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Emma Walmsley

GSK Exercises Right To Buy Out Novartis Consumer Healthcare JV

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GlaxoSmithKline PLC has announced that it will buy out the 36.5% stake **Novartis AG** holds in the GSK-Novartis Consumer JV, which was created in 2014 as part of a three-part transaction between the two companies, for $13bn (£9.2bn). Under the original deal, Novartis had a put option, exercisable from March 2, 2018 to March 2, 2035, to require GSK to purchase its stake (or specified tranches of it) in the joint venture.

Last week, GSK announced that it had pulled out of the bidding to acquire the **Pfizer Inc.** consumer health business (*Also see "GSK Drops Out Of Auction For Pfizer's Consumer Health Unit" - Scrip, 23 Mar, 2018.*). Commenting on the transaction, GSK CEO Emma Walmsley said in a statement to the London Stock Exchange: "The proposed transaction addresses one of our key capital allocation priorities and will allow GSK shareholders to capture the full value of one of the world's leading Consumer Healthcare businesses. For the Group, the transaction is expected to benefit adjusted earnings and cash flows, helping us accelerate efforts to improve performance. Most importantly it also removes uncertainty and allows us to plan use of our capital for other priorities, especially pharmaceuticals R&D."

The GSK statement claims that "with category-leading power brands, increased focus on science-based innovation and improved operational efficiencies, GSK Consumer Healthcare is well positioned to deliver sales growth, operating margin improvements and attractive returns." GSK expects the transaction to be accretive to adjusted earnings in 2018 and thereafter, and to strengthen cash flow generation with operating margins approaching "mid-20's" percentages by 2022 at 2017 CER (constant exchange rates).

In 2017, GSK's Consumer Healthcare business delivered sales of £7.8bn having grown 4% on a three-year CAGR basis (2015-2017 at 2014 CER), since 2015, with an overall improvement in operating margins from 11.3% in 2015 to 17.7% in 2017.

GSK will start a strategic review of Horlicks and its other consumer healthcare nutrition products to support funding of the transaction, and to drive increased focus on OTC and Oral Health categories. Combined sales of these products were approximately £550m in 2017.

As the majority of Horlicks and other nutrition product sales are generated in India, where they are sold by GlaxoSmithKline Consumer Healthcare Ltd, a public company listed on the National Stock Exchange (NSE) and Bombay Stock Exchange (BSE), the strategic review will also include an assessment of GSK's 72.5% shareholding in the company.

The company reiterated how India remains a priority market for GSK investment and growth. "The Consumer Healthcare business will continue to invest in growth opportunities for its OTC and Oral Health brands, such as Sensodyne and Eno. The Group is also actively investing in its Pharmaceutical and Vaccines businesses, including building new manufacturing capacity in Vemgal, Karnataka and Nashik."

GSK expects the outcome of the strategic review to be concluded around the end of 2018. There can be no assurance that the review process will result in any transaction.

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from the editor

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The end of the quarter sees a flurry of M&A excitement, but it's got nothing to do with the activity that President Trump's tax reform has been expected to trigger, and plenty more to do with the long-running, stop-start consolidation in the consumer health sector.

Merck KGaA continues to dangle its consumer business forlornly without attracting a buyer, and Pfizer is now in a similar position, the deadline for bids having come and gone without resulting in an offer.

In the meantime, the deal that has actually materialized had been on the cards for a while, with Novartis's 17-year put option on its minority stake in its joint venture with GlaxoSmithKline finally having gone live earlier this month and the new CEOs of both companies each taking the helm looking more likely than their respective predecessors to go through with the transaction that gives GSK sole control.

If GSK, like Sanofi, has decided to double down in the consumer segment, overall big pharma interest is geared towards the exit. Watching Bayer struggle with the Merck & Co consumer products business it bought in 2014 doesn't make for inspiring viewing for those on the fence.

That mix and match deal Novartis and GSK completed three years ago is paying off for the Swiss firm now in that it has been able to offload a non-core asset in a buyer's market for a decent price. That money will be useful to Vas Narasimhan as he shapes the Swiss firm into a drug maker fit for the digital age.

Scrip

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GSK Drops Out Of Auction For Pfizer's Consumer Health Unit
https://bit.ly/2uoTpI2
The acquisition of Pfizer's consumer health business, which includes big named products such as Advil painkillers and Centrum multivitamins, has proven too big and too costly for GSK investors to stomach.

MIFID II May Hit Small & Midcap EU Biotech Investment
https://bit.ly/2pJJgzX
New EU regulation designed to offer greater protection and more transparency for investors could have serious implications for Europe's small to midcap biotechs just as the European Investment Bank predicts a potential €40bn funding shortfall in key bioclusters by 2021.

Merger Buzz Boosts Shares Of India's Troubled Fortis
https://bit.ly/2GbWfBp
Shares of Indian hospital chain Fortis Healthcare have risen some 16% in the past month, fuelled by investor hopes of a takeover battle for the financially troubled company. US hedge fund Elliott Management is now said to have entered the fray and be buying up stock.

Seattle Genetics Says Adcetris Sets New Standard In Frontline Lymphoma
https://bit.ly/2IWDdkq
The market for a new FDA-approved indication in frontline classical Hodgkin lymphoma could be worth $650m to $750m, some analysts say.

Finance Watch: The Curious Case Of Proteostasis' Short Attack
https://bit.ly/2I9CjzV
Proteostasis planned to raise cash this week, but scrapped the offering after an investor that shorted the stock published a scathing report. Also, Arena raised more than $350m in an offering after its positive Phase II etrasimod data, and venture capital flows to biopharma firms with big ideas.

Tech Transfer Roundup: ProQR Partners With Foundation Fighting Blindness On Rare Vision-Loss Disorder
https://bit.ly/2GAAGxM
Galderma unveils seven-year partnership with Mount Sinai and Northwestern in atopic dermatitis. Beacon/Takeda and Zealand/UniQuest tie-ups both address gastrointestinal diseases.

inside:

Roche Gains With Tecentriq IMpower131 NSCLC Data, But For How Long?

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Boosting its chances of being first to market a drug in that setting, **Roche** on March 20 reported positive progression-free survival (PFS) headline data from the IMpower131study evaluating its PD-L1 inhibitor *Tecentriq* (atezolizumab) in first-line squamous cell lung cancer.

But whether Roche can keep that lead will only become clear when data from the program mature on overall survival (OS), which is expected later this year.

'These are positive data for Tecentriq in NSCLC and bode well for its chances of being the first PD-1/PD-L1 inhibitor approved in combination with chemotherapy for squamous patients'

Other rivals are in the meantime closing in, with readouts soon from **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) Phase III KEYNOTE-189, and **Bristol-Myers Squibb Co.**'s CheckMate-227 study of *Opdivo* (nivolumab) and *Yervoy* (ipilimumab) in first-line NSCLC.

Roche said an interim analysis from the IMpower131 study, which is comparing Tecentriq plus chemotherapy (carboplatin and *Abraxane* [albumin-bound paclitaxel; nab-paclitaxel]) against chemo alone, met its co-primary endpoint of PFS in the initial treatment of people with advanced squamous non-small cell lung cancer.

OS NOW DATA AWAITED

Overall survival data are not yet "mature" and will be presented at an upcoming oncology congress, Roche said without elaborating. Analysts believe that will occur at ASCO 2018, which takes place in the first week of June.

Analysts noted that squamous cell NSCLC is a big, poorly treated market representing some 30% of all diagnosed first-line lung cancer patients. It's a different market from the non-squamous setting, which is most frequently discussed with upcoming immuno-oncology trials such as Keynote 189, Checkmate 227, **AstraZeneca PLC**'s MYSTIC and the Roche IMpower130/132 studies, analysts at Credit Suisse said in a note to investors.

"These are positive [IMpower131] data for Tecentriq in NSCLC and bode well for its chances of being the first PD-1/PD-L1 inhibitor approved in combination with chemotherapy for squamous patients," said Datamonitor Healthcare oncology lead analyst Hardik Patel. "Although the squamous population only accounts for between 25% to 30% of all NSCLC patients – and Keytruda is already approved for first-line PD-L1+ squamous patients as a monotherapy – approval in this setting would be a significant opportunity for Roche given the historic unmet need in this population," Patel said.

It will be important for IMpower131 to also show a significant benefit in terms of overall survival in order to guarantee Tecentriq's approval for this label expansion and allow it to compete with Keytruda monotherapy, Patel told *Scrip*.

He noted that PD-1/PD-L1 inhibitors typically perform better in terms of OS than PFS, due to issues with so-called pseudo-progression.

"The observation of a significant benefit in PFS in IMpower131 is a positive indicator. Nonetheless, improvements in PFS do not always translate into improvements in OS, and data from the Phase II POPLAR study in previously treated patients showed Tecentriq had a much smaller impact on OS in the squamous population versus the non-squamous population. Thus, we await further data from the IMpower131 trial to fully elucidate Tecentriq's outlook in first-line squamous population," Patel said.

The situation is similar with the drug's Phase III IMpower150 trial, testing it in combination with *Avastin* (bevacizumab) and chemotherapy for non-squamous patients, with positive PFS data shown and OS data yet to come.

In contrast, Merck has already announced Keytruda's Phase III KEYNOTE-189 study testing the drug in combination with **Eli Lilly & Co.**'s *Alimta* (pemetrexed) and chemotherapy for non-squamous patients met both PFS and OS endpoints. Data for that trial will be presented April 16th at the AACR conference in Chicago, Patel said.

Analysts at Credit Suisse therefore said Roche's lead acquired from the PFS data from IMpower131 "is likely to be short-lived" with Merck a fast follower in squamous first-line lung cancer with the near-identical Keynote-407 study due to report in 2018. They also noted that a subgroup of squamous patients was included in Merck's Keytruda monotherapy Keynote-024 study.

Adding to the commercial uncertainty is the "challenging" nature of the Tecentriq+carboplatin+nab-paclitaxel regimen, the analysts said.

"Abraxane is administered on days one, eight and 15 of each 21-day cycle of carboplatin+Tecentriq. Giving weekly chemo would be challenging for both patients and health authorities in many countries, in our view. We believe that there is limited use of Abraxane in lung cancer today for this reason," Credit Suisse analysts said in a March 20 reaction note. Another hurdle is the fact Abraxane is still a branded chemotherapy with generics not expected until 2022, increasing the cost of this regimen.

A potential solution to that situation, the analysts said, are the results of the third arm (Arm A) of the IMpower131 study comparing Tecentriq plus carboplatin plus paclitaxel (not Abraxane) versus chemo alone.

"This chemo regimen is administered once every 21 days and is much more acceptable to patients and healthcare systems. Under the terms of the IMpower131 statistical protocol, Arm A can only be analysed once Overall Survival is mature for Arm B versus Arm C," Credit Suisse said.

Merck's Keynote-407 similarly gives the investigator's choice of paclitaxel or Abraxane, they added.

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Weak Rova-T Data May Imperil AbbVie's Larger Cancer Ambitions

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AbbVie Inc. avoided calling the Phase II TRINITY data it unveiled March 22 for rovalpituzumab tesirine (*Rova-T*) in small cell lung cancer a failure, but market analysts took no such precautions, with one saying the unconvincing data might "unravel AbbVie's oncology strategy."

The dire prognosis came from Leerink Partners analyst Geoffrey Porges, but he wasn't alone in seeing the unimpressive data for Rova-T as bad news for AbbVie's oncology plans. Sanford Bernstein analyst Tim Anderson wrote the drug off as "a dud" – adding, "so much for the $6bn Stemcentrx acquisition."

An antibody-drug conjugate, Rova-T is the centerpiece of AbbVie's $5.8bn buyout in 2016 of **Stemcentrx Inc.**, a deal that brought it a host of cancer candidates, seven more of which are in early-stage clinical trials. The transaction also carries the potential for another $4bn in earn-outs for Stemcentrx shareholders.

While *Imbruvica* (ibrutinib) and *Venclexta* (venetoclax) give AbbVie a viable hematologic cancer portfolio to build upon, the Stemcentrx assets were intended to anchor a solid tumor pipeline. Analysts questioned the deal value at the time – and that skepticism looks prescient today.

William Blair & Company analyst Katherine Xu noted March 22 that the Stemcentrx buy "to a large extent represents AbbVie's solid tumor oncology franchise. While third-line SCLC only accounts for an expected $200m-$400m of the Rova-T peak sales projected by AbbVie, the TRINITY data "cast doubt on Rova-T's potential not only in SCLC, but also other indications, and brings into question the validity of the Stemcentrx acquisition."

At the very least, the TRINITY data likely push back the approval timeline for Rova-T from a possibility of approval during the second half of 2018 to now second-half 2020 at the earliest, she added.

DISAPPOINTING DATA, AGAIN

In an analysis of 177 third-line SCLC patients with high expression of the cancer stem cell antigen DLL3, Rova-T yielded an investigator-assessed best overall response rate (ORR) of 29%, an independent review committee assessment of ORR of 16%, a duration of objective response of 4.1 months and median overall survival of 5.6 months. These data are not terribly differentiated from use of chemotherapy in the third-line setting, which offers estimated overall survival of four to five months, Leerink's Porges pointed out in a March 22 note.

Worse, these mediocre efficacy results are offset by a safety profile for Rova-T that Porges calls "unacceptable." AbbVie reported that adverse events of fatigue, photosensitivity, pleural effusion and decreased appetite all were seen in more than 30% of the trial participants.

Those safety findings render a potential one month of added survival benefit inconsequential, Porges argued. "These systemic side effects for what is supposed to be a targeted cancer treatment are concerning and call into question the chemistry of Rova-T, and the Stemcentrx platform in general," he wrote. Porges added that with the safety profile and efficacy data roughly equivalent to current standard of care, Rova-T's approvability in general might now be in question.

The Phase II data were already in a limited population; the high delta-like protein-3 (DLL3) subgroup was identified as having the best response out of a Phase Ia/Ib program, but the overall response disappointed and raised early questions about the Stemcentrx acquisition.

SOLID TUMOR PROSPECTS ON SHAKY GROUND

AbbVie had estimated peak global sales of $5bn for Rova-T by 2025, as it expected the drug to prove beneficial in a number of tumor types that express DLL3, including breast, ovarian and colorectal cancers. Porges noted that sales projection makes up roughly 11% of the $47bn in sales the pharma is predicting in 2025 for products other than *Humira* (adalimumab), which is responsible for a majority of the company's revenue currently and likely will face biosimilar competition in the US and Europe by then.

Although long skeptical of AbbVie's sales projections for Rova-T, Porges said failure in the TRINITY study compounded by safety questions would eliminate roughly $1.5bn in consensus peak revenue potential for the pharma. In addition, these results could effectively "remove upside opportunities and catalysts for label expansions, and would lower the credibility of AbbVie's business development team," he contended. With oncology the key business growth segment for AbbVie following the end of patent protection for Humira, the company's entire strategy now faces doubts, he said.

Along with the data from the Phase II TRINITY study, AbbVie also revealed that following discussions with US FDA, it will not seek accelerated approval of Rova-T in third-line SCLC as previously planned.

AbbVie acknowledged the results are "not what we hoped for," but added that it still holds optimism for the results of two ongoing Phase III studies known as MERU and TAHOE, which are evaluating the ADC in first-line and second-line SCLC.

TRINITY DATA NOT A TOTAL SURPRISE

Bernstein's Anderson said expectations for TRINITY were lowered in late 2017 when AbbVie announced a delay in its plans to file Rova-T for approval. "Dosing in TRINITY had to be limited to only two infusions, because of safety concerns (which speaks to safety issues, and simultaneously plays against efficacy, because of limited patient exposure to the drug)," he noted.

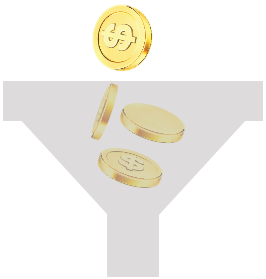
AbbVie Biotech Ventures Head Scott Brun, during an appearance at the Barclay's Global Healthcare Conference on March 15, seemed to be trying to lower expectations about Rova-T's trial performance. At the same time, Brun pointed to the high incidence of relapse in SCLC and noted the lack of any approved therapy for the second- and third-line settings. At present, response rates for relapsed SCLC patients tend be in the single digits, he said, with median survival of about two months.

Published online 22 March 2018

EUROPEAN VENTURES 2017

Life science opportunities in Europe see fewer venture capitalists than in the US, and financial markets are not unified. Digital health now extends life science opportunities beyond biotech and medtech, but investors have wider choices, still.

$3.97 bn



221
BIOTECH & MEDTECH COMPANIES

$13.19 bn

386
BIOTECH & MEDTECH COMPANIES

EUROPEAN FIRMS GET LESS VC FUNDING ON AVERAGE[1]

Venture capital flowed more gently and sporadically in Europe (as usual)

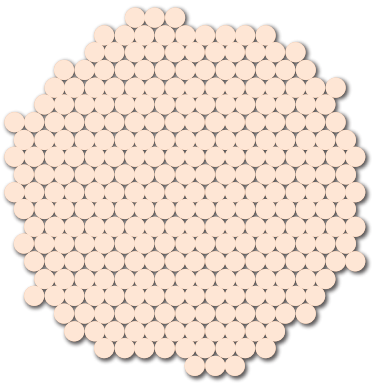
BIOTECH AND MEDTECH INVESTING IS CHEAPER IN EUROPE: COMPARING AVERAGE FINANCING ROUNDS

	A ROUND	B ROUND	C+ ROUND
Europe	$11.4m	$18.94m	$35.4m
USA	$29.4m	$40.89m	$42.44m

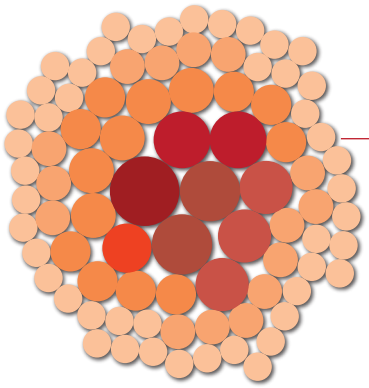
EUROPE'S LOW EXPOSURE TO LIFE SCIENCES

At least **372** investors were involved in the 221 rounds surveyed for 2017: **287** only got involved once

1
LIFE SCIENCE INVESTMENT



1+
LIFE SCIENCE INVESTMENT



Most Active Investors (Biotech And Medtech) By Rounds In Europe

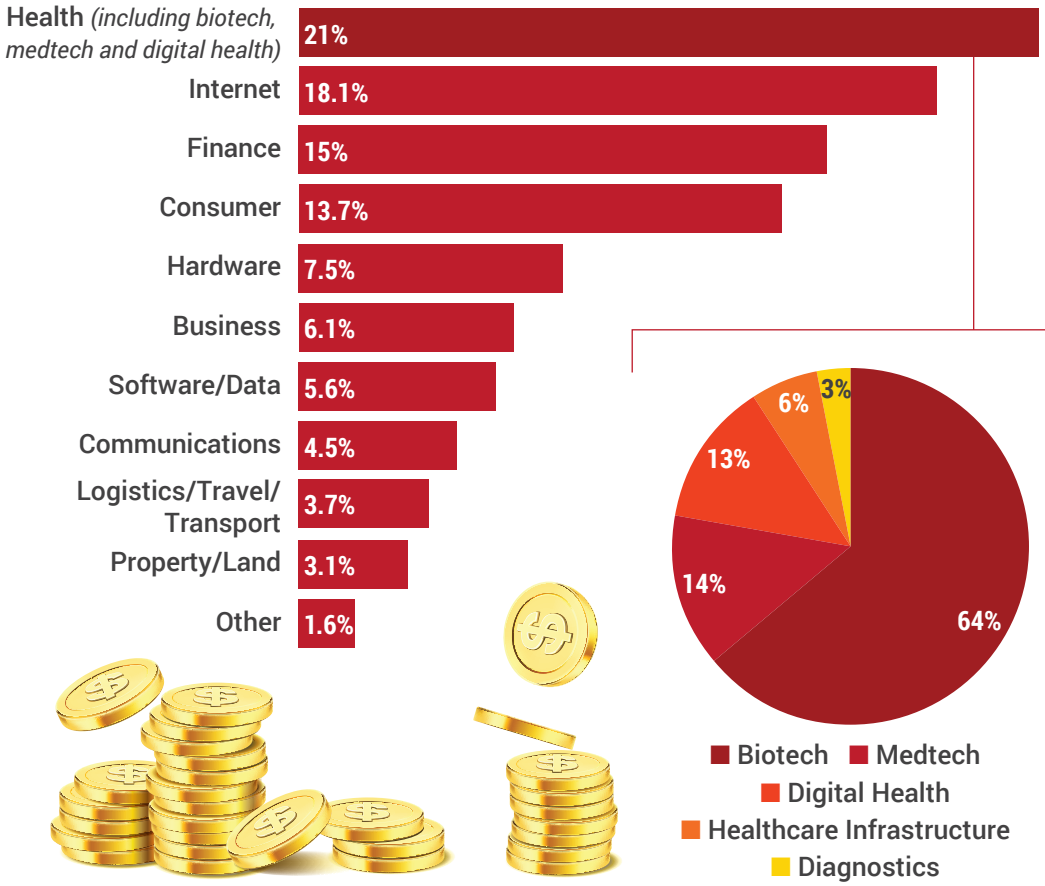
- **12** High-Tech Gruenderfonds
- **9** OrbiMed, Novo AS
- **8** Kurma Partners, Life Sciences Partners
- **7** Sofinnova, Boehringer Ingelheim Venture Fund, Seventure Partners
- **6** Johnson & Johnson Development Corp.
- **5** Forbion Capital Partners

IN EUROPE

80%
of venture capital doesn't go to healthcare

Biotech only accounts for 14% of Europe's $22.2 bn VC investment; medtech only 3%

VENTURE CAPITAL IN EUROPE[1]



SOURCES: [1]FinSMEs, Strategic Transactions, Scrip

The Ups And Downs Of US Drug Pricing Policy

CATHERINE KELLY catherine.kelly@informa.com

The possibility of US pricing reform has long been a concern for the biopharmaceutical industry, especially as it seemed to be a favorite topic for US President Donald Trump. But while 2017 seemed to be more talk than action, this year could be a different story.

Much of the action, whether in Congress or the regulatory realm, is favorable to industry interests. However, there have been a few setbacks and more may come.

Through the end of 2017, the biopharma industry appeared to be influencing the drug pricing debate in Washington, D.C. in a way that was not only deflecting calls for government price controls but was also advancing industry priorities.

The debate had "shifted to where it should be," which was to focus on "all the factors that bear on what patients pay out of pocket," Pharmaceutical Research and Manufacturers of America President and CEO Stephen Ubl told the J.P. Morgan Healthcare Conference at the start of the year.

Ubl reflected on how different the drug pricing debate is now than was feared a year ago, when Trump rocked the investor conference with comments about how the pharmaceutical industry was "getting away with murder."

Biopharma had successfully (and once again) countered calls from Democrats to empower HHS to negotiate drug prices in Medicare Part D and to allow importation of cheaper drugs from abroad. As alternatives, industry has offered policies that target practices by payers and providers that contribute to higher costs.

"I spend a lot of time trying to persuade policy makers to [reject] Medicare negotiated drug prices or reimportation," Ubl said. "Instead we are talking about things like moving toward outcomes-based contracting, alternative payment models, sharing rebates and discounts with patients at the point of sale, generic competition and reforming the 340B program.

"These are all market-based policy solutions that can reduce out-of-pocket costs and we are beginning to see policy makers pick up these ideas."

PROGRESS ON 340B REFORM

That's true. Industry has pushed hard to rein in the drug discounts required under 340B. The program, which operates under section 340B of the Public Health Service Act, requires manufacturers to provide hospitals that serve uninsured or underinsured patients a significant break – up to 50% – on prescription drug prices.

Until recently, lawmakers have been reluctant to disrupt the program because of its focus on needy patients. But there is growing recognition that the program has expanded well beyond its original intent and sentiments are changing. The Senate has begun to move on the issue with an oversight hearing in the Health, Education, Labor and Pensions Committee March 15.

