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UniQure is among the companies tipped for takeover in 2020

Gene Therapy Companies Among Top M&A Targets In 2020

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The remarkable promise of a single infusion to potentially cure life-limiting diseases has made gene therapy one of the outstanding developments in biopharma in recent years – and big pharma companies have already bought up several pioneers in the field.

The most notable of these was Novartis AG's acquisition of AveXis in April 2018 for $8.7bn, a move which was followed by a flurry of smaller deals in 2019, including Roche's protracted purchase of Spark Therapeutics and Astellas's $3bn swoop for Audentes.

Investor confidence in gene therapy companies cooled in the second half of 2019, as the difficulty of bringing gene therapies to market and making them profitable became apparent – illustrated by the limited sales of Spark's Luxturna and Bluebird's manufacturing problems with Zynteglo.

Nonetheless, Novartis and AveXis' Zolgensma has enjoyed a strong launch in the US market, reinforcing the view that gene therapies can be blockbusters, if all the commercial hurdles and manufacturing challenges have been dealt with.

Analysts are now predicting another mini-wave of gene therapy acquisitions in 2020, with a number of well-established and early-stage companies tipped for acquisitive interest from big biopharma.

Top of the list in terms of market cap is BioMarin – the company filed its hemophilia A gene therapy valrox with the EMA and FDA in December, but already has an established rare disease portfolio.

However at its current value of $15.19bn, it is above the bolt-on acquisition 'sweet spot' and would require a bold move ahead of valrox's anticipated approval towards mid-2020.

Another company frequently mentioned as a takeover target in recent years has been Sarepta. It has confounded sceptics by gaining FDA approval for not one but two Duchenne muscular dystrophy treatments, despite the fact that its trial data shows limited proof of efficacy.

Just before the festive period, Roche swooped to pay $1bn upfront for the rights to commercialize SRP-9001, Sarepta's investigational micro-dystrophin gene therapy for Duchenne muscular dystrophy (DMD) outside the US.

This move consolidates further Sarepta's financial future, and makes a bid from a potential acquirer - such as Pfizer, mooted in the past – much less likely.

Meanwhile, looking at it from the perspective of those in need of acquisitions to bolster their pipelines, there are a few oft-named candidates.

Analysts at William Blair have identified Novo Nordisk as one of the most likely movers in 2020, as the Denmark-headquartered firm is keen to make up lost ground in hemophilia. The most likely vehicle for that would be Netherlands-based UniQure, which currently looks likely to be first to file a gene therapy for hemophilia B.

Another company which has sent out clear signals of buying intent in the field is Takeda. Even though the company is still paying off its $62bn acquisition of Shire, it has identified cell and gene therapy as key to its future, and may well splash more cash in order to accelerate its current early-stage presence in the field.

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from the editor

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Gene therapy generated a lot of headlines in 2019, and we can be pretty certain it will continue to do so in 2020. While many of us were taking a break from work, deal making in the space continued, and David Meek departed the leadership of Ipsen to join gene therapy start-up FerGene (p8).

As reported on p6, Sarepta pocketed more than $1bn from licensing rights to its clinical-stage gene therapy for Duchenne muscular dystrophy SRP-9001. It stands to receive substantially more from Roche if the product progresses to market, and the deal doesn't even cover the US, where Sarepta retains rights. This contrasts with the $1m Sarepta paid to Nationwide Children's Hospital just over a year ago to exercise its option on the candidate, and the $29m in milestones it agreed.

Clearly, large companies have deep pockets when they see an opportunity in a potentially important field, and gene therapy is attracting a lot of interest. Our cover story reflects on significant M&A undertaken in the gene therapy space and considers which companies might be ripe for a takeover, as well as sounding some notes of caution. The race for gene therapies is a gold rush but newcomers beware: do your due diligence before buying your picks and shovels, or risk repenting at leisure. With so many advanced therapies rapidly progressing through the pipeline, we are likely in for some big setbacks as well as important steps forward.

I wish all our readers all the best for what looks like being an exciting 2020.

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Bispecifics Could Be A Threat To CAR-Ts, But Efficacy May Trump Convenience

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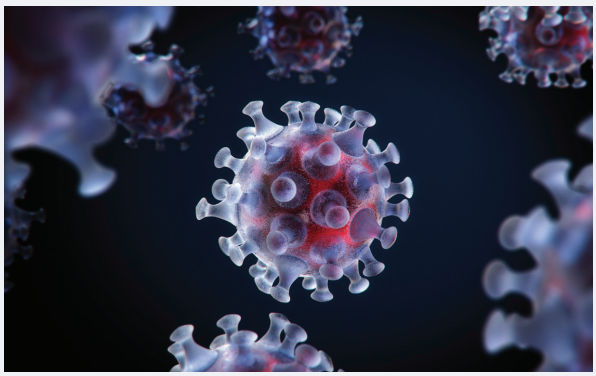

Bispecific antibodies that are designed to target cancer cells and engage T-cells gained momentum at the recent American Society of Hematology (ASH) conference, prompting the question of whether these candidates could steal market share from chimeric antigen receptor T-cell (CAR-T) cell therapies that have generated a lot of excitement over the past few years.

It is probably too early to tell if bispecifics will offer efficacy and safety that beats the response rates seen with CAR-T therapies to date, including the two approved CD19-targeting CAR-T products – Novartis AG's Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel) from Gilead Sciences Inc.'s subsidiary Kite Pharma Inc. However, bispecifics may have safety advantages, with lower rates of severe cytokine release syndrome (CRS) and limited neurotoxicity.

"I think one of the more exciting themes of the meeting is how bispecific antibodies are encroaching on the domain of CAR-T cells," ASH secretary Robert Brodsky, of the Johns Hopkins University School of Medicine, said during a preview of this year's conference. "More follow-up needs to be done to see the durability and to see the tolerability, but if bispecific antibodies can do what CAR-T cells do, that would be a big advance."

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To read the rest of this story go to: https://bit.ly/2N48FAR

inside:

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Gene therapy M&A 2016-2019

BUYER	ACQUIRED	TRANSACTION	LEAD CANDIDATE AND INDICATION	LEAD CANDIDATE STATUS	ACQUISITION ANNOUNCED
Pfizer	Bamboo	$645m*	Hemophilia A and B, Duchenne	Preclinical	August 2016
Novartis	Avexis	$8.7bn	Zolgensma for spinal muscular atrophy	Approved	April 2018
Roche	Spark Therapeutics	$4.3bn	Luxturna for Leber congenital amaurosis (LCA)	Approved	February 2019
Biogen	Nightstar Therapeutics	$867m	NSR-REP1 for rare retinal disorder CHM	Phase II	March 2019
Vertex	Exonics Therapeutics	$245m	Gene editing - Duchenne	Preclinical	June 2019
Astellas	Audentes Therapeutics	$3bn	AT132 for rare neuromuscular disease XLMTM	Filing in 2020	December 2019

Selected gene therapy M&A. Source: companies, Scrip. * Dependent on milestones

Gene therapy - potential M&A targets in 2020

GENE THERAPY COMPANY	MARKET CAP	LEAD GENE THERAPY CANDIDATE	LEAD CANDIDATE STATUS
BioMarin	$15.19bn	Valrox - hemophilia A	Filed with FDA, EMA
Sarepta	$9.62bn	SRP-9001 - Duchenne	Phase I
Bluebird Bio	$4.86bn	Zynteglo - beta thalassemia	Approved in Europe, under FDA review
UniQure	$3.13bn	Etranacogene dezaparvovec (AMT-061) - hemophilia B	Phase III
Regenxbio	$1.51bn	RGX-314 - wet AMD and diabetic retinopathy	Phase IIb Q1 2020
Sangamo Therapeutics	$970m	SB-525 for hemophilia A	Phase III commences in 2020 (Pfizer partnership)
Krystal Biotech	$958m	KB103 - Dystrophic epidermolysis bullosa (DEB)	Phase I/II
Precision Biosciences	$705m	Chronic hepatitis B (in vivo gene correction)	IND in 2020
Voyager Therapeutics	$517m	VY-AADC - advanced Parkinson's disease	Phase II
AskBio	Privately held	ACTUS-101 - Pompe disease	Phase I/II
PassageBio	Privately held	GM1 - GM1 gangliosidosis	IND enabling H1 2020
Encoded Therapeutics	Privately held	ETX101 - SCN1A+ Dravet syndrome	Preclinical

Alexion is another frequently-cited likely bidder in gene therapy, as these new approaches could encroach on its existing franchises in rare diseases.

William Blair analysts say Alexion could make a play for Krystal Biotech or PassageBio.

The latter has clear links with Alexion – its current interim CEO Stephen Squinto was a co-founder of Alexion, and until recently served as its Executive Vice President and Chief Global Operations Officer.

Gilead is well known for its large cash reserves and need for additional pipeline firepower to revive its business, and is seen as a potential suitor for Precision Bioscience or Sangamo. It has been working with both companies since 2018, and their close proximity in the San Francisco area would make either a good cultural fit.

Finally, AbbVie is also looking to keep spending, even after its $63bn acquisition of Allergan. William Blair predicts it could make a move for Voyager, PassageBio or Encoded Therapeutics. AbbVie and Voyager launched a $1.5bn gene therapy collaboration in early 2019 in Parkinson's disease and other diseases characterized by the abnormal accumulation of misfolded alpha-synuclein protein.

Such an acquisition could help it establish a lead in neurodegenerative diseases, providing another new therapeutic avenue to pursue for its post-Humira future.

However there is plenty to be cautious about in this still cutting-edge field. This has been amply illustrated by a sharp rise in the number of clinical holds imposed by the US FDA on gene therapies. This reached eight in 2019, including the latest for Solid Biosciences' SGT-001 in December, this time related to toxicity.

Another key long-term factor acquirers will look to is manufacturing capacity and expertise. This is a vital competence when looking to expand beyond limited rare disease therapies and into more lucrative fields which require greater gene therapy manufacturing capacity.

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Sarepta Secures $1.15bn From Roche In Ex-US DMD Gene Therapy Deal

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Sarepta Therapeutics Inc. CEO Doug Ingraham said that out-licensing ex-US rights to its Duchenne muscular dystrophy (DMD) gene therapy SRP-9001 to Roche eventually will bring the company more than $10bn in benefit. Initially, Sarepta gets $1.15bn under the deal announced on 23 December that, when combined with cash on hand, will give the company $2.5bn to advance its plans for being a global gene therapy leader.

The agreement comes barely a week after Roche closed its acquisition of gene therapy specialist Spark Therapeutics Inc. following US Federal Trade Commission clearance of the $4.8bn transaction. *(Also see "Roche/Spark Deal Clears FTC In A Sigh Of Relief For Pharma Dealmakers" - Scrip, 16 Dec, 2019.)* The Sarepta deal also gives the Swiss big pharma a gene therapy candidate in a therapeutic area where Roche recently ended development of a late-stage drug, RG6206 (talditercept alfa), an anti-myostatin adnectin.

To access SRP-9001, Roche initially will pay a $750m upfront fee and buy Sarepta stock at $158.59 per share for a total of $400m. In addition, it will fund half of SRP-9001's global clinical development costs, invest up to $1.7bn in regulatory and sales milestone fees, and pay royalties estimated to be a mid-teens percentage of the product's ex-US sales.

Ingraham said during a 23 December conference call with analysts and investors about the Roche agreement that "assuming success, the non-risk-adjusted payments inclusive of royalties could reasonably exceed $10bn" and he declared the deal "the largest licensing transaction in cell or gene therapy history" as well as "the largest single-asset, ex-US license of any kind in all of biopharma history."

The deal will accelerate the delivery of DMD gene therapy to patients outside the US, the CEO noted.

"With its existing infrastructure, expertise and shared mission, Roche will accelerate our ex-US plans," he said. "And more than that, Roche broadens our ambition, as they will get to territories that Sarepta would be challenged to address in a similar timeframe even with our most ambitious approach."

Sarepta's stock closed up 7.5% at $135.58 per share on 23 December after the deal was announced.

"We believe it is remarkable that Sarepta was able to secure such economics for ex-US rights on a development-stage program," Needham analyst Chad Messer wrote in a same-day note. "Notably, despite having two approved drugs in the US, Sarepta does not currently have ex-US sales infrastructure. We believe the size and quality of this deal reflect the excitement surrounding the gene therapy field and the quality of Sarepta's DMD program."

A LARGE RETURN ON SAREPTA'S ACADEMIC COLLABORATION

The combined $1.15bn Sarepta will receive from the initial upfront cash payment and equity investment is quite a large return on the company's relatively small costs related to licensing SRP-9001. It

Roche will lead SRP-9001 commercialization in all countries outside the US

entered into a research and development agreement with Nationwide Children's Hospital in January 2017 for SRP-9001, which delivers the microdystrophin-encoding gene directly to muscle tissue for production of microdystrophin. *(Also see "Sarepta Snaps Up Gene Therapy Approaches to DMD" - Scrip, 12 Jan, 2017.)*

DMD is a rare disease caused by a lack of the protein dystrophin, which leads to muscle weakness and early death. Sarepta already leads the DMD market with two approved exon-skipping antisense oligonucleotides – Exondys 51 (eteplirsen), approved in 2016, and Vyondys 53 (golodirsen), approved on 12 December. Sales of both drugs could be usurped by a potentially curative DMD gene therapy.

When Sarepta exercised its option for SRP-9001 in October 2018, it agreed to pay $1m up front plus up to $29m in milestone fees plus low single-digit royalties, according to Biomedtracker. The company reported positive dystrophin-producing results in the first four patients treated with the gene therapy in a Phase I/IIa study and outlined plans for a pivotal trial in July 2018. *(Also see "Sarepta Outlines A Fast Path Forward For Its DMD Gene Therapy" - Scrip, 19 Jun, 2018.)* More detailed results from those four boys with DMD were reported in October 2018. *(Also see "Sarepta Commits To Rapid, Thorough Pivotal Study For DMD Gene Therapy Based On Functional Improvements" - Scrip, 4 Oct, 2018.)*

Messer noted that Sarepta expects to finish treating the 40 patients in the ongoing study by the end of 2019 with results expected 48 weeks after dosing completion at the trial's two US sites. An international pivotal trial is expected to begin in mid-2020.

"This licensing agreement [with Roche] instills added confidence in Sarepta's gene therapy programs and removes any remaining financial overhang for Sarepta, in our view," SVB Leerink analyst Joseph Schwartz wrote in a 23 December note. "To the extent that Roche likely critically evaluated Sarepta's manufacturing and clinical probability of success, the deal may bode well for the ability to produce enough SRP-9001 via Sarepta's hybrid adherent-based approach and SRP-9001's likelihood to succeed in the ongoing '102 and upcoming '103 studies."

BIG MONEY TO FUND SAREPTA'S BIG ASPIRATIONS

Sarepta will leverage its upfront funding from Roche to fund its massive investment ongoing in gene therapy infrastructure, including both manufacturing and R&D for SRP-9001 and gene therapies outside of DMD.

The company has committed itself to becoming a leader in the field and has added several programs to its gene therapy pipeline through business development. It agreed to buy partner Myonexus Therapeutics Inc. in February based on early clinical trial success for SRP-9003 (MYO-101) in limb-girdle muscular dystrophy.

"As we will have as much as $2.5bn of cash available after closing [in the first quarter of next year] to drive our strategy as we commence 2020, this partnership provides us both resources and, importantly, focus to execute our plans," Ingraham said during a conference call on the Roche deal. "Our aspiration is to be the global leader in rare genetic medicine; continuing our RNA commercial success, while advancing our current and next-generation RNA platforms; and continuing the rapid construction of our enduring gene therapy engine."

Out-licensing ex-US rights for SRP-9001 to Roche allows Sarepta to focus on its pipeline of RNA-targeting antisense therapies and its gene therapy ambitions without having to build out ex-US infrastructure – including commercial access, government affairs and regulatory capabilities – which Ingraham said would be "distracting" for the company. However, Sarepta will manufacture and provide clinical trial and commercial supplies of SRP-9001 to Roche.

William Blair analyst Tim Lugo said in a 23 December note that the deal with Roche "is well structured and highly strategic for Sarepta, providing significant upfront resources to support the continued development of its deep pipeline consisting over 20 gene therapy candidates, while allowing it to retain control of the development plan for SRP-9001."

The company's agreement with Roche gives the big pharma firm an option to acquire ex-US rights to certain other DMD-specific programs in Sarepta's portfolio in exchange for additional milestone fees, cost sharing and royalty payments. However, Ingraham indicated that any further deals are not on the near-term horizon.

"That option cannot be exercised for two years," the CEO said, later noting that Sarepta currently is not considering any ex-US deals for other gene therapies in its portfolio.

As for conducting deals to in-license or buy assets for its own growing rare disease portfolio, Ingraham said Sarepta still will consider opportunities that align with the company's priorities.

"We're going to be thoughtful going forward about finding opportunities if we think that they make economic sense and are compelling to bolster our pipeline," he noted. "We've been looking as well to providing additional tools for our Gene Therapy Center of Excellence so that we can ensure that we can continue to advance with gene therapy."

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Astellas Strengthens Next-Gen IO Hand With $665m Xyphos Buy

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Following on from the early December announcement that it is paying $3bn for US gene therapy company Audentes Therapeutics Inc., Astellas Pharma Inc. has bought the privately held US immuno-oncology (IO) bioventure Xyphos Biosciences, for $120m upfront.

The structured acquisition could be worth up to $665m in total factoring in future development milestone payments including the initial sum paid upon closing, which has already made South San Francisco-based Xyphos a wholly owned subsidiary of the Japanese firm.

The transaction gives Astellas access to Xyphos' proprietary ACCEL (Advanced Cellular Control through Engineered Ligands) cell therapy technology platform, which has already generated XYP-117, a lead "convertibleCAR" therapy in preclinical development, which is currently scheduled to enter the clinic in 2021.

Astellas is already working in the I-O area as a primary focus of its R&D strategy and has said that new modalities and technologies are of strategic interest. It currently has several antibody therapies in early clinical development that came from the 2015 acquisition of Potenza Therapeutics Inc., including the anti-TIGIT antibody ASP837. "Combining this [Xyphos'] technology with our capabilities in cell therapy that we have been working on so far, we can create next-generation high-function cells," said Astellas president and CEO Kenji Yasukawa.

TECH PLATFORM

Xyphos has developed technology to direct cells of the immune system to target single or multiple tumor antigens while controlling immune cell proliferation and endurance. The proprietary molecules can be delivered to natural immune cells or to engineered chimeric antigen receptor (CAR) cells.

The patented CAR technology modifies the NKG2D receptor, which exists on natural killer (NK) cells and some T-cells. The change renders the receptor inert and unable to bind to any of its natural ligands, which occur on stressed cells.

Through further protein engineering, several natural ligands of NKG2D have been modified to bind exclusively to the otherwise inert NKG2D receptor and various functional molecules such as antibodies to specific tumor antigens are attached to the modified ligand.

The ligand-directed functional molecules then bind exclusively to immune cells expressing the inert CAR on their surface, forming the proprietary "convertibleCAR" cells. These can then be directed and "switched on" by the ligand-bound

antibody to seek, become activated by and attack a targeted cancer cell. As activity can be tightly controlled from outside the CAR-cell, Xyphos believes this may potentially lead to safer, better modulated and more efficacious treatments with fewer off-target effects, potentially with fewer of the proliferation risks of first-generation CAR-Ts. The convertibleCAR cells might also be modified to new targets should tumor expression profiles change.

Xyphos is not alone in the next-gen CAR-T control field however, as several other firms including Autolus Ltd. are working on better modulated therapies. *(Also see "'Serial Killer' CAR-T Could Help Autolus Bounce Back" - Scrip, 28 Nov, 2019.)* Other pipeline assets at Xyphos include the preclinical CD20-targeting therapy XYP-217, for relapsed/refractory non-Hodgkin's lymphoma, and XYP-317, an HER-targeting therapy in the discovery phase for solid tumors.

EXEC TEAM

Xyphos' management team includes co-founder James Knighton as CEO, who has previous experience at Chiron and DuPont Merck, while chairman and co-founder David Martin is a former senior vice-president of R&D at Genentech Inc.

Xyphos, founded in 2017 from the split of AvidBiotics Corp. (at which Knighton was co-founder and president), has not disclosed much about its previous investors, but an undisclosed minority stake was acquired by the Parker Institute for Cancer Immunotherapy in 2018.

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Blow To Ipsen As FerGene Nabs CEO Meek

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David Meek Moves From Pharma To Biotech

Source: FerGene

FerGene, launched less than a month ago by Ferring Pharmaceuticals AS and private equity giant Blackstone Life Sciences, has pulled off a coup by poaching David Meek, CEO of Ipsen, to head up the new gene therapy company.

As revealed by *Scrip* at the end of November, Ferring, which is best known as a leader in reproductive medicine and women's health, decided to partner with Blackstone and set up a new enterprise to advance nadofaragene firadenovec, its gene therapy for patients with high-grade, Bacillus Calmette-Guérin unresponsive, non-muscle invasive bladder cancer. Earlier this month, the new company unveiled results from a Phase III trial of nadofaragene firadenovec, showing that the therapy met its primary endpoint with 53% of patients achieving a complete response at three months, and 24% continuing to show a CR at 12 months. *(Also see "Fledgling Pharma FerGene Makes Quick Debut With Gene Therapy Candidate" - Scrip, 6 Dec, 2019.)*

A biologics license application for the gene therapy has been accepted for filing by the US Food and Drug Administration and been granted a priority review. FerGene is preparing its US commercialization plans and bringing Meek on board, with his 30 years of industry experience, is a key step.

Meek has only been CEO at the French pharma group since 2016, having previously been president of oncology at Baxalta Inc., but FerGene said that he had "transformed Ipsen into a global biopharma growth leader with initiatives to transform external innovation, Ipsen's R&D operations and build out the company's footprint in countries like the US and China."

Blackstone's Paris Panayiotopoulos, a co-chair of FerGene, cited Meek's "deep knowledge of the US oncology market" which makes him "the ideal fit" to head the new group. His experience "will be instrumental as we advance a breakthrough investigational gene therapy that offers the potential to meaningfully improve the standard of care for a patient population which has seen little innovation over the past twenty years," Panayiotopoulos added.

Meek, who will also take on the role of president at FerGene, will start work on 14 January after stepping down from Ipsen, effective 31 December. Previously, he was chief commercial officer of Endocyte Inc. from 2012 to 2014 and prior to that served in various executive leadership roles at Novartis AG and Johnson & Johnson.

While FerGene is thrilled with its high-profile hire, Meek's departure from Ipsen has come as a shock to industry observers and a setback for the Paris-based firm, creating an unexpected void at the top.

Ipsen has appointed chief financial officer Aymeric Le Chatelier as interim CEO. Le Chatelier, who joined the company in 2014 without any previous experience in pharma, will be supported by "the newly-

created office of the CEO," comprised of chief operating officer Harout Semerjian and Richard Paulson, CEO of Ipsen North America, "to ensure a smooth transition." The board has asked its nominations committee to "immediately conduct a search process in order to identify the future CEO."

The timing of Meek's departure is not great for Ipsen. It comes days after the FDA placed late-stage trials of palovarotene in two rare bone disorders – fibrodysplasia ossificans progressiva and multiple osteochondromas – on partial clinical hold.

Ipsen gained access to palovarotene, a retinoic acid receptor gamma selective agonist, when it acquired Canada's Clementia Pharmaceuticals Inc. in February for $1.04bn. The FDA freeze, revealed on 6 December, followed reports of patients experiencing early growth plate closure affecting zones of cartilage at each end of long bones while taking the drug.

Analysts at Jefferies issued a note after the partial hold explaining that "removing the MO indication and restricting chronic FOP treatment to older patients could cut our peak sales to $270m, from $1.85bn." Ipsen shares fell back as palovarotene is seen as a key element to boost the firm's maturing pipeline.

Meek, a 56-year-old American, has been lauded for aggressively trying to restock said pipeline. In October, Ipsen in-licensed global rights to Blueprint Medicines Corp.'s BLU-782, an ALK2 inhibitor to treat FOP as monotherapy and potentially in combination with palovarotene. *(Also see "Ipsen Doubles Down On FOP With Blueprint Pact" - Scrip, 16 Oct, 2019.)*

In a recent interview with *Scrip*, Ipsen chief business officer Ivana Magovcevic-Liebisch said that "external innovation is critical for our future growth because we don't really have in-house discovery research any longer." She added, "We need to continuously fill our pipeline and do so at all stages…you need to plant a lot of seeds to ensure that you have a successful pipeline, not least because our commitment is to bring one product or one meaningful indication to the market every year." *(Also see "Ipsen CBO: We Are Seeking Fresh Rare Disease Buys" - Scrip, 25 Nov, 2019.)*

Achieving that goal will be quite a challenge for Meek's successor.

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2019 Drug Launches: New Specialty And Rare Disease Blockbusters Take Shape

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Several drugs with big commercial potential launched in the past year, even though many of the new entrants were for niche, rare diseases. The year 2019 was an exciting one for novel drugs, despite the fact that the number of new molecular entities approved by the US Food and Drug Administration was less than in 2018, a banner year.

The US FDA approved 53 novel drugs and biologics in 2019 as of 30 December, many of which were drugs for rare diseases. (see table on page 10).

Novartis AG's Zolgensma and Pfizer Inc.'s Vyndaqel/Vyndamax (tafamidis) were among the early commercial standouts, suggesting the two big pharmas may have new blockbuster-sized rare disease brands on their hands.

STRONG LAUNCHES IN RARE DISEASE

Zolgensma generated $160m in the third quarter, after launching in June. It's the first gene therapy that could become a serious commercial success, approved for spinal muscular atrophy and carrying a substantial $2.1m price tag. *(Also see "It's Official: Novartis SMA Gene Therapy Zolgensma Is World's Most Expensive Drug" - Scrip, 24 May, 2019.)*

Meanwhile, Vyndaqel got off to a strong start, impressing investors after management had cautioned that low diagnosis rates for the rare disease it treats, cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM), would slow early uptake. *(Also see "Pfizer Vyndaqel Launch Surprises With An Early Burst Out Of The Gate" - Scrip, 29 Oct, 2019.)* Vyndaqel launched in the US in May and generated $87m in the US from launch through the third quarter, and $259m worldwide in the first nine months of the year. It is approved for transthyretin amyloid polyneuropathy in Europe and for ATTR-CM in Japan.

"Tafamidis could be much bigger than analysts model, by a factor of 2-3x," Wolfe Research analyst Tim Anderson

Some Notable Launches In 2019

- Two new drugs for sickle cell disease, an area that has seen a dearth of innovation, Novartis' Adakveo (crizanlizumab) and Global Blood Therapeutics' Oxbryta (voxelotor)
- Novartis' gene therapy for spinal muscular atrophy, Zolgensma (onasemnogene abeparvovec)
- The first triple combination for cystic fibrosis, which expands applicability to approximately 90% of patients, Vertex Pharmaceuticals' Trikafta (elexacaftor/tezacaftor/ivacaftor)
- Two novel drugs for types of depression, a category that hasn't seen significant innovation in a decade, Johnson & Johnson's Spravato (esketamine) and Sage's Zulresso (brexanolone).

said in a 4 December note. He forecasts blockbuster-level sales for the drug in 2021.

"You begin to see this mix of the old world and the new world," ZS Associates principal Pratap Khedkar said of the years' top launches. "The old world is sunsetting – it's still there though, you can't ignore it – but increasingly about half your focus has to be large molecules and things like gene therapy, which brings in much bigger challenges around things like pricing, distribution, logistics, things that are not easy for pharma."

Novartis and Pfizer appear to be succeeding with their respective launches in part by laying out strong value propositions for the drugs so that they have secured market access despite high prices.

Some of the years' rare disease launches have gone slower, like Sanofi's experience with Cablivi (caplacizumab) for acquired thrombotic thrombocytopenic purpura (aTTP), a rare blood-clotting disorder. Cablivi was an important element of Sanofi's €3.9bn acquisition of Ablynx NV in 2018. Cablivi generated €40m ($44.5m) in the first nine months of 2019 after launching in April. The company has acknowledged it will need to build the market from scratch as there have been no approved therapies for aTTP and many patients go undiagnosed.

SKYRIZI PLAYS TO ABBVIE'S STRENGTHS

A notable launch outside of the rare disease space is AbbVie Inc.'s Skyrizi (risankizumab), a second-to-market IL-23 inhibitor for plaque psoriasis behind Johnson & Johnson's Tremfya (guselkumab). After launching in May, Skyrizi generated $139m through September, an impressive early result given the competitive nature of the biologic dermatology category. *(Also see "AbbVie's Humira Succession Plan Begins Taking Shape With Skyrizi US Approval" - Scrip, 24 Apr, 2019.)* AbbVie's strength and market power in immunology and skin disorders with Humira (adalimumab) have clearly given Skyrizi a leg up at launch, posing a competitive threat to IL-23 and IL-17 rivals like Tremfya, Novartis Cosentyx (secukinumab) and Eli Lilly & Co.'s Taltz (ixekizumab).

Strength in a therapeutic area is considered a commercial advantage for new launches. "The data that we have is clear that companies that have a strong market position in terms of relative market share have higher Phase III success rates, faster time to peak sales and higher peak sales," Bain & Co. partner George Eliades said.

Generally, $200m in first year sales is considered a solid indication a drug is on a blockbuster path, though in recent years, the

The Class Of 2019: Select US Drug Launches

A look at some of the notable drugs that launched in 2019

COMPANY	DRUG	LAUNCH MONTH	FIRST FDA APPROVED INDICATION	2019 REVENUES
Johnson & Johnson	Spravato	March	Treatment-resistant depression	N/A
Sanofi	Cablivi	April	Acquired thrombotic thrombocytopenic purpura (ATTP)	€40m ($44.5m)
Novartis	Mayzent	April	Relapsing multiple sclerosis, including SPMS	$4m*
Amgen	Evenity	April	Osteoporosis in women at high risk of fracture	$87m**
Johnson & Johnson	Balversa	April	Advanced urothelial cancer with FGFR3 or FGFR2 mutations	N/A
AbbVie	Skyrizi	May	Plaque psoriasis	$139m
Pfizer	Vindaqel/Vyndamax	May	HTTR-CM	$259m**
Novartis	Zolgensma	May	Spinal muscular atrophy	$160m*
Sage Therapeutics	Zulresso	June	Postpartum depression	$1.5m*
Novartis	Piqray	June	HR+, HER2- advanced breast cancer with PI3KCA mutations	$43m*
Roche	Polivy	June	R/R diffuse-large B-cell lymphoma (DLBCL)	CHF21m ($21.5m)
Roche	Rozlytrek	August	ROS1-positive metastatic non-small cell lung cancer	CHF4m ($4.1m)
AbbVie	Rinvoq	August	Rheumatoid arthritis	$14m
Novartis	Beovu	October	Wet age-related macular degeneration	N/A
Vertex	Trikafta	October	Cystic fibrosis	N/A
Novartis	Adakeveo	November	Vaso-occlusive crises associated with sickle cell disease	N/A
Beigene	Brukinsa	December	Mantle Cell lymphoma	N/A
Global Blood Therapeutics	Oxbryta	December	Sickle cell disesae	N/A
Alnylam	Givlaari	December	Acute hepatic prophyria	N/A

Footnotes: *revenues reported only for third quarter 2019 **Vyndaqel/Vyndamax generated $87m in the US since launch and $259m worldwide and Evenity generated $15m in the US since launch and $87m worldwide.

Source: Pink Sheet US Performance Tracker and company filings

launch trajectory for some new drugs has lengthened as competition has grown and market access barriers have intensified.

"In many cases when launches struggle, it is because the payer angle has not been thought through enough," ZS' Khedkar said. "If the coverage is less than 50% by the end of the first year than that is really, really hard to make that launch successful." Then a vicious payer/physician cycle builds in which physicians lose their confidence in the drug and don't advocate for it, leading payers to feel they can put more restrictions in place, he said.

As Bain's Eliades pointed out, physician and patient experience with a product is also becoming more important for brands looking to separate themselves in crowded therapeutic areas, which requires drug companies to step back and make sure they are offering the best service.

"In a competitive space, the product profile only accounts for about half of the drivers of physician loyalty and the other half is the experience of using the product," Eliades said. Some of that experience also harkens back to market access and steps drug companies can take to make sure physicians can clear the payer restrictions that might be in place for a certain drug as smoothly as possible.

For most of the 2019 launches, particularly those that launched later in the year, it's still far too soon to judge early commercial success. Investors and other stakeholders will be keeping an eye on initial indicators for drugs like Adakveo and Oxbryta in sickle cell disease, Novartis Beovu (brolucizumab) for wet AMD and AbbVie's Rinvoq (upadacitinib) for rheumatoid arthritis, all of which launched in the second half of the year.

CANCER DRUGS, BUT NOT AS MANY AS SOME YEARS

Several new drugs for cancer also hit the market that could have strong commercial potential, though there were fewer cancer drug approvals than some prior years. Ten cancer drugs were approved by FDA's Center for Drug Evaluation and Research (CDER) in 2019 as of 30 December. In 2018, CDER approved 17 cancer drugs, nearly double the amount.

> "If payer coverage is less than 50% by the end of a drug's first year on the market, it is really, really hard to make that launch successful."
> – Pratap Khedkar

Novartis' PI3K inhibitor Piqray (alpelisib) launched in June as the first treatment for HR+, HER2- breast cancer with PIK3CA mutations. It generated $43m in the third quarter, a solid start. Roche's Polivy (polatuzumab vedotin-piiq) was approved in June for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and generated CHF21m ($21.5m) through September.

A late approval came through from FDA on 23 December for AstraZeneca and Daiichi Sankyo's Enhertu (famtrastuzumab deruxtecan-nxki) for advanced HER2-positive breast cancer patients who have received two or more anti-HER2 based regimens in the metastatic setting. The accelerated approval was swift, based on the results of a Phase II trial. Enhertu, an antibody drug conjugate, is expected to be a big commercial opportunity, given strong efficacy data in patients who have run through most therapeutic options, but that launch will be tracked in 2020.

Some drugs have gotten off to a noticeably lackluster start. In depression, J&J's Spravato for treatment-resistant depression and Sage Therapeutics Inc.'s Zulresso for postpartum depression have both been slow to get off the ground, though both drugs have risks associated with them resulting in controlled distribution that was expected to slow the launch timeline. J&J has not disclosed Spravato revenues, generally a sign the sales are not yet material to the company's top-line. Sage reported Zulresso sales of just $1.5m in the third quarter, its first full quarter on the market.

Spravato needs to be administered in a certified treatment center. Though patients can self-administer the drug, they have to be monitored for at least two hours by a health provider and make arrangements to get home after treatment. Zulresso is administered through a 60-hour I.V. infusion and requires continuous inpatient monitoring for sedation and loss of consciousness.

All in all, the year's class of new drugs seems to include some bigger commercial standouts than 2018, which saw a record number of drug approvals, but mostly for rare diseases and niche cancers with limited early commercial potential. The greatest potential for a near-term commercial winner last year was for the new CGRP drugs for migraine, but three new drugs launched simultaneously, creating a challenging launch environment for the expensive biologics that has persisted into 2019.

In contrast, the class of 2017 had several early blockbuster contenders that have proven their commercial power in 2019, drugs like Sanofi/Regeneron Pharmaceuticals Inc.'s Dupixent (dupilumab), Roche's Ocrevus, GlaxoSmithKline PLC's Shingrix and AstraZeneca PLC's Imfinzi – so there's plenty of time for the commercial debuts of 2019 to shine.

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With Vascepa's New CV Claim, Amarin Targets Patients On Other Triglyceride-Lowering Agents

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Amarin Corp. PLC's plan for promoting Vascepa's (icosapent ethyl) new cardiovascular risk reduction claim includes convincing practitioners to switch patients currently using other triglyceride-lowering agents that have failed to demonstrate a CV outcome benefit.

Amarin finally has reeled in the big indication for Vascepa in the US

"A significant part of our education process will also emphasize that with an FDA-approved indication, it makes little sense for patients to continue being treated with earlier generation products, which while they might have lowered triglyceride levels have all failed to demonstrate cardiovascular risk reduction in clinical studies," chief medical officer Craig Granowitz said during a 16 December investor call. "This includes, but is not limited to, fenofibrates, niacin and omega-3 mixtures."

Company officials discussed promotional plans for the long-awaited CV benefit claim on the call, as well as their view of the expansive label awarded by the US Food and Drug Administration 13 December.

The agency approved Vascepa as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥150mg/dL) and established CV disease or diabetes and at least two additional risk factors. *(Also see "Sales Already Growing As Vascepa Secures Cardio Approval" - Scrip, 16 Dec, 2019.)*

The CV benefit claim, based on results from the REDUCE-IT outcomes trial, has been a decade in the making. *(Also see "Vascepa Advisory Committee Is Latest Outpost In Product's Remarkable Regulatory Journey" - Pink Sheet, 11 Sep, 2019.)* It significantly expands Vascepa's indicated use beyond its initial 2012 approval for treatment of adults with severe hypertriglyceridemia (TG levels of >500mg/dL), an indication that encompasses only about two million to three million US adults.

Although the new indication is not as broad as Amarin originally sought, it encompasses use for both secondary and primary prevention of CV events. At an advisory committee meeting in November, the majority of panelists favored an indication encompassing secondary prevention in patients with existing CV disease and primary prevention in diabetics with additional risk factors for CV disease, despite reservations about the strength of the efficacy data in the primary prevention setting. *(Also see "Amarin's Vascepa Positioned For Broad CV Risk Reduction Claim Following US FDA Panel Nod" - Pink Sheet, 14 Nov, 2019.)*

LABELING PROVIDES LEEWAY

It is difficult to precisely quantify the size of the patient population covered by the new labeling claim, Granowitz told investors.

Approximately 38 million patients in the US are on statin therapy, and approximately 12 million statin-treated patients have TG levels of at least 150mg/dL, he said. "More than half of these patients are also estimated to have established cardiovascular disease or diabetes and multiple other cardiovascular risk factors," Granowitz said.

In addition, millions of patients are statin-intolerant and have CV risk factors, he said. "Both high-risk, statin-treated and statin-intolerant patients are covered by the new label for Vascepa and are potential candidates to be helped by this important preventative care treatment option."

Amarin execs said the expanded labeling gives prescribers significant leeway in determining the additional risk factors to be considered when prescribing for diabetics, as well as discretion for use in statin-intolerant patients.

Guidelines and professional society statements also provide a broader view of patients that could benefit from Vascepa, such as those with TG levels between 135mg/dL and 150mg/dL, Granowitz said.

STOP CALLING IT A 'FISH OIL PRODUCT'

Even ahead of the labeling expansion, Amarin has seen Vascepa sales soar with release of the results from REDUCE-IT, in which Vascepa reduced the risk of a five-point major adverse CV event (MACE) endpoint – CV death, myocardial infarction, stroke, coronary revascularization and hospitalization for unstable angina – by 25%. *(Also see "Amarin's Vascepa Momentum Builds Ahead Of Next Week's FDA AdComm" - Scrip, 5 Nov, 2019.)*

However, because Vascepa is the first and only drug approved for this new indication and most of Amarin's resources were directed to R&D while the REDUCE-

IT study was ongoing, most physicians currently have little visibility or detailed knowledge about the drug, Granowitz said. "Once physicians learn about the details of Vascepa and its clinical results, they typically become very supportive. The FDA-approved label should make this easier and more direct."

Amarin will support the new label with medical education programs and publications designed to expand knowledge and awareness of Vascepa and its effects, which REDUCE-IT showed go beyond merely lowering triglycerides, he said.

Promotional efforts also will emphasize how Vascepa, an omega-3 fatty acid drug product containing purified ethyl ester of eicosapentaenoic acid derived from fish oil, differs from fenofibrates, niacin, omega-3 mixtures and dietary supplements, Granowitz said, adding that one goal is getting people to stop referring to Vascepa as a "fish oil product."

"Only Vascepa has been demonstrated to lower cardiovascular events," he said. "Fish oil supplements, other omega-3 products and other products in general which are available today have not proven such benefits. And many other companies have failed trying to demonstrate the benefits demonstrated in the REDUCE-IT study."

With final labeling now in hand, Amarin said it plans to seek advisory comments from the FDA's Office of Prescription Drug Promotion prior to running direct-to-consumer ads for the new indication. The company anticipates launching a DTC campaign in mid-2020.

Amarin also is increasing the size of its sales force to 800 representatives. A national launch meeting is planned for the week of 13 January, which will limit the time company executives can spend at the J.P. Morgan Health Care Conference in San Francisco the same week, CFO Michael Kalb said.

CV DEATH MISSING FROM INDICATION ...

Company execs downplayed any concerns about the absence of CV death risk reduction from the indication statement.

CV death was a component of both the five-point MACE primary endpoint and the three-point MACE secondary endpoint in REDUCE-IT.

Although Vascepa showed a 20% reduced risk of CV death, several FDA advisory committee members recommended against a claim specific to this endpoint because the magnitude of benefit was not as large or statistically robust as other components of the MACE composite. *(Also see "Amarin Heads Into Vascepa Expansion Labeling Talks After Positive US FDA Panel Review" - Scrip, 15 Nov, 2019.)*

Steven Ketchum, president of R&D and chief scientific officer, noted the clinical studies section of labeling includes the five- and three-point MACE composite results, as well as a breakdown of the individual components.

"While we would have liked CV death to also appear in the indication for use statement, this label does not prevent communication of the information in the tabular display of the REDUCE-IT clinical efficacy results and promotion," Ketchum said. "It's hard to imagine a prescribing physician who would choose to not prescribe the drug because CV death is not listed in the indication statement."

... BUT OTHER PARAMETERS ADDED IN

At the advisory committee meeting Amarin sought a broad indication: to reduce the risk of CV death, myocardial infarction, stroke, coronary revascularization and unstable angina requiring hospitalization as an adjunct to statin therapy in adults with elevated TG levels (≥135mg/dL) and other risk factors for CV disease.

The approved indication is narrower – with limitations specific to TG levels of 150mg/dL or greater, use of maximally tolerated statin therapy, and existence of CV disease or diabetes plus two risk factors.

The REDUCE-IT study criteria required that patients with established CV disease be at least 45 years old, and diabetics be at least 50 years old and have at least one additional CV risk factor. However, the new indication is not restricted by age.

SVB Leerink's Ami Fadia said the expanded indication closely follows the advisory committee's feedback but also allows for appropriate physician discretion.

At the advisory committee meeting "there were concerns of Vascepa becoming a 'cardio-candy,' which we believe prompted FDA to require the diabetes +≥2 risk factors for primary prevention language," the Leerink analyst said. The TG cutoff of 150mg/dL also is in line with panel feedback, although based on multiple medical society guidelines, the inherent variability in TG levels and electronic medical record data, physicians can be expected to use Vascepa in some patients with TGs<150 mg/dL, Fadia said.

"On statin use, we noted some AdComm commentary on requiring maximally tolerated statin therapy, and this was included in the indication, although we note that this does not demand a specific statin dose, and there is no specific cholesterol level required for use."

NO PLANS TO 'SIGNIFICANTLY INCREASE' PRICE

Amarin has increased its total net revenue guidance to a range of $410m-$425m for 2019 and is projecting total net revenue for 2020 in the range of $650m-$700m, mostly from sales of Vascepa in the US.

These projections are based on anticipated growth in volume. "Assuming that managed care rapidly moves to ensure patient access to Vascepa, it is our intention to not significantly increase Vascepa's price," Kalb said.

Vascepa is priced at a wholesale acquisition cost of $303.65 for a 30-day supply.

"We are aware of third-party economic analysis, which supports that the price of Vascepa could be doubled and that the product would remain cost-effective," Kalb said, adding that the current price is similar to that of Pfizer Inc.'s blockbuster statin Lipitor (atorvastatin) before it went generic.

"Affordable pricing works well for that drug, and we are seeking to follow their model," he said. "Beyond 2020, we believe that Vascepa total net revenue will grow to reach multiple billions of dollars. However, the history of other therapies for chronic conditions suggest that growth builds over multiple years. Accordingly, at this time, we are not providing guidance regarding annual revenue levels beyond 2020."

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Sales Already Growing As Vascepa Secures Cardio Approval: **https://bit.ly/2SXKvvG**

Allergan's Oral CGRP Inhibitor Ubrelvy Approved For Migraine Attacks

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Allergan PLC's oral calcitonin gene-related peptide (CGRP) inhibitor Ubrelvy (ubrogepant) will be the first oral CGRP inhibitor to reach any market and it is the first drug in its class indicated to stop a migraine headache after it starts following the drug's 23 December approval by the US Food and Drug Administration.

All three monoclonal antibodies against CGRP that are available in the US – Amgen Inc./Novartis AG's Aimovig (erenumab), Teva Pharmaceutical Industries Ltd.'s Ajovy (fremanezumab) and Eli Lilly & Co.'s Emgality (galcanezumab) are approved for migraine prophylaxis, not for acute (on-demand) treatment of migraine attacks. But while Ubrelvy gives Allergan and its acquirer AbbVie Inc. – under a $63bn merger that's expected to close early in 2020 – a first-in-class oral treatment for migraine headaches, competition is close behind. *(Also see "AbbVie Pounces On Chance To Buy Revenues In $63bn Mega-Deal For Allergan" - Scrip, 25 Jun, 2019.)*

Ubrelvy is the second oral drug approved in 2019 for the acute treatment of migraine headaches after the US FDA approved Lilly's Reyvow (lasmiditan) in October. Reyvow will launch after Lilly receives US Drug Enforcement Administration controlled substance classification of the serotonin (5-HT)1F receptor agonist; a DEA decision was expected within 90 days of FDA approval.

Reyvow and Ubrelvy could launch around the same time, since the 90-day wait for DEA scheduling of Lilly's drug should end in January and Allergan expects its drug to be available in the US during the first quarter of 2020. Also, Biohaven Pharmaceutical Holding Co. Ltd. expects an FDA decision on its oral CGRP inhibitor rimegepant in the first quarter of 2020.

ALLERGAN HAS AN EDGE WITH BOTOX IN MIGRAINE

Despite the near-term launch of multiple oral drugs for acute migraine treatment, Allergan's experience with Botox (onabotulinumtoxinA) in chronic migraine prevention puts the company in a good position to capitalize on its investment in Ubrelvy, which was licensed from Merck & Co. Inc. in 2015 along with atogepant, a second oral CGRP inhibitor that Allergan has in Phase III for migraine prevention. *(Also see "Allergan migraine portfolio grows with Merck CGRP antagonists" - Scrip, 8 Jul, 2015.)*

Botox probably is best known as a wrinkle-reducer, given the product's dominance in the medical aesthetics market. *(Also see "Medical Aesthetics: Key Players In A Largely Untapped Market" - Scrip, 10 Sep, 2018.)* However, the neurotoxin now makes more money from therapeutic uses than from aesthetics; migraine is Botox's biggest therapeutic indication. Allergan reported $928.7m in Botox sales during the third quarter, up 5.6% in the third quarter of 2018, including $525.5m in Botox Therapeutic and $403.2m in Botox Cosmetic sales.

In an interview before Ubrelvy's approval, Allergan's Aimee Lenar, vice president of gastroenterology and central nervous system marketing, noted that while there are about 8m migraine patients who take prescription medications to stop a migraine attack, there hasn't been a new acute treatment for migraine headaches in the US for more than 20 years.

She said about 15m prescriptions are written annually for the last major class of acute and preventative treatments to hit the market – the long-generic triptans.

"Given our incumbency in neurology, we have very good relationships with neurologists, but have also talked to a number of primary care physicians as well who are very active treaters of migraine and what we have heard loud and clear is that patients need a multi-modal approach to therapy," Lenar said. "For the acute treatment of migraine, patients are taking multiple options, both prescription and/or over-the-counter. An agent like this, ubrogepant, with this particular mechanism that this group of doctors would become more familiar with, it would become a much-needed option."

Botox, Ubrelvy and atogepant are key assets in Allergan's neuroscience franchise – one of the stand-out businesses in the company's portfolio. Neuroscience is seen as a key therapeutic area going forward for AbbVie as well as it looks for products to make up for revenue it stands to lose when top-selling biologic Humira (adalimumab) faces biosimilars in the US in 2023. AbbVie executives have cited Allergan's CGRP inhibitors as well as Vraylar (cariprazine) for schizophrenia and bipolar I disorder as particularly valuable assets in the companies' combined neurology portfolios. *(Also see "AbbVie Will Use Allergan Revenue To Fund Combined Firm's Large R&D Pipeline" - Scrip, 27 Jun, 2019.)*

MIGRAINE MARKET TOUGH TO PENETRATE

Given the size of the migraine market – Allergan noted there are 31m people who suffer from these debilitating headaches in the US – Ubrelvy has the potential to be a big-seller. However, the migraine market has proven to be tough to crack for the first round of CGRP inhibitors.

Companies selling these injectable treatments for the prevention of chronic and episodic migraine headaches have reported meager sales to date. Amgen, who with Novartis had a first-to-market launch with Aimovig, reported a decline in sales from $83m in the second quarter to $66m in the third quarter. *(Also see "Amgen's Q3 Sales Beat Consensus, But Two Key New Drugs Fell Short" - Scrip, 29 Oct, 2019.)*

Aimovig remains the top-selling CGRP inhibitor, however, as Lilly reported $48m in third quarter sales, which was up from $34m in the prior quarter. *(Also see "Lilly's Diabetes Franchise Poised For A Shakeup As Conterno Steps Down" - Scrip, 23 Oct, 2019.)* Teva's Ajovy turned in $25m in third quarter sales. *(Also see "Teva Turnaround Hung Up By The Uncertain Cost Of Settling Opioid Cases " - Scrip, 7 Nov, 2019.)*

Allergan will hit the ground running with a multi-modal advertising campaign to drive migraine patients into their neurologists' or primary care doctors' offices to seek access to Ubrelvy.

In the company's experience, Lenar told *Scrip*, "patients are very responsive to direct-to-consumer advertising. We do that today for Botox in terms of traditional television and robust digital and social initiatives and we plan to do that for ubrogepant as well." She noted that direct-to-consumer advertising for the injectable CGRP inhibitors in migraine prevention appear to be activating patients.

In a 23 December note on the approval, SVB Leerink analyst Marc Goodman called the drug's label "favorable," pointing out there is no "black box" warning about liver safety and said that bodes well for the class, including Biohaven's rimegepant. He added that key opinion leaders surveyed by Leerink "have indicated that they are also eager to try the oral CGRPs for their convenient dosing and good safety to date, and we believe both Ubrelvy and rimegepant could be substantial products as a result."

Ubrelvy is approved for 50mg and 100mg doses, based on Phase III trials of each dose, and the label outlines parameters for repeat dosing, which Goodman said is "a nod to its favorable safety." The label does outline acute therapy and its limitations, while clarifying that Ubrelvy is not indicated for prevention of migraine, the analyst added. Finally, he noted that the labeling outlines suggested use with the lower dose, 50mg, in patients with severe hepatic or renal impairment, including circumstances where a second dose could be warranted.

That label language "could foreshadow favorable labeling for rimegepant's potential approval given that, on a numerical case-by-case basis, we would argue that rimegepant has more "placebo-like" numbers versus that of Ubrelvy from clinical trials," Goodman wrote.

Allergan has not announced its pricing strategy for Ubrelvy.

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Astellas, Seattle Genetics Break Ground With US ADC Approval

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The US Food and Drug Administration (FDA) has granted accelerated approval to Astellas Pharma Inc. and Seattle Genetics Inc.'s first-in-class antibody-drug conjugate (ADC) Padcev (enfortumab vedotin-ejfv), providing a new treatment option for later-stage patients with a form of cancer that can currently be very difficult to treat.

The novel therapy, which targets the nectin-4 cell surface protein highly expressed in bladder cancer, has been cleared for the treatment of adults with locally advanced or metastatic urothelial cancer who have previously received a PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy, either as neoadjuvant therapy before surgery or adjuvant therapy post-surgery or in a locally advanced or metastatic setting.

While there have been other approvals in bladder cancer, Padcev is both the first treatment and first ADC to be approved specifically for this set of urothelial cancer patients, who have had limited options after the failure of initial therapies. Around 80,000 people are diagnosed annually with bladder cancer in the US, of which urothelial malignancy accounts for 90% of all cases and can also be found in the renal pelvis, ureter and urethra.

After binding to nectin-4, the ADC releases the anti-tumor agent monomethyl auristatin E into the malignant cell, which causes cell reproduction cycle arrest and programmed cell death (apoptosis).

Astellas and Seattle Genetics appear to be pretty much alone in the nectin-4 space. The only other company working on ADCs against this target is Bicycle Therapeutics Ltd., which has a couple of candidates for solid tumors but still at the preclinical stage, Biomedtracker shows.

The regulatory clearance was granted under the FDA's Accelerated Approval Program and based on tumor response rate; the scheme allows approval based on a surrogate endpoint if a drug fills an unmet medical need for a serious condition. The FDA also granted Padcev Priority Review and Breakthrough Therapy designation and the approval came approximately three months before the March 15th, 2020 PDUFA date.

Under the accelerated approval program, continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials. In Padcev's case, a global Phase III confirmatory clinical trial (EV-301) is already underway that is also intended to support further global registrations.

In the US, marketer Astellas noted it will be offering access and reimbursement support to patients through the PADCEV Support Solutions scheme.

PIVOTAL TRIAL RESULTS

The pivotal Phase II EV-201 trial for enfortumab vedotin-ejfv enrolled 125 patients with difficult-to-treat locally advanced or metastatic urothelial cancer, including those whose disease had spread to the liver, who had received prior treatment with a PD-1 or PD-L1 inhibitor and platinum-based chemotherapy.

The primary endpoint was confirmed objective response rate (ORR), which was 44% per a blinded independent central review (55/125; 95% confidence interval [CI]: 35.1, 53.2). 12% of patients treated with single-agent Padcev experienced a complete response, meaning no cancer could be detected at the time of assessment, while 32% had a partial response (ie, a decrease in tumor size or extent of cancer in the body).

The median duration of response, a secondary endpoint, was 7.6 months (95% CI: 6.3, not estimable).

The most common serious adverse reactions were urinary tract infection (6%), cellulitis (5%), febrile neutropenia (4%) and diarrhea (4%). The most common adverse reactions (≥20%) were fa-

tigue (56%), peripheral neuropathy (56%), decreased appetite (52%), rash (52%), alopecia (50%).

KEYTRUDA COMBO PROMISE?

The enfortumab ADC also gained a lot of attention at the recent European Society for Medical Oncology (ESMO) cancer congress in Barcelona, Spain, after promising Phase I results in combination with the PD-1 inhibitor pembrolizumab (Merck & Co. Inc.'s Keytruda) in the first-line setting in urothelial cancer. 45 previously untreated patients with locally advanced or metastatic urothelial cancer ineligible for treatment with cisplatin-based chemotherapy were treated with the combo. The ORR was a very high 71%.

In the pivotal KEYNOTE-052 trial that supported the approval of Keytruda monotherapy in first-line bladder cancer patients not eligible to receive platinum-based chemotherapy, Keytruda showed a 28.9% confirmed ORR, 8.1% of which were complete responses. The ORR was also higher than historical data for cisplatin-based combinations in first-line bladder cancer.

Astellas and Seattle Genetics have disclosed that they see the combination of enfortumab vedotin with Keytruda in front-line bladder cancer as even more crucial to the ADC's commercial success. In a late September comment following the "remarkably positive" top-line combination data, analysts from Informa's Biomedtracker said it will be interesting to see how the companies decide to proceed with registration-enabling studies for the combo.

"Keytruda's monotherapy use in first-line bladder cancer is currently limited to patients not eligible for cisplatin-based therapy and whose tumors express PD-L1 (combined positive score ≥10), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. The results shown here [in the combo study] are in a cisplatin-ineligible population, and at this time this seems to be the population that the company will move forward with," they predicted.

"However, with such promising response data, it would seem that a trial testing the combination beyond the cisplatin-ineligible population studied here could be a possibility. This in principle would maximize the number of patients treatable with the combination," they observed, saying that such plans (so far not confirmed) would be monitored.

Keytruda by itself has just been recommended by an FDA panel for treatment of adults with Bacillus Calmette-Guerin-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma-in-situ with or without papillary tumors, who are ineligible for or have elected not to undergo cystectomy.

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Lynparza Gets US OK For Pancreatic Cancer

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The US Food and Drug Administration has approved AstraZeneca PLC and Merck & Co. Inc.'s Lynparza (olaparib) for use in a third tumor type, pancreatic cancer, less than two weeks after its advisory panel gave a narrow nod to the new indication.

The PARP inhibitor has been approved for the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. The approval makes Lynparza the first targeted medicine in biomarker-selected patients with advanced pancreatic cancer; it is already approved in breast and ovarian cancer indications.

On 17 December, the FDA's Oncologic Drugs Advisory Committee (ODAC) voted narrowly (seven to five) in favor of Lynparza's approval, based on the pivotal POLO study which showed a near doubling of progression-free survival (PFS) in this subset of pancreatic cancer patients. In POLO, which was presented at the ASCO meeting in June and simultaneously published in the *New England Journal of Medicine*, the median PFS for Lynparza patients was 7.4 months compared with 3.8 months for those on placebo, with more than twice as many patients remaining progression free at both one year (34% vs. 15%) and two years (22% vs. 10%).

> Lynparza will get to plow a new market but the opportunity is relatively small.

Discussion at the panel meeting centered around two points: the lack of an overall survival benefit and the clinical relevance of the 3.6 month increase seen in PFS. The US agency usually likes to see an OS benefit before approving drugs for pancreatic cancer, but AstraZeneca argued that the gBRCAm study population (encompassing between 4% and 7% of pancreatic cancer patients) was too small to power the trial for OS.

With the US agency deciding in favor of approval on the back of PFS data alone, Lynparza will get to plow a new market. The opportunity is relatively small: SVB Leerink analysts say in a 30 December reaction note it is worth at peak $155m in the US and around $50 in the EU, comprising a relatively modest share (about 4%) of their $5.1bn worldwide peak sales forecast for the product. But, they maintain, it "could create a 'halo effect' for oncologists, potentially reinforcing the drug as the PARP of choice across multiple tumor types."

Patients will be selected for therapy based on an FDA-approved companion diagnostic for Lynparza, Myriad's BRACAnalysis CDx. An EU approval application for Lynparza in pancreatic cancer is under review.

Published online 31 December 2019

J&J's Spravato Gets EU Okay For Drug-Resistant Depression: **https://bit.ly/2tA59ra**

FDA CRL Delays ViiV's Long-Acting Cabotegravir Regimen

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The unexpected arrival of a complete response letter from the US Food And Drug Administration (FDA) means ViiV Healthcare will not be able to launch its long-acting double drug HIV-1 treatment next month, as it had confidently planned.

ViiV's head of R&D Kimberly Smith had told *Scrip* in an interview earlier in December that FDA approval of the combination was expected "imminently" and that the company was getting its manufacturing and commercialization processes "up and running" in preparation.

"Let's just imagine an army of Santa's helpers running around the manufacturing facilities making sure that everything is ready to go," Smith had said, reflecting confidence of an approval.

But on 21 December ViiV Healthcare in a brief statement said the reasons for the FDA complete response letter "relate to chemistry manufacturing and controls," and meant that "we will not meet our PDUFA action date of Dec. 29." Cabotegravir is an integrase strand transfer inhibitor developed by ViiV Healthcare (as a long-acting intramuscular injection version of its approved drug dolutegravir), while rilpivirine is a non-nucleoside reverse transcriptase inhibitor developed by Janssen Pharmaceuticals Inc. The long-acting regimen designed for monthly injection is an investigational product and not approved anywhere in the world.

"Patients have been hearing about the coming of this product for more than three years. This combination will offer people who have HIV a very unique and arguably transformative product, and many of them have told us that this product will have a tremendously positive impact on their lives," Smith had told *Scrip* earlier in December.

Not everyone has been as enthusiastic as Smith about the transformative and positive potential of the new monthly injection.

Analysts at SVB Leerink predicted in a 5 December note to investors that the approach would only take a small share of the HIV market. They acknowledged in their comments that "the major developers are all pivoting to the exploration of injectable treatment options, what could allow once monthly, or even less frequent, injectable treatments to control or prevent HIV infection," But they said the approach was "a strategy born of necessity, rather than demand" given all-in-one oral pills are approaching genericization.

While the long-acting injectable approach "sounds promising enough in theory," SVB Leerink's analysts said that "in fact [it] will impose large painful intramuscular injections on patients, and may result in even worse compliance than once daily tablets."

"It is hard for us to see that more than a relatively small minority of providers or patients will opt for such treatments," the analysts concluded.

ViiV Healthcare did not provide details about the FDA concerns that the group will need to address before an eventual approval can occur. Sources within the company did say that the FDA CRL reflected issues more to do with process controls rather than safety issues.

The company said it would now work closely with the FDA to resolve the agency's concerns, but could offer no guidance as to when that process would be completed.

The AIDS specialty company was founded in late 2009 and is majority owned by GlaxoSmithKline PLC, with Pfizer Inc. and Shionogi & Co. Ltd. as shareholders.

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Sub Q Entyvio Hits Speed Bump After US Complete Response:
https://bit.ly/2SX52Am

GSK Files Its BCMA Drug In Multiple Myeloma

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GlaxoSmithKline PLC has submitted a biologics license application to the US Food and Drug Administration for its anti-B-cell maturation antigen (BCMA) therapy, backed by detailed pivotal Phase II DREAMM-2 results showing the antibody-drug conjugate in late-stage multiple myeloma patients produced a good 31% response rate.

GSK on 16 December said full results from its DREAMM-2, published in *The Lancet Oncology*, were consistent with those seen in a similar subset of patients in the DREAMM-1 study, a Phase I/II in heavily pre-treated patients. *(Also see "Good DREAMM-1 Data Keeps GSK On Track For Multiple Myeloma Filing This Year" - Scrip, 25 Mar, 2019.)*

If approved, GSK's belantamab mafodotin, also known as GSK2857916, will be the first anti-BCMA agent available in the US.

Multiple myeloma is the second most common blood cancer and is generally considered treatable, but not curable, and often becomes refractory to available treatments.

BCMA has become an interesting new drug target in multiple myeloma, and GSK is ahead of other pharma companies developing a BCMA-targeting therapy for the disease.

BCMA normally promotes plasma cell survival by transduction of signals from

two known ligands, BAFF (B-cell activating factor) and APRIL (a proliferation-inducing ligand). This pathway is important for myeloma cell growth and survival.

"There is a lot of enthusiasm in the multiple myeloma community over BCMA as a target and belantamab mafodotin is positioned to be the first approved therapeutic targeting BCMA." Datamonitor Healthcare analyst David Dahan told *Scrip*.

Belantamab mafodotin uses a linker technology licensed from Seattle Genetics Inc. GSK is conducting a series of studies testing the effect of belantamab mafodotin as third-line monotherapy in relapsed/refractory multiple myeloma, as well as in combination with standard and novel treatments in the first- and second-line setting, as part of its broader DREAMM clinical development program.

GSK's anti-BCMA agent was granted breakthrough therapy designation from the FDA and PRIME designation from the European Medicines Agency in 2017. GSK is expected to file for EU approval in the first half of 2020. *(Also see "Myeloma BCMA Therapy In Spotlight: EMA Considers Fast Tracking GSK Filing " - Pink Sheet, 13 Nov, 2019.)*

Celgene Corp./bluebird bio Inc.'s BCMA-targeting CAR-T therapy, ide-cel, is likely to be the second anti-BCMA agent to market, as Celgene expects to file a US biologics license application to the FDA in the first half of 2020.

Belantamab mafodotin and competing ide-cel are being evaluated in fourth-line or later multiple myeloma patients.

The DREAMM-2 study evaluated 2 doses (2.5mg/kg and 3.4mg/kg) of belantamab mafodotin. The 196 patients in the study had previously received a median of seven lines of treatment and were refractory to a proteasome inhibitor, and an immunomodulatory agent, and had failed prior treatment with an anti-CD38 antibody.

Analysts at Jefferies said that, while the pivotal DREAMM-2 data confirmed belantamab mafodotin's likely role as salvage therapy in multiple myeloma, it left doubts about its use as an early treatment, due in part to concerns over ocular toxicity.

Still, Jefferies gave GSK's belantamab mafodotin a 80% probability of approval and predicted a commercialized product eventually generating worldwide peak sales of some $1.5bn, assuming use is largely in third-line and salvage treatment.

Published online 17 December 2019

Novartis Culls Fevipiprant After LackLUSTER Data

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Having already flopped as a treatment for moderate sufferers, Novartis AG has pulled the plug on its asthma drug fevipiprant following data which showed that the once-daily pill was not effective in sicker asthmatics either.

The Swiss giant announced topline results from pooled analyses of its Phase III LUSTER-1 and LUSTER-2 studies which show that fevipiprant, a prostaglandin DP2 receptor antagonist, did not meet the clinically relevant threshold for reduction in rate of moderate-to-severe exacerbation compared to placebo over a 52-week treatment period for either of the doses tested, 150mg or 450 mg). The studies included patients who had inadequately controlled moderate-to-severe disease despite receiving inhaled mid-to-high dose corticosteroids and at least one additional controller and while the drug was generally well tolerated, "the totality of these results do not support further development of fevipiprant in asthma," Novartis stated.

The LUSTER studies were part of the VIBRANT Phase III program, which also included the ZEAL-1 and ZEAL-2 studies, negative topline results from which were announced in October. The data revealed that fevipiprant had failed to reach the primary efficacy endpoint of forced expiratory volume (FEV1) improvement in two Phase III trials in patients with moderate asthma.

Fevipiprant Fails To Stand Up In Asthma Studies

Novartis seemed to believe the candidate would have a better chance of success in severe disease and as recently as the firm's R&D day on 5 December, research chief John Tsai spoke about the potential of the drug. He noted that uncontrolled Global Initiative for Asthma (GINA) 4/5 patients, particularly those with high blood eosinophils, were the target population for fevipiprant, which could have provided an alternative to inhaled corticosteroids.

Tsai said at the R&D meeting in London that fevipiprant was also being evaluated in asthmatics with nasal polyps and in chronic obstructive pulmonary disease patients. A spokesperson confirmed to *Scrip* that the COPD studies will also be terminated but based on the safety and tolerability findings from the program to date, the ongoing fevipiprant study for nasal polyps will continue as planned. *(Also see "Early Assets Excite At Novartis R&D Day" - Scrip, 6 Dec, 2019.)*

Bryan Garnier analyst Eric Le Berrigaud issued a note on 16 December claiming that "several times we called for caution about fevipiprant," starting back in the fall last year when the broker spoke to a specialist "who was not convinced at all by the drug they had in trials [as] the results were far less spectacular than with biologics."

He added that despite the ZEAL failures, successful LUSTER trials would have created "a multi-blockbuster product" in reference to Merck & Co. Inc.'s now-genericized asthma drug Singulair (montelukast) and concerns about its neuropsychiatric adverse events, "but we associated high peak sales potential with a low probability of success of 30%."

Le Berrigaud went on to say that while "we can imagine Novartis had high hopes for the drug but likely over a pretty long period of time," the company "pushed a lot against evidence and history in the DP2 class." Other drugs that have failed in this class for asthma include AstraZeneca PLC's AZD1981, Amgen Inc.'s AMG853, Actelion Pharmaceuticals Ltd.'s setipiprant and Boehringer Ingelheim International GmbH's BI 671800.

Despite the setback, Novartis said it would continue to invest into respiratory medicines, citing the once-daily triple combination inhaler QVM149 (indacaterol, glycopyrronium and mometasone) and dual inhaler QMF149 (indacaterol/mometasone). The company presented positive top-line results in October for uncontrolled asthma from the IRIDIUM and PALLADIUM Phase III trials. *(Also see "Novartis Primed To Re-Energize Respiratory Business, Rivals Close In" - Scrip, 2 Oct, 2019.)*

The Novartis spokesperson also told *Scrip* about QBW251, a "transformational oral therapy for COPD" which is in a Phase IIb study, and CSJ117, an inhaled formulation of a monoclonal antibody fragment targeting thymic stromal lymphopoietin (TSLP). The latter is a potential first inhaled biologic for severe asthma, which should start Phase IIb studies in 2020.

FUTURE OF RESPIRATORY IN DOUBT?

In terms of the pipeline, Le Berrigaud argued that with the culling of fevipiprant, Novartis's presence in the respiratory field is "weaker than ever." He added: "Of course, Novartis has new inhaled products coming but history says that from a commercial and marketing perspective, it has always proven difficult to compete against GlaxoSmithKline PLC and AstraZeneca."

He claimed that fevipiprant was a differentiated product but "Novartis no longer has this type of drug and the R&D subcommittee will have to ask itself the right questions going forward because the field can be expensive to invest in." The analyst concluded by saying that "the prospect of having no oral drug after inhaled and before biologics in severe asthma is very good news" for Sanofi's Dupixent (dupilumab), which inhibits the interleukin-4 and IL-13 proteins, as well as GSK's Nucala (mepolizumab) and AstraZeneca's Fasenra (benralizumab), which are IL-5 inhibitors for severe eosinophilic asthma *(Also see "Sanofi's €10bn Dupixent Plan: 'We're Going To Put The JAKs Properly In Their Place'" - Scrip, 12 Dec, 2019.) (Also see "AstraZeneca Gains US OK For Fasenra In Patient-Friendly Form " - Scrip, 4 Oct, 2019.)*

GOSSAMER SINKS

The decision to terminate fevipiprant has not only hurt Novartis. Gossamer Bio Inc., which also has a DP2 antagonist called GB-001 in Phase II development for rhinosinusitis and asthma, saw its shares fall in response to the LUSTER data, closing down 37% to $15.96 on 16 December. Data from Gossamer's moderate-to-severe eosinophilic asthma trial of GB-001 are due in early 2020. *Published online 17 Dec 2019*

Gilead's Bad Luck In NASH Continues With ATLAS Failure

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Gilead Sciences Inc.'s hopes for being a player in non-alcoholic steatohepatitis (NASH) combination therapy took a hit on 16 December, as the Phase II ATLAS trial investigating monotherapy and combinations of three different drug candidates failed to meet statistical significance with any cohort on a fibrosis-reduction endpoint – raising questions about whether Gilead has a path forward with any of the agents studied in ATLAS.

This is the second major R&D setback for Gilead in NASH this year, as in February its ASK1 inhibitor selonsertib failed to meet a primary endpoint of reducing fibrosis score by one stage or more without worsening of NASH in a Phase III trial. *(Also see "In NASH, Gilead Swung For The Fences And Struck Out Again" - Scrip, 12 Feb, 2019.)* Selonsertib is one of three experimental NASH compounds Gilead has been studying in ATLAS, along with Phase II cilofexor, an FXR agonist, and Phase II firsocostat, an ACC inhibitor. *(Also see "Gilead Increasingly Seems Focused On Combo Therapy In NASH" - Scrip, 12 Apr, 2019.)*

Gilead reported that in top-line data from the 392-patient ATLAS, no two-drug combo or monotherapy arm had achieved statistical significance compared to placebo on the endpoint of one-stage or more fibrosis reduction without worsening of NASH. The study's selonsertib monotherapy arms were discontinued before the readout due to the Phase III failure in February – Gilead no longer lists the drug as a NASH candidate, although it is studying the agent in diabetic kidney disease.

Eleven patients (15.5%) in the selonsertib/firsocostat arm (n=71) in ATLAS achieved the primary endpoint (p=0.62), while 13 patients (19.1%) hit the endpoint in a selonsertib/cilofexor arm (n=68) (p=0.26) and 14 patients (20.9%) hit the mark in a cilofexor/firsocostat arm (n=67) (p=0.17). The 33-patient firsocostat arm had a 12.1% success rate (p=0.94), while 11.8% succeeded in the cilofexor monotherapy arm (p=0.96).

Gilead noted, however, that the cilofexor/firsocostat arm did achieve statistical significance in multiple measures of fibrosis and liver function, including a two-stage or greater improvement in non-alcoholic fatty liver disease score

(NAS), and one point or greater reductions in liver fat, hepatocellular ballooning and lobular inflammation. The combo also produced statistically significant improvements from baseline on a number of non-invasive tests of fibrosis, liver injury and liver function, including AST, ALT and bilirubin levels as well as the ELF (enhanced liver fibrosis) blood test.

FDA drug development guidance for NASH established two surrogate endpoints for pivotal trials - one stage or greater improvement in fibrosis score without worsening of NASH or resolution of NASH without worsening of fibrosis. *(Also see "NASH Drug Development Guidance Encourages Sponsors To Adopt Innovative Trial Designs" - Pink Sheet, 4 Dec, 2018.)*

OPINIONS VARY ON GILEAD'S NEXT STEPS IN NASH

Jefferies analyst Michael Yee offered hope for the cilofexor/firsocostat doublet in a 16 December note, pointing out that expectations for the ATLAS study weren't very high to begin with, as the size of the various cohorts made it difficult to meet statistical significance on the primary endpoint.

"While failing to achieve the primary endpoint, the study showed several signals of efficacy in the combo cohorts which in our view justify a discussion with regulatory agencies and the potential initiation of a larger Phase IIb study," he wrote. "While NASH will not be a driver for shares of Gilead in the near-term, we like the optionality that it presents."

SVB Leerink analyst Geoffrey Porges acknowledged the slivers of hope presented by the ATLAS secondary endpoint findings but wondered what value those data really offer to Gilead. In a 16 December note, he asserted that Gilead might continue to pursue NASH R&D but only if the costs aren't prohibitive and that NASH would remain a very secondary position compared to the company's ambitions in cancer immunotherapy.

"The company indicated that they will continue to examine the data and speak with regulators to determine if a potential path forward exists for this program," Porges said. "These results seem to validate our belief that NASH is a very complex disease that seems a relatively low probability investment for Gilead investors."

JMP Securities analyst Liisa Bayko focused on what Gilead's latest NASH stumble means for other companies in the space, saying the ATLAS data offer "positive read-through" for Intercept Pharmaceuticals Inc. with obeticholic acid and Madrigal Pharmaceuticals Inc. with resmetirom. *(Also see "Intercept's NASH Drug Delayed By April Advisory Committee, But Firm Is Ready For Launch" - Scrip, 16 Dec, 2019.)*

"Intercept [OCA] continues to be the only NASH medicine with proven anti-fibrotic effects and while there are differences in mechanism and development stage between selonsertib, cilofexor and firsocostat and Madrigal's resmetirom (THR-beta agonist), we view the disappointing data of a later-stage competitor as an incremental positive."

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Intercept's Early NASH Efforts Will Stress Advanced Fibrosis: **https://bit.ly/36y1fgP**

BioMarin Eyes Late 2021 Launch As Achondroplasia Drug Succeeds In Phase III

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BioMarin Pharmaceutical Inc. will meet with regulators in the first half of 2020 to discuss filings for vosoritide in the treatment of achondroplasia – the most common cause of short stature, or dwarfism – now that the drug has succeeded in a 121-patient Phase III clinical trial.

The company said on 16 December that children who were treated with the therapy gained 1.6cm more in height over a year of treatment than those who received a placebo; a Phase II/III study in babies and toddlers is ongoing. Most side effects were mild with transient injection site reactions as the most frequent adverse events (AEs); there were no serious AEs.

Hank Fuchs, BioMarin's president of research and development, told *Scrip* that given feedback the US Food and Drug Administration solicited from patient advocates and key opinion leaders last year, the company will seek approval to treat children with achondroplasia based on vosoritide's Phase III efficacy in children ages 5 to 14 and safety data from a study under way in newborn through five-year-old patients. The timing of BioMarin's filings will be based on feedback from the FDA and other regulators during the first half of 2020, but Fuchs said the company anticipates a product launch later in 2021.

San Rafael, CA-based BioMarin did not report any secondary endpoint results for vosoritide – a once-daily injection of an analog of C-type natriuretic protein (CNP) – and provided minimal top-line data for the Phase III study's primary endpoint, which was the change in growth velocity from baseline to 52 weeks versus placebo. Secondary endpoints included changes in height Z-scores (a measure of growth versus age-appropriate expectations) and assessments of upper-to-lower limb body ratios.

"Lack of secondary endpoint data in today's data release is not surprising, in our view, as our previous expert discussion indicated it would take about one to two years to detect meaningful changes in these endpoints," Jefferies analyst Eun Yang wrote in a same-day note.

BioMarin intends to provide more detailed data in a future medical meeting presentation or medical journal publication. Nevertheless, the company's stock closed up 4.2% at $83.50 based on the top-line release.

The results did not show how many centimeters patients grew in the vosoritide and placebo groups, only that children who were injected with the drug gained 1.6cm more than those who received a placebo. Fuchs said a 1.6cm gain is close to a normal increase in growth velocity.

"For achondroplasia, which is the most common form of disproportionate short stature, all of the morbidity results from a mutation [in the fibroblast growth factor receptor 3 (FGFR3) gene] that affects bone growth," he explained. "So, measuring a near-normal correction of bone growth means that – in addition to the potential for statural or height benefits – over time, the improvement in bone health and growth will translate into other health benefits for achondroplasia."

Complications of achondroplasia include spinal cord compression, sleep apnea, bowed legs, mid-face hypoplasia, permanent sway of the lower back, spinal stenosis and recurrent ear infections. Some of these conditions may require surgery and can lead to early mortality.

PHASE II HEIGHT GAIN WAS SLIGHTLY GREATER

While the Phase III result for vosoritide is slightly below the 2cm placebo-adjusted gain observed in 10 children treated with the same 15µg/kg dose in the company's Phase II study, "this may in part be attributed to differences in baseline characteristics between the trials," William Blair analyst Tim Lugo said in a same-day note.

"For example, patients in the Phase III trial had a mean age of 8.7 years at enrollment compared with 8 years for those in the Phase II trial, and the Phase III trial also had a lower proportion of patients with a rating of 1 on the Tanner scale (a measure of sexual maturity; 79.3% vs. 100%) and different distribution of sex (52.9% male vs. 40% male), which may have contributed to a slightly higher baseline [annual growth velocity (AGV)] of 4.2cm/year vs. 4cm/year in the Phase II trial," Lugo continued.

He said the Phase III results should support approval in achondroplasia, which has no approved therapies, and forecast that vosoritide likely will achieve blockbuster status with annual sales approaching $1bn by 2026.

Jefferies analyst Yang predicted about $410m in sales for vosoritide in 2023 assuming an annual list price of about $160,000, based on prior comments from BioMarin that a $100,000-$200,000 range would be appropriate.

However, Oppenheimer analyst Leland Gershell noted that a competing therapy with less frequent dosing from Ascendis Pharma AS is in development with a Phase II study under way in two- to 10-year-old achondroplasia patients.

"While we expect vosoritide to be the first drug approved for this condition, ASND's once-weekly CNP analog being just a few years in development behind causes us to hold a tempered view of vosoritide's longer-term prospects," Gershell said on 16 December.

But BioMarin has the benefit of having longer-term efficacy data for the patients treated in its Phase II open-label extension study. The company reported 4.5-year results during its R&D day in November in comparison with age- and gender-matched children from a natural history study it conducted, which showed that patients treated with vosoritide for 54 months gained 9cm compared to expected growth in this population.

LONGER, EARLIER TREATMENT IS BIOMARIN'S GOAL

Vosoritide is being tested in children under the age of 18 whose growth plates have not closed, which represents about 25% of the achondroplasia population and is the intended commercial population.

"If you're 17 years of age, you've only got your growth plates open another year, so the maximum benefit you could get is that 1.6cm," Fuchs said. "Whereas if you start when you're zero years of age, the final adult height in an achondroplastic individual is around 50cm of deficiency, so the earlier you start the better you are going to be. Where exactly that time of most appropriate and safe start is is going to be informed by the [Phase II/III] study we have ongoing."

Patients in the completed Phase III study already have experienced some degree of the effects of achondroplasia on their growth plates, but BioMarin sees this trial as "a stepping stone into a larger universe of opportunity, which is the longer that you give it the better the outcomes are going to be and the earlier you give it the better the outcomes will be," Fuchs said. "What [the data] today shows is that it's unequivocally vosoritide that's doing the work compared to placebo."

The company divided its ongoing placebo-controlled Phase II/III study in 70 babies and toddlers into three parts; the first cohort is enrolling children from 2 to 5 years of age, the second includes children from six months to 2 years old, and the third is enrolling babies from zero to 6 months of age.

"Since this is the period of maximum change in the body in terms of both elongation but also things that happen at the base of the neck and the spinal canal, this is the population in whom we hope to make the most profound effect over a longer period of time; those data are probably a year or so behind where we are today with today's [Phase III data] announcement," Fuchs said.

BioMarin has not reported data to date that show how the long-term growth velocity gains in the Phase II study translated into effects on achondroplasia-related conditions, like spinal cord compression, bowed legs and sleep apnea, but five-year results are expected soon that may shed some light on vosoritide's efficacy beyond height gains, the company told *Scrip*.

BioMarin believes its data to date are sufficient for approval, however, after an advisory committee the US FDA hosted in May 2018 about clinical trials in achondroplasia, Fuchs said.

The feedback then supported growth velocity as the primary endpoint for studies in the disease, but advisory committee members also wanted drug developers to study sleep apnea, ear infections, quality of life and other complications of achondroplasia. The committee also said they would have preferred a two-year study to support BioMarin's filing for vosoritide instead of the one-year trial the company conducted.

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Scrip's **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

PIPELINE WATCH, 20 DECEMBER 2019–2 JANUARY 2020

Event Type	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)
Phase III Top-Line Results	Poxel/ Sumitomo Dainippon	imeglimin	Diabetes Type 2	TIMES 2; Positive Results	0
Phase III Top-Line Results	Lexicon Pharmaceuticals, Inc.	Zynquista (sotagliflozin)	Diabetes Type 2	SOTA-EMPA; Primary, Secondary Endpoints Achieved	0
Phase III Top-Line Results	Stealth BioTherapeutics Inc.	elamipretide	Primary Mitochondrial Myopathy	MMPOWER-3; Missed Primary Endpoints	0
Phase III Top-Line Results	Axsome Therapeutics, Inc.	AXS-07 (meloxicam/rizatriptan)	Migraine, Acute	MOMENTUM; Met Co-Primary Endpoints	10
Phase III Top-Line Results	Sol-Gel Technologies Ltd.	Twyneo (tretinoin/benzoyl peroxide)	Acne	SGT-65-04, 05; Positive Data	3
Phase III Top-Line Results	Incyte Corp.	itacitinib	Graft vs. Host Disease	GRAVITAS-301; Missed Primary Endpoint	0
Phase III Top-Line Results	Novan Therapeutics	SB206	Molluscum Contagiosum	B-SIMPLE1, 2; Mixed Results	0
Phase III Trial Initiation	ContraFect Corporation	exebacase	S Aureus Bacteremia, Endocarditis	DISRUPT; A Direct Lytic Agent	34
Phase III Trial Initiation	Bausch Health/Novaliq GmbH	NOVO3 (perfluorohexyloctane)	Dry Eye Disease	NVU-003; First-In-Class Tear Film Stabilizer	27
Phase III Trial Initiation	Phathom Pharmaceuticals	vonoprazan	H. pylori Infection	PHALCON-HP; w/amoxicillin, clarithromycin	61
Phase III Trial Initiation	Akari Therapeutics, Plc	nomacopan	Transplant-Associated Thrombotic Microangiopathy	Pediatric HSCT-TMA; Complement/Leukotriene Inhibitor	37
Phase III Trial Initiation	BioXcel Therapeutics, Inc.	BXCL501 (dexmedetomidine)	Agitation in Schizophrenia, Bipolar Disorder	SERENITY I,II; Sublingual, Adaptive Studies	39
Phase III Trial Initiation	Mithra Pharmaceuticals SA	Donesta (estetrol)	Menopause Symptoms	E4 Comfort; In Europe, Russia, South America	0

Source: Biomedtracker | Informa, 2020

Knighthood For AstraZeneca's Mene Pangalos

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AstraZeneca's R&D chief Mene Pangalos has been awarded a knighthood in the New Year 2020 Honours List in recognition of his services to UK science.

Pangalos was among over 1,000 people to be awarded on 28 December, the knighthood being one of the highest honors bestowed by the Queen.

Since joining AstraZeneca in 2010, Pangalos has overseen a renaissance in the company's pipeline, and is credited with being the driving force behind an almost five-fold improvement in R&D productivity over the period.

Drugs developed and launched in the period include cancer treatments Lynparza and Tagrisso, both now blockbusters, which have helped revive the company's fortunes.

Also named in the New Year Honours List were many famous names, such as musