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What Will Novartis Do With $13bn Cash Pile From GSK?

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Novartis AG CEO Vas Narasimhan has only been in the hot seat for a couple of months but is wasting no time in transforming the firm into a pure pharma player, selling its stake in a consumer healthcare joint venture with **GlaxoSmithKline PLC** for $13bn.

The Swiss major would appear to have got a good deal, given that the figures that had been mentioned for the 36.5% stake had been in the region of $9-12bn. Narasimhan certainly thinks so, saying in a statement that while its consumer healthcare JV with GSK is progressing well, "the time is right for Novartis to divest a non-core asset at an attractive price." He went on to say that "this will strengthen our ability to allocate capital to grow our core businesses, drive shareholder returns and execute value-creating bolt-on acquisitions." Narasimhan also stressed his often-repeated message about building "the leading medicines company, powered by digital and data."

The news comes as no great surprise, given that the JV, created in 2015 as part of a three-part transaction between the two companies, gave Novartis a put option, exercisable from March 2, 2018 to March 2, 2035, to require GSK to purchase its stake, or parts of it. Many analysts thought that an asset swap might have taken place but the Swiss major has only waited 25 days to exercise its option and take the cash. The question now is what Novartis will do with the money.

Eric Le Berrigaud, an analyst at Bryan Garnier, said in an investor note March 27 that $13bn "is a touch above our estimated transaction price." He added that the sale will provide Novartis "with more financial flexibility to be used exceptional share buy-backs or access to more strategic alternatives i.e. broadening the range of targets for potential bolt-on acquisitions fitting its core businesses." It is "strategically good for Novartis given that it simplifies and focuses its organization."

Analysts at Deutsche Bank noted that the deal would be dilutive to the tune of around 3.5% per year to core earnings per share unless Novartis deploys the cash elsewhere. They wrote that "disappointingly, the company is vague in this regard, discussing only its standard capital allocation policy, rather than any pre-prepared statement for a commitment to reduce the dilution through a share buy back. As such, Novartis management has the ability to create shareholder value through this transaction but the jury remains out for now."

The jury appears to be in at Société Général, where analysts issued a note saying that the $13bn price tag "is a positive surprise" as they had valued the stake at $10.6bn. They wrote that they expect Narasimhan "to refocus the company on innovation," believing that Novartis will give more details about its plans to redeploy the cash with its first quarter results on April 19.

Ian Hilliker, an analyst at Jefferies said in a note that as the consumer healthcare sector "does appear to be facing more difficult times at present, with increased competition, or price pressure from e-commerce, this looks to be a strategically well-timed decision for Novartis." Noting that the initial disposal of the JV stake will be dilutive, he said "we would expect that Novartis will look to redeploy some of these proceeds fairly quickly to help mitigate any dilution. It is

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BROUGHT TO YOU BY THE EDITORS OF **PHARMASIA NEWS, START-UP** AND **SCRIP INTELLIGENCE**

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J&J's Price Pledge
What's the whole story? (p13)

Amazon's Adventures
Expansion into healthcare a major disruption (p10)

from the editor

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Looking back at the first quarter of 2018, defining themes and stories in the pharma space have included the corporate tax reform in the US that was finally passed at the end of 2017, and the increasing encroachment of digital technology and data in the world of healthcare.

President Trump's tax reform prompted fresh expectations of a new wave of M&A, which has yet to materialize in any serious way: there have been few >$1bn transactions and no mega-mergers, and aside from the Celgene-Juno buy the larger deals have been predominantly ex-US (Sanofi buying Ablynx and Bioverativ, GlaxoSmithKline buying Novartis out of their consumer health joint venture). Watch this space, though, Takeda's revelation that it is thinking about making an offer for Shire could kick start a competitive flurry (p7). Tax reform is also prompting other investment: companies including Pfizer and Merck & Co have outlined plans to return cash to shareholders, invest in capital projects and pay employee bonuses, for example.

As for digital disruption, minds have become increasingly focused on the possibility that Amazon will transform the drug distribution system (p10); the online retail giant's partnership with JP Morgan and Berkshire Hathaway in January remains shrouded in mystery but is significant as its first foray into health care. That sense of looming disruption to current distribution models in the US is compounded by government threats of cost controls. Changing business models and consolidation in the PBM sector, with pharma veterans being brought into prominent leadership positions, indicates how seriously the market incumbents are taking the threat (p18).

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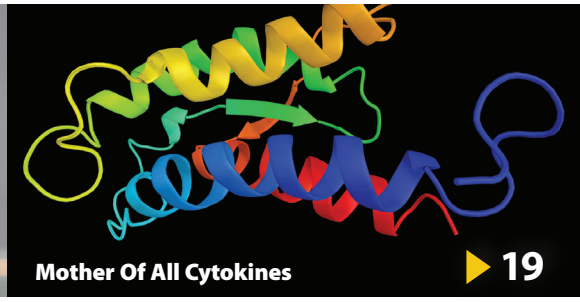

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GSK Gains Clarity For Pharma Focus Through Novartis Consumer JV Buy

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It's hard to imagine that spending $13bn (£9.2bn) could lift a weight from someone's shoulders, but that's what **GlaxoSmithKline PLC** has done with its purchase of **Novartis AG**'s 36.5% stake in the companies' Consumer Healthcare Joint Venture.

GSK said on March 27 that buying Novartis' share of the JV, which became a possibility this month under the companies' 2014 agreement to combine their OTC drug and nutritional products businesses, "removes this uncertainty and improves the Group's ability to plan allocation of capital to its other priorities."

GSK has made pharmaceutical research and development, with a renewed focus on oncology, a top priority, so buying Novartis' share of the consumer health JV clarifies how much the company can spend on R&D, including business development.

"Very importantly, the transaction removes an inherent uncertainty for [GSK] with the removal of the Novartis split, and this will allow us the planned use of our capital for other priorities, especially pharma R&D," GSK CEO Emma Walmsley said during a March 27 call with analysts and investors. "As I've said, strengthening and investing in our pharma pipeline is critical to support the company for its next wave of growth."

The company will provide an update on its pharma R&D strategy during its second quarter 2018 earnings report, scheduled for July 25. This will be a key period for GSK, which should know more by then about whether its pharma revenue will be hit by generic versions of its blockbuster asthma therapy *Advair Diskus* (fluticasone/salmeterol).

Capturing 36.5% more of the revenue flowing in from the consumer health business, combined with revenue from new products, could help GSK offset declining sales of Advair. Walmsley sold the buyout of Novartis' stake in the consumer health JV as giving investors a greater share of profits from a business that's doing well and has room for growth.

"The buyout of the Novartis stake means GSK shareholders will capture the full value of a business we believe is well positioned to deliver future sales growth and continued operating margin improvement," she told the call.

CONSUMER REVENUE A BOOST AS PHARMA IS CHALLENGED

The consumer health JV launched in 2015 as part of a $28.5bn three-way deal announced in 2014 that included combining Novartis' and GSK's consumer health franchises to create a business with about $10bn in annual sales. The arrangement gave GSK a majority 63.5% stake in the JV and a commitment to buy out Novartis' share if it chose to divest its interest between March 2, 2018 and March 2, 2035. In the deal, Novartis also bought GSK's oncology business for $16bn, GSK bought Novartis' vaccines unit for $5.25bn, and Eli Lilly & Co. bought Novartis' animal health business for $5.4bn under the original set of transactions.

The combined consumer health business generated sales of £7.8bn ($11bn) in 2017 with a three-year compound annual growth rate of 4% between 2015 and 2017. The unit's operating margins have improved during that period from 11.3% in 2015 to 17.7% in 2017, and GSK forecasts even greater improvement into the mid-20% range by 2022.

But while consumer health always has been an important business for the company, GSK is staking its future on pharma R&D and has invested in people and other resources under Walmsley to strengthen its prescription drug business.

The CEO described the company as "a world leader in consumer" during GSK's 2017 fourth-quarter earnings call on Feb. 7, but said "our first priority remains pharma and both investing in the launches and the execution under way, but also more specifically prioritizing the pipeline in pharma. We will not do anything that cuts across that prioritization."

That seems to suggest that GSK will not invest in consumer health outside of its commitment to Novartis under the companies' 2014 agreement. The British drug maker had been interested in acquiring **Pfizer Inc.**'s consumer health business, but pulled out of the bidding March 23 – just four days before announcing the buyout of Novartis' consumer health JV stake.

"While we will continue to review opportunities that may accelerate our strategy," Walmsley said in a statement March 23, "they must meet our criteria for returns and not compromise our priorities for capital allocation."

HIV, RESPIRATORY, VACCINES AND ONCOLOGY

Among the company's existing pharma priorities are:

- The respiratory franchise, including *Breo Ellipta* (fluticasone/vilanterol), *Anoro Ellipta* (umeclidinium/vilanterol), *Trelegy Ellipta* (fluticasone/umeclidinium/vilanterol) and *Nucala* (mepolizumab). Trelegy was the first triple-combination inhaled therapy approved in the US for chronic obstructive pulmonary disease (COPD) in September. The franchise's next FDA endorsement in COPD may be a supplemental approval for Nucala.
- HIV via **ViiV Healthcare** , including the key assets *Tivicay* (dolutegravir) and *Triumeq* (dolutegravir/abacavir/lamivudine), which are facing intense competition from new products launching out of Viiv's main rival **Gilead Sciences Inc.**
- Vaccines, a franchise boosted by FDA approval for the shingles vaccine *Shingrix*, which is expected to steal significant market share and become the preventative therapy of choice.
- And oncology, where Walmsley has vowed to boost the pharma business with a renewed focus on cancer drugs and brought in ex-**Genentech Inc.** executive Hal Barron to drive home this strategy.

Business development also will be important for GSK's pharma growth, but don't expect any mega-mergers from the UK big pharma.

Walmsley said during the company's call about buying out Novartis' consumer health JV stake: "I've been clear that our first priority is to invest in our organic growth, which starts with pharma and R&D, and perhaps that will include some early-stage [business development.]"

She indicated that there will be more commentary in that regard during GSK's R&D update as part of its second quarter earnings report in July.

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GSK's Horlicks Review Plan – Some Early Expectations In India

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GlaxoSmithKline PLC's decision to potentially divest the popular malted milk drink *Horlicks*, which is largely sold through its publicly listed Indian subsidiary, **GlaxoSmithKline Consumer Healthcare**, isn't about market-related pressures, the UK multinational's top brass has emphasized.

"I want to be absolutely clear that this has, for a long time, been a winning and performing brand, primarily in India. There is no issue at all around critical mass in the categories of which it competes. This is about an efficient use of GSK's capital," GSK CEO Emma Walmsley stressed in an investor call March 27.

Walmsley explained that GSK has wanted to focus within the consumer business on the science-based brands within OTC and oral health; and by announcing in combination with the Novartis deal the strategic review of Horlicks, it allowed GSK to maintain the flexibility that it required "to support our other priorities for capital allocation and support our existing profile, the priority there being pharma R&D".

GSK on March 27 announced a strategic review of Horlicks and its other consumer healthcare nutrition products to support the deal to buy out Novartis' stake in the duo's consumer healthcare joint venture; the "assessment" of GSK's 72.5% shareholding in GlaxoSmithKline Consumer Healthcare forms part of this review.

A LEADING MARKET SHARE

GSK Consumer Healthcare Ltd is the category leader in the Indian health food drinks segment. The popular drink Horlicks, which some years ago was reported to have outsold Pepsi in India, commands a market share of 44.1% (by value) as per Dec 2017 MAT (moving annual total) data from AC Nielsen. Horlicks extensions account for over a 16% share.

Competitors like **Danone**'s *Protinex* and Abbott's *Pediasure* and *Ensure*, though, have been making their presence felt in the category, while other factors including the availability of other healthy substitutes such as oats are said to have impacted the segment overall.

Putting Horlicks and the Indian arm (Horlicks accounts for the bulk of the company's revenues) on the block is expected to generate significant interest.

Deutsche Bank analysts, in a report dated March 27, said that a price of more than three times sales could be achievable based on similar deals in the sector, indicating "possible proceeds of over £1.7bn given 2017A sales of £550m".

