receptor that interestingly is impacted by both IL-4 and IL-13,” the Biomedtracker analysts pointed out. ▶

Published online 1 November 2017

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2017

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Financing Deal of the Year

This Scrip Award seeks to reward successful and creative fundraising by pharma and biotech companies.

Abzena's public placing of £25m

Abzena's April £25m fundraising represented over 50% of the group's total market capitalization at the time, and will transform its growth plans. Capacity at its UK and US businesses had been reached but the new capital will fund a transformational growth plan, aimed at >40% CAGR revenue growth over three years.

BiomX's Series A financing of \$24m

This Series A financing, led by OrbiMed, Johnson & Johnson Innovation – JJDC, Inc. and Takeda Ventures, allows BiomX to benefit from the input, expertise and guidance of J&J and Takeda – highly valuable for a new start up. The proceeds will be used to advance the pipeline and continue to enhance its proprietary microbiome modulation platform technologies.

Inventiva's €48m initial public offering

Inventiva completed this €48m IPO on Euronext Paris in February, decisively breaking the European drought in IPOs. The deal was completed slightly below its objective for funds raised, but still widely regarded as successfully completed because of the significant headwinds from challenging market conditions. Inventiva attracted several highly regarded investors from the US and Europe.

Pharming's €104m financing

Pharming raised €104m through a combination of new equity, straight debt and new convertible bonds to finance the reacquisition of the US commercial rights to Ruconest from Valeant Pharmaceuticals. The deal accelerates Pharming's development into a profitable specialty pharmaceutical company with its own independent commercial infrastructure, and accelerates operating profitability.

Verona Pharma's \$89m NASDAQ listing

UK-based Verona listed on NASDAQ in April when it expanded its footprint in the US market with a global offering that raised \$89.3m. It also raised £44.7m as part of a significantly oversubscribed private placement of equity securities in July 2016, which brought in a number of new cornerstone specialist UK, European and US healthcare funds.

INC Research/inVentive Health's Best New Drug Award

In this category, the judges will be looking for the small-molecule or biological product that represents the best advance in its therapeutic area.

Astex Therapeutics/Novartis's Kisqali (ribociclib)

Kisqali provides a first-line treatment for HR+/HER2- advanced breast cancer in combination with an aromatase inhibitor. It belongs to a class of drugs that help slow the progression of cancer by inhibiting two proteins called cyclin-dependent kinase 4 and 6. About 30% of those affected by early-stage breast cancer will go on to develop advanced disease.

Merck KGaA/Pfizer's Bavencio (avelumab)

Bavencio is a fully human monoclonal antibody targeting the programmed death-ligand 1 protein. It is the first FDA-approved treatment for Merkel cell carcinoma, a rare type of skin cancer. Previously the only options available to patients with Merkel cell carcinoma were surgery, radiation, or chemotherapy, which often prove to be insufficient in metastatic or recurrent patients.

Roche's Ocrevus (ocrelizumab)

This humanized monoclonal antibody is the first approved drug to have shown efficacy in primary progressive multiple sclerosis as well as relapsing remitting disease. It is designed to target CD20-positive B cells, thought to be a key contributor to myelin and axonal damage. The B-cell-targeting mechanism is unique among current therapies, and may account for its broad efficacy.

Sanofi/Regeneron Pharmaceuticals' Dupixent (dupilumab)

Dupixent is the first biologic to be approved for use in atopic dermatitis. It gained US FDA approval for adults with moderate-to-severe disease who are not adequately controlled by, or cannot use, topical therapies. The injectable monoclonal antibody is directed against the IL-4R α , which blocks signaling from both IL-4 and IL-13 to inhibit the inflammatory response.

Shire's Xiidra (lifitegrast)

Xiidra is the first prescription therapy approved in the US for both the signs and symptoms of dry eye disease. As the first drug in its class, it captured 20% market share within six months of launch. It inhibits T-cell inflammation by blocking two key surface proteins that mediate the chronic inflammatory cascade associated with dry eye disease.

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Behind The NASH Leaders, Pursuers Already Anticipating Second-Wave Improvements

JOSEPH HAAS joseph.haas@informa.com

The unmet need in non-alcoholic steatohepatitis (NASH) has prompted numerous companies to aggressively pursue the opportunity. And while there is fierce competition to be first to market, the companies trailing the vanguard of drug development are aiming to improve on that first wave.

There are four companies already in Phase III in NASH – **Intercept Pharmaceuticals Inc.**, **Genfit SA**, **Allergan PLC** and **Gilead Sciences Inc.** – and 19 others that have advanced at least to Phase II in the fatty liver disease, according to Biomedtracker.

At the recent American Association for the Study of Liver Diseases meeting several of the sponsors still in Phase II seemed to be positioning their candidates as ones that may offer a step up in benefits similar to what was seen in hepatitis C as the first-generation protease inhibitors gradually were surpassed by other direct-acting antivirals and ultimately combination therapies.

At different ends of the biopharmaceutical industry spectrum, big pharma **Bristol-Myers Squibb Co.** and privately held biotech **NGM Biopharmaceuticals Inc.** both are addressing the fibroblast growth factor (FGF) hormone pathway with their candidates and believe reducing liver fat could result in a cascade of liver health benefits for patients. NGM even thinks it could end up with a NASH therapy that would return the liver to normal health in 26 weeks or less, rather than requiring the lifelong, chronic therapy generally expected for this major unmet medical need.

Private biotech **Cirius Therapeutics Inc.**, meanwhile, is addressing the metabolic nature of NASH by attempting to come up with a mitochondrial therapy that will provide benefits similar to those seen with **Takeda Pharmaceutical Co. Ltd.** and **Eli Lilly & Co.**'s **Actos** (pioglitazone) in diabetes, only with a cleaner safety profile.