And Sen. Chuck Grassley, R-Iowa, introduced a bill March 1 that would require hospitals to publicly disclose the spread between the 340B discounts it receives and the amount they are reimbursed for the same drugs.

Along the same lines, CMS finalized a rule in November that will sharply reduce Medicare Part B reimbursement for drug that have been purchased with 340B discounts, which may undercut the incentives for some providers to participate.

In the House, the Energy & Commerce Committee issued a report on 340B in January, informed by a series of hearings, that recommended increased oversight of hospitals benefitting from the discounts.

Biopharma has also made progress with its arguments that rebates contribute to high list pricing. The Administration is supportive of changes to the rebate model that could undercut payers' incentives in demanding the price concessions.

Rebates are currently collected by PBMs and passed back to payers, which have used them to keep premiums down across their membership. However, the transactions are not transparent and it is unclear how much of a benefit patients receive from rebates.

Manufacturers have promoted the idea that rebates should be passed through to consumers at the point of sale and CMS recently issued a request for information on how such a program might work.

The concept got a big boost recently with insurer **UnitedHealthCare**'s announcement that it would begin passing through rebates at the point-of-sale in its fully-insured commercial plans.

These were positive developments and a testament to the industry's efforts at educating the public and lawmakers about very complicated issues. But then February came and the industry got a nasty surprise.

HIGHER REQUIRED DISCOUNTS ON BRANDS

Tucked into the interim budget legislation enacted early in the month was a provision adapted from an Obama-era proposal that increased the 50% discount required on branded drugs provided to Medicare Part D beneficiaries in the coverage gap to 70% beginning in 2019.

It appears to have been added to the budget package by Senate Democrats and agreed to by Republicans in order to get the votes for the must-pass budget extension.

The justification for the increase was that it funded effectively "closing" the Part D coverage gap a year earlier than it would otherwise. But as manufacturers' liability in the gap increased under the provision, the plans' responsibility for costs decreased from 25% to 5%, leading to claims that the provision's main accomplishment was shifting a major financial responsibility from plans to manufacturers.

Unofficial estimates of the impact on manufacturers range from $20bn to more than $40bn over 10 years. And now the industry is scrambling to get the provision repealed or revised in a way that would be less onerous.

PhRMA is strongly opposed to the increased discount requirement, arguing it will "save Part D insurance plans over $40bn – roughly seven times what Medicare Part D beneficiaries will save."

Congress should "repeal the harmful Part D changes in the recent budget deal and instead pursue additional reforms to improve affordability and predictability for seniors," the trade group added.

Change is certainly possible but the discount increase was scored by the Congressional Budget Office as saving the government around $10bn over 10 years, (an estimate most analysts think is too low) and Congress will not want to give up those savings.

Less than a week later, industry was rattled again by a raft of drug pricing proposals coming out of the White House, some in a white

paper authored by the Council on Economic Advisors titled, "Reforming Biopharmaceutical Pricing at Home and Abroad," and others in the president's 2019 federal budget proposal.

The proposals, many of which have been circulating among policy experts for years, aim to curb drug costs in Medicare Part D, Part B and in Medicaid.

They stop short of direct price controls like authorizing HHS to negotiate drug prices directly with manufacturers in Part D or allowing for the importation of cheaper drugs from abroad. But many proposals would address drug costs in ways that might impede access to brands or otherwise reduce sales and so are worrisome.

For example, the CEA paper proposes allowing Part D sponsors to offer more restrictive formularies by requiring coverage of just one, rather than two, drugs per category or class. It would also exclude the (now 70%) manufacturer discount in the coverage gap from counting toward the calculation of beneficiary out-of-pocket costs, a move aimed at discouraging use of brands when a less expensive option is available.

The president's budget proposes a pilot test in Medicaid in which up to five states would be able to operate closed formularies to enhance the program's leverage in negotiating prices directly with manufacturers. Currently, Medicaid must cover all drugs all long as manufacturers provide the statutorily-defined Medicaid rebate.

Still, both documents are aspirational – most of the changes would need to be implemented through legislation. So they don't present a near-term threat. And not all of the proposals would be negative for the industry. Some have been strongly supported by pharma, like the plan in the president's budget to require that a portion of manufacturer rebates be applied to Part D beneficiary cost sharing at the point-of-sale, or adding an out-of-pocket spending cap for beneficiaries in Part D.

CREATES ACT

Also percolating in Congress is legislation aimed at curbing manufacturers' efforts to block the development of generics. The CREATES Act would target alleged abuses of the risk mitigation and evaluation strategies (REMS) process in which branded drug firms prevent generic companies from obtaining samples of branded drugs.

The bill would also allow generic firms to sue brand companies for failing to sell sufficient quantities of their drug to support an ANDA. The bill has some bipartisan support. But there are also Republican objections, fanned by the branded drug industry, focused especially on the litigation provision.

Driven by the President's rhetoric about drug pricing, the issue is a priority in Washington. But with a pharma-friendly Republican majority in Congress, the industry is well-positioned to influence the direction of the debate.

And the Trump Administration has appointed former biopharma executives and consultants to the key regulatory and policy roles that would be involved in efforts to lower drug costs.

They include FDA Commissioner Scott Gottlieb, who worked extensively with the biopharma industry as a consultant and investment advisor. Alex Azar, formerly with **Eli Lilly & Co.**, was confirmed as HHS secretary Jan. 24.

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CHMP Nod For Ipsen's Mainstay Cabometyx In First-Line RCC

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Ipsen's cancer therapy *Cabometyx* (cabozantinib) has won CHMP endorsement for approval in Europe in a new indication, first-line renal cell cancer (RCC) – an important step for a product that Ipsen expects to be the backbone of its broader oncology portfolio.

Sotirios Stergiopoulos, Ipsen's global medical affairs and chief medical officer, R&D, told *Scrip* that when Ipsen started development almost 13 years ago, there were no targeted treatments available for patients with kidney disease. "We now have options to treat our patients with," he said. "The significance here with Cabometyx is that it has taken out what had been the standard of care for so many years."

Pfizer Inc.'s *Sutent* (sunitinib) has been the standard of care option for first-line RCC treatment – but Stergiopoulos said it had been dethroned.

The European Medicines Agency's scientific committee, the CHMP, granted a positive recommendation for Cabometyx's label extension into first-line RCC during its March round of assessments. The drug is already approved in Europe for use in thyroid cancer (sold as *Comtriq*) and second-line RCC.

In the US, where cabozantinib is developed and sold by **Exelixis Inc.**, the drug is approved for thyroid cancer and first- and second-line RCC. Furthermore, a filing has already been accepted by the FDA for use of the drug in liver cancer. Ipsen expects to submit the product to the EMA for a label extension into liver cancer in the second quarter of this year.

ONCOLOGY BACKBONE

Cabometyx has a big part to play in Ipsen's wider oncology R&D strategy. There was a significant amount of research ongoing for the drug and it could be used in combination treatments down the line, Stergiopoulos said.

"Cabometyx has a major role for the company as we grow in oncology," he said. "It's going to be a significant component of what we doing going forwards."

Exelixis, for example, is already exploring use of the drug in combination with checkpoint inhibitors. However, Stergiopoulos said the company would not limit the potential of combinations to only checkpoint inhibitors.

EXPANDING CABOMETYX'S REACH

Ipsen awaits approval for the label extension in RCC from the European Commission, which is expected to follow the CHMP's decision. In studies, patients treated with Cabometyx saw up to a 52% reduction in progression of disease, Stergiopoulos noted. "For people like me, that have been in this field for many years, that is quite drastic."

Stergiopoulos said it was premature to speculate on the value of the label extension to Ipsen in Europe. "It's too early to say, but for us this is a win for the patients." He added that "Cabometyx has really contributed to the very strong growth of Ipsen."

"We are working closely with health authorities to ensure that eligible patients can access this new treatment. We want to work hand-in-hand to get this option out there," Stergiopoulos noted.

After approval in first-line RCC, Ipsen will look more broadly at its development programs to see where else it can take Cabometyx. "We have a lot more work to do to really optimize this treatment," Stergiopoulos said.

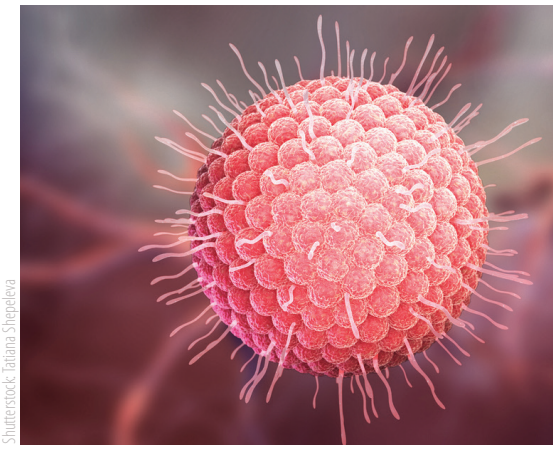
Ipsen and Exelixis have a number of trials ongoing for Cabometyx, including Phase II programs in ovarian cancer, melanoma, non-small cell lung cancer, solid tumors, breast cancer, uterine cancer, bladder cancer and sarcoma. The pair signed an executive licensing agreement back in 2016 that gave Ipsen exclusive commercialization rights for current and future cabozantinib indications outside of the US, Canada and Japan.

"We've had a significant commitment from the company to really look at how we bring this therapy to as many patients as possible," Stergiopoulos said, noting that Ipsen has three large R&D centers in the UK, US and France.

Published online 23 March 2018

GSK Secures Approvals For Shingrix

Officials at the European Commission and Japan's Ministry of Health, Labour and Welfare (MHLW) have approved *Shingrix*, the **GlaxoSmithKline PLC** non-live, recombinant subunit vaccine, for the prevention of shingles in adults aged 50 years or older. The EC has also approved Shingrix for the prevention of post-herpetic neuralgia (PHN) for the same patients.



Shutterstock: Tatiana Shepeleva

The approvals are expected to put more pressure on *Zostavax*, the **Merck & Co. Inc.** shingles vaccine, which saw a dramatic drop off in sales in the US following FDA approval of Shingrix in October 2017 and the subsequent recommendation by US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices naming Shingrix as the preferred vaccine for the prevention of herpes zoster and related complications for immunocompetent adults aged 50 years and older.

MSD saw a 45% year on year decline in US sales of Zostavax in the fourth quarter from $221m in 2016 to $121m in 2017. In the same period, GSK reported sales of $22m. Since 2015, MSD has seen US sales of Zostavax fall from $592m in 2015 to $518m in 2016 and $422m in 2017. Datamonitor Healthcare analysts forecast that global sales of Shingrix could hit $687m by 2025.

CONTINUED ON NEXT PAGE

Datamonitor Healthcare analyst Michael Haydock thinks that Zostavax sales could drop off faster than originally forecast. "I can't see the 5EU countries continuing to recommend two different vaccines in the long term, particularly when one vaccine is clearly superior to the other. Instead, I suspect we will find that the 5EU countries will just procure one recommended vaccine (Shingrix), as they will presumably get a better price per dose if they exclusively reimburse it," he told *Scrip*.

Japan Use Case

For Japan, Haydock believes Shingrix may have an open goal as Zostavax is currently not routinely recommended in the elderly. "I assume the reason Zostavax isn't used is because it is not deemed cost effective in Japan, its efficacy declines with age, but Shingrix should have a stronger case given its superior efficacy," he added.

In the ZOE-70 study, Shingrix was shown to be 97% effective in preventing herpes zoster in those aged over 50 years, and 90% effective in adults aged over 70 years. Conversely, Zostavax's efficacy declines steeply with age, with the CDC estimating it is only 38% effective in those aged above 70 years, and protection also wanes substantially within four years post vaccination.

GSK declined to provide details of how it intends to roll out the vaccine – in Japan it is registered to the **Japan Vaccine Co. Ltd.**, a joint venture of GlaxoSmithKline and **Daiichi Sankyo Co. Ltd.** – saying it will be able to provide more information on launch plans in due course following national level discussions. "GSK looks forward to launching the vaccine on a country by country basis as and when we are in a position to provide sustainable supply to meet local demand," a GSK spokesperson told *Scrip*.

mike.ward@informa.com, 23 March 2018

Hyperkalemia Market Hots Up In EU With Okay For AZ's Lokelma

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It has taken longer than expected but **AstraZeneca PLC** has now received European approval for *Lokelma* (sodium zirconium cyclosilicate), which will go head-to-head in the hyperkalemia space with **Vifor Pharma Group**'s *Veltassa* (patiromer).

The European Commission's green light for Lokelma, previously known as ZS-9, comes two months after the EMA's Committee for Medicinal Products for Human Use (CHMP) issued a positive opinion of the drug for the treatment of adults with hyperkalemia, a condition characterized by elevated potassium levels in the blood associated with cardiovascular, renal and metabolic diseases. The approval is based on four trials, the data from which showed that for patients receiving Lokelma, the median time to achieving normal potassium levels in the blood was 2.2 hours, with 98% achieving normal levels within 48 hours from baseline – it also demonstrated sustained potassium control for up to one year.

The road to approval has not been a smooth one, however. The CHMP's recommendation at the end of January involved the re-adoption of an original opinion from back in February 2017. That earlier decision from the CHMP was not converted into a marketing approval because of concerns about Lokelma's manufacture at a site in Texas. Those problems resulted in the FDA issuing a second complete response letter in March 2017, after it had inspected the aforementioned manufacturing facility; another review is underway across the Atlantic (AstraZeneca did not have to submit any additional clinical data) and a decision is expected in the first half of 2018.

For the moment, the hyperkalemia battlefield will be in Europe, where Vifor got approval for Veltassa in July last year. The Swiss company has started rolling out the drug, which it expects to be a blockbuster, in the UK, Norway and Denmark and a launch in the key German market is planned for the second quarter of 2018.

AstraZeneca believes it has a best-in-class treatment on its hands, however, having previously noted that Lokelma is not systemically absorbed, has a rapid onset of action and is stable at room temperature. BMO Capital Markets analyst Alex Arfaei said in a March 22 note that Lokelma appears to demonstrate comparable efficacy and safety compared to Veltassa but "in the context of severe hyperkalemia, a faster onset of action is clinically important."

He wrote that the EU approval for Lokelma is incrementally positive for AstraZeneca "and further demonstrates the strength of their underappreciated pipeline." Arfaei added that BMO conservatively estimates a 65% probability of approval in the US as "we believe most of the manufacturing issues should be addressable by AstraZeneca" – he is predicting sales of around $1.1bn by 2022, with 25-30% of them coming from the EU.

AstraZeneca got hold of Lokelma when it bought ZS Pharma Inc for $2.7bn in 2015, a price tag that comes closer to being justified if the product becomes a blockbuster. Arfaei wrote that Lokelma, along with the commercial potential of the PD-L1 inhibitor *Imfinzi* (durvalumab), the next-generation EGFR inhibitor *Tagrisso* (osimertinib), the PARP inhibitor *Lynparza* (olaparib) and the BTK inhibitor *Calquence* (acalabrutinib), plus other assets such as the renal disease drug roxadustat and the asthma therapy *Fasenra* (benralizumab), shows that "overall, AstraZeneca's pipeline, particularly in oncology, is delivering."

Published online 23 March 2018

MEETING GROWTH CHALLENGES ROUNDTABLE PANEL PART 2:

Aligning Science, Talent And Expertise

BY MIKE WARD

Developing products that are clinically meaningful requires more than a novel approach to an unmet medical need. A panel of biotech executives and venture investors discuss how to meet the challenges of building a sustainable business from day one.

Starting up life science companies has probably never been easier. Our understanding of disease biology continues to grow, the pool of experienced biotech executives with the battle scars of entrepreneurship has never been deeper, and the cash pile to bankroll their development continues to grow. The challenge these days is what do company executives have to do to ensure they can translate their ground breaking ideas into sustainable businesses that develop products that make a meaningful difference to patients.

Scrip spoke with Gil Van Bokkelen, chairman and CEO of Athersys, Inc., Daniel R. Orlando, chief operating officer of Vericel Corporation, Robert McNeil, general partner and managing director of Sanderling Ventures and CEO of Dalcor Therapeutics, Ali Fattaey president and CEO of Curis, Inc., Mei Mei Hu, co-founder and CEO of United Neuroscience, Inc., Gregory Hanson, CFO of MabVax Therapeutics Holdings, Inc., and Dennis Podlesak, partner at Domain Associates LLC, in a roundtable interview about the challenges company executives face as they try to build their business. Sponsored by Freyeur & Trogue, Impactiv and rbb Communications, the roundtable took place during the J.P. Morgan Healthcare Conference in San Francisco.

Translating Ideas Into Real Products

Translating a promising discovery into a product that helps patients requires input from various stakeholders, many of whom are not part of the original research and more often than are actually outside the company. The challenge for investors and management teams is to ensure that the nascent business has access to the right expertise at the appropriate time.

"It is about marrying promising technology with great talent. One doesn't do well long term without the other. Great technology without the right management team probably won't get very far or funded or succeed. Conversely, great talent without really valuable technology tends not to go far either," noted Domain's Podlesak.

For entrepreneurs, CEO and companies, he added, it is about accessing the right experience. "In some cases it is the formation of the early management, in others its augmented by great key opinion leaders."

Indeed, scientific founders may have great ideas and science but that is different from developing a drug. "That requires a much more comprehensive development plan – what are the studies you are going to have to do preclinically? What are your clinical plans? How many drugs fail because they don't get the dose right? Because they didn't have a great clinical plan to get the endpoint for approval?" questioned United Neuroscience's Hu.

"There is the raw drive to get the idea, then there is the task of translating it into a drug and then there is the executive decision of assessing which programs to pursue based on unmet clinical need and/or good payer coverage. That takes different skills and why it is a team effort. I don't know a single person who can do all of that," she added.

Often that means having different people at the helm as the company evolves from research idea to discovery program, development plans and finally product delivery either to a pharma partner or to patients directly. That decision is often made by experienced executives in venture capital syndicated.

"Before Adennyx was created I met with the French founder in Paris and he had this idea about how we can prevent chronic pain and it was one of those big ideas that is hard to get your head around. We actually studied the company for almost two years before we invested. We took all that work that he had done and sent it to Stanford where we replicated all of the clinical work, including a lot of the preclinical work, to validate the model. And while we were figuring out whether it was something we wanted to invest in we started surrounding the company with key opinion leaders and experts in the area of pain – some of whom eventually became part of the management team," noted Podlesak.

The challenge is how investors convince the scientists with great ideas that they may not be the right people to advance a program. "Our job is to make sure that it is something worthwhile.

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Curis Inc.

Robert McNeil
Managing Director
Sanderling Ventures & CEO
Dalcor Therapeutics

Daniel R. Orlando
COO
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Gil Van Bokkelen
Chairman & CEO
Athersys Inc.

Gregory Hanson
CFO, MabVax Therapeutics
Holdings Inc.

We then have to put together a team that can grow cost effectively and develop the compound into something that you can submit an IND and take it into the clinic and do all the studies," added Sanderling's McNeil.

DalCor was created in such a way. In 2012 he had discussions with investigators at the Montreal Heart Institute led by Jean-Claude Tardif and Marie Pierre Dubé who had made an interesting observation about dalcetrapib, a CETP inhibitor that was being developed by Roche and Japan Tobacco. The companies had conducted a large, double blind cardiovascular study, dal-Outcomes, randomized over 15,000 patients already taking statins for cholesterol control but the study results were equivocal. While the drug was well tolerated, there was no significant reduction in CV events in the dalcetrapib group, and the dalcetrapib development program was terminated.

The Montreal team, however, found a significant association between the effects of dalcetrapib in altering CV events and the allelic polymorphism at the rs1967309 location in the adenylate cyclase type 9 (ADCY9) gene. When comparing dalcetrapib with placebo, patients with an AA polymorphism had a 39% decline in cardiovascular events, while GG had a 27% increase, and GA had a neutral effect, in the cohort of dal-Outcomes patients.

"They described what they had seen having conducted a GWAS on dalcetrapib. It was a compelling argument right there so I said OK here is $50M let's go. We put together a $150M round because we were going to go directly into a Phase III study. We know now we have retrospectively a gene – ADCY9 – and we know prospectively that it reduces atherosclerosis the same amount as statins. The scientist stayed in his lab and the rest of us went out and figured how to put together all you need to have: a board, an executive steering committee to run a 5,000 patient trial," he noted.

Dalcor in-licensed dalcetrapib from Roche in 2015 and raised $50M in a series round in the same year and $100M in a series B round in 2016. The company is conducting a double-blind, randomized, placebo-controlled, multicenter Phase III clinical trial that will enroll 5,000 patients recently hospitalized with ACS and who express the AA genotype at variant rs1967309 in the ADCY9 gene, determined by an investigational companion diagnostic test developed by Roche Molecular Systems (RMS). The primary endpoint of the study, which started in 2016, is the time to first occurrence of any component of the composite of cardiovascular death, myocardial infarction and stroke. The trial will be conducted at 880 sites in 33 countries.

Advice offered by both McNeil and Podlesak to biotech boards is find the right marriage of both science and talent. "One of the great things about our space is it is so rich in talent that you don't always have to have it residing inside the company. In fact, a lot of companies that grow up very nicely start out using the right external resource to help them navigate their path forwards," added Podlesak.

Aligning With Key External Stakeholders

One key group that biotechs need to engage with as they pursue the development path to market and even sustainability are the regulators. And the advice is to get in early as they are more receptive and helpful than some may think.

"It wasn't too long ago that we were talking about how tough it was to work with the FDA – and why isn't anything getting out? You are now seeing guidance and breakthrough designations and different approaches that make it easier to develop drugs that both the FDA and companies think have the potential to be really advantaged treatments," noted Domain's Podlesak.

Indeed, the metrics bear this out. In recent years there has been a significant increase in the number of new chemical entities being approved year on year by the FDA and other regulatory bodies. In 2017, the FDA approved 46 new molecular entities, while the European Medicines Agency gave the green light to 28 new products containing 29 new active substances.

Regulators are taking a more pragmatic view around approvals to get to help patients as quickly as possible and biotechs are being encouraged to open communication as early as possible.

"The first thing start-ups should do is develop a very firm understanding of the indication they are addressing and the status of existing treatments. Second, they have to meet with regulators to get their perspective on what they find acceptable in terms of different development approaches. I would argue that we have never been in a better time with respect to the transition and evolution of the way that the FDA and other regulators are actually viewing highly innovative therapies," added Athersys' Van Bokkelen.

During the J.P. Morgan meeting, the Alliance for Regenerative Medicine revealed in its state of the industry report some of the dramatic progress taking place. "These are all reflections of an evolution in thinking at the FDA, EMA, Japan's MHW and other regulatory bodies that has been occurring in the past four to five years. That has been underpinned by the efforts of a lot of stakeholders including advocacy groups such as ARM and BIO that have met with FDA leadership in Washington DC," noted Van Bokkelen. "I think the regulatory environment has changed dramatically. Under Dr Gottlieb's leadership it is going to continue to evolve in very important and effective ways."

Companies should see the regulators as potential allies and not antagonists. "We have got to stop punishing the FDA every time something bad happens, making the FDA the scapegoat when the unexpected happens. It is not productive – it may be good political theatre but it does not help new medicines get developed," he added.

The interaction with should be both as early as possible and open-minded. "You know the one thing the FDA and other regulators hate most? It is coming to them with the mentality that you want to cut as many corners as possible, spend less, and take less time to do what needs to be done. They hate that," he cautioned.

"If you approach them with a rational intelligent model then the FDA will work with you in a very productive way. I think more and more companies are learning that there is a right way to do it and a wrong way to do it – come at them with a pitchfork or an adversarial mindset – that you want to cut as many corners as fast as you can – then they are going to resist," he warned.

Interestingly, there was a consensus among the panellists that biotechs might find it easier to work pragmatically with the regulators than the multinationals. Progress with CAR-T has been achieved without the need for enormous studies being conducted. Regulators have been willing to draw on a lot of relevant data from real clinical experience.

Tapping Real World Data & Evidence

One of the ways in which the FDA has demonstrated its willingness to being open-minded is the conversations it is having around how companies might utilize real world data and evidence. The challenge, however, is that real world data can mean different things to different people.

"The FDA expects you to be very clear about the type if real world data you are going to utilize. How did you obtain it? How are you prospectively going to use it and gather trial data in the context of enabling them to make an objective decision about whether your therapy is safe and effective. Unfortunately, a lot of people talk about real world data and they don't know what that are talking about because they have never had to make the case and present it to regulators and explain to them how they are going to use it," argued Van Bokkelen.

While it sounds like a relatively simple thing – accessing the data in electronic medical records or health records from clinics around the world – the reality is that data are not collected or created in a way that is universally acknowledged. But there are ways that companies can use real world evidence, benchmarked against standard of care, that can move the needle and speed things up.

The challenge is how investors convince the scientists with great ideas that they may not be the right people to advance a program.

Real world data and evidence, however, is mostly collated to inform pricing and reimbursement discussions. – I have a commercial background and have for more than a decade used real world outcomes sourced through the many payers to leverage for better contracts. That is the traditional use – use in clinical studies has not really changed. When you go to the FDA now they still want the placebo-controlled demonstration and clear differentiation and safety and efficacy.

That is a view that Vericel's Orlando concurs with. "If you ask me where I really want to see RWE is for getting expanded use and expanded indications. Why would we not all pursue the real clinical data to support the payers – its expensive for payers, physicians and everybody loses. Instead of us pursuing that next clinical study, if we were allowed to use real world data we would be able to expand that authorization of products appropriately and reduce costs in general," he noted.

With his commercial background Orlando has been using real world outcomes to leverage for better contracts with payers and while acknowledging that the FDA has been very helpful to Vericel with its pediatric indication for Epicel, Orlando believes that the FDA's appetite to allow real world data to expand labels is still not in place.

"Use in clinical studies has not really changed. When you go to the FDA now they still want the placebo-controlled demonstration and clear differentiation and safety and efficacy. They want you to go back and make huge investment and do placebo-controlled trials. Some of the markets are a bit smaller so it is not realistic for small companies to do that," he added.

The FDA still has a very strong orientation towards wanting data from double blind randomized placebo-controlled studies. Companies can augment that with real world clinical experience and patient testimonials but the regulators are still reluctant to make arbitrary decisions about only one treatment group, that by definition is open label, and compare that to ad hoc datasets that companies may have constructed without giving them full transparency about where the data came from or the limitations associated with it. A position that the roundtable participants recognized is perfectly rational.

Recognizing The Value Proposition

Where real world data and evidence is gaining traction is in the pricing and reimbursement arena, so companies, irrespective of their maturity or the development stage of their programs need to lay the foundations for payer discussions. That is something venture capitalists consider when evaluating potential investments.

"I think that it has to be both early and through the entire process – although the way through to post-approval – that the ability to validate these around empirical data becomes critically important because it helps fine tune and refine the decision making. If a drug can get approved in Europe but it can't be sold at a price where it has to compete favorably with generic drugs – even if it is better – it will probably never end up being a drug there," warned Domain's Podlesak.

To be investable, companies need to understand the therapeutic area, its market dynamics and the competitive environment. Not only today but what will it look like at the time of approval for the decade plus post-approval. Consequently, management need to understand how payers will perceive value throughout the entire drug development, approval and post-marketing process.

"It has now become more a part of the investment thesis. So when we see things that are really well presented – it is not about providing $10M to run a clinical study but is $20M needed to show how it would be attractive to pharma and payers in the therapeutic area," he added.

This is the second installment of a multi-part coverage of the Meeting Growth Challenges Roundtable, sponsored by Freyeur & Trogue, Impactiv and rbb Communications, conducted during the J.P. Morgan Healthcare Conference in San Francisco.

Alnylam And Regeneron Gene R&D Pact On NASH

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Regeneron Pharmaceuticals Inc. and **Alnylam Pharmaceuticals Inc.** are joining forces to investigate genetic factors underlying chronic liver disease, identify new therapeutic targets and then progressing likely RNAi candidates, sharing the costs and potential profits equally from any resulting products.

The move reflects the promise that RNA interference (RNAi) therapeutics offer in specifically targeting and silencing genes involved in the cause or pathway of human disease.

Regeneron, which has made early research in genetics a priority, said it enlisted Alnylam's RNAi expertise after identifying for the first time a variant in the HSD17B13 gene associated with lowered risk of chronic liver diseases.

Research on the hepatocyte-expressed, genetically validated HSD17B13 target upon which the pact is based was published in the *New England Journal of Medicine* on March 22.

The duo hopes to find ways to mimic the naturally occurring 'loss-of-function' genetic variation in HSD17B13 that's found in people who are protected from nonalcoholic steatohepatitis (NASH) progression.

Under the pact, Regeneron will contribute research on the HSD17B13 target. Alnylam will leverage its RNAi therapeutics platform to identify compounds directed to this target.

"We are pleased to join together with an equally science-minded company with a novel RNAi therapeutic approach that appears well-suited to impact this particular target," Regeneron's Chief Scientific Officer George Yancopoulos said in a statement.

Regeneron and Alnylam said they intended to enter into a separate, fifty-fifty collaboration to further research, co-develop and commercialize any therapeutic product candidates that emerge from these discovery efforts.

This is Regeneron and Alnylam's second recent collaboration founded on genetic exploration.

In January 2018, Alnylam, alongside **AbbVie Inc.**, **AstraZeneca PLC** and **Pfizer Inc.** joined Regeneron's pre-competitive consortium to sequence 500,000 individuals in the UK Biobank health resource and subsequently make the data publicly available to the global research community. Each committed $10m in return for a limited period of exclusive access to the sequenced data.

Alnylam meanwhile is preparing to commercialize its first RNAi therapeutic, pencilled in for later this year. The US biotech is preparing its strategy for the potential approval and launch of lead product patisiran, for the treatment of hereditary ATTR amyloidosis, in mid-2018.

"As we transition Alnylam toward commercialization in rare diseases, the prospect of collaborating with a scientific leader like Regeneron on innovative medicines for more prevalent diseases like NASH makes perfect strategic sense," Alnylam CEO John Maraganore said, adding: "We believe the exquisite specificity afforded by the RNAi mechanism of action and our industry-leading, proprietary GalNAc-conjugate approach for delivery to the liver is an unparalleled combination for developing an RNAi therapeutic toward genetically-validated targets in NASH."

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Celgene Further Commits To Neuroscience With Prothena Pact

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Celgene Corp. has taken its cheque book out to sign a second neurodegenerative disease pact this month, paying $100m upfront and a $50m equity investment to team up with **Prothena Corp. PLC** and develop therapies to tackle conditions such as Alzheimer's and amyotrophic lateral sclerosis.

The multi-targeted collaboration will focus on three proteins implicated in neurodegenerative diseases. The first target is tau in Alzheimer's, progressive supranuclear palsy, frontotemporal dementia (FTD), chronic traumatic encephalopathy and other tauopathies.

The second target is TDP-43, a protein implicated in ALS and FTD, among others, and the third is an undisclosed target. Cashwise, the $50m stake represents the purchase by Celgene of 1.2 million Prothena shares at $42.57 each, a 26% premium on the company's closing price on March 20.

The deal gives Celgene an exclusive right to license clinical candidates in the US at the time of any investigational new drug filing, and if exercised, can be expanded to global rights at completion of Phase I. This would trigger potential payments of $135m per program, plus regulatory and commercial milestones of $562.5m per program, plus royalties ranging from high single-digits to high teens.

The collaboration has met with the approval of analysts. Edward Thomason at PharmaVitae told *Scrip* that it adds to Celgene's neuroscience pipeline, and offers synergies with the firm's portfolio of next-generation immunomodulators and expertise in protein homeostasis. He noted that "although the market is skeptical of neurodegenerative disease development right now, it is a logical long-term investment that offers synergies and high potential value if successful."

The Prothena deal expands on current protein homeostasis collaborations and programs focused on oncology, namely with **Nurix Inc.**, **Cleave Biosciences Inc.** and **Forma Therapeutics Holdings LLC**, Thomason added. However, he pointed out that it is the first partnership of Celgene to fully focus on the neuroscience therapy area, and PharmaVitae expects more deals to follow as Celgene builds this new portfolio beyond ozanimod in multiple sclerosis, which surprisingly got hit with a refuse-to-file letter from the FDA

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last month, and ahead of the patent expiry on its multiple myeloma mega-blockbuster *Revlimid* (lenalidomide) in 2022.

Thomason went on to say that controlling protein homeostasis and manipulating the ubiquitin-proteasome system has potential across therapy areas and there is a growing body of literature supporting how it can be utilized to regulate neurodegeneration. While the Prothena deal is focused on targeting tau aggregates in Alzheimer's, "it has potential utility in multiple neurological disorders including other tauopathies, as well as in Parkinson's disease, aging and Huntington's disease."

He concluded by saying that PharmaVitae sees the deal as supportive of Celgene's long-term diversification and it expects the company to build "a strong position in the neuroscience therapy area over the next decade."

Thomason's views were echoed by Michael Yee at Jefferies who issued an investor note stating that Celgene is a leader in developing therapies that target critical pathways in protein homeostasis and is an ideal partner for these disease areas for Prothena. He added that the partnership was consistent with Celgene's distributed model of R&D and adds new and developing resources in neuroscience, acknowledging that this is very early stage – Prothena's tau antibody is not in the clinic yet and the next one – TDP-43 is probably another year behind that.

There has been much debate over the wisdom of companies investing heavily in the neurodegenerative disease area, especially in the challenging areas of Alzheimer's and ALS where the lists of failures are long. However, analysts at JMP Securities who wrote in a note that "we view this collaboration as a significant step toward Celgene realizing its long-alluded-to plans to enter the neurodegenerative space," added that they saw "the back-end weighted nature of the agreement as favourable…as it affords the company the means by which to mitigate the risk inherent in developing drugs for neurodegenerative diseases, while probing what we believe to be high-potential targets."

As for what the deal means for Prothena, the Ireland-domiciled company spun out of Elan in 2012 after the latter was acquired by **Perrigo Co. PLC**, Jefferies' Yee wrote that on top of the cash boost, the link-up "validates our long-term pipeline thesis on the novel and deep science" at the firm. In particular, he pointed out that Prothena's scientists were involved in the development of the MS blockbuster *Tysabri* (natalizumab) and in original amyloid beta Alzheimer's work.

Analysts at Barclays said in a note that the agreement allowed Prothena "to pursue higher risk/ higher reward programs in neuroscience, without compromising the investment required" to bring the firm's amyloidosis drug NEOD001 through Phase IIb and III trials and into potential commercialization. As for Celgene, they said "we still would like to see an additional late-stage acquisition to bolster near-term sales" beyond the acquisitions earlier this year of Juno and **Impact Biomedicines**.

Earlier this month, Celgene paid $101m, including an equity investment, to **Vividion Therapeutics Inc.** as part of a collaboration focused on developing small-molecule therapies across several therapeutic areas that function through the ubiquitin proteasome system, such as cancer, inflammatory and neurodegenerative diseases.

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Ilumya Is Sun's New Branded Specialty Drug Pillar

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Sun Pharmaceutical Industries Ltd. is breaking into the branded biologics space in a competitive therapeutic category – plaque psoriasis – dominated by power players like **AbbVie Inc.**, **Johnson & Johnson** and **Novartis AG**. The company announced March 21 that the US FDA approved *Ilumya* (tildrakizumab-asmn) - the company's first biologic – for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Ilumya binds to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor, inhibiting the release of pro-inflammatory cytokines and chemokines. Ilumya will go up against J&J's first-in-class IL-23 blocker *Tremfya* (guselkumab), approved by FDA in July 2017, in a category that already is crowded.

J&J also markets the entrenched IL-12/23 blocker *Stelara* (ustekinumab), while another class of drugs – IL-17 inhibitors – have emerged as a new blockbuster category for psoriasis, including Novartis' *Cosentyx* (secukinumab), **Valeant Pharmaceuticals International Inc.**'s *Siliq* (brodalumab) and **Eli Lilly & Co.**'s *Taltz* (ixekizumab). Meanwhile, the anti-TNFs like AbbVie's *Humira* (adalimumab), J&J's *Remicade* (infliximab) and **Amgen Inc.**'s *Enbrel* (entanercept) have dominated the biologics market for a decade.

Into this fiercely competitive space walks Sun Pharma, an Indian drug manufacturer best known for selling generics, including a broad portfolio of dermatology products. Like other generic drug manufacturers, the company has come under pressure recently from challenging pricing dynamics in the US generic drug market.

Ilumya is a key asset in the company's strategy to build a portfolio of patent-protected specialty drugs. The focus on psoriasis makes sense for Sun, which is ranked fourth in the US dermatology market in terms of prescription volume. "Many dermatologists write prescriptions for our products every day," the company said. It has a dermatology field force that will support the launch of Ilumya.

The company's commercial success for Ilumya may come down to pricing and contract negotiations with payers. Sun declined to discuss its pricing strategy, noting "We don't disclose pricing strategy until the product is available." The company also declined to say when the product will be made available to patients.

Managing Director Dilip Shanghvi, who founded Sun in 1983, acknowledged that formulary coverage will be a major challenge for tildrakizumab, during a fiscal year third quarter sales and earnings call Feb. 14.

The cost of biologics for psoriasis are high, and payers might roll out a welcome mat for a more affordable option. J&J launched Tremfya at a wholesale acquisition cost of $9,684 for a 100 mg pre-filled syringe, or roughly $58,100 annually. The price was in line with Cosentyx, which launched at a list price of around $58,000 a year.

CONTINUED ON NEXT PAGE

Sun also sees other advantages for Ilumya, including dosing every 12 weeks versus dosing every eight weeks with Tremfya. Chief Medical Officer Simon Lowry said in an interview with *Scrip* at the American Academy of Dermatology meeting in February that there is still plenty of room for new competition, because available medicines have only penetrated about 20% of psoriasis patients eligible for treatment.

But Tremfya appears to have an advantage when it comes to efficacy, though it's difficult to compare across trials. The Ilumya approval was based on the results of two pivotal Phase III trials, Resurface 1 and Resurface 2, enrolling 926 patients. The co-primary efficacy endpoints were number of patients with Psoriasis Area Sensitivity Index 75 (PASI 75) responses compared to placebo and the proportion of participants with a Physician Global Assessment (PGA) score of clear or minimal with at least a 2-grade reduction from baseline at week 12 compared to placebo. The second study also included a comparator arm with Amgen's Enbrel versus which Ilumya demonstrated superiority.

At 12 weeks, 64% and 61% of patients achieved PASI 75 scores in Resurface 1 and 2, respectively, and 14% and 12% achieved PASI 100, or total skin clearance.

In the two Phase III trials included in labeling for Tremfya, 73% and 70% of patients achieved PASI 90 scores, but at 16 weeks, rather than 12 weeks. Tremfya also demonstrated superiority to Humira, which is widely used for psoriasis.

Sun gained the global commercial license to Ilumya in 2014 from **Merck & Co. Inc.**, which said at the time that it was prioritizing its R&D pipeline, including a big investment behind the PD-1 inhibitor *Keytruda* (pembrolizumab). Sun paid Merck $80m up front when Ilumya was in Phase III. Merck completed the development and regulatory activities, funded by Sun. Merck is eligible to receive an undisclosed payment based on the regulatory approval, as well as milestone fees and tiered royalties on sales.

Sun partnered tildrakizumab with **Almirall SA** for development and commercialization in Europe in July 2016. Almirall paid $50m up front plus milestone fees. A regulatory filing has been submitted in Europe.

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Morphosys Seeks US Listing

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MorphoSys AG, the Munich-based antibody biopharmaceutical company, has unveiled plans to also list on Nasdaq with a public offering of American Depositary Shares (ADSs), each equivalent to 0.25 of an ordinary share. The company's F-1 registration statement reveals a plan to raise a maximum of $150m.

By listing the ADSs on Nasdaq, Morphosys hopes to increase its visibility in the US. Currently listed on the Frankfurt Stock Exchange, US investors account for about 49% of the company's shareholder base. "While we do have US investors as shareholders, listing on Nasdaq would enable us to access additional investors. We picture ourselves as being a US commercial organization in the future so need to raise our profile in the market. Raising it with the US investor community is part of that process," CEO Simon Moroney told *Scrip*.

Morphosys intends to use the net proceeds from the offering, together with a portion of its cash and cash equivalents, available-for-sale financial assets, and current financial assets classified as loans and receivables (in aggregate of €312.2m as of Dec. 31, 2017) develop its proprietary clinical pipeline, initiate pre-commercial and commercial activities and advance earlier stage product candidates

Highest priority will be given to further development of its lead candidate MOR208, an IgG1 kappa antibody targetingCD19, in-licensed from **Xencor Inc.** in 2010.

The company is earmarking $225m for further development of MOR208, which is currently being evaluated for relapsed or refractory diffuse large B-cell lymphoma (DLBCL), in combination with other compounds including: with *Revlimid* (lenalidomide) for patients ineligible for high-dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT); with *Treanda* (bendamustine) for patients ineligible for HDCT and ASCT; and in chronic lymphocytic leukemia with either *Zydelig* (idelalisib) or *Venclexta* (venetoclax) in patients who have relapsed after prior therapy with a Bruton's tyrosine kinase inhibitor.

MOR208 was granted breakthrough therapy designation by the FDA in October 2017 based on interim data from the L-MIND study. "Since getting the breakthrough designation we have had very productive discussions with the FDA and can see a path to approval of MOR208 in DLBCL," CEO Simon Moroney told *Scrip*.

In addition, the company is looking to develop MOR208 in other treatment lines and hematological malignancies, as well as exploring opportunities, either on its own or with a partner, in additional oncology indications, including solid tumors, with an initial focus on non-small cell lung cancer.

Morphosys is currently finalizing different commercialization strategies for MOR208. No decision has yet been made as to whether the company will go it alone or seek a partner to share co-development responsibilities and co-promotion rights in the US. "We see commercialization of MOR208 in the US as a catalyst for our transformation into a fully integrated biopharmaceutical company," he added. The company is earmarking approximately $90m to build US commercial capabilities for MOR208. "We are looking to build out a commercial organization ready to promote MOR208," he noted. If all goes to plan that could be as early as the first half of 2020.

Beyond MOR208, the company expects to spend approximately $20m financing the clinical development of MOR202, its anti-CD38 antibody, in multiple myeloma and in NSCLC in combination with a checkpoint inhibitor, $30m on the clinical development of MOR106, Ylanthia-derived antibody against IL-17C, a 50/50 co-development with **Galapagos NV**, in atopic dermatitis, and a further $45m on other discovery programs and the development of its technology platforms.

Morphosys expects to use the remainder of any net proceeds from the offering, together with its existing funds for general corporate purposes. This could include in-licensing, acquisition or investment in complementary technologies, products, businesses or assets, either alone or together with a collaboration partner. However, the company says it has no current plans, commitments or obligations to do so.

The company says that the money from the offering coupled with what it already has in hand will be sufficient, based on current plans, to meet any obligations through to 2020. *Published online 23 March 2018*

TCR2 Raises $125m To Make T-Cell Therapies Available To More Cancer Patients

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TCR2 Therapeutics Inc. believes that its technology platform for the development of T-cell receptor (TCR)-based therapies can make the cancer treatments available to more patients, including people with solid tumors, and now it has $125m to take at least two candidates into the clinic.

Cambridge, Mass.-based TCR2 announced March 21 that it closed a Series B venture capital round to pursue clinical proof-of-concept for its platform. With the new round and its $44.5m Series A, the company has raised $169.5m since it emerged from stealth mode at the end of 2016.

While two chimeric antigen receptor T-cell therapeutics have been approved to date for hematological malignancies – **Novartis AG**'s *Kymriah* (tisagenlecleucel) and **Gilead Sciences Inc.** subsidiary **Kite Pharma Inc.**'s *Yescarta* (axicabtagene ciloleucel) – CAR-T therapies haven't been as successful in solid tumors.

TCR2 CEO Garry Menzel noted in an interview that TCR2 may have an alternative T-cell therapy format that overcomes one of the field's big challenges. "TCR approaches have been able to work to some degree in solid tumors, most recently in the data from **Adaptimmune Therapeutics PLC**," he told *Scrip*, noting some very early clinical results the UK-based company unveiled recently in liposarcoma.

SOLID TUMOR HURDLE

"You now have about 25 to 30 CAR-T players and you have about five to six TCR players," including **bluebird bio Inc.**, Kite, **Celgene Corp.**'s recently acquired **Juno Therapeutics Inc.**, Novartis, **GlaxoSmithKline PLC** and TCR2, Menzel said. "The reason for that is TCR – that's the whole T-cell receptor – seems to be required for responses in solid tumors."

He noted that the TCR's "full repertoire" is needed so that it can be appropriately active in a hostile tumor microenvironment as compared to CAR-T therapies that use a T-cell receptor fragment. And companies that do have TCR programs run into the same problem – a requirement that the antigen targeted by a T-cell therapy must be present in the context of human leukocyte antigen (HLA).

"That brings with it two challenges, the first of which is that there are more than a dozen subtypes of HLA, and that limits the addressable market, because you have to screen a lot of patients to find the right subtype that you can treat," Menzel said. "The second is that HLA is downregulated in many cancers, which ultimately blinds the T-cell to that target, and that presents a risk of relapse."

TCR2's approach doesn't require the targeted antigen to be present in the context of HLA.

"The way that we do that is we tether the tumor antigen domain directly to one of the subunits on the T-cell receptor, which bypasses HLA and attaches directly to a surface antigen," Menzel explained. "We don't make the entire T-cell receptor – we make a subunit, a tether and a binding domain, and then basically transduce that with lentivirus into a T-cell. The T-cell then makes the whole T-cell receptor for us, incorporating our piece into it, and expresses on the surface of the cell a whole TCR with a tether and a binding domain. We call that a *TRuC*, which is short for T-cell Receptor Fusion Construct."

The CEO added that TCR2 is "the only company that we know of, to date, that is able to figure out how to get around the HLA problem when utilizing a full T-cell receptor."

HUMAN PROOF-OF-CONCEPT

TCR2 is working on investigational new drug (IND) application-enabling studies so that it can file an IND with the US FDA and start its first human proof-of-concept study this year. That clinical trial will test TC-210, which targets mesothelin for the potential treatment of ovarian cancer, mesothelioma, cholangiocarcinoma and non-small cell lung cancer (NSCLC).

The company has three other programs. One of those combines TC-210 with a proprietary PD-1 switch, which fuses the extracellular portion of PD-1 and the intracellular portion of CD28. When attached to a TRuC, TCR2 can turn the T-cell suppressive signal PD-1 into a positive CD28 signal to enhance T-cell functions. TRuC plus the PD-1 switch is designed specifically to treat lung cancer, but Menzel noted that if there is synergy between TC-210 in combination with an available PD-1/PD-L1 inhibitor then the company will not take its PD-1 switch into the clinic.

A third program in development at TCR2 is a dual TRuC targeting both CD19 and CD22 for hematological malignancies. The fourth, known only as Program X because the targeted antigen has not been disclosed, will be developed to treat solid tumors.

Program X will move into IND-enabling studies in 2018 and it will be the second TCR2 program to enter the clinic. However, Menzel said it's possible that the company could take a third program into the clinic with its $125m Series B round, which is expected to last through 2021.

KEEPING OPTIONS OPEN

TCR2 has not entered into any partnerships with other biopharmaceutical companies to help with the development or funding of its programs, with the exception of a license for a piece of technology that serves as an add-on to its TRuC platform. The company also doesn't have any immediate plans to enter into a partnership, especially now that it's raised a large Series B round, but that doesn't mean its executives aren't open to such negotiations. "We have kept all of our options opened," Menzel said, adding that TCR2 wanted to get its TRuCs into a state of development with sufficient proof that they would work before pursuing partnerships.

"The financing allows us to independently prosecute our technology into 2021," he said. "For us, in looking for a partner, it's not so much an issue of capital, although that's always important. It's more an issue of capability, that someone could provide us a relationship that could help us get through the challenges you face with T-cell therapy."

TCR2 expects to double in size from its current headcount of about 30 employees during the next year, hiring translational, clinical, manufacturing and other specialists as it pursues human proof-of-concept.

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Perfect Pitch: Rheos Raises $60m To Tune Immune Cells In Autoimmune Diseases

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Rheos Medicines Inc. came out of stealth mode on March 22 with $60m in Series A venture capital from Third Rock Ventures to fund the development of precision medicines for autoimmune and inflammatory diseases and cancer based on the company's insights into immune cell metabolism – though it will seek partners to move ahead with cancer programs.

Cambridge, Mass.-based Rheos is building a drug discovery and biomarker identification platform that includes its proprietary Immune Cell Encyclopedia (ICE), which maps the metabolic pathways of different types of immune cells, and the company's own data and methods for sorting patients into subsets that take into account heterogeneity in immune-mediated diseases.

Interim CEO Abbie Celniker, a Third Rock partner, told *Scrip* that Rheos' initial drug development focus will be autoimmune and inflammatory diseases, and it will seek partners for cancer programs. The company will use its Series A cash to move assets from early research into preclinical development, so that they're ready for the clinic by the time more capital is needed.

FINE-TUNING IMMUNE CELLS FOR PRECISION MEDICINES

"The idea behind Rheos is to bring precision medicine to patients with inflammatory and autoimmune diseases by finding targets to tune the immune system and identifying biomarkers to help us understand the best patients to treat with an immune cell tuning drug," Celniker said.

"At the heart of what we're doing, we're taking advantage of the knowledge that our founders bring to us about which cells drive which inflammatory and autoimmune diseases and then we will interrogate the cells' biology to understand the targets and these biomarkers," she continued.

Rheos' scientific founders include Chief Scientific Officer Laurence Turka, who left research and teaching roles at **Harvard Medical School** and **Massachusetts General Hospital** to join the company. Its scientific founders bring expertise in autoimmune and inflammatory diseases, immune cell metabolism, autoimmune disease biomarker identification, translational immunology, and T-cell biology from universities and research institutes in the US, UK and Germany.

They've already contributed to Rheos' product pipeline, which includes therapeutic programs focused on CD4 and CD8, T-cell subtypes that are involved in multiple diseases of interest, including inflammatory bowel disease, psoriasis, vitiligo and cancer. Such programs will look for pathways involved in dysregulation of immune cell metabolism that can be fine-tuned with small molecule drugs.

"Where you're tuning immune function, you're tuning it to a steady state so that it's not driving an immune response when you don't need one," Celniker said. "In cancer, you can imagine tuning it up so you have a more robust immune response."

Turka likes to compare immune cells to people – both get their energy from proteins, fats or carbohydrates. And just like people perform differently based on whether they had salad or pizza for lunch, immune cells can be tuned up or down by changing where they get their energy or how they use their energy, he said in an interview.

As Rheos builds its Immune Cell Encyclopedia – a first-of-its-kind effort, according to Turka, assembled with patient samples from various universities and research institutions – the company will look at what makes one lymphocyte in one state different from another type of lymphocyte in the same or another state. He said that will allow for identification of novel drug targets and biomarkers in complex, heterogeneous diseases.

"All of lupus isn't the same and all of scleroderma is not the same. Patients can be categorized by one type of dysregulation in an immune cell and others will be categorized by another type of dysregulation," Turka said.

PRECISE RATHER THAN BROAD TREATMENTS

Currently available medicines for autoimmune and inflammatory diseases present a challenge for the health care system, because the medicines suppress the immune system rather than modulate part of it, causing infections, malignancies and other safety issues. They're also used on broad patient populations when only some patients will respond and many lose response over time.

"Patients are suffering the continuous guessing game that physicians have to play, and based on what will be reimbursed," Celniker said. She noted that the promise of a precision medicine approach to autoimmune and inflammatory diseases is better justification for why patients should be put immediately onto a specific drug.

"The promise, too, is the simplicity of the [Rheos] approach. It makes perfect sense to imagine that cells' behavior can be regulated by a metabolic pathway," Celniker said.

She noted that there are not a lot of competing drug development efforts right now looking at immune cell metabolism, but larger pharmaceutical and biotechnology companies appear to be very interested in this space, based on their outreach to Rheos' scientific founders over time.

The company has about 15 full-time employees based in Cambridge and anticipates actively hiring more personnel over the next year, but Celniker pointed out that Rheos is "also very focused on getting the right people into the company at the right time," including a CEO.

Celniker, who's also the interim CEO for Third Rock-funded **Goldfinch Bio**, said the search for a full-time Rheos CEO is under way. Goldfinch launched at the end of 2016 with a $55m Series A round.

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Abuse-Deterrent Opioids: Where Are They Now?

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The commercial market for abuse-deterrent opioids was thought to have blockbuster potential eight years ago, when drug makers started investing heavily in the therapeutic space on the heels of FDA's approval of an abuse-deterrent formulation of **Purdue Pharma LP**'s big seller *Oxycontin XR* (oxycodone). Flash forward to 2018 and the millions of dollars invested in the development of abuse-deterrent opioids appears to have gone up in smoke.

Back in 2010, pharma did not foresee the road blocks ahead, banking on the assumption that in the face of an opioid addiction crisis, the US FDA, payers and physicians would welcome the arrival of new opioids that are harder to abuse. But the abuse-deterrent technologies used in the products only reduce, not eliminate, the potential for abuse, and generally via intranasal or intravenous abuse. They can't altogether prevent the risk of dependency that comes with taking opioids orally as prescribed.

As a result, FDA has put in place high approval standards for new opioids that could suggest less chance for abuse, payers have been unwilling to spend more money on them, and physicians have been reluctant to prescribe them over cheaper generics when it means there will be access hurdles standing in the way. All this comes on a backdrop of a national strategy to reduce the number of opioid prescriptions generally in the US.

A report released by the Tufts Center for the Study of Drug Development released in July 2017 found that 96% of all opioid products prescribed in the US in 2015 lacked abuse-deterrent properties. Despite the challenges there are some two dozen applications for abuse-deterrent opioids pending at FDA, according to the Tufts report, though FDA declined to confirm the number of pending NDAs.

FDA has approved 10 opioids with abuse-deterrent claims consistent with its guidance, but the recent announcement by **KemPharm Inc.** that it is seeking a generic drug partner to sell its newly approved brand-name opioid *Apadaz* (benzyhydrocodone/acetaminophen) – at a price on par with generics – put a spotlight on just how disappointing the commercial market for abuse-deterrent opioids is, particularly when FDA doesn't approve the product with abuse-deterrent claims. There are other examples, too, that highlight how the prospects for the market have been diminished.

Purdue, **Pfizer Inc.** and a few small specialty players are soldiering on. Even Pfizer has faced big financial setbacks in the field, though the pharma giant is large enough to absorb them without taking a direct hit. Pfizer spent $3.3bn to buy the pain specialist **King Pharmaceuticals Inc.** in 2010 in a bid to move into the abuse-deterrent opioid space, building on its success in pain with *Celebrex*. It's fair to say the acquisition never delivered as expected.

Pfizer did manage to get one product from King's pipeline, *Embeda* (morphine/naltrexone), onto the market with abuse-deterrent claims in 2014, but Pfizer doesn't break out sales of Embeda, which generally means the sales are not material. The long-acting oxycodone formula *Remoxy* that Pfizer had its eyes on at King was eventually returned to its original owner, **Pain Therapeutics Inc.**, which is still pursuing development with FDA. Another product, *Troxyca ER* (oxycodone/naltrexone extended-release), developed internally by Pfizer, was approved by FDA with abuse-deterrent properties in 2016, though the company has not yet launched the product and would not say if it plans to.

PAYERS LIKE ABUSE-DETERRENCE – AT A GENERIC PRICE

For the pain specialists forging on, the hope is that the continued emphasis on the opioid epidemic will spur a change in payer attitudes toward valuing abuse-deterrent products as part of a comprehensive solution to the crisis. Some states have introduced legislation requiring payers to reimburse for abuse-deterrent products, which could help to open access. And some drug makers say they are seeing more traction in the market when it comes to improved market access.

But brand manufacturers are also racing against the clock, in a sense, because FDA recently released a final guidance late last year on the development of generic abuse-deterrent opioids.

Payers, meanwhile, are interested in reimbursing abuse-deterrent opioids – but at a lower price, and ideally one that is comparable to current generic opioids. "If the price point is equal, replacing a generic product with an abuse-deterrent formulation is a sensible approach," said Steve Cutts, vice president of pharmacy services and clinical strategy for the pharmacy benefit manager of **Magellan Health Services Inc.**. As it stands, he said, the cost of abuse-deterrent opioid far exceed the generic alternative.

This is the opportunity KemPharm has opted to pursue, changing tack as the reality of the FDA-approved labeling for Apadaz and commercialization challenges set in. Apadaz cleared FDA Feb. 23 without abuse-deterrent claims but, like many newer opioids, with reference to abuse-deterrent properties mentioned in labeling.

As KemPharm's Chief Business Officer Gordon "Rusty" Johnson acknowledged in an interview, "There was this initial period of time post-2010 when there was a great deal of enthusiasm for abuse-deterrent opioids. But the commercial reality has been a much tougher slog."

Now KemPharm is hoping to partner with a generic drug maker or a PBM to help launch Apadaz at a generic price point to replace the generic benzyhdrocodone market.

"It's a good example of innovative thinking on the part of a manufacturer," Magellan's Cutts acknowledged of the KemPharm strategy.

INVESTMENTS THAT HAVEN'T PAID OFF

KemPharm, like other niche specialty players, went public on the back of the promise of abuse-deterrent opioids. The company raised $59.9m in an IPO in April 2015, with a stock price of $11 per share, but opened March 20 at $6.85. The company spent $23.4m developing Apadaz from 2014-2016 and $46.3m total in R&D costs during that time, according to filings with the Securities & Exchange Commission.

Egalet Corp. is another pain-focused player that went public in February 2014, raising $58.4m in a public offering of stock at $12 per share and a coinciding private placement. The company's stock is now trading at less than $1. Egalet successfully got two opioids to the US market, the oxycodone

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A Snapshot Of Abuse-Deterrent Opioids In A Challenging Market

DRUG MANUFACTURER/OPIOID	FDA APPROVAL STATUS	WHERE IS IT NOW?
Pfizer's *Embeda* (morphine/naltrexone)	August 2009; updated with AD-claims in 2014	Marketed, but Pfizer does not break out sales; $61.1m in 2016 US sales reported by IQVIA
Purdue's *Oxycontin* (oxycodone)	2010; reformulated with AD properties and approved with claims in April 2013	Marketed; a blockbuster and one of the most commercially successful AD opioids but Purdue does not report financials
Egalet's *Oxaydo* (oxycodone)	June 2011; launch delayed until Sept. 2015; formulated to deter intranasal abuse; no labeling claim	Marketed; Egalet announced combined Oxaydo, *Aramyo* and *Sprix* sales of $26.1m in 2016
Endo's *Opana ER* (oxymorphone)	Crush-resistant formulation launched in 2012, though FDA never approved AD claims	No longer marketed; withdrawn from the market in 2017 at request of FDA because of intravenous abuse concerns
Collegium's *Nucynta ER* (tapentadol)	Approved in August 2011 and launched by Janssen, designed with AD properties but no claims; DepoMed acquired rights from Janssen in 2015 for $1.05bn in cash	Nucynta products generated $239.5m in 2017; DepoMed has decided to stop making opioids and gave commercial rights to Collegium in a 2018 deal for $10m in cash and a minimum $135m annual payment for four years
Pernix's *Zohydro ER* (hydrocodone)	Reformulated with AD properties in Feb. 2015 after initial approval was deemed controversial; no FDA-approved AD claims	Originator Zogenix off-loaded Zohydro ER to Pernix in 2015 for $100m plus cash; it generated $18m in first nine months of 2017
Mallinckrodt's *Xartemis XR* (oxycodone/acetaminophen)	Approved in 2014 formulated with AD properties, but not with AD claims	Discontinued in mid-2017
Purdue's *Targiniq ER* (oxycodone/naloxone)	Approved in 2014 as the second opioid with AD claims	Never launched; Purdue says it continues to monitor market conditions
Purdue's *Hysingla ER* (hydrocodone)	Third opioid approved by FDA with AD claims in November 2014	On the market; Purdue does not break out sales
Biodelivery Sciences' *Belbuca* (buprenorphine)	Endo secured FDA approval for Belbuca in 2015, but without abuse deterrent claims	Endo returned rights to Belbuca to BDSI and took a $40m impairment charge; generated $17.6m in first nine months of 2017
Daiichi-Sankyo/Inspirion's *MorphaBond ER* (morphine)	Approved in October 2015 with AD claims	Daiichi signed on as a commercial partner in 2016 and MorphaBond launched in November 2017
Pfizer's *Troxyca ER* (oxycodone/naltrexone extended-release)	Approved in August 2016 with AD claims	Pfizer hasn't launched Troxyca and would not comment on commercial plans.
Teva's *Vantrela ER* (hydrocodone extended-release)	Approved January 2017 with AD claims	Teva has not launched Vantrela and said it has no plans to at this time
Daiichi-Sankyo/Inspirion's *Roxybond* (oxycodone immediate-release)	Approved in April 2017 with AD claims	Daiichi-Sankyo plans to commercialize
Collegium's *Xtampza ER* (oxycodone)	Approved in April 2016, with AD claims	Xtampza ER generated sales of $28.5m in 2017
Egalet's *Arymo ER* (morphine)	Approved in January 2017 but tentative approval for a new AD claim was in December 2017, pending patent exclusivity issue set to expire in October	Marketed; Egalet announced combined Oxaydo, Aramyo and Sprix sales of $16.9m in 2016
KemPharm's *Apadaz* (benzhydrocodone/acetaminophen)	Approved February 2018 with AD properties, but no claims	KemPharm said it is seeking a generic partner and plans to launch at generic pricing
Pain Therapeutics' *Remoxy* (oxycodone extended-release)	Pending at FDA with Aug. 7 action date	Pfizer once owned rights but after two rejections by FDA it returned rights to Pain in 2014; Pain got a third FDA rejection in 2016 but resubmitted in Feb. 2018

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

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

Selected clinical trial developments for the week 16–22 March 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III RESULTS PUBLISHED			
Array Biopharma Inc.	encorafenib plus binimetinib	melanoma	COLUMBUS; *The Lancet Oncology*, March 22nd, 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
Regeneron Pharmaceuticals Inc.	*Eylea* (aflibercept)	diabetic retinopathy without diabetic macular edema	PANORAMA; reversed disease progression.
Roche	*Tecentriq* (atezolizumab) plus chemotherapy	squamous non-small cell lung cancer, first-line	IMpower131; positive PFS results.
Heron Therapeutics Inc.	HTX-011 (meloxicam/ bupivacaine) extended-release	post-surgical pain	EPOCH 1, 2; pain and opioid use reduced.
UPDATED PHASE III RESULTS			
Spark Therapeutics Inc./ Novartis AG	*Luxturna* (voretigene neparvovec)	Leber's congenital amaurosis	Improved symptoms.
Shire PLC	*Natpara* (rhPTH)	hypoparathyroidism	RACE; long-term safety and efficacy.
Radius Health Inc.	*Tymlos* (abaloparatide) then alendronate	osteoporosis	ACTIVExtend; positive data.
Shield Therapeutics PLC	*Feraccru* (ferric maltol)	iron deficiency	AEGIS-CKD; positive post-hoc analyses.
PHASE III INITIATED			
Shire PLC	SHP647	ulcerative colitis	As induction therapy.
Helsinn Group	*Akynzeo* (fosnetupitant/ palonosetron) iv	chemotherapy-induced nausea and vomiting	In breast cancer patients; oral form already marketed.
PHASE III ANNOUNCED			
Isofol Medical AB	*Modufolin* (arfolitixorin)	colorectal cancer	ISO-CC-007; dose selection concluded.
UPDATED PHASE II RESULTS			
Reata Pharmaceuticals Inc.	bardoxolone methyl	pulmonary arterial hypertension	LARIAT; positive effects on walking time.
Gamida Cell Ltd.	*NiCord* (nicotinamide expanded cord blood)	bone marrow transplant	Immune reconstitution observed.
Millendo Therapeutics Inc.	ATR-101	congenital adrenal hyperplasia	Signs of efficacy.
Sellas Life Sciences Group Inc.	*Zeltherva* (galinpepimut-S)	multiple myeloma	Sustained clinical benefit.
Novo Nordisk AS	*Ozempic* (semaglutide)	obesity	Significant weight loss observed.
Progenics Pharmaceuticals Inc.	*Azedra* (iobenguane I-131)	neuroendocrine tumors	Tumor biomarker data positive.

Source: Biomedtracker

CONTINUED FROM PAGE 20

product *Oxaydo*, developed with abuse-deterrent technology in 2015, as well as the extended-release morphine product *Arymo ER* in January 2017, but uptake has been slow.

Egalet reported total product sales of $26.1m in 2017, including a third product, *Sprix* nasal spray. It also reported a net loss of $69.4m for the year. The company spent millions on R&D, $75.2m from 2015-2017, according to an SEC filing.

During the company's fourth quarter sales and earnings call March 12, CEO Bob Radie said the future comes down to payer acceptance.

"Payers have been resistant to want to put these products into preferred positions and in many instances, across all of the different payer types, commercial/government, we see, oftentimes, payers creating hurdles, making it difficult for prescribers to get this." Nonetheless, the company insists it is making progress securing market access for Arymo ER. In February, the company said one of the largest regional payers in the Northeast gave Arymo ER a preferred placement on its formulary.

Another drug maker, **Pernix Therapeutics Holdings Inc.**, launched the extended-release hydrocodone product *Zohydro* with abuse-deterrent technology in 2015, after the original developer **Zogenix Inc.** backed out of the space. Zohydro generated $24m in 2017, a decline of 3% due to a reduction on price. The company's net loss was $77.1m. Continued net losses at a similar pace will be hard to sustain.

Purdue's Oxycontin has been the exception to the rule when it comes to abuse-deterrent opioids. The company was able to succeed where others failed because of the initial popularity of extended-release oxocodone and early FDA approval of an abuse-deterrent formulation, along with the agency's corresponding decision to ban generics. That gave Purdue a stronghold on the market in a scenario that hasn't materialized in other opioid classes, where cheap generics have been readily available.

Purdue, being privately held, doesn't release financial information publicly, but analysts put Oxycontin revenues at around $2bn.

A rival drug maker, **Collegium Pharmaceutical Inc.**, which markets the competing abuse-deterrent oxycodone product *Xtampza ER*, said Oxycontin sales were $1.7bn in 2017, about 15% of the US market share for all extended-release and long-acting opioid prescriptions. Collegium is hoping to chip away at Oxycontin's hold on the market. Xtampza ER generated $28.1m in 2017, the company reported, and prescriptions are growing. Prescriptions for Xtampza ER grew 37% in the fourth quarter versus third quarter to 38,044. The company's stock price also is on the rise, since it went public at $12 per share in May 2015, raising $80m in gross proceeds. The stock opened March 20 at $26.62.

Collegium is one company that is doubling down on the abuse-deterrent space. It recently acquired the *Nucynta* franchise, including immediate-release and extended-release products, from **DepoMed Inc.**. The company paid $10m up front and a $6m inventory payment upon closing, as well as an annual license fee of $135m for four years, plus royalties on sales over $233m.

To put a reality check on the deal, DepoMed bought the Nucynta franchise from **Johnson & Johnson** for significantly more in 2015: $1.05bn in cash.Those are deal dynamics that hurt.

DepoMed, meanwhile, is laying off 40% of its workforce. By cutting its pain sales force and eliminating brand spending on Nucynta, the company said it would reduce expenses by $70m. That's one of the big challenges for a small pain specialist trying to compete in this niche space – building out and investing in a commercial sales team. It's the pitfall KemPharm hopes to avoid.

But at this point, the list of opioids with abuse-deterrent claims that are on the market is almost eclipsed by the number of new opioids that have been discontinued or held from the market. Only time will tell if any new products get on stronger financial footing.

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Eric Cornut has been appointed chair of Italian pharma group **Menarini**, taking over from ***Lucia Aleotti***, the owner manager who runs the company with her brother, vice president Alberto Giovanni Aleotti. Cornut was chief ethics, compliance and policy officer at Novartis from 2014 until his retirement in 2016. He also served as interim director general of the European Federation of Pharmaceutical Industries and Associations (EFPIA) in 2016-17. The siblings in charge of Menarini will not reduce their involvement in the company, but will spend more time seeking strategic acquisitions. They were convicted of fraud and tax evasion in 2016.

Emergent BioSolutions Inc. has promoted ***Robert G. Kramer Sr.*** to the newly created position of president and chief operating officer, and appointed ***Richard S. Lindahl*** as its new executive vice president and chief financial officer. Kramer joined the company in early 1999 shortly after its founding and has held a variety of executive level positions, including president of Emergent's Lansing, Michigan manufacturing site and, most recently, executive vice president, administration and chief financial officer. Lindahl most recently served as CFO at CEB Inc.

Novo Nordisk has appointed ***Pinder Sahota*** general manager and corporate vice president for the UK. Previously, Sahota was responsible for developing the commercial & market development strategy for key brands across Europe in his role as senior vice president of market and commercial development for Europe at Smith & Nephew based in Baar, Switzerland. Pinder succeeds interim general manager Nick Bailey.

Sienna Biopharmaceuticals Inc. has appointed ***John W. Smither*** as chief financial officer. He will succeed ***Richard Peterson***, who has resigned for personal reasons, effective Mar. 29. It has also appointed of ***Caroline Van Hove*** as the company's first chief commercial officer. Smither was Sienna's CFO from January 2016 to March 2017, and subsequently has served as an independent consultant in the biopharmaceutical industry. Previously, he served as CFO of Kythera Biopharmaceuticals, Inc. Van Hove has 20 years of diverse experience in the pharmaceutical, consumer and medical device industry, managing sales and marketing, commercial excellence, public relations and corporate affairs functions.

The Medicines Company has appointed ***Christopher Visioli*** as chief financial officer and treasurer, effective immediately. Visioli succeeds William B. O'Connor who is retiring after serving as chief accounting officer and then chief financial officer for a total of 13 years. O'Connor will remain with the company as an advisor through 2018, assisting Visioli in transition. Visioli will report directly to CEO ***Clive Meanwell***.

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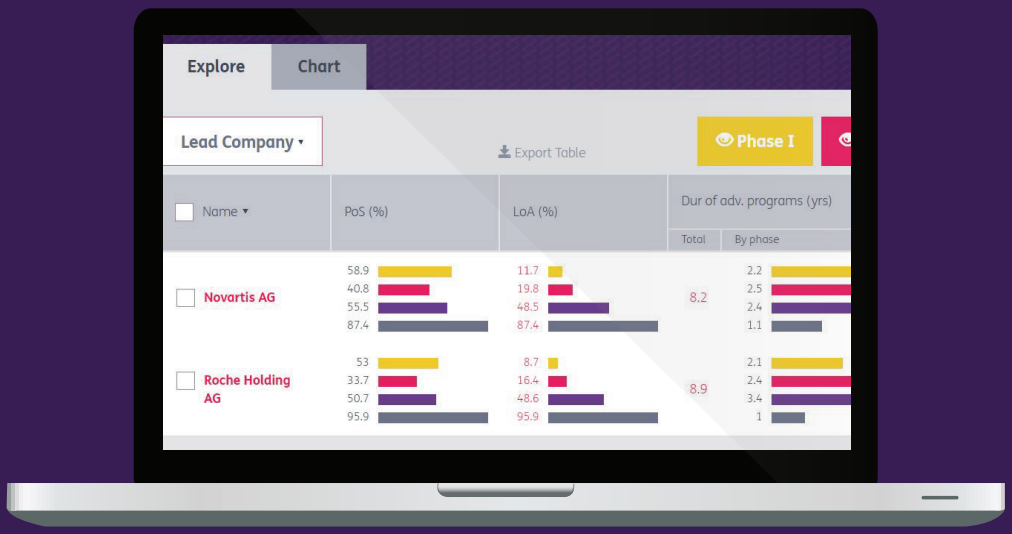

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