Navroz Mahudawala, managing director of Candle Partners, a boutique investment banking firm, told *Scrip* that the Indian subsidiary GSK Consumer Healthcare Ltd. is richly valued at around 43-44 times TTM (trailing twelve months) earnings and would be a key driver for the global sale as it is the key market after the US.

"It's unlikely we would witness a separate deal at the India level; this would be part of the global sale process wherein a global buyer would look at the business as a consolidated piece," Mahudawala said.

A board meeting of GSK Consumer Healthcare is scheduled for March 28, though this had been announced by the Indian arm on March 20 – the company told *Scrip* it is part of the original plan for the financial year.

Some analysts believe **Reckitt Benckiser Group PLC**, which recently pulled out of the race for **Pfizer Inc.**'s consumer healthcare business, could possibly take a hard look at Horlicks and the nutrition products business in India. This would be against the backdrop of Reckitt's interest in expanding in India, and the **Mead Johnson Nutrition Co.** deal.

Both Reckitt and GSK recently pulled out of the race for Pfizer's consumer health business, GSK just days before announcing the buyout of Novartis' consumer health JV stake.

Others speculated about **Nestle SA** as a potential suitor, though there is no official word on any interest by the firm.

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CONTINUED FROM COVER

quite possible that part of the timing of the decision to execute the put may have been triggered by an imminent bolt-on deal."

It will be interesting what areas Novartis will look at for these bolt-ons deals, and oncology seems likely to be one of them. In January, the company concluded the $3.9bn acquisition of radiopharmaceutical specialist Advanced Accelerator Applications SA, four days after the French group's *Lutathera* (lutetium Lu 177 dotatate) won FDA approval to treat somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors.

Given Narasimhan's interest in data, Novartis can also be expected to continue to invest more of its cash pile in digital deals in the clinical space. Earlier this month, the Basel-headquartered giant expanded its alliance with **Science 37** to launch up to 10 new virtual trials using the latter's technology which uses mobile devices and telemedicine services, days after linking up with **Pear Therapeutics Inc.** in a prescription digital therapeutics collaboration aimed at treating patients with schizophrenia and multiple sclerosis.

This month also saw the appointment of chief digital officer Bertrand Bodson, who has only been with Novartis since January, onto its executive committee, the group's main decision-making body. Given the culture switch at the top of Novartis, it is possible that rather than collaborations with digital players, it may choose to bring some of its digital partners in-house, just as **Roche** did through its recent purchase of Flatiron Health Inc.

The sale of non-core assets is not expected to stop with the GSK deal and the status of Novartis' Alcon unit is back in the spotlight. The eye care division returned to growth in 2017 and at the company's annual results meeting in January, Narasimhan said that a decision on whether to spin off or sell is unlikely before 2019 but a clue as to its future may emerge in the coming months.

There is little chance of Novartis' generics arm Sandoz going under the hammer, as biosimilars is very much a core business. However, in response to continuing pricing pressures in the US, the company will continue discontinuing or divesting certain non-complex generics.

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Takeda's Interest Likely To Flush Out Further Shire Suitors

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Takeda Pharmaceutical Co. Ltd.'s statement that it is considering making an approach to **Shire PLC** may force the hand of other big pharma companies. Several firms, including **Pfizer Inc.** and **AbbVie Inc.**, are viewed as in the market for larger transactions as they face increased pressure on their current growth prospects, and Shire's position at the lower end of the large biopharma set makes it a more digestible, but still transformative target for the biggest companies in the sector.

Furthermore, with Takeda already carrying debt and of a similar market cap size to Shire, it is quite possible that any offer it eventually decides to make will be outbid should another firm decide also to act opportunistically on Shire's current low valuation. Takeda's bid would likely be equity-heavy, giving those with the ability to offer an all-cash buyout additional leverage.

"We expect most large pharma companies have a takeout model of Shire and Takeda's announcement will force them to make a decision," Bernstein analysts commented in a March 28 note.

Under the leadership of Flemming Ørnskov, Shire has been building a position as a powerhouse in rare disease therapies, executing a series of transactions culminating in the $32bn purchase of **Baxalta Inc.** in 2016, which added a large hemophilia franchise to its business. However, its share price has been in decline ever since.

SHIRE CHALLENGES

The sustainable growth of the hemophilia business has been called into question as rival and new entrants in the space are threatening the established order with innovative therapeutic options. In 2017, hematology accounted for $3.8bn in product sales out of a total of $14.4bn across Shire's business.

Aside from the external challenges faced by the former Baxalta business and the complexity of the integration process, Shire has also struggled with market access for its much-touted *Xiidra* (lifitegrast) dry eye treatment, and that product's potential could be constrained by generic versions of **Allergan PLC**'s *Restasis* (cyclosporine ophthalmic) expected to hit the US market later this year.

Shire's stock closed the US trading day March 28 up 12% to $144.53 per share. Its market capitalization stood at around £32.5bn ($46bn) by mid-afternoon on the London Stock Exchange, where its share price soared after Takeda's interest became public knowledge. Takeda's market cap on the Tokyo Stock Exchange at close of trading on March 28 was around ¥4.37tn ($41.4bn).

Takeda highlights the synergy between its business and Shire's in the former's core areas of oncology, gastroenterology and neuroscience, as well as the potential Shire would afford it to build its business in the US. However, the Bernstein analysts noted that "the strategic logic is not apparent," citing a mismatch in portfolio and operational footprint aside from a "modest overlap in GI and enhancing the Shire portfolio in Japan." They think the deal looks "stretched" financially, and lacking in the "opportunity for large cost synergies."

However, as Jefferies analysts pointed out in a March 28 reaction note, "Shire's leading global position in rare diseases would likely be attractive for most large pharma/biotech." They flagged up the company's Phase III candidates, adding: "We believe many of these are underappreciated and could drive longer-term upside." In particular, they highlighted SHP621 for eosinophilic esophagitis, SHP647 for ulcerative colitis and maribavir for cytomegalovirus, as well as Phase II SHP607 to prevent chronic lung disease in premature infants, as "underappreciated".

Shire recently announced it was internally splitting into two distinct divisions, focused on rare diseases and neuroscience (mainly consisting of its mature attention deficit/hyperactivity disorder franchise), with operational metrics for each to be reported separately from the first quarter of 2018. The move is intended to create "enhanced optionality," which could include the sale or spin-out of the neuroscience business, something to be decided in the second half of this year.

As recently reported in *Scrip*, a number of larger companies are viewed as potentially in the market for large acquisitions, including Pfizer, AbbVie, **Merck & Co. Inc.**, **Roche** and **Amgen Inc.**. **Novartis AG** has since agreed to sell its minority stake in the consumer health joint venture with **GlaxoSmithKline PLC** for $13bn, which adds to its war chest for acquisitions. However, CEO Vas Narasimhan has expressed an interest in bolt-on deals and in building up the company's data/digital capabilities; Shire would be a surprising target for the Swiss firm.

AbbVie was on the verge of buying Shire for $55bn in 2014, but withdrew its offer after the Obama Administration's tax rule change to crack down on the gathering trend for so-called tax-inversion mergers, a tactic used by US firms to shift their domicile to that of an acquired firm and thus break free of the unattractive tax regime endured by US-domiciled companies. The Trump Administration's tax reform legislation passed late 2017 has eased the US corporate tax rate, however.

Since then, though, AbbVie has been coming under increasing pressure to define its longer-term prospects, especially since not everyone shares CEO Richard Gonzalez's longer-term bullish views on eventual biosimilar erosion of the company's cash cow, *Humira* (adalimumab) – the world's best-selling drug, with 2017 sales of $18.4bn. AbbVie has seen its own share price rise significantly since the end of 2014 but just last week it took a major hit, falling 13% on March 22, its single biggest daily fall since listing, after it reported disappointing Phase II lung cancer data for *Rova-T*, one of the drugs earmarked as a multi-billion blockbuster to help offset the eventual decline of Humira. The news once again highlighted AbbVie's vulnerability.

PFIZER'S POTENTIAL MOTIVATIONS

Pfizer CEO Ian Read has made no secret of the fact that the company is in the market for transformative transactions, so it should not be ruled out as a potential rival to Takeda. However, Shire may not be the best fit for the company. Shire's Irish domicile gives it a low tax rate, but that is a less attractive incentive in the aftermath of US tax reform. Nevertheless, Shire could give Pfizer a welcome boost in rare diseases, an area it previously has flagged as one to build up.

Shire confirmed on March 28 that it had not yet received an approach from Takeda. The Japanese pharma has until April 25, 2018, to announce either a firm intention to make an offer, or that it does not intend to make an offer, under the rules of the London Stock Exchange.

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Availability More Than Strategy Driving Takeda's Shire Interest?

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Takeda Pharmaceutical Co. Ltd.'s ambitions of becoming a major global Japan-based pharma company could take another turn if it decides to confirm an offer for **Shire PLC**, which would open up new frontiers in rare diseases and further build out its limited late-stage pipeline.

But any such move also appears to go against some of the past signals and stated intentions of Japan's largest pharma firm, raising questions around the reasons behind any formal bid for the UK-based company, the go/no-go deadline for which is 5pm UK time on April 25.

So far, Takeda has confirmed it is only in the early stages of "considering making an approach to Shire" about a possible formal offer, in line with its open policy of continuous consideration of opportunities to enhance corporate growth and the pipeline, a statement that led to a spike in Shire shares on March 28.

Takeda's head office in Tokyo declined to make any further comments beyond those given in a formal statement, which said that that it sees any transaction strengthening its core therapeutic areas, specialty portfolio and R&D pipeline, driving financial value, and improving its US presence to "align with the market opportunity" there.

STICKING BY CRITERIA?

Takeda has not been shy of making major acquisitions in the past, spending tens of billions of dollars to put Millennium, ARIAD and Nycomed under its roof, along with TiGenix, Syrrx and a slew of other smaller deals over the years. The first two were aimed at strengthening its position in oncology, now a core area of focus along with gastrointestinal, neuroscience and vaccines. But with estimates running up to $70bn, any bid for Shire would be in a different league and by far its biggest ever M&A deal; and Takeda's current cash and equivalent holdings are less than a tenth of that figure, raising analyst concerns over financing.

General investors also seem to have mixed views on the prospect of a deal, with Takeda's shares falling by around 6.8% to JPY5,158 ($48.38) in morning trading in Tokyo on March 29. While a bid could take the company into the global top 10 pharma firms by revenue, financing and strategic fit concerns appeared to be weighing heavily.

Weber has always stressed that there are strict criteria for any M&A transaction, including financially that it must not adversely affect Takeda's credit rating or policy for dividends.

Current CEO Christophe Weber has always stressed that there are strict criteria for any M&A transaction, including financially that it must not adversely affect Takeda's credit rating or policy for dividends. One question being asked is therefore how Shire could be swallowed without changes to this position.

Geographically also there appears to be some misalignment with past stated strategy. Takeda's apparent focus for its next deal appeared to have been on creating a "balanced footprint" in Asia and the emerging markets, and the company said more than a year ago that it had set aside a budget of around $450m for a small potential emerging market deal. There has been consistent speculation about a transaction in India or China.

Any bid for Shire would therefore seem to detract from this intended development track, as geographically, the main advantage would come from Shire's existing position in the US, where Takeda already has a strong business but may see potential from high-priced specialty drugs.

THERAPEUTIC ALIGNMENT?

Therapeutically, while an acquisition would bring Takeda a desired increased commercial presence in the global specialty medicines area through Shire's marketed products, some of these – for example in hemophilia and dry eye – are outside its current main focus areas, which it has said in the past it has considered very carefully on a global basis.

In R&D there is perhaps a stronger case, given that Takeda has said it is refocusing on specialty areas. It has relied mainly on rejuvenated internal labs and in-house research effort over the past few years to achieve this, along with around 75 academic and industry partnerships signed over the same period.

But the late-stage R&D pipeline is still far from overflowing and is dominated by oncology, namely the ALK inhibitor brigatinib, antibody-drug conjugate brentuximab vedotin, and proteasome inhibitor ixazomib, and Shire would certainly bring more strength to the general portfolio. Shire's investigational assets such as SHP 647 for ulcerative colitis, which would complement Takeda's commercialized would-be blockbuster *Entyvio* (vedolizumab), might therefore be an attraction.

Neither should commercial and revenue pressures be discounted. The first US generic competition to multiple myeloma drug *Velcade* (bortezomib) is due to start in November (litigation notwithstanding), bringing close to a billion dollars in market revenues under threat.

Takeda's current Vision 2025 business plan envisages sustaining growth year-on-year and it may see Shire as a way of ensuring this against this tide, despite reservations about the strategic fit both geographically and therapeutically.

Perhaps the increasing rarity of a sizable company being available at a reasonable valuation is what is driving Takeda's interest; maybe its last and best chance in a potential bid for global glory. But for now, all the suitor is stressing is that there is no certainty that an approach, even if made, will actually lead to any transaction.

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Japan Nod Positive For Hemlibra But Shadows Linger

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Japan's Ministry of Health, Labour and Welfare has issued a conditional approval to **Chugai Pharmaceutical Co. Ltd.**'s first-in-class antibody *Hemlibra* (emicizumab), for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with congenital Factor VIII deficiency (hemophilia A) who have Factor VIII inhibitors.

The product is approved in a range of once-weekly subcutaneous injection formulations from 30mg to 150mg and is awaiting a reimbursement price to be granted under Japan's national health insurance scheme, after which it can be launched nationally. This usually happens within several months.

Shutterstock: Natalie Ilina

The Factor VIIIa-mimetic bispecific monoclonal antibody binds to Factor IXa and X to provide the cofactor function of Factor VIII, and was developed using Chugai's in-house technology. It's current business plans envisage expediting commercialization and use in a variety of settings to maximize access and sales, and the company recently told *Scrip* that the product is expected to become an important growth driver globally.

After simultaneous filings in the US, EU and Japan, Hemlibra was approved in the US (where it has orphan and breakthrough status) last November through the **Genentech Inc.** arm of Chugai's global partner and majority owner **Roche**, and was approved by the European Commission (through Roche) this February, in both cases for patients with Factor VIII inhibitors.

Although the company has so far stopped short of providing global sales projections, Datamonitor forecasts worldwide sales of $1.15bn in 2025 in the US, Japan and five major European markets. The subcutaneous injection, which gives a longer half-life and lower dosing frequency (initially once weekly but potentially once a month), is seen as a particular benefit for patients.

Globally, emicizumab has the potential to "revolutionize" hemophilia treatment by a single drug, Datamonitor says, as it may be used by patients in multiple settings. Chugai also points out that emicizumab is effective regardless of the existing presence of Factor VIII inhibitors, which it also has a low likelihood of inducing. 25-30% of severe hemophilia A sufferers develop inhibitor antibodies to Factor VIII replacement therapies, after which treatment with such therapies becomes compromised.

JAPAN CONDITIONS

The new Japanese approval is based on the previously reported HAVEN 1 study in adolescents and adults and the HAVEN 2 study in children under 12, both of which showed reduced bleeds in inhibitor patients.

In Japan, around 5,000 people suffer from hemophilia A, and Datamonitor predicts sales in this country alone will reach $352m in 2025; Chugai is predicting a modest JPY2bn ($19m) globally for emicizumab this calendar year.

As a condition of approval, the ministry has required a risk management plan, and all-patient postmarketing surveillance data to be collected in around 100 people initially, and until it is satisfied about safety and efficacy and over whether additional post-launch data are needed.

This is a common requirement for novel drugs and aims to confirm limited clinical trial data in a wider population of actual patients.

GLOBAL PLANS, FACTORS

Chugai has conducted a suite of supporting studies, and the HAVEN 3 Phase III trial in adolescent/adult non-inhibitor patients receiving episodic or prophylactic Factor VIII agents and emicizumab in weekly and every two week dosing regimens reached its primary bleeds and key secondary endpoints last November. Positive interim results from HAVEN 4 in non-inhibitor/inhibitor patients with dosing every four weeks were reported in December.

Chugai says filings in the three major markets for haemophilia A patients without inhibitors is a priority to help maximize emicizumab in its potential indications.

On the downside, Datamonitor notes that the antibody is not in development for hemophilia B (given that it specifically mimics Factor VIII), and is unlikely to developed as an on-demand therapy as intravenous Factor VIII or VIIa or other bypassing agents would be quicker and more cost-effective in this situation. (The Japanese label states specifically it should not be used for on-demand hemostatic treatment.)

One other possible cloud is that one death, from rectal haemorrhage, was reported in HAVEN 1, raising doubts over whether concomitant use of bypassing agents results in increased thrombosis risk.

Such concerns "may thus affect the drug's uptake among the hemophila A population, particularly in the inhibitor segment," Datamonitor states. Roche and Chugai may therefore need to work to provide reassurance on the safety profile and mitigation strategies, it adds.

Another overhanging cloud in the US is an injunction by Shire subsidiary Baxalta Inc. against the sale of Hemlibra there, in a dispute relating to patent rights.

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Amazon And The Case For Major Health Care Disruption

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When it comes to **Amazon**'s anticipated expansion into health care, insights are only speculation, but experts at CNBC's Healthy Returns conference in New York on March 28 made the case for major disruption. From drug delivery by drone to breaking the insurance formulary model altogether, panelists talked about some of the changes the online retailer could bring to the sector.

Amazon, with its broad consumer reach, best-in-class distribution model and foothold in technology, could be a formidable competitor to some in the drug distribution system. In other cases, Amazon could be an interesting partner. For drug manufacturers, the entry of Amazon into health care could present new opportunities for cutting costs out of the system and getting drugs to patients in a more convenient way.

Faisal Mushtaq, the CEO of pharmacy data aggregator **Truveris**, said Amazon has a unique opportunity to fundamentally disrupt the health care delivery system, because big changes will not negatively impact its top and bottom line the way it would impact existing health care players.

"Amazon and other innovators – it could be Google, for example – have an ability to disrupt things because they are not moving any of their cash," he said. "They have enormous potential to aggregate the demand side, which is all the employers, and potentially cash-paying customers, and then all the suppliers, which are the pharmaceutical companies."

The biggest potential changes are probably years out, however. "I think they have a big play, and I think they are still in the formative stages, [figuring] out what they are going to do," he said.

Julie Grant, a partner at the health care investment firm Canaan Partners, said Amazon appears to be putting in place an infrastructure for broad expansion in health care. She pointed to some of the company's recent hires like Missy Krasner, the former managing director of data solution provider **Box**'s health care and life sciences group, as laying the foundation for big health care expansion.

"We've seen the sales force team expand to the life sciences sector, where they are now storing data for large amounts of genomics sequencing," Grant said. "It hints at a strategy to have an infrastructure play across the entire health ecosystem."

Amazon, of course, has been keeping its health care plans hush-hush. The company did reveal a partnership with investment firm Berkshire Hathaway and banking giant J.P. Morgan in January to explore initiatives to lower the cost of health care and improve the quality of care for employees. But even those plans are being held close to the vest.

THE BUSINESS MODELS MOST AT RISK

Some industry observers have speculated that the highly regulated drug distribution and reimbursement models are too complicated for a novice like Amazon to wade into too deeply.

But the panelists at the CNBC conference said they think Amazon has a long-term view and that the US health care system is craving disruptive change that will take costs out of the system and make health care delivery more convenient. Additionally, any initiatives to improve price transparency around drugs and other health care services would be welcomed by patients, the panelists noted.

"Even if the state-by-state regulations on drug distribution are complex and how you get a pharmacy license, and all of these bells and whistles behind the scenes, I think these guys can do it," Grant said. She said she would advise Amazon to focus on a single simple solution initially that could impact millions of lives to build trust – something as simple as offering a fixed price for an expensive generic drug and taking it out of the PBM structure.

Harvard Business School fellow and former **Medtronic PLC** CEO Bill George, agreed the PBMs and other middlemen are the most at risk from Amazon. He pointed to wholesalers like **McKesson Corp.**, **Cardinal Health Inc.** and **AmerisourceBergen Corp.** as potential casualties of an Amazon health care entry.

"That is an incredible level of distribution. We don't need all of these layers in the system, and we need to do much more directly, and why shouldn't we," he said. "I have my prescription from my doctor. Why shouldn't I be able to receive the medications directly?"

Insurers and PBMs are already in the midst of intense consolidation. Most recently, the health insurer **Cigna Corp.** announced plans to buy **Express Scripts Holding Co.**, the largest independent PBM in the US for $67bn in cash and stock.

"I think that was a movement out of weakness, and not of strength," George said of the proposed Cigna/Express Scripts merger.

Sweeping changes would require a longer view and broader changes to the US health care system.

BIGGER CHANGES REQUIRE BIGGER CHANGES

"If Amazon is going to get really advanced in terms of pricing and giving us that transparency, we actually need a change in the insurance product structure," Grant said. "A self-insured employer with a lot of demand can do that, but it requires a very big change in the way we administer benefits."

"We have a lot of really broken systems in the US health care system that have bad problems trying to solve bad problems," she added. "They really could change that. It's not going to happen tomorrow, but they could basically make PBMs irrelevant."

Thinking long-term, Mushtaq also speculated about potential changes to insurance structures. "Maybe we are looking at a future where there is an open market where – way down in the future – there is a spot market for prices where pharmaceutical companies are bidding for business for employers and their patients in real-time based on net prices," he said.

He said he hoped Amazon wouldn't resort to improving a broken system. "Don't try to optimize on the edges," Mushtaq advised. "You have an opportunity to redo, to replace the architecture."

For now, George said speculation about Amazon will move others to action, calling it the "Amazon catalyst."

"They will catalyze a lot more activity, catalyze value-based health care and catalyze employers to get involved," he said.

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FDA Refuse-To-File Letter Delays Alkermes Depression Drug

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Alkermes PLC's hopes to launch a potential blockbuster depression drug later this year have been dashed. The company announced April 2 that it received a refuse-to-file letter from the US FDA for a new drug application (NDA) for ALKS 5461 for major depressive disorder in patients with an inadequate response to standard antidepressants.

The FDA is requesting additional clinical trials before reviewing the application, which suggests a lengthy delay and is particularly problematic for Alkermes given that several other drug developers are circling in on the treatment-resistant depression market.

The refuse-to-file (RTF) letter surprised some investors mainly because management has sounded confident about FDA acceptance and approval later this year, though some investors had remained skeptical because of the data package. During the company's fourth quarter call in February, CEO Richard Pops talked about 2018 as being a year of investment to lay the foundation for growth ahead of the launch of ALKS 5461.

The company's stock opened 19% lower on April 2 on the news at $46.75, and closed down nearly 33% at $45.23. Investors will not be reassured by the fact Pops sounded so surprised about the turn of events during a same-day conference call.

"We have had many interactions with FDA over many years, culminating in a pre-NDA meeting last summer, which led to the commencement of our rolling submission," he said. "While we expected there to be questions during the review process, in none of these interactions did FDA raise concerns which would lead us to expect an RTF."

Alkermes initiated the rolling NDA submission in August 2017, a pathway open because the drug had a fast track designation from the FDA, which is intended to help facilitate a faster review of drugs that treat serious conditions or address unmet medical needs. In that way, the letter is unexpected because Alkermes had the opportunity to meet with the FDA and agree on the content and timing of the NDA submission.

At the same time, some investors and analysts had remained skeptical that the FDA would approve the NDA based on the results of a single Phase III trial. The regulatory approach was considered risky since one trial, FORWARD-5, was positive, but two prior Phase III trials had failed.

The package included data from four randomized placebo-controlled studies, including Phase II studies, with over 1,500 patients. Another Phase III trial is ongoing. As Barclays analyst Douglas Tsao put it in a same-day research note, "While we didn't think approval of ALKS 5461 was a certainty, we're surprised that the FDA refused to accept the NDA to review based on a lack of sufficient evidence considering Alkermes' management's confidence in recent months."

MORE CLINICAL STUDIES NEEDED

The letter cites concerns from the FDA about insufficient evidence of overall effectiveness, which doesn't bode well for a quick turnaround of the NDA. A substantial delay could put Alkermes at a competitive disadvantage, given that several rival drugs are advancing through late-stage development in depression, including **Johnson & Johnson**'s esketamine for treatment-resistant depression and **SAGE Therapeutics Inc.**' brexanolone for postpartum depression.

Evercore ISI analyst Umer Raffat highlighted the competitive dynamics in an email to investors. "This FDA delay compresses the timelines further amidst several competitor programs making meaningful progress in the depression space," he said. "As a result, we are lowering our peak sales potential (and probability of success) to $800m from $1.2bn."

The FDA is requesting additional clinical trials be completed for ALKS 5461 prior to resubmission. The agency has also requested a bioavailability study be conducted to generate additional bridging data between ALKS 5461 and the reference drug buprenorphine.

"This is surprising and troubling to us," Pops said, since the results of the data had been previously shared with FDA in two separate meetings and presented at a major medical meeting.

"FDA did not express their view that the evidence of effectiveness was insufficient to support a full review of the NDA," he said. "We obviously disagree with FDA's conclusions, and we expect them to only render final judgement after a complete review of the NDA."

Alkermes plans to appeal the FDA's decision. Pops said the company will immediately request a Type A meeting with the FDA to determine the next steps. The company said it may also need to revise its 2018 financial guidance.

The company forecast in February that revenues would grow to $975m to $1.015bn this year, driven by currently marketed drugs *Vivitrol* and *Aristada*, but Alkermes also expected a substantial increase in SG&A expenses driven by commercial investment in ALKS 5461.

ALKS 5461 is a novel oral medicine that acts as an opioid system modulator. It is positioned as an add-on therapy for patients with MDD who don't respond adequately to current therapies. It is a fixed-dose combination of the partial mu-opioid receptor agonist and kappa-opioid receptor antagonist buprenorphine and a mu-opioid receptor antagonist samidorphan.

This is the second publicly announced high-profile RTF letter handed out by the FDA recently. **Celgene Corp.** received a RTF for an application seeking approval of ozanimod in multiple sclerosis in February.

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Pfizer May Enjoy Cardiomyopathy Success With Tafamidis

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Pfizer Inc. may have an unexpected blockbuster opportunity on its hands, as it reported significant cardiovascular outcomes data March 29 from a Phase III study of tafamidis meglumine in transthyretin-mediated cardiomyopathy. Approved overseas as *Vyndaqel*, tafamidis has been tied up since 2012 at the US FDA for the related indication of familial amyloid polyneuropathy (FAP). Informa Pharma Intelligence's Biomedtracker called the top-line data from Pfizer's Phase III ATTR-ACT study "quite encouraging," while an Evercore ISI analysis hailed the findings as "a very rare late-stage pipeline surprise … especially for Pfizer." Evercore analyst Umer Raffat added in his March 29 note that Pfizer could realize peak annual sales above $1bn for tafamidis in cardiomyopathy, from a drug that analyst consensus values at virtually nothing.

Although tafamidis is available in Europe and Japan as an approved therapy for transthyretin familial amyloid polyneuropathy, the FDA issued a complete response letter related to its US regulatory filing in June 2012, requesting a second efficacy study to establish substantial evidence of effectiveness.

Asked about its regulatory plans now for tafamidis, a Pfizer spokesperson told *Scrip*, "We are currently reviewing the full dataset and look forward to engaging with health authorities on these data, including the FDA." There is no approved drug therapy for transthyretin cardiomyopathy.

The Pfizer data came one day after **Alnylam Pharmaceuticals Inc.** revealed subgroup analysis data from its Phase III APOLLO study of patisiran showing that the RNA-interference drug candidate was associated with significant improvements in measures of cardiomyopathy, such as cardiac structure and function. Alnylam has patisiran under regulatory review for hereditary transthyretin-mediated amyloidosis (hATTR) in both the US and EU.

Patisiran is being assessed in the US under priority review with breakthrough therapy status for hATTR; it has a PDUFA date of Aug. 11. **Ionis Pharmaceuticals Inc.**'s antisense candidate inotersen also is under review in the US and EU for hATTR, with a July action date in the US.

POOLED FOR TWO DOSAGES

Unlike Alnylam's intravenously administered candidate, tafamidis is a once-daily, oral meglumine salt. Approved elsewhere in a 20 mg dose, the 441-patient ATTR-ACT study employed three arms, investigating both 20 mg and 80 mg daily doses of tafamidis against placebo. Pfizer said pooled data from the two cohorts receiving study drug demonstrated a statistically significant reduction in the combination of all-cause mortality and the frequency of cardiovascular-related hospitalizations after 30 months compared to placebo.

Pfizer pointed out that transthyretin cardiomyopathy is believed to be substantially under-diagnosed, as well as a disease of significant mortality. The average life expectancy following diagnosis ranges from three to five years, the pharma said.

Mat Maurer, a Columbia University trial investigator, noted in the company's top-line data announcement that right now clinicians are limited to managing the symptoms of transthyretin cardiomyopathy

In his note, Evercore's Raffat said the Pfizer trial was undertaken at very high risk, because of previous trial failures in this indication and because the primary endpoint measured outcomes. One notable failure in transthyretin cardiomyopathy came in 2016 when Alnylam's revusiran, a predecessor to patisiran, failed a Phase III study in hATTR with cardiomyopathy due to an imbalance in mortality, causing the Boston-area biotech to shelve the drug.

Raffat added that key questions remain about the Pfizer data, including a need for clarity on how the 20 mg dose performed compared with the 80 mg dose. If Pfizer determines that an 80 mg dose is needed for optimal efficacy, however, this could give the pharma an opportunity at a longer patent life beyond the 2029 expiry for the 20 mg dose and enable it to price the drug differently than the roughly $180,000 annual charge for Vyndaqel in Europe.

He also said that further examination of the data should clarify whether the drug provided a clear benefit on all-cause mortality, suggesting that using mortality and hospitalization as a combined outcomes endpoint yielded a less clear result. Assessing the drug's market potential for the transthyretin cardiomyopathy indication, Raffat tied together a separate pair of estimates – Pfizer's projection that the disease has a less than 1% diagnosis rate currently and that there may be about 1,000 diagnosed patients worldwide, along with Alnylam's estimate of roughly 40,000 cases globally of hereditary familial amyloidotic cardiomyopathy. Put together, this enabled the analyst to model a peak of 5,000 diagnosed patients. If 30% of those were treated with tafamidis and the drug was priced at $750,000 a year, that could yield peak sales of $1.125bn, Raffat said.

Biomedtracker's analysis brought up concerns similar to Raffat's in terms of a deeper understanding of the efficacy data. "More details are needed on the magnitude and how much each [cardiovascular outcome] component was impacted," it said. "It will also be interesting to see if there are any differences in subgroups with the hereditary and wild-type forms, both of which were included in the study."

The Alnylam data, part of a presentation at the International Symposium on Amyloidosis in Tokyo March 28, showed that for 56% of the APOLLO enrollment that met predefined cardiac requirements (n=126), patisiran showed statistically significant improvement compared to placebo in cardiac structure and function measures of cardiomyopathy.

In addition, the drug produced a significant reduction in levels of a cardiac stress biomarker, NT-proBNP, at nine and 18 months compared to placebo. Alnylam pointed out both that cardiomyopathy is the leading cause of death in patients with hATTR amyloidosis and that higher levels of NT-proBNP are associated with increased mortality in cardiac amyloidosis patients.

JMP Securities analyst Michael King said in a March 28 note that these findings support JMP's expectation that patisiran will be used in hATTR patients with cardiomyopathy.

Biomedtracker's analysis of the Pfizer data suggested that patisiran and Ionis' inotersen might compete with tafamidis for cardiomyopathy use, even if approved specifically for polyneuropathy, because many hATTR patients will develop polyneuropathy and cardiomyopathy as their disease progresses.

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J&J Price Pledge: Average Doesn't Tell The Whole Story

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Johnson & Johnson's Janssen unit issued a US Transparency Report earlier this month that touted a 4. 6% year-over-year decline in average net price of its drugs in 2017 due to discounts and rebates to payers and providers. While Janssen's report did not include price changes for individual drugs, Bernstein analysts looked at figures on specific products and concluded that the average was pulled down by drugs affected by generic and biosimilar competition, not just discounts forced by pharmacy benefit managers.

"Our cursory look suggests the price decline has nothing to do with PBMs [pharmacy benefit managers] and more to do with asset mix and the way JNJ chose to calculate things," Bernstein analyst Ronny Gal said in a March 26 note.

Gal points to price changes on six drugs, which J&J says represent less than one-third of its US sales in 2017.

Janssen reported that its average list price (wholesale acquisition cost) increased 8.1% in 2017 while the average net price (wholesale acquisition cost minus rebates, discounts and returns) declined 4.1%. The company said that payers drive deep discounts and rebates in today's competitive marketplace.

Gal pointed out that the company's average sales price (ASP) declined for products facing competition while J&J raised prices materially where it could, notably for the multiple myeloma treatment *Darzalex* (daratumumab) and the cancer drug *Imbruvica* (ibrutinib), which it shares with **AbbVie Inc**.

In 2017, J&J reported US sales of $884m (an 87.2% year-over-year increase) for Darzalex and $881m (a 37.2% increase) for Imbruvica. Gal stated that the price of Darzalex was raised 7.5% in the last 12 months and Imbruvica was up 9.7%, and both products have no (or very limited) commercial rebates.

Those increases fall within J&J's pledge to keep annual price increases to less than 10%.

The ASP, which is reported by the Centers for Medicare & Medicaid Services, is a calculation of the weighted average of manufacturer's sales price for a drug for all purchasers, net of price adjustments like rebates. The ASP reporting has a six-month delay.

As for drugs facing competition, Gal said that in the second half of 2017, the average sales price of *Remicade* (infliximab) began to come down because of biosimilar competition. The ASP for April 1, 2018 is 83.287 versus 87.149 for Aug. 30, 2017, a 4.4% decline, he stated. Accounting for the six-month delay in ASP reporting, he said the price began to decline in the third quarter of 2017.

Remicade was 21% of J&J US pharma sales in 2017, the company confirmed. In its fourth quarter and full year 2017 sales and earnings report, J&J reported Remicade sales dropped by 9% for 2017 to $6.3bn and 10% to $1.5bn in the fourth quarter.

Gal said J&J included branded *Concerta* (methylphenidate extended-release) in its math, where prices declined 50% in 2017 in a generic market. He also said J&J had to give material discounts on its diabetes drug *Invokana* (canagliflozin) ($994m) where Lilly's SGLT2 had better results, and it discounted *Eprex* (epoetin alfa) ($675m) to lock contracts away from Roche's *Mircera* (methoxy polyethylene glycol-epoetin beta).

"In short, JNJ has ran into few tough competitive situations and accounted for products facing generic/biosimilar competition in its product mix," Gal stated. "More than a statement on pricing trend, it is a reminder that pharma is by far the most sophisticated player when it comes to presentation of data and managing the public debate on pricing."

Asked about the source of his data, Gal said that for Remicade he used the reported ASP from CMS and for the realized price of Concerta he used the reported US revenue divided by total prescriptions from IMS (now **IQVIA**). For J&J's oncology drugs he used the list prices from Price Rx.

In response to Gal's note, Janssen said in a statement that the data disclosed in its second annual US Transparency Report clearly demonstrate that in 2017 the aggregate net price of its medicines in the US decreased. "Our analysis takes into account relative product sales volume in the calculation of aggregate price change. While price changes varied by product, as a whole our net price realized was -4.6%."

The statement adds, "The Bernstein analysis mistakenly concludes that our negative price change was driven by changes in the price of a select set of products that represent less than 1/3rd of our US sales. It's important to note that in addition to negotiated discounts and rebates we pay across our broad portfolio, all products sold to many government programs are subject to mandatory discounts.

"Furthermore, because Remicade (infliximab) faced increased marketplace competition and corresponding downward pricing pressure in 2017, we made the point in our Transparency Report that even excluding Remicade our aggregate price change was negative."

STATE LAWS REQUIRING MORE TRANSPARENCY

J&J is among several companies that began issuing reports on average list price and average net price changes last year. The information comes as the pharma industry has faced sharp criticism for drug costs and a growing number of state laws are requiring more detailed disclosures about drug pricing.

Oregon Governor Kate Brown (D-OR) signed the latest bill into law on March 13. The measure, HB 4005, requires manufacturers to annually report to the state's Department of Consumer and Business Services on the prices of prescription drugs and costs associated with developing and marketing them. Drug makers must report information when the price was $100 or more for a one-month supply or for a course of treatment lasting less than one month, and if there was a cumulative increase of 10% or more than the price of the drug during the previous calendar year.

At least five other states have enacted drug pricing laws in the last two years, including California, Vermont, Florida, Louisiana and Nevada, and numerous other states have introduced similar bills.

In December 2017, the Pharmaceutical Research and Manufacturers of America filed suit to block implementation of California's law, SB 17, which requires manufacturers to provide 60-day notice to purchasers if the price of Rx drugs with a wholesale acquisition cost (WAC) of more than $40 for a course of therapy increases more than 16% over a two-year period. The reporting requirement went into effect on Jan. 1.

Politico reported on March 25 that companies have begun reporting WACs to California purchasers in response to the law.

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Ipsen Dreams Of Capital Position In Oncology

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Sotirios Stergiopoulos

Ipsen is putting words into action to become a "powerhouse" in oncology drug development; the company will sign new deals soon to bring in external innovation into its reorganized R&D unit.

Sotirios Stergiopoulos, Ipsen's global medical affairs and chief medical officer, R&D, told *Scrip* in a recent interview that Ipsen has been working in oncology since the '80s but lately has upped its efforts in this space.

"Between the experience and innovation that we have we are now considered one of the world's top 20 pharma specialists in oncology," Stergiopoulos said, adding that Ipsen still wants to improve its position against its oncology peers.

Cabometyx (cabozantinib), a product partnered with **Exelixis Inc.**, is set to become the backbone of Ipsen's oncology portfolio. "Cabometyx has a huge role and what is critical for us is that it keeps moving forwards in new indications and as we expand our pipeline," Stergiopoulos said, adding that the ability to combine Cabometyx was key.

In the US, the drug is approved for thyroid cancer and first- and second-line renal cell cancer (RCC). Furthermore, a filing has 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, and recently won a CHMP recommendation for the drug in first-line RCC. It is also approved for thyroid cancer in Europe.

Still, Stergiopoulos, who is also president of the board of governors of the Accreditation Council for Medical Affairs (ACMA), said "the strength of any company's pipeline, especially companies in oncology, is the use they can get not only as single agents but also from combining their pipeline."

Ipsen was moving at "lightspeed" to gather information, enrich its pipeline and attract some of the best people in the field, Stergiopoulos said."We have our goal of becoming a research and development powerhouse. We have added a significant amount of people to the company that are leaders in the oncology world, in R&D and in our commercial organization," he said.

Among several recent executive appointments at Ipsen, in 2017 the company named Harout Semerjian president and head of specialty care international region and global franchises. Semerjian joined the company from **Novartis AG**, where he focused on oncology and specialty care; in his last role at the Swiss big pharma Semerjian was senior VP and global launch head of breast cancer therapy *Kisqali* (ribociclib).

As well as Cabometyx, Stergiopoulos highlighted *Onivyde* (irinotecan sucrosofate), partnered with **Shire PLC**, as an important brand for Ipsen's oncology strategy. The drug is approved in pancreatic cancer and is in late-stage development for small cell lung cancer; other early-stage trials are ongoing in gastric and colorectal cancer and solid tumors.

"More than 30 studies over the past 10 years failed in pancreatic cancer and there had been no formal approvals for new therapies in pancreatic cancers for a long time," Stergiopoulos note when talking about Onivyde progress so far.

Ipsen "has very solid programs moving forwards and we are going to be contributors to the oncology space for many years to come," Ipsen's CMO said.

DEALS, DEALS, DEALS

In order to achieve its ambitious goals though, Ipsen – like many of its pharma peers – needs to replenish and expand its R&D pipeline. The company expects to agree licensing deals or small asset acquisitions in oncology in the coming year to grow its development portfolio. Currently, around 86% of Ipsen's sales come from specialty care products and 60% of these sales come from its oncology brands.

"We are open to licensing and acquisitions, we are looking at how potential new treatments can move forward and be complementary to our pipeline," Stergiopoulos said.

This time around, the ideal license agreement would be more of a global deal, unlike its setup with Exelixis for Cabometyx. Under their 2016 pact, Ipsen holds the exclusive commercialization rights for current and potential future cabozantinib indications outside of the US, Canada and Japan. "We'd like more of a global deal but its dependent on the asset and partnership. We value our partners significantly, as shown through our work with Exelixis," he noted.

Ipsen is open to different deal options and modes of action in oncology, Stergiopoulos said the company was assessing both broad cancer treatments and immuno-oncology approaches. "We're going to take it compound by compound," he said.

The company's preference is mid- to late-stage investigational cancer therapies, but it won't turn a blind eye to earlier stage oncology assets. "You never know what you might end up missing if you exclude earlier stage programs," Stergiopoulos added.

Success of a powerhouse R&D company looks like an effective and efficient R&D pipeline that brings therapies to patients sooner rather than later, he said. "I'd like to see significant momentum to keep going, to further deliver on our already strong growth."

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Edge 'Devastated' By Phase III Failure of EG-1962, Set To Downsize

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Edge Therapeutics Inc. was left with a decimated stock price on March 28 after announcing that its only clinical candidate, EG-1962 (nimodipine microparticles), failed in a Phase III study in aneurysmal subarachnoid hemorrhage, due to better-than-expected performance in the control arm.

Developed with the company's *Precisa* technology platform, EG-1962 is a novel polymeric microparticle containing nimodipine suspended in a diluent of sodium hyaluronate administered through an external ventricular drain. The drug has had fast track and orphan drug designation with the FDA.

Subarachnoid hemorrhage is bleeding in the area between the brain and the thin tissues that cover the brain. In 75% of cases, the condition results in brain damage or death.

The calcium channel blocker nimodipine is available as an oral therapy in generic and branded form and represents the standard of care.

Generic nimodipine gel capsules have caused problems in the past because health providers were extracting product from the capsules with a syringe, to administer the drug intravenously instead of with the oral syringe as intended, resulting in life-threatening medication errors. **Arbor Pharmaceuticals Inc.**'s *Nymalize* was approved in 2013 for use as an oral solution of nimodipine, eliminating the use of needles and promising safer administration.

The biodegradable polymer-based design of EG-1962 was intended to support sustained drug exposure for 21 days with a single dose. That compares to dosing every four hours for 21 days for standard-of-care nimodipine. It was also thought that Edge's therapy would offer better a better safety profile.

The Phase III NEWTON 2 study was designed to test EG-1962 with oral placebo against oral nimodipine with a single dose of intraventricular normal saline in 374 patients with aneurysmal subarachnoid hemorrhage. Treatment was given for up to 21 days. The primary endpoint was the proportion of patients with a favorable outcome – defined as a score of 6 to 8 on the Extended Glasgow Outcome Scale at the 90-day mark. The goal was to show a statistically significant 18%-20% improvement for the primary endpoint at the time of an interim analysis and a 10%-15% improvement by the end of the study.

In a Feb. 20 note modeling peak US sales of $350m, Credit Suisse analyst Martin Auster had said that even a 5%-10% absolute improvement on favorable outcomes on the Extended Glasgow Outcome scale would be "clinically meaningful and support broad adoption."

EFFICACY ENDPOINT TO BE MISSED

However, the company announced March 28 that following treatment of the first 210 trial participants, the drug had a low probability of hitting the primary endpoint, based on the outcome of a prespecified interim analysis. An independent data monitoring committee recommended that the study be stopped due to the low likelihood for demonstrating significant efficacy over control, but safety was not an issue in the trial, according to Edge.

"It's important to note the observed improvements in functional outcome in the control group were unexpectedly higher than response rates in past clinical studies with a similar patient population," CEO Brian Leuthner explained during a March 28 investor call. The exec said that the company is "devastated" by the outcome.

Edge will stop the study and will be analyzing the data going forward.

The company's stock price was a casualty of the NEWTON 2 news, plummeting by 91.6% to a close of $1.31 on March 28.

"Edge will assess the next steps for the company, but anticipates in the near term reducing the scope of its operations, including the size of its workforce, in order to preserve its cash resources, which were $88.1m as of Dec. 31, 2017," Edge said in a statement.

Chief Financial Officer Andrew Saik said the company has been spending about $4m to $5m per month and obviously needs to evaluate its cash burn going forward; the company will provide more guidance regarding a controlled shutdown of NEWTON 2 in May.

FAILURE TOOK EDGE BY SURPRISE

Edge said that the result was a surprise because the drug had demonstrated efficacy in the randomized, open-label, Phase I/II NEWTON study in a similar population of 72 patients with subarachnoid hemorrhage.

The company announced in February 2016 that the drug cut 3.5 days in time spent in the intensive care unit and doubled the likelihood of favorable outcomes. In the Phase I/II study, the median length of stay in the ICU was 13.5 days for those treated with EG-1962 vs. 17 days for nimodipine.

In the EG-1962 arm, 60% of participants had a score of 6 through 8 on the Extended Glasgow Outcome Score at 90 days vs. 28% on oral nimodipine. The patients in the EG-1962 arm also benefited from fewer cases of vasospasms, cerebral ischemia, use of rescue therapies and hypotension.

"At this time, we see limited opportunity for further development of EG-1962," JMP Securities analyst Jason Butler said in a March 28 note.

Aside from EG-1962, Edge only has one other candidate in its pipeline – EG-1964, which is a formulation of the pancreatic trypsin inhibitor aprotinin still in the discovery phase.

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Ablynx's Lupus Candidate Hits End Of Road

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Ablynx NV's anti-IL-6 nanobody, vobarilizumab, has failed to meet its primary endpoint in a Phase II trial in lupus and further development of the molecule is unlikely after patient deaths – the news is a blow to **Sanofi**, which recently agreed to acquire the Belgian biotech for its Nanobody platform technology.

In the Phase II STEADY trial, vobarilizumab failed to meet the primary endpoint of dose response at 24 weeks in patients with systemic lupus erythematosus (SLE). None of the treatment doses tested showed efficacy on the mBICLA endpoint (Modified BILAG-based Composite Lupus Assessment).

"We are disappointed that vobarilizumab didn't show a dose response in the analysis of the study's primary endpoint, however, vobarilizumab was well tolerated in all tested dose groups, confirming its favorable safety profile," Ablynx's chief medical officer, Robert Zeldin, said in a statement.

Ablynx will now analyze the full data set for vobarilizumab, which targets the interleukin 6 pathway, but analysts do not anticipate any further studies of the drug in lupus.

Despite lower treatment-related serious adverse events and infection rates in the vobarilizumab treatment groups compared to placebo (2% and 2.8% versus 6.5% and 6.5%), the discontinuation rate due to adverse events was higher for vobarilizumab (12.4% vs. 6.5%) in the Phase II trial.

Bryan, Garnier & Co analysts highlighted in a March 26 note that "two deaths reported in the vobarilizumab group are likely to stop further investigations of the drug in this indication."

Despite these safety issues in the STEADY trial, the analysts said Ablynx's deal with Sanofi was not at risk. They highlighted that Sanofi's offer mainly reflected the potential of caplacizumab in acquired thrombotic thrombocytopenic purpura (aTTP) and was not dependent on the outcome of the trial in lupus.

Sanofi's acquisition of Ablynx is expected to close by the end of the second quarter this year.

While vobarilizumab was not a key attraction for Sanofi, the Phase II asset held promise and therefore contributed to Ablynx's high price tag of €3.9bn.

END OF ABBVIE PACT?

Its deal with Sanofi stands strong, but analysts expect Ablynx's development partner for vobarilizumab, **AbbVie Inc.**, to definitively drop the drug candidate following the negative Phase II data in SLE. AbbVie will review the complete dataset from the Phase II STEADY SLE study

to determine whether to exercise its option to license vobarilizumab. Should AbbVie exercise the option, it would trigger a payment to Ablynx. If the option is not exercised, Ablynx's agreement with AbbVie would be terminated.

AbbVie had already decided not to exercise its opt-in for vobarilizumab in rheumatoid arthritis, because of the crowded and competitive market for IL-6 inhibitors in RA.

In July 2016, Ablynx reported positive Phase IIb monotherapy data for vobarilizumab in moderate-to-severe RA. The company said at the time, that Phase IIb results confirmed the favorable safety profile of vobarilizumab and the potential for convenient monthly administration. An open-label extension study in RA patients is currently ongoing (94% roll-over rate) and results are expected in the second half of 2018.

Data from the extension study, if positive, could help Ablynx secure a new partner for vobarilizumab in RA to replace AbbVie, or justify further development of the drug by Sanofi.

STEADY TRIAL DETAILS

The multi-center, randomized, double-blind, placebo-controlled Phase II STEADY trial was initiated in August 2015 and enrolled 312 patients with moderate-to-severe, active seropositive SLE across the US, Europe, South America and Asia.

Patients were assigned to one of four dose groups of subcutaneously administered vobarilizumab (75 mg every 4 weeks, 150 mg every 4 weeks, 150 mg every 2 weeks, 225 mg every 2 weeks) or placebo. Patients were evaluated for efficacy up to and including Week 48 and for safety up to and including Week 58.

The primary endpoint of the study was the percentage of patients who achieved a response at Week 24 according to the modified BICLA score – a composite measure of lupus disease activity across all body systems.

SLE is a complex, multi-organ, autoimmune disorder characterized by the production of pathogenic autoantibodies and tissue deposition of immune complexes, which result in widespread tissue damage.

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Sanofi's Keeney 'Open Dialogue' With Asian Start-Ups

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As young start-ups in the Asia-Pacific region make headway in developing new therapies in exciting areas such as gene therapy and immunology, large drug firms like **Sanofi** continue to watch the region's R&D horizon closely with an eye on potential collaborations. The French multinational is not averse to considering early-stage assets in its areas of focus, their generally higher risk profile notwithstanding.

Adam Keeney, Global Head, External Innovation and R&D Strategy at Sanofi, indicates that the company is not "overly concerned" about the risks that come with early-stage assets and is "very agnostic" as to where the partner is located. What is critical is the "opportunity, the excitement" around the technology or science and the "comfort" with the partnership/collaboration, he maintained.

"What is important is the quality of the asset. We have quite now an expertise in how to assess and evaluate early-stage opportunities. The APAC [Asia-Pacific] overall but particularly the markets of China, Korea and Japan provide a lot of promise and we are going to be, over the next year or so, thinking more about how do we increase our presence and investments in the area," Keeney told *Scrip* in a recent telephone interview. He also underscored the "thorough" due-diligence activity that precedes any potential deal.

Keeney referred to ongoing projects from companies in the APAC region, such as Sanofi's deal with **JHL Biotech Inc.** around novel biologics/biosimilars and a number of research collaborations with key institutions in China and Japan.

"That's a good testament to the fact that we had confidence in the company [JHL] to be able to bring forward the opportunities to fit with our strategy in the region, particularly in China. We have quite active efforts there in terms of understanding the science and where it is going, particularly in Japan where there is lot of strong immunology research that we are particularly interested in," he added.

In December 2016, Sanofi and JHL struck a deal to collaborate for the development and commercialization of biological therapeutics in China and with potential international expansion prospects. Sanofi acquired exclusive rights to JHL's proposed biosimilar rituximab and options to certain pipeline products.

OPEN DIALOGUE

Keeney also noted the increased start-up activity in China where a lot of new money is being invested. "We have good contact with a lot of those management teams understanding the assets they are working on. So, we have a good open dialogue with inventors, investors, entrepreneurs in that region."

Interestingly the young Chinese firm **Harbour BioMed**, which is focused on immuno-oncology and immunological diseases and has been in the spotlight over the recent past after it closed a Series A+ round financing, is led by ex-Sanofi executives. Harbour Biomed's founder CEO Dr. Jingsong Wang was previously Head, China Research and Development Center and the Head of Translational Medicine, Asia Pacific, at Sanofi.

Sanofi is also keen to build on its linkages with academia in the APAC region. Senior officials have previously indicated to Scrip that Sanofi expects to expand its iAwards program, which aims to help convert successful and high potential academic projects into sponsored research programs and subsequently create in-licensing and start-up opportunities, in Asia.

DIGITAL HUB

Meanwhile, Sanofi's R&D hub model also positions the APAC region as its digital hub and Keeney sees prospects for potential collaborations in the region and to use the opportunity that the region provides both in terms of patient access and clinical trial development.

"From the R&D perspective we are piloting novel technologies around patient recruitment, or thinking further about how we could generate novel sets of data; how do we think about APAC patient populations as opportunities to think about different types of treatments for different populations more locally leveraging the fact that we have a significant R&D infrastructure in the APAC region through the hub," Keeney explained.

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Welcome To The PBM Realm, Derica Rice and Andrew Witty

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Yet another exposé about the drug cost conundrum that the pricing strategies of pharmacy benefit managers (PBMs) pose for the industry was detailed mid-March in the Financial Times. This report, down to the penny, showed how many of the widely used drugs incur as much as a three-fold spread in their cost between the manufacturer and the consumer by the time all the middlemen interests are served. The FT investigation of the death of a 38-year-old Texas teacher who delayed filling her *Tamiflu* prescription when she was asked to pay at the upper end of this spread puts this conundrum in sharp relief.

This negative publicity came only a few days after two leading PBMs announced that they had persuaded experienced biopharma industry leaders to lead their organizations.

These two PBM appointments coincided with President Trump promising to unveil his healthcare cost control plans 'next month' - presumably in April 2018. This can be expected to complicate the vision and the strategy of these two pharma executives as they switch sides.

Derica Rice leaves his position as the CFO and EVP of Global Services at **Eli Lilly & Co.** in Indianapolis to become president of **CVS Health Corp.**'s Caremark PBM, where he will run operations as well as drive strategy, business development and client relationships.

Andrew Witty stepped down from his board position at UnitedHealth Group to become CEO of Optum, an increasingly important part of **United Healthcare Services Inc.** that includes its leading PBM unit. Witty was well known as the longtime CEO of **GlaxoSmithKline PLC** until he stepped down last year.

FURTHER IRONY

As ironic as these two appointments seem, the irony is only more striking when juxtaposed with the three industry veterans who are guiding healthcare policy for the US government: FDA Commissioner Scott Gottlieb, who worked with a long roster of biopharma, HHS Secretary Alex Azar, also from Lilly, and Joe Grogan, Associate Director for Health Programs in the Office of Management and Budget, who previously worked at **Amgen Inc.** and **Gilead Sciences Inc.**. These three are among the key advisers to President Trump in shaping the government plans to rein in healthcare costs.

Needless to say, the pace of change that promises (or threatens) to reshape the healthcare systems in the US only reflects the reshaping of the health care industry underway globally. China, for example, is feverishly rewriting the script as to how its citizens will obtain their healthcare. The nation is merging ministries, harmonizing regulations to global standards, and reducing import tariffs, among numerous initiatives. The EU, Japan, and many other countries are trying to reinvent their health care systems.

For the US health care system, the two PBM leadership changes only magnify the implications of two big mergers in this space, that of CVS acquiring the insurer **Aetna Inc.**, and **Cigna Corp.** acquiring the **PBM Express Scripts Holding Co.**, which more or less aim to mirror the business model of the UnitedHealth. Assuming the two mergers will be consummated, these two behemoths, along with Optum, will control a large part of healthcare for a majority of Americans, directing the way biopharma products are bought, distributed, priced, and paid for in the US. And these organizations also harbor ambitions to do the same beyond the US shores.

The biopharma industry is caught in the middle, hardly able to stay true to its business model, other than to continue to price its products higher, often just so that they can offer discounts attractive enough to land a spot on the formulary that one of these PBMs control.

WHAT GAMBIT?

Witty and Rice have lived through this landscape for more than a decade, but on the other side. Consumers may argue that it is difficult to distinguish which is the dark side, but these two now have an opportunity to put their principles into practice, and demonstrate the true colors of all the key stakeholders to everyone. The obvious question is why? Why would these two biopharma leaders join their industry nemesis? They have consistently argued how the rebates to which pharma companies are forced to agree lead to high list prices and distort the market place, while earning the industry a black mark.

The second question is what? What could Witty and Rice be expected to focus on as their legacy, now that they are closing the circle, moving from the industry to the PBMs?

A part of the answer emerges from the recent UnitedHealth announcement that it would begin passing through rebates at the point-of-sale in some of its healthcare insurance plans. Witty sat on the board of UnitedHealth at the time of this decision, and surely would have had some influence over it. All the other PBMs, including CVS Caremark and Cigna Express Scripts, will have no choice but to follow. Indeed, Aetna did so just days after. The industry trade group PhRMA has advocated such a rebate pass-through as a means of lowering drug spending, and in the process better aligning list prices with market forces.

Having influenced this rebate pass-through decision while on the board, Witty would now have to implement it broadly, though it may well impact Optum's bottom line. The challenge is no different for Rice and all the other management teams at competing PBMs.

While the rebate pass-through is a step biopharma has long advocated, this PBM initiative could take away an important deflecting shield. They may no longer be able to point a finger to the lack of PBM rebate transparency for high drug prices, inviting more direct actions, including in the threatened action by President Trump. The recently enacted US Government $1.3tn budget and earlier Congressional actions include some provisions that may add fuel to this trend.

To blunt this risk, the biopharma leaders advocate a number of initiatives, ranging from outcomes-based cost of medicines, to more innovative installment payment models for high-cost therapies, to increasing ge-

neric competition, and other market driven initiatives – rather than price controls, Medicare Part D authority for price negotiations, or reimportation that the industry fears may stifle innovation.

STRANGE BEDFELLOWS IN A TANGLED WEB

Market driven or otherwise, the PBMs would remain a major influencer in this debate, and likely be involved in implementing many parts of any legislation from the US Congress or presidential decrees, not to mention any payer group cost control initiatives. Hence it becomes important to ponder the priorities with which Witty and Rice are planning to address the challenges facing PBMs, from lack of transparency, to pricing and rebate strategies that continue to encourage use of brand-name drugs long after their patents expire (and in the process thwart generic competition), to inequitable – or at least undisclosed – sharing of the benefits their clout yields.

Many of these issues plaguing the PBMs are in place also because they are profitable to many of the biopharma companies, their loud complaints notwithstanding, especially those innovators whose products have lost patent protection and who now need to perpetuate use of their branded drugs as long as possible – at times regardless of cost. Therefore, this relationship of strange bedfellows will test both of these gentlemen in their new assignments. Their vision and strategy may also be interrupted by whatever grand plan President Trump announces in April, no matter how quickly he changes his mind.

This month, perhaps there is a reason for some optimism for biopharma, partly thanks to the incursions pharma executives are making into the PBM world, and also because of the other three industry veterans in high places shaping government health care policy. But let us stay tuned as to what next month may bring. Time will tell if the biopharma industry is able to refine its business model with the help of good friends in high places.

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Viren Mehta founded and is managing member of Mehta Partners, LLC, a globally integrated boutique providing strategic insights to senior management teams in the biopharmaceutical sector for nearly 30 years.

Scrip's Rough Guide To IL-2: Mother Of All Cytokines

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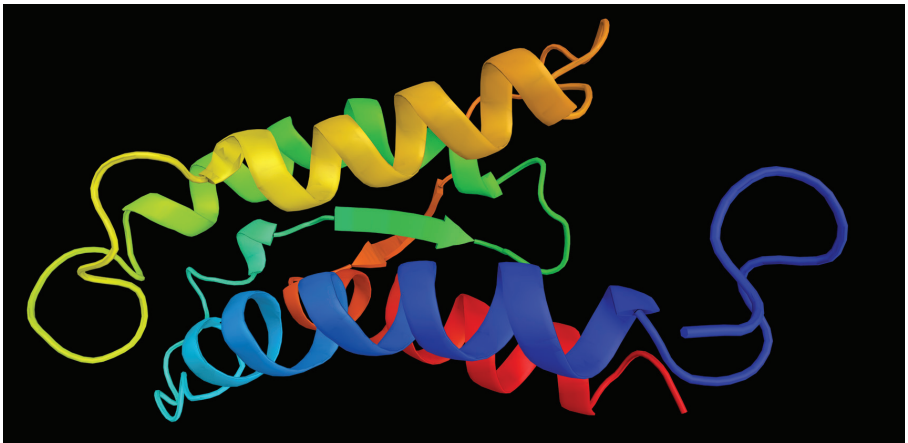

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Interleukin-2 is a small protein that stimulates cell signaling in the immune system

Interleukin-2 traditionally has been associated with nasty toxicities like the potentially fatal, flu-like cytokine release syndrome, but these days – with **Nektar Therapeutics**' NKTR-214 up on a pedestal – it's drawing feverish interest from investors.

Interleukin-2 (IL-2) is a type of cytokine, a small protein made by immune cells that is central to cell signaling and drives the generation of lymphocytes. It may be targeted for treatment of autoimmune diseases and cancer, though in very different ways, such as where the mechanism is targeted, dose level and frequency of administration. (This rough guide focuses on use in oncology.)

Per a high-priced deal announced Feb. 14, Nektar will be working closely with **Bristol-Myers Squibb Co.** to develop and commercialize its NKTR-214, a pegylated formulation of IL-2, with Bristol's PD-1 inhibitor *Opdivo* (nivolumab) and CTLA-4 inhibitor *Yervoy* (ipilimumab). The thinking is that the stimulating effect of IL-2 will work well in combination with checkpoint inhibitors to take the brakes off the immune system, playing a role in priming the immune system and boosting performance in patients with low expression of the PD-L1 biomarker, who tend to not fare so well with PD-1 therapy. The deal covers 20 indications for nine tumor types and the partners say development will be rapid, with Phase III studies in melanoma and renal cell carcinoma kicking off in the middle of the year.

The IL-2 mechanism has been used for a long time in cancer, though not commonly. **Nestle Health Science SA/Novartis AG**'s high-dose human recombinant IL-2 *Proleukin* (aldesleukin) was approved in 1992 for renal cell carcinoma and 1998 for melanoma – but requires intravenous administration in hospitals with intensive care units and is considered prohibitively toxic. Proleukin's labeling has an extensive boxed warning for capillary leak syndrome, a rare condition that can cause a severe, sudden drop in blood pressure, which in turn can cause organ failure and death. Capillary leak syndrome is caused by cytokine-release syndrome, an intense activation of the immune system leading to unrestricted growth of immune cells with damaging, life-threatening effects.

Sumanta Pal, a kidney cancer specialist at the City of Hope hospital in Duarte, Calif., and a spokesperson for the American Society of Clinical Oncology (ASCO), explained that Proleukin has only been suitable for the patients in the best condition – those who are young and with limited metastases – with access to academic centers. He also noted that low-dose IL-2 approaches have not panned out.

But Proleukin has some limited activity. Labeling indicates a 15% objective response rate (ORR), including a 7% complete response (CR) rate, in renal cell carcinoma, and a 16% ORR and 6% CR rate in metastatic melanoma,

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based on single-arm studies. Tim Turnham, former executive director of the Melanoma Research Foundation and now vice president at the MK&A pharma consultancy, commented that he knows one metastatic melanoma patient who has no evidence of disease 10 years or more out from treatment, but another who chose IL-2 over a new checkpoint inhibitor and died right after treatment due to a massive stroke. He noted the treatment-related death rates in the pivotal studies were 2% in melanoma and 4% for renal cell carcinoma. The cases illustrate the dilemma cancer patients face as they consider whether to take a drug with significant side effects in the hope of a cure, Turnham said.

What was exciting about the Proleukin development was that around 10% of responses were durable, and therefore some patients seemed to be "cured," Michael Atkins, a leading researcher in immunotherapy and deputy director at the Georgetown Lombardi Comprehensive Cancer Center in Washington, D.C., told *Scrip*. This kept the field of cancer immunotherapy alive as researchers worked to discover why some patients did well and others did not, based on the stimulatory and suppressive cells in the tumor microenvironment, culminating in the development of the CTLA-4 and PD-1 checkpoint inhibitors, Atkins said.

At least three companies have developed innovative candidates designed to minimize the toxicities of IL-2 for oncology indications – Nektar (NKTR-214), **Alkermes PLC** (ALKS 4230) and Roche (RG7461 and RG7813) – making drugs not only usable as single agents but in combination with checkpoint inhibitors. However, the IL-2 pipeline is pretty sparse for cancer as well as immunology. Novartis AG's IL-2 receptor targeting *Simulect* (basiliximab) is approved for preventing kidney transplant rejection. **Servier SAILTOO Pharma'**s ILT101, which stimulates regulatory T-cells, is in Phase II for lupus and type 1 diabetes, and other drugs aimed at the target are in preclinical development for autoimmune diseases. Nektar is teaming up with **Eli Lilly & Co.** to develop Nektar's Phase I IL-2-stimulating candidate NKTR-358 in multiple autoimmune indications.

In cancer, Nektar has clearly made progress faster than Roche and Alkermes, Evercore ISI analyst Umer Raffat commented during a Feb. 21 webinar about IL-2.

Phase I single-arm dose-escalation data for 25 patients with a range of cancers, including melanoma, renal cell carcinoma and colorectal cancer, were presented at the Society for Immunotherapy of Cancer (SITC) meeting in 2016. Researchers reported that in a particular dosing cohort of 5 patients with renal cell carcinoma, there was one unconfirmed partial response, with a 30% reduction in tumor burden, and one additional patient with reduced tumor burden per RECIST.

Response rates in the Phase I/II PIVOT dose-escalation study reported at the SITC meeting in November 2017 for NKTR-214 with Opdivo in 38 patients with melanoma, renal cell carcinoma and lung cancer were very impressive – in the mid-60s for first-line metastatic melanoma, for example, but the sample size was very small, particularly for non-small cell lung cancer, with only five patients. Updated data reported by the company on March 2 show that the response rate in renal cell carcinoma has been improving over time and has reached 60% for patients negative for PD-L1 expression across tumor types.

At this point the numbers are small, so it is not fair to say the data are transformative for the field – but they are highly encouraging, Pal told *Scrip*. One big challenge in kidney cancer is that the "bar has risen tremendously" for treatment in the last 12 months, with high response rates for dual checkpoint inhibitors and other new combinations coming to the fore, the researcher said .

However, Nektar believes that its safety profile could be differentiating. In the PIVOT study, the Grade 3+ adverse event rate for 150 patients treated to date was only 11% across dose cohorts and there were no treatment-related Grade 3+ dropouts.

MOTHER OF ALL CYTOKINES

The Bristol/Nektar deal propels NKTR-214 as "one of the more differentiated assets in the exciting and burgeoning field of immuno-oncology," William Blair analyst Andrew Hsieh said in a Feb. 14 note. Barclays analyst Geoff Meacham suggested that IL-2 could become a "central leg in immuno-oncology development."

In a very short time – from the time of the SITC meeting to before the Bristol deal – Nektar's market capitalization rose by $8bn, Brad Loncar, CEO of Loncar Investments, said in an interview with *Scrip*. Importantly, the drug showed a benefit in patients who were PD-L1-negative, a population that has been very hard to treat to date with checkpoint inhibitors. Given the PD-L1-negative data, Loncar believes that the deal price tag was "100% worth it" for Bristol-Myers Squibb.

The Bristol deal value raised some eyebrows given the only data were in such a small number of patients, but on the other hand it also reflects the history of IL-2.

IL-2 is the mother of all cytokines, driving the proliferation of T-cells – "it's where T-cells begin their lives, so it is a natural target as an adjunct to cancer immunotherapy," commented Ira Mellman, vice president of cancer immunology at Roche's **Genentech Inc.**.

In contrast with many new IO mechanisms, IL-2 is well validated, which Loncar says "puts NKTR-214 in a class of its own among thousands of combination studies involving checkpoint inhibitors that are now under way."

Nektar believes that NKTR-214 has the potential for use as a backbone in combination with a wide variety of therapies, including vaccines and cellular therapies, in addition to checkpoint inhibitors, and has retained rights to explore broad development.

Nektar was working on IL-2 at a time when everyone was chasing after the "shiny new thing" in immuno-oncology and wound up with an asset that everyone in the industry now wants to be a part of, Loncar said.

There are many validated targets that are important for generating T-cell immunity but for which there are no drugs, because there is a perception they are not safely druggable, Mellman pointed out."Everybody does the same thing to an alarming extent in drug development," but not everything has to be a shiny new target, he said.

Toxicity has been a big limitation for IL-2, but "it has always been the case that if someone could figure out a way to safely dose it, then it would by definition be of interest to any T-cell based immunotherapy," he added.

Asked to comment on the small size of the IL-2 pipeline and the sudden huge interest in the mechanism for cancer, Georgetown's Atkins noted that a lot of people have thought that IL-2 is not selective enough and that cytokines have been viewed as "1980s/1990s news." The thinking has been that antibodies were going to be better than cytokines and that targeting immunosuppressive factors in the tumor microenviroment will yield more than agonist approaches, the clinician added.

HOW THEY WORK

The binding of IL-2 to the IL-2 receptor triggers both the pro-inflammatory response and anti-inflammatory response, which historically has made Proleukin dosing very complex and difficult; a result of the opposing pathways being activated concurrently is a very narrow therapeutic window, commented William Blair's Hsieh.

There are three main components of the IL-2 receptor – IL-2Rα (or CD-25), IL-2Rβ (or CD-122), and IL-2Rγ (or CD-132). At high doses, IL-2 binds to the dimer IL-2Rβγ, which subsequently activates tumor-killing T-cells (pro-inflammatory). However, IL-2 also binds to the trimeric form, IL-2αβγ, which has a higher affinity than the dimeric receptor, resulting in regulatory T-cells (anti-inflammatory), which is undesirable in the context of cancer therapy, the analyst explained.

NKTR-214 MECHANISM OF ACTION

NKTR-214 consists of recombinant IL-2 conjugated as a prodrug with six PEG chains attached using chemically releasable linkers. In its fully pegylated form, NKTR-214 is essentially inactive. The PEG chains slowly and irreversibly dissociate from NKTR-214 to gradually reveal biological activity; the 2-PEG and 1-PEG forms are the most active, according to the company. This slow release of PEG chains in the blood allows less frequent dosing, stops over-activation of the immune system and overcomes traditional IL-2 toxicity such as capillary leak syndrome, Nektar explained. It also provides preferential binding to CD-122 to promote the generation of tumor-killing CD8+ T and natural killer (NK) cells and minimizes regulatory T-cells in the tumor.

"When NKTR-214 is injected, it is inert, so the T-cells all over the body don't get over-activated and shocked, which can lead to cytokine release syndrome with Proleukin. [This is] a feature that is completely unique and an important differentiating factor that can only be achieved with Nektar's specific pegylation chemistry," Jonathan Zalevsky, research and chief scientific officer at Nektar, said in an interview. "Being able to control that rate of activation is absolutely essential," he added.

But the drug doesn't completely prevent binding to CD-25, which is important because this binding and stimulation of development of regulatory T-cells has some positive effects in terms of immune response. However, with NKTR-214, the regulatory T-cells are generated in the periphery, where they can still play a positive role, but not in the tumor, where their presence would interfere with the drug's activity, the exec explained.

Alkermes used a different approach to block binding to the high-affinity form of the IL-2 receptor. Its ALKS 4230 is a fusion protein that includes human recombinant IL-2 glued to the IL-2α receptor. This prevents ALKS 4230 from binding to the IL-2 receptor when the CD-25 is present, but still allows binding to the intermediate affinity form of the receptor where CD-25 is not present.

"This promotes the selective expansion of natural killer and CD8 cells without corresponding expansion of regulatory T cells," the company explained. Alkermes started a Phase I single-ascending dose study in May 2016 and was expected to release data that year. It later moved the timing of the release of clinical data to May 2017 and then 2018.

During his Feb. 21 webinar, Raffat noted the explosive growth in interest in Alkermes – following the Bristol/Netkar tie-up, Alkermes' market capitalization rose by $1.5bn.

However, Raffat also highlighted the slow pace and recruitment of Alkermes' Phase I study and questioned whether intravenous dosing for five consecutive days in the hospital setting, as currently required for the drug, was a gating factor for development.

At the moment, Alkermes is primarily evaluating safety and pharmacodynamic response and said that it is already starting to see the expansion of immunostimulatory T-cells. The company plans to start a multi-ascending dose study later this year to identify a dose or multiple doses to take forward in multiple Phase II trials.