FOCUSING ON METABOLIC APPROACHES

Through two name changes and a revised focus from diabetes to NASH, San Diego-based Cirius has focused on attenuating pyruvate metabolism by a mechanism other than peroxisome proliferator activator receptor (PPAR) agonism – the mechanism employed both by Actos and by Genfit's Phase III NASH candidate elafibranor. In fact, based on years of study, Cirius co-founder and R&D head Jerry Colca believes that pioglitazone's benefit in diabetes may derive from multiple mechanisms.

"Even though these drugs were called PPAR gamma agonists [and] everybody thought that was what they did, [Colca] realized they probably work through many mechanisms and that there's probably one mitochondrial target that's giving you the efficacy," Cirius Chief Business Officer Brian Farmer told *Scrup*. "In fact, the PPAR gamma is probably just along for the ride and creating some safety issues." In the case of Actos, those issues include the risk of weight gain and cardiovascular disease.

Like pioglitazone, Cirius' MSDC-0602K works as an insulin sensitizer, which the biotech thinks will prove to play a key role in addressing the multi-factorial disease state found in NASH patients.

"We think people look at our compound as a new approach, a little different than what other people are doing," Farmer said. "Most other [NASH] compounds are focused on single, downstream anti-fibrotic and anti-inflammatory targets. Ours, we think, is more metabolic-focused on the underlying disease and would affect many different pathways."

CONSIDERING REGIMENS

Like most companies working in NASH, Cirius is thinking ahead to its drug's potential as both monotherapy and as part of a combination regimen, such as the ones that eventually ascended to standards-of-care in HIV and HCV. Cirius hopes '0602K will emerge as a "cornerstone, the metabolic piece," with perhaps an anti-fibrotic agent added on, the exec said.

But, initially, it is only studying '0602K as a monotherapy, even though the company knows combo therapy likely will be the wave of the future in NASH. Farmer said Cirius first wants to see if it can replicate the 45% resolution of NASH seen in its earlier trials, including one in diabetes patients, compared to the 20%-30% resolution commonly seen with other NASH candidates.

For now, Cirius, which raised a \$30m Series A financing in April, is working to enroll a 340-patient, 55-site Phase IIb study of '0602K in the US. It will test three doses of the small molecule drug against placebo, given once-daily for 52 weeks, with a liver biopsy before and at the end of treatment. The endpoints will look at histology, liver fibrosis and inflammation, like the ones being used in the ongoing Phase III trials, Farmer said.

Cirius expects to complete enrollment by mid-2018 and produce data toward the middle of 2019. "We're going well, we've enrolled about a third of the patients," Farmer said. "NASH is a tough space to enroll – everyone's been having trouble. It's tough – unfortunately it requires and will require for a while two liver biopsies to be in a trial, one at the beginning, one at the end, to get really conclusive evidence."

"It's hard to know sometimes who's going to have the fibrosis or not, so some patients are given a biopsy and then told they can't be in the study," he added. "And then there's just a lot of competition, a lot of studies going on."

REDUCING LIVER FAT VIA THE FGF PATHWAY

Bristol also switched focus from diabetes to NASH with its candidate, a pegylated FGF21 hormone analogue formerly known as ARX618, in-licensed in 2011 from **Ambrx Inc.** Bristol's Fibrosis Lead Rose Christian told *Scrup* the compound provides pleiotropic effects, both reducing fat and enabling the use of fat as energy source. The company has biomarker data indicating an anti-fibrotic effect from a pair of Phase II studies, one in diabetes patients and one in NASH patients.

Both Bristol and NGM, which is developing the FGF19 analogue NGM282, presented Phase II data at the European Association for the Study of Liver Disease meeting earlier in 2017, offering evidence of multiple, substantial benefits in NASH patients, but based on im-

aging and biomarker data rather than the standard of biopsy data. NGM now is working on an extension of its Phase IIb study to obtain biopsy data from about 20 patients, while Bristol recently had an end-of-Phase II meeting with the US FDA, where Christian said the company “teed up some pretty novel [trial] designs.”

Bristol also is partnered with **Nordic Bioscience AS** to study the use of collagen turnover markers – such as ProC3 – to measure fibrosis levels in patients. ProC3 is one of several biomarkers widely used in NASH studies as the industry searches for non-invasive methods for diagnosis, prognosis and assessing how patients respond to therapy.

“There have been studies in a number of different liver fibrosis categories – initially in HCV patients – that show that patients who have much higher levels of ProC3 are more likely to have persistent levels of fibrosis even after they were cured, and were much more likely to progress to the need for a transplant or even HCC [hepatocellular carcinoma],” Christian explained. “We found that higher ProC3 levels in our NASH study, even with just 75 patients, predicted those who would have higher fibrosis scores but also better response. There’s going to be a huge need for that in the future; it’s very analogous to measuring HbA1C levels in diabetes patients.”

Bristol’s agreement with Nordic Bioscience is not exclusive – Christian said the pharma is not looking to develop a proprietary companion diagnostic for NASH, but it does hope to help advance the validation process for ProC3. Bristol would like to see ProC3 on the market as a NASH diagnostic by the time its drug is ready to launch.

BRISTOL’S BIOMARKER FINDINGS

In the first Phase II study in diabetes patients with fatty liver, Bristol saw an improvement in metabolic parameters and a reduction in fibrosis based on biomarkers. In the study in NASH patients, the company used liver biopsy to confirm that subjects had NASH but it did not perform an end-of-treatment biopsy for endpoint data.

“Back in early 2015, everyone thought it would take a year and a half at least for liver fibrosis to improve ... and I thought based on my understanding of collagen and bone biology, you should see a change a lot faster than that,” Christian said. In reviewing MRI scans of patients who had had bariatric surgery, Bristol saw that that liver fat levels reduced within four weeks. This led Christian to assume that Bristol’s drug could show fat-reducing benefit in four months or less.

Bristol took a lot of meetings at the AASLD meeting in Washington, DC, to find out the latest thinking on NASH combination therapy, Christian added. That remains a consensus expectation because nobody yet has a candidate with the demonstrated ability to reduce fat, lower fibrosis score and improve the metabolic markers of NASH.

“Every one of those is a driver for NASH progression and is going to have to be addressed, whether by a monotherapy or a combination of drugs that can each hit one aspect,” she explained. “Based on our animal models, we know FGF21 reduces liver fat, we saw this in early toxicology studies as well as in NASH models ... and we know it has metabolic effects.” She added that Bristol also has observed anti-inflammatory effects and an anti-fibrotic impact based on magnetic resonance elastography (MRE) scans, which measure liver stiffness.

In another study, Bristol saw a 30% reduction in ProC3 with 16 weeks of treatment, which is associated with more than a one-stage reduction in fibrosis score. Christian said these data have been presented at a conference but not yet published, but Bristol feels “very confident with these results.”

“In terms of our drug development approach, what makes sense is to start looking at FGF21 in some other some other fibrotic liver diseases, such as patients with cured HCV infection,” she added. “A lot of them still had persistent fibrosis after cure and are at risk for transplant or [HCC]. That’s not treated by hep C [therapy] alone. I think that’s a target for combo therapy. Also, there is alcoholic liver disease. Right now, not many trials are actively looking at that, and the effect of alcohol consumption on inflammation and fat accumulation in the liver is very similar to that of NASH and may respond to similar therapies.”

PROFOUND EFFECTS

NGM President Jeff Jonker says his company has produced Phase II data indicating reduction of liver fat and improvement in fibrosis and inflammation in a study very similar in design to Bristol’s NASH study and one conducted by Gilead with its ACC inhibitor GS-0976. But NGM282 showed benefits – based on imaging and biomarker data, not liver biopsy – that were “profound” compared to those other two candidates, he asserted. A healthy liver has about 5% fat content, whereas a typical NASH patient has 15% fat content in his or her liver. In 12 weeks of treatment, NGM282 was able to show roughly 10% absolute reduction in liver fat, essentially returning the liver to a normal healthy state. Jonker cited one patient with three times to four times the normal amount of liver fat whose reading was 3.6% at the end of 12 weeks of treatment with NGM282.

NGM also saw positive indications from the ProC3 biomarker and reduced levels of ALT, typically very elevated in NASH, the exec told *Scrip*. Still, he acknowledged the limited value of imaging and biomarker data in a disease setting where liver biopsy remains the standard for diagnosis and determining the effect of treatment.

“All of that is great and exciting, [but] it also is still uncorrelated. The imaging and biomarkers are kind of aligned with the biopsy data, but we’re not quite there yet, so we can’t do a victory dance with just imaging and biomarker data,” Jonker said. The company recently decided to augment its Phase IIb data in 82 patients by initiating a 66-patient extension, in which about one-third will undergo a liver biopsy at the end of treatment.

NGM’s thesis is that reducing liver fat will result in a cascade of benefits ultimately resulting in the liver healing itself. Jonker attributed this to developing a drug that mimics the powerful and quick effects normally occurring hormones can present in the human body. He noted that the liver is one of the few regenerative organs in the human body.

Therefore, NGM’s hope is that NGM282 might become a monotherapy that more or less resolves NASH in a 12- or 26-week period, rather than chronic therapy. In Phase IIb, 80% of patients responded to therapy, while the other 20% saw their disease state stabilize. Such benefits probably won’t apply to patients with cirrhotic livers, Jonker explained, but for NASH patients with earlier-stage disease, NGM is looking to change the expected paradigm of NASH therapy.

“If this is what you can do in 12 weeks, there is, I think, a real possibility that you could resolve NASH and reverse fibrosis in a very short period of time,” Jonker said. “We would think from looking at our data and thinking about what our Phase III design might be that a realistic endpoint for us might be 26 weeks. Most of the studies are 52, 72 or even 96 weeks, but those are fairly mildly active agents. If you have something that is this potent, I don’t know. Nobody expected to see these data. Nobody thought at 12 weeks you could do this!” ▶

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Stock Scan October: Generics Pull Pharma Down

JOHN HODGSON john.hodgson@informa.com

The 2% average stock decline among the Top 50 publicly traded drug companies represents a fall in market capitalization across the largest pharma companies of \$50bn.

Furthermore, the fall in values occurred despite general market revivals in Asia in October.

Eleven out of the Top 50 pharma stocks rose in value more than 5% in the month, and seven of those were domiciled in Asia.

In contrast, 14 big pharma stocks fell more than 5% in October and 11 of those were North American companies. Indeed, nine stocks fell more than 10% in the month, and all but one of those are based (operationally) in the US or Canada.

FIRST, THE GOOD NEWS

October was a tumultuous month for **Mylan NV**. Although the company's stock price at the end of the month was 13.8% up on its position at the start, Mylan had been 22.3% up the month until the last day of October following the FDA approval of its high and low dose formulations of generic *Copaxone* (glatiramer acetate). When that news broke, Mylan's stock rose 16.2% on the day (Oct. 4) then rose a further 4% over the next two and remained buoyant. But on Oct. 31, the company's president and executive director, Rajiv Malik, was named in connection with a price-fixing investigation being conducted by 45 US state Attorneys-General. That pulled Mylan down over 6%.

Five of the eleven stocks that rose more than 5% during the month were Japan-domiciled companies, swept up in a 9.9% rise across the Japanese market. Only **Sumitomo Dainippon Pharma Co. Ltd.** came out ahead of the rise in the Nikkei 225 index, however. Risers **Eisai Co. Ltd.**, **Astellas Pharma Inc.**, **Otsuka Pharmaceutical Co. Ltd.** and **Kyowa Hakko Kirin Co. Ltd.** actually fell back relative to the market trend. **Mitsubishi Tanabe Pharma Corp.** declined 3.3% even while other stocks were rising.

Indian pharma stocks also performed well during October with the Nifty Pharma index up 6.6% through October, slightly ahead of the Nifty 50 index of the large cap compa-

Big Pharma* Stock Trading Trends - October



-2%

Mean monthly fall across the top 50 public pharma companies



-\$50,000,000,000

\$50 billion market cap fall across pharma



-31%, -\$35bn

Celgene's stock decline

*Top 50 Companies By Annual Prescription Drug Sales



+16.2%

Biggest daily price rise - Mylan on the approval of generic Copaxone



+\$1,365

Winnings from daily pharma bets starting with a \$1,000 stake ...



-\$743

... or losings with the wrong stocks on the wrong day at the wrong price

There was lots of negative activity among generics stocks in October. Much of it came in reaction to Endo's questionable decision to challenge FDA Commissioner Scott Gottlieb's apparent encouragement of drug compounding, something likely to lead to undercutting of generic drug pricing

nies which includes **Cipla Ltd.**, **Dr. Reddy's Laboratories Ltd.**, **Lupin Ltd.** and **Sun Pharmaceutical Industries Ltd.**

Sun led the group with a 9.9% rise over the month as the FDA completed its inspection of the company's plant at Dadra. Sun's stock also rose over 5% in the two days following the US FDA's approval of the ANDA for generic *Coreg CR* (carvedilol phosphate).

Cipla was the other big Indian winner in October: its stock ended 7.1% up on the month, with a rise of 5.4% in two days when its ANDA for sevelamer carbonate tablets (a generic version of Genzyme's *Renvela*) was approved by the FDA on Oct. 27.

Novo Nordisk AS had contended that its new GLP-1 analog semaglutide could become the new standard of care in type 2 diabetes and that was reinforced in October

by decisions at the FDA. The agency's publication of briefing documents on Oct. 17 ahead of its Endocrinologic and Metabolic Drug Advisory Committee meeting pushed Novo's stock price up 5%. A second rise of 2% followed the 16-0 committee vote in favor of approval on Oct. 18. Rival **Eli Lilly & Co's** stock moved only marginally down on both occasions as investors had already factored in the impact on *Trulicity* (dulaglutide) sales in August when Novo first announced its clinical findings.

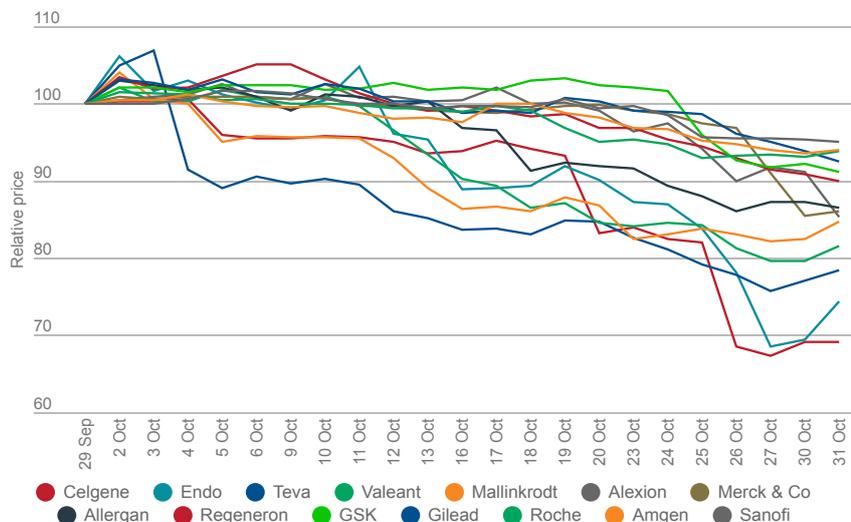
... AND NOW, THE BAD NEWS

There was lots of negative activity among generics stocks in October. Much of it came in reaction to **Endo International PLC's** questionable decision on Oct. 12 to challenge FDA Commissioner Scott Gottlieb's apparent encouragement of drug com-

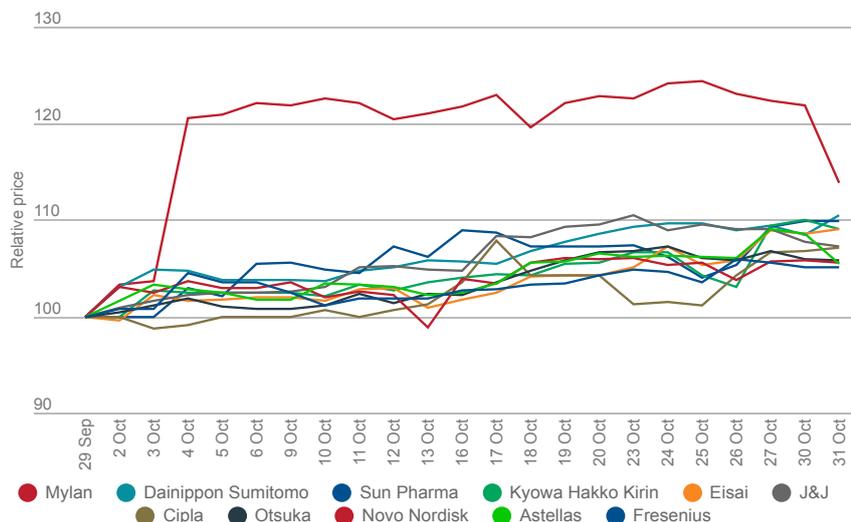
Winners and Losers In October

Hover over legend to highlight a company. Y axis shows price relative to start of month.

Losers



Winners



*Top 50 Companies By Annual Prescription Drug Sales

Why Stocks Moved

Company	Up	What happened
Mylan	13.8%	FDA approves high and low dose generic Copaxone
Dainippon Sumitomo	10.5%	9.9% rise in Nikkei 225 during Abe re-election run-up
Sun Pharma	9.9%	FDA inspection completed; ANDA for generic Coreg CR
Kyowa Hakko Kirin	9.1%	9.9% rise in Nikkei 225
Eisai	9.0%	9.9% rise in Nikkei 225
J&J	7.2%	Q3 results and analyst upgrades
Cipla	7.1%	ANDA approval for generic Renvela
Otsuka	5.8%	Trails 9.9% rise in Nikkei 225
Novo Nordisk	5.6%	FDA advisors recommend semaglutide
Astellas	5.4%	Trails 9.9% rise in Nikkei 225
Fresenius	5.1%	Shareholder approval for acquisition of NxStage Medical

Company	Down	What happened
Celgene	-30.8%	Crohn's program ended; Lower sales of Otezla, Revlimid reported
Endo	-25.6%	Filed suit against FDA for encouraging compounding
Teva	-21.6%	Mylan's Copaxone generic approved; fallout from compounding debate
Valeant	-18.4%	Fallout from compounding debate
Mallinckrodt	-15.3%	Fallout from compounding debate
Alexion	-14.7%	Disappointing Q3 reporting
Merck & Co	-14.0%	Withdrew Keytruda application for first-line lung cancer in Europe
Allergan	-13.5%	District Court decision raises patent threat to Restasis
Regeneron	-10.0%	Delays due to manufacturing and protocol issues in two partnered projects

pounding, something likely to lead to undercutting of generic drug pricing.

Endo itself fell 11% after filing the suit and continued to decline as the implications of raising its head above the parapet became clear. The company's stock ended 25.6% down on the month. **Teva Pharmaceutical Industries Ltd., Valeant Pharmaceuticals International Inc.** and **Mallinckrodt PLC** were among the companies dragged.

Teva suffered twice in the month, its stock having declined over 14% following Mylan's approval for generic Copaxone.

Away from generics, **Merck & Co. Inc.** was 14% down on the month. Most of the decline came at the end of the month with falls of 6% on two consecutive days as the company withdrew its European application for first-line use of *Keytruda* (pembrolizumab) in lung cancer, often a way of pre-empting a negative opinion from the EMA's CHMP. Merck's stock was not helped by the virtually simultaneous announcement from **Bristol-Myers Squibb Co.** of the expansion of *Opdivo* (nivolumab)'s label in Europe.

Merck's decline wiped \$24bn off the company's market valuation. But the biggest loss of value during the month was at **Celgene Corp.** where poor third-quarter results including lower than expected sales of *Otezla* (apremilast) and *Revlimid* (lenalidomide) precipitated a 30% stock devaluation, equating to the loss of \$35bn billion in market capitalization over the month. The stock lost over 10% when the company abandoned its clinical program with mongersen in Crohn's disease and fell another 14% as the company reported its Q3 results.

Investors were disappointed with **Alexion Pharmaceuticals Inc.**'s Q3 results, too, sparking an 8% decline in the stock over two days as the figures came out.

Meanwhile **Allergan PLC** declined 9% over three days following a US District Court decision that could open its dry-eye medication *Restasis* (cyclosporine ophthalmic emulsion) to patent challenges much earlier than investors had expected.

Regeneron Pharmaceuticals Inc. declined 10% over the month, a move attributable to likely setbacks in projects partnered with Teva and **Sanofi** in osteoarthritic pain and rheumatoid arthritis, respectively. Both setbacks are likely to be temporary. ▶

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Influenza And Beyond: Sanofi Pasteur R&D Chief Talks Strategy

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John Shiver has led vaccine research at Sanofi Pasteur for more than four years, having joined the company from **Merck & Co. Inc.**, where he was vice president of the US drug major's vaccine research franchise. In an exclusive interview with *Scrip* he outlines the integration process for **Protein Sciences Corp.**, a business Sanofi purchased earlier this year for \$650m, and discusses the biggest challenges currently facing human vaccine developers – of which Sanofi Pasteur is the world's largest.

Sanofi acquired privately owned Protein Sciences, of Meriden, Connecticut, in July this year for \$650m up front and up to \$100m in undisclosed sales milestones. Protein Sciences has developed technology to manufacture vaccines using recombinant proteins produced via the infection of insect cells with engineered baculoviruses. This contrasts with the majority of currently marketed products, which are produced in eggs, a process that takes longer and has the potential to be affected by supply constraints.

Shiver said Sanofi Pasteur will further develop and explore the use of this technology in other vaccine channels while also using its vast commercialization network and expertise to better sell Protein Sciences' lead vaccine, *Flublok* – a US FDA approved influenza vaccination aimed at older patients of 50 years plus.

"Flu vaccines have been around for many decades; most vaccines in the world are made with eggs... Certainly, though, there is an interest to innovative and improve technology," Shiver said. "Protein Sciences, through the work they did over many years, has become the first company to develop and license a recombinant flu vaccine."

After failing to get significant market traction for its trivalent seasonal influenza vaccine that was approved in the US in January 2013, Protein Sciences won FDA approval for a quadrivalent version, *Flublok QIV*, in October 2016.

Shiver called *Flublok QIV* an "advance for flu protection technology" with "a lot

of potential for improving flu vaccination overall and certainly in specific populations." Sanofi Pasteur will provide assistance and expertise by tying *Flublok QIV* to its substantial commercial network and salesforce – which is something that Protein Sciences, as a smaller company, did not have before.