"Once we have our dose, that will enable us to move into the dose-expansion phase. I know there is a lot of impatience to enroll these programs, but I think ultimately a methodical, step-wise approach is important. Obviously, we don't want to compromise quality for time," Alkermes Chief Medical Officer Craig Hopkinson told *Scrip*.

Alkermes also plans to submit an IND for a subcutaneous formulation later this year and start a Phase I study in early 2019.

"Over the coming months, we will have a far better understanding of how this works and what the future studies need to look like," Hopkinson said.

ROCHE'S IL-2 VARIANTS

Meanwhile, Roche has two IL-2-targeted candidates in Phase I. With both, Roche has modified IL-2 so that it doesn't bind to CD-25 and then fused it to an antibody targeted at the tumor bed. This delivers IL-2 to the presumptive site of action on the tumor without stimulating CD-25 on the capillary endothelium or on regulatory T-cells. The design is somewhat like an antibody-drug conjugate.

Roche's RG7461 (RO6874281) is a targeted immunocytokine combining an engineered interleukin-2 variant (IL2v) with an antibody against fibroblast activation protein (FAP), a protein expressed in several cancers. In December 2015, Roche started a Phase I study (NCT02627274) of 180 patients testing the drug once weekly alone and then in combination with *Herceptin* (trastuzumab) in breast cancer and with Lilly's *Erbitux* (cetuximab) in head and neck cancer. The company initially indicated that top-line results would be released in 2017, but the estimated primary completion date was later changed to September 2019.

In January, Roche started a Phase II study (NCT03386721) testing RG7461 in combination with its PD-L1 inhibitor *Tecentriq* (atezolizumab) in 40 patients. In that study, the combination is initially given once weekly, then every two weeks. The primary completion date is February 2019.

Roche's RG7813 (RO6895882, cergutuzumab amunaleukin) is a targeted immunocytokine combining an engineered cytokine (IL2v) with an antibody against carcinoembryonic antigen (CEA), a protein expressed in several cancers.

Results from a Phase I study (NCT02350673) were set for release in 2017 but are now expected in 2018. In that trial, the drug is given every two weeks.

The attention on Nektar has rekindled interest in IL-2 as a potential therapeutic but Genentech's Mellman said that doesn't mean that anybody has nailed the issue with a best-in-class approach.

"It's still much too early to say if that is really the case. There may very well be a lot of room in the field to create other molecules that will have more favorable characteristics both in terms of dosing and safety on one hand and efficacy on the other hand," he said.

Since the mechanism addresses a fundamental aspect of immune response, if it can be done safely it could be deployed broadly across a large number of cancer indications – "the sky's the limit," Mellman said.

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

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

Selected clinical trial developments for the week 23–29 March 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III SUSPENDED			
Edge Therapeutics Inc.	EG-1962	aneurysmal subarachnoid hemorrhage	NEWTON 2; missed efficacy endpoint at interim analysis.
PHASE III RESULTS PUBLISHED			
Merck & Co. Inc.	doravirine	HIV/AIDS	DRIVE-FORWARD; *The Lancet HIV*, March 25, 2018.
Boehringer Ingelheim GMBH	*Stiolto Respimat* (tiotropium/olodaterol)	COPD exacerbations	DYNAGITO; *The Lancet Respiratory Medicine*, March 28, 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
Pfizer Inc.	*Vyndaqel* (tafamidis)	transthyretin cardiomyopathy	ATTR-ACT; met primary endpoint.
Biohaven Pharmaceuticals Holding Co. Ltd.	rimegepant	migraine	BHV-3000-301, -302; achieved both primary endpoints.
UPDATED PHASE III RESULTS			
Roche	*Tecentriq* (atezolizumab) plus bevacizumab	non-small cell lung cancer, first-line, non-squamous	IMpower150; overall survival improved.
Alnylam Holding Co.	patisiran	hATTR amyloidosis	APOLLO; subgroup analyses.
Ionis Pharmaceuticals Inc./Akcea Therapeutics Inc.	inotersen	hATTR amyloidosis	NEURO-TTR; OLE; sustained benefit.
PHASE III INITIATED			
Polyphor Ltd.	murepavadin	Pseudomonas infections	PRISM-MDR; in ventilator-associated pneumonia.
CSL Ltd.	CSL112	atherosclerosis	AEGIS-II; in post-MI patients.
Urovant Sciences Ltd.	vibegron	overactive bladder	EMPOWUR; in adults.
PHASE II INTERIM/TOP-LINE RESULTS			
Ablynx NV/AbbVie Inc.	vobarilizumab	systemic lupus erythematosus	STEADY; missed dose response primary endpoint.
MediciNova Inc.	MN-166 (ibudilast)	methamphetamine dependence	Missed primary endpoint, well tolerated.
Altimmune Inc.	NasoVAX, intranasal vaccine	pandemic flu	Immune responses observed, well tolerated.
Esperion Therapeutics Inc.	ETC-1002 (bempedoic acid) as add-on to a PCSK9 inhibitor	dyslipidemia	Lowered LDL-C, and well tolerated.
Allecra Therapeutics GMBH	AAI101 plus cefepime	urinary tract infections	CACTUS; effective and well tolerated.
AnaptysBio Inc.	ANB020	peanut allergy	Positive data.
Flex Pharma Inc.	FLX-787	multiple sclerosis spasticity	Reduced spasm frequency, well tolerated.
hVIVO/PepTcell Ltd.	Flu-v, universal flu vaccine	influenza	Reduced symptoms, encouraging results.
Verona Pharma PLC	RPL554 inhaled	COPD maintenance	Positive results.

Source: Biomedtracker

China Roundup: Innovent I/O Setback, Adagene, Hua Bag Millions, WuXi Relisting

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Innovent Biologics Inc. has withdrawn an approval filing for its lead immuno-oncology asset with the China FDA, dealing a setback to the Chinese biotech unicorn, which is valued at around $1bn.

Suspensions over quality issues for the molecule, IBI308, prompted Innovent Bio to put out a statement in late December, saying the PD-1-targeting drug's clinical development is fully compliant with regulations and rules, the data are complete and reliable, and the filing was based on its efficacy and safety profile.

Innovent Bio obtained a clinical trial approval from the China FDA in August 2016 and filed a subsequent new drug approval for IBI308 just 15 months later in December 2017, for Hodgkin's lymphoma. Since then, the company seemed to be in for a smooth ride after obtaining fast-track review status, but apparent issues with the filing - the first for a PD-1 checkpoint inhibitor submitted by a domestic biotech company - seem to have led to the withdrawal.

With more than 100 PD-1/PD-L1 assets under development, China bioventures are racing to develop and launch therapies in the immuno-oncology space in a market with an increasing cancer incidence. **Bristol-Myers Squibb Co.** filed for the approval of Opdivo (nivolumab) in the country in November 2017.

ADAGENE, HUA MEDICINE

On the financing front, antibody discovery firm **Adagene Inc.** has completed a $50m oversubscribed Series C financing, led by Sequoia China and backed by New World TMT, AVIC Trust, King Star Capital and Gopher Asset Management, as well as other investors.

Suzhou-based Adagene is the latest Chinese biotech to receive multiple millions in financing. Founded by Peter Luo in 2012, Adagene completed its Series A of $8m in December 2014 and a B round of $28m in January 2016. Fidelity Asia and WuXi Apptec were among the early investors. The inflow of funding has allowed Adagene to use its Dynamic Precision Library (DPL) platform to develop a pipeline consisting of several IND-ready immuno-oncology assets, an IND filing for one of which is expected in the first half of 2018.

Investment in biotech startups is catching fire in China, and on the heels of Adagene, Shanghai-based **Hua Medicine Ltd.** has also closed a combined Series D and E financing of $117.4m. In this combined round, new investors including Blue Pool Capital Limited, GIC Private Limited and AVICT Global joined existing investors ARCH Venture Partners, Eight Roads, F-Prime Capital Partners, Venrock, WuXi AppTec Corporate Ventures, Ally Bridge Group, Harvest Investments, and co-founders and management.

The large new funding will support Hua to complete two Phase III trials and the planned commercial launch in China of dorzagliatin (HMS5552), a new generation glucokinase activator (GKA) that treats type 2 diabetes.

With the funding under its belt, Hua is also poised to file an initial public offering soon. (See upcoming Finance Watch for more on Hua's fundraising and plans.)

Published online 3 April 2018

Scott A. Smith, **Celgene**'s president and chief operating officer, is leaving the company, effective immediately. His abrupt departure follows a series of product setbacks for the firm, and his major responsibilities will be assumed by chairman and CEO ***Mark J. Alles***. Smith had served as president and COO since in April 2017. He joined Celgene in 2008 and had held several senior positions, including as vice president, global marketing, inflammation and immunology (I&I), senior vice president, global head of I&I and president, global I&I. Celgene said it was now modifying its executive team structure "to enhance leadership focus on building Celgene for continued long-term success". In addition to existing responsibilities, Alles will now be responsible for strategic leadership of its global hematology and oncology franchise, global Inflammation and Immunology franchise, manufacturing, regulatory, and clinical development.

Abeona Therapeutics Inc., a clinical-stage biopharmaceutical company focused on developing novel cell and gene therapies for life-threatening rare genetic diseases, has appointed ***Dr. Carsten Thiel*** chief executive officer. ***Dr. Timothy J. Miller*** will remain president and assume the position of chief scientific officer in charge of the company's expanding clinical and preclinical research programs. Thiel brings 25 years of proven global biopharmaceutical industry experience, including rare and orphan diseases, and most recently served as the executive vice president and chief commercial officer of Alexion Pharmaceuticals, Inc.

Kleo Pharmaceuticals Inc., a biotechnology company pioneering a new class of immunotherapies, has appointed ***Dr. Luca Rastelli***, chief scientific officer, effective immediately and reporting to CEO ***Doug Manion***. Rastelli has more than 20 years of oncology drug discovery, development, and business development experience. Most recently, he was vice president, for oncology at BioXcel Therapeutics and he was previously at Boston Scientific, CuraGen, Sopherion and EMD Serono (Merck Serono).

Sir Marc Feldmann has been appointed executive chairman of **Hemogenyx Pharmaceuticals Plc**, a biotechnology company developing novel therapies to transform bone marrow, or blood stem cell, transplantation for the treatment of blood diseases, effective April 9. He was previously chairman of the company's scientific advisory board. Meanwhile, chairman Robin Campbell will become a non-executive director and Adrian Beeston, non-executive director, will step down from the board, both with immediate effect.

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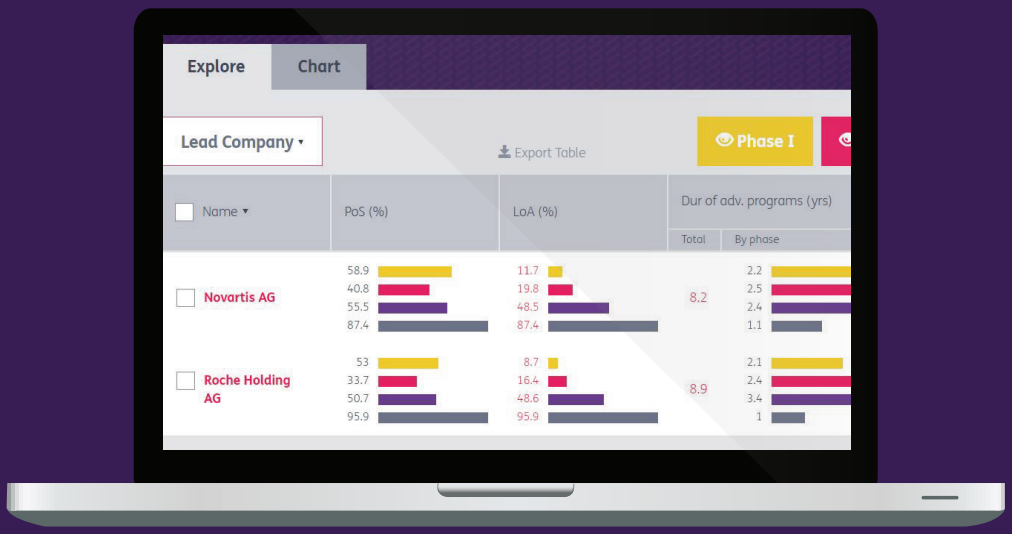

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