"As a small biotech, Protein Sciences wasn't in the position to market *Flublok* to the full benefit of the product because they lacked a salesforce and that type of commercial experience," Shiver said. He noted that the acquired business has other strengths. "They developed a brand-new product, the first recombinant flu vaccine on the US market, the only one in the world in fact, but Sanofi Pasteur is very strong in understanding the overall flu market."

AGE-SPECIFIC MARKETING IN FLU

Sanofi Pasteur expects to market *Flublok QIV* specifically at those aged 50-64. The French pharma group will target its own influenza vaccine, *High Dose Fluzone*, at people over 65. "Individuals aged 50 and over, just because of age, have four times more influenza disease than younger populations," Shiver noted.

While *High Dose Fluzone* was shown to be around 24% more protective than standard dose flu vaccine in patients over 65, *Flublok* (in clinical studies) outperformed the standard of care vaccine by around 40%. Protein Sciences' product was most efficacious in people aged 50 to 64, Shiver said, adding that the two products were "complementary" to each other. "We can now take advantage of the learnings from our high-dose vaccine and apply that to selling *Flublok* in the 50-64-year-old age group," he said. Sanofi Pasteur will use both products to cover the entire higher risk, older patient population, Shiver noted. Shiver added that acquiring *Flublok* saves Sanofi Pasteur from having to complete further clinical studies for *High Dose Fluzone* specifically in the 50-64 age group, which would have taken time, investment and required the use of a signifi-

cant amount of its manufactured supply of the *Fluzone* product.

PIPELINE PROGRAMS

Protein Sciences also brings into Sanofi Pasteur several early-stage vaccine programs, including:

- *Panblock*, a recombinant candidate in clinical development for pandemic flu vaccination;
- *FluNhance*, a recombinant neuraminidase-based product which is being studied as an efficacy-enhancing additive for flu vaccines;
- D3252, another recombinant vaccine candidate, in preclinical development for severe acute respiratory syndrome (SARS); and a preclinical Zika vaccine.

Shiver said his group was taking its time to assess these vaccine candidates, as well as some of the collaborative partnerships Protein Sciences had previously formed. He wants to be able to understand the programs better and see how candidates fit within the overall strategy of Sanofi Pasteur. "I would call these programs 'work-in-progress,'" Shiver said. "We have established dialog with the Protein Sciences team and we will educate each other on our pipelines so that collectively we can make the best decisions for Sanofi Pasteur overall on what to do with these projects."

Recombinant vaccine R&D is an area where Sanofi Pasteur was not established before the Protein Sciences acquisition. "We have a new product platform, and there are not that many new platforms in the world on licensed vaccines," he said.

As for Sanofi Pasteur's pipeline, Shiver highlighted a few of its many vaccine clinical programs. Sanofi is continuing to move its products from three strains of flu to four with the high dose formulation – *QIV* compared with *TIV*. This formulation is currently in Phase II. Within flu, Sanofi Pasteur is also developing a broadly protective vaccine, "the next generation flu vaccine." Current vaccines provide yearly, seasonal protection and efficacy can vary year-to-year depending on the strains that emerge;

depending on how good the match is between the circulating virus and what is in the vaccine. “Our intent is to develop a vaccine that can give longer protection, as well as better protection, as flu viruses drift naturally,” Shiver said. “This is still in the earlier stages of research but it is an important program and I am excited about the progress we are making.”

Meanwhile, he noted that Protein Sciences was not the only significant deal made by Sanofi Pasteur this year. In March, the firm joined up with **MedImmune LLC**, the global biologics R&D arm of **AstraZeneca PLC**, for the development of a vaccine against respiratory syncytial virus (RSV) – the most common cause of lung inflammation and pneumonia in infants.

Sanofi paid €120m up front – and will pay up to €495m to AstraZeneca in development and sales-related milestone payments – for the rights to develop and commercialize monoclonal antibody MEDI8897 for the prevention of RSV-associated illness in newborns and infants. The two companies will share all costs and profits equally. MedImmune continues to lead all development activity up to the first approval, and AstraZeneca will retain MEDI8897 manufacturing activities. Sanofi Pasteur will lead the commercialization activities for MEDI8897, which received fast-track designation from the FDA in 2015.

MEDI8897 is a next generation passive immunization for babies and infants; it is based on AstraZeneca’s approved RSV product *Synagis* (palivizumab), which is used in babies at high risk. “The next generation product has many potential advantages over that initial product,” Shiver said, adding that he hopes the vaccine will be applicable to all babies to protect them against the first season, and perhaps second season, of RSV they will face.

GAPS IN THE PIPELINE

When asked about future deal-making to bulk up Sanofi Pasteur’s pipeline, Shiver described the world as full of opportunity. “We certainly try to identify what we think are the most important diseases and make sure we have programs to apply against those,” he said, “which is why we have one of the largest pipelines in the vaccine pharmaceutical world.”

He added that as well as asset acquisitions and licensing deals, Sanofi Pasteur seeks partners for its in-house clinical-stage

vaccines. “Most of our projects eventually have some type of significant partnership by the time licensure occurs,” he noted. “No one can do everything and we are always vigilant for new opportunities for both existing and emerging diseases that could come from perhaps a biotech or government laboratory, really anywhere in the world is making progress,” Shiver added. More than half of Sanofi Pasteur’s programs are partnered in some way.

CHALLENGES FACING VACCINE DEVELOPERS

One of the biggest challenges for vaccine developers is the time it takes to get a product from the lab to market. In parallel, Shiver highlighted several trickier diseases that have thwarted vaccine researchers in the past and remain hard to tackle today.

“A better pertussis vaccine could have a huge impact,” Shiver said. Current pertussis vaccines – immunizations for children and teens that protect against whooping cough – work quite well but they do have some shortcomings. The older generation pertussis vaccines do not have great tolerability and the world has moved away from them. Pertussis is now included in the common combination childhood vaccine called DTaP.

However, Shiver said the goal is a better pertussis vaccine with strong and long-lived efficacy, that would boost protectivity without the need for more vaccinations, and with a safe and tolerable profile. “This is an area where most of the vaccine world agrees innovation is needed.”

Human immunodeficiency virus (HIV) is another difficult vaccine development area. Sanofi has an HIV vaccine in the clinic in partnership with **GlaxoSmithKline PLC**, as well as the National Institutes of Health (NIH) and the Gates Foundation. The product is an improved version of a previous HIV vaccine candidate, it is currently in repeat efficacy studies. “The previous trial of our HIV vaccine candidate showed around 60% protectivity after a couple of years and around 30% protectivity after three of four years, so we have proof-of-concept a HIV vaccine can work but it’s not good enough yet to go straight to product,” Shiver said, noting that this vaccine candidate was still a few years away from results.

Other areas where Shiver believes Sanofi Pasteur is making slow progress in difficult diseases include: staphylococcus, cytomeg-

alovirus and *Clostridium difficile*. The company’s first-in-class vaccine for clostridium difficile is currently in Phase III; the large-scale trial includes over 200 sites. “I have a lot of optimism that we will get to an endpoint soon with this study, which is a difficult trial to conduct, and hopefully that endpoint is favorable.”

Vaccine R&D is a slow-moving vehicle in part because large numbers of people are involved in clinical trials, but also companies are vaccinating healthy people to prevent diseases with low incidence rates.

SEEKING SPEED WITHOUT SACRIFICE

“It is a constant goal that I have, and a big priority for R&D in general, to find ways to speed up development without sacrificing patient safety or making premature judgments on the performance of a vaccine,” Shiver said. Sanofi Pasteur, he said, was modelling different types of trial designs, using new translational methods, and investing more in efforts to speed up development times.

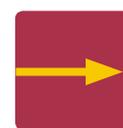
To get more information about how vaccines are impacting a disease in early-stage studies, Shiver’s team is becoming more reliant on biomarkers. The company uses vaccine biomarkers that “may not be validated, so to speak, but are likely to be highly associated with a disease. These can help inform in early studies if we are on the right track or not.”

Increasingly the group is bringing machine learning into the process, which allows data to be viewed in different ways, analysis that can better inform and speed up decision-making. In October 2017, Sanofi Pasteur signed an agreement for research into vaccine biomarkers with **BERG** – an artificial intelligence focused biotech company. Under this agreement, BERG will generate and model data using its proprietary Interrogative Biology platform to assess potential biomarkers of seasonal influenza vaccination outcomes. BERG’s technology uses AI to produce data driven analysis of high throughput molecular and clinical information.

“It doesn’t do the world much good, and it doesn’t do Sanofi Pasteur much good to have a full and interesting pipeline if we can’t get these vaccines to the finish line, and get them there sooner than later,” Shiver said. “We must fail faster and know when success looks more imminent, it works both ways.” ▶

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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 27 October–2 November 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Biogen/Ionis Pharmaceuticals Inc.	<i>Spinraza</i> (nusinersen)	spinal muscular atrophy	ENDEAR; the <i>NEJM</i> online, Nov. 2, 2017.
Phase III Completed			
Celgene Corp.	ozanimod	multiple sclerosis	RADIANCE Part B; superior efficacy versus Avonex, well tolerated.
Phase III Interim/Top-line Results			
Alnylam Pharmaceuticals Inc./Sanofi	patisiran	hereditary ATTR amyloidosis with polyneuropathy	APOLLO-OLE; met primary and secondary endpoints.
Roche	etrolizumab	Crohn's disease, ulcerative colitis	BERGAMOT, HICKORY; well tolerated, clinical improvement.
Alkermes PLC	ALKS8700	multiple sclerosis	EVOLVE-MS; well tolerated.
ViiV Healthcare	fostemsavir	HIV/AIDS	BRIGHT; positive results in heavily pretreated patients.
AstraZeneca PLC/Leo Pharma AS	tralokinumab	asthma, severe and uncontrolled	STRATOS 2, TROPOS; no effect on steroid use, exacerbations.
Astellas Pharma Inc./FibroGen Inc.	roxadustat	chronic kidney disease with anemia	In Japanese patients on dialysis, positive efficacy.
Daiichi Sankyo Co. Ltd.	pexidartinib	tenosynovial giant cell tumor	ENLIVEN; reduced tumor size.
Sanofi/Regeneron Pharmaceuticals Inc.	<i>Dupixent</i> (dupilumab)	asthma, severe steroid-dependent	VENTURE; improved lung function, reduced asthma attacks.
AbbVie Inc./Neurocrine Biosciences Inc.	elagolix	pain associated with endometriosis	Elaris EMIII, IV Ext.; well tolerated long term.
ReGenTree LLC	RGN-259	dry eye	ARISE-2; mixed results.
Updated Phase III Results			
Alnylam Pharmaceuticals Inc./Sanofi	patisiran	hereditary ATTR amyloidosis with polyneuropathy	APOLLO; met primary and secondary endpoints .
Anthera Pharmaceuticals Inc.	<i>Sollpura</i> (liprotamase)	exocrine pancreatic insufficiency	SOLUTION; non-inferior to control.
Ionis Pharmaceuticals Inc.	inotersen	hereditary ATTR amyloidosis	NEURO-TTR; met co-primary endpoints .
Paion AG	remimazolam	used during bronchoscopy	Safe and effective sedation.
Agile Therapeutics Inc.	<i>Twirla</i> (AG200-15)	contraception	SECURE; well tolerated, effective.
Shionogi & Co. Ltd.	lusutrombopag	thrombocytopenia	L-PLUS-2; effective and safe.
Allergan PLC	ulipristal acetate	uterine fibroids	Venus II; reduced bleeding.
Shire PLC	lanadelumab (SHP643)	hereditary angioedema	HELP; provided sustained protection.
Theravance Biopharma Inc./Mylan NV	revefenacin	chronic obstructive pulmonary disease	Improved health status of patients.
Roche	<i>Ocrevus</i> (ocrealizumab)	multiple sclerosis, primary progressive	ORATORIO (MS); clinical benefit shown.
Sanofi	<i>Lemtrada</i> (alemtuzumab)	multiple sclerosis	Benefit maintained over five years.
Teva Pharmaceutical Industries Ltd./Active Biotech AB	<i>Nerventra</i> (laquinimod)	multiple sclerosis	CONCERTO; mixed results.

Source: *Biomedtracker*

Amgen, Novartis May Screen 30,000 Patients To Find 2,000 For Alzheimer's Trial

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The most pressing issue for a new Alzheimer's disease prevention study conducted by **Amgen Inc.**, **Novartis AG** and the Banner Alzheimer's Institute may be recruitment rather than its results.

The partners are collaborating on the Phase II/III trial, which is testing whether the oral drug CNP520 can prevent, slow or potentially stop Alzheimer's progression. Representatives of the companies and institute announced on Nov. 2 that the clinical trial, called Generation Study 2, has launched and is enrolling patients.

CNP520 is a beta-site APP-cleaving enzyme-1 (BACE) inhibitor. Amgen traded some rights to a calcitonin gene-related peptide (CGRP) inhibitor for migraine headaches to Novartis in 2015 for shared global rights to CNP520. Both companies are collaborating on CNP520's development.

While Generation Study 2 potentially faces long odds – all trials looking to reduce the accumulation of amyloid in the brains of Alzheimer's patients have failed – the researchers also seemed concerned during their announcement about finding participants. They noted that Alzheimer's trials often are delayed by the specific recruitment criteria – and for Generation Study 2 they want

patients who are not cognitively impaired. Ana Graf, Novartis Global Program Head, said researchers likely will have to screen up to 30,000 people to find the 2,000 needed for the trial. They are looking for patients aged 60-75 years old, who are at risk for clinical symptoms due to their age and carry at least one copy of the APOE4 gene. Graf added that trial sites will work with Banner's genetic screening program to help find patients.

"We expect that [the sites] will do outreach, that in the US they will also work with the GeneMatch program to be able to efficiently recruit subjects," she said.

GeneMatch is the Banner trial recruitment program that uses genetic testing to match volunteers with trials.

Indeed, the screening effort symbolizes one of the problems associated with Alzheimer's prevention efforts.

Patient screening is among the major problems, in part because it is expensive. But given past failures at modifying disease progression or symptom treatment, prevention is seen as the next avenue to fight the disease.

Generation Study 2 will include 1,200 patients on two potential doses of active treatment and 800 on placebo. Screening

is expected to last 12 weeks. Treatment duration should be five to seven years, followed by three months of follow-up. The event-driven trial is expected to be completed in 2024. It already has been initiated in the US and Spain. About 180 sites will be needed globally, including 80 in the US, Graf said.

Vissia Viglietta, Amgen Executive Director and Global Development Lead, said she believes this trial has a better chance of success than previous amyloid studies, because it is looking at pre-symptomatic patients.

She said previous trials targeting amyloid may have failed because of design problems, including enrichment criteria that did not allow for enrollment of the best patients.

"We truly believe that an amyloid-targeting agent, given the fact that amyloid is accumulating 20 years prior to the symptoms, has to target the pre-clinical population," Viglietta said. "That's why we believe that the prevention trial in pre-symptomatic individuals will have a chance to be successful."

Informa's Biomedtracker gives CNP520 a 50% chance of approval, which is 2% below average for drugs at similar stages of development for neurological diseases. ▶

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APPOINTMENTS

Dr Brett P. Monia, a founder of **Ionis Pharmaceuticals Inc.**, and head of drug discovery and the company's inotersen program, is to become the company's chief operating officer, effective Jan. 15, 2018. He will replace B. Lynne Parshall, who will become senior strategic advisor to Ionis and remain a member of the board of directors of Ionis and Akcea Therapeutics Inc.

ThromboGenics NV has appointed **Dr Susan Schneider** as chief medical officer, and Vinciane Vangeersdaele as chief commercial officer. Schneider brings nearly 15 years of experience in clinical drug development to ThromboGenics. Most recently, she was vice president and therapeutic area head of retina and glaucoma at Aller-

gan PLC. Vangeersdaele has over 15 years' experience in a variety of pharmaceutical sales and marketing leadership roles, the latest being the head of the ophthalmology franchise Europe at Novartis AG.

Zelluna Immunotherapy, a biotechnology company specializing in T-cell receptor immunotherapies, has appointed **Miguel Forte** as CEO. Forte has extensive commercial experience in the regenerative medicine, cell therapy, medical and regulatory affairs industries, and is currently chief commercialization officer and chair of the commercialization committee for the International Society of Cellular Therapy. Previously, he worked for the European Medicines Agency, Bristol-Myers Squibb

Co., Abbott Laboratories Inc. and Wellcome Laboratories (now part of GlaxoSmithKline PLC), Nabi Pharmaceuticals and UCB Group.

Therapix Biosciences Ltd., a specialty clinical-stage pharmaceutical company developing cannabinoid-based treatments, has appointed its chair, **Dr. Ascher Shmulewitz**, to the role of interim chief executive officer, effective immediately. Shmulewitz has served as chair of Therapix since January 2014 and has been on the company's board since February 2013. As one of Therapix's key founding investors, Shmulewitz brings significant experience in cannabinoid-based medicine and has a well-established track record leading biopharmaceutical companies.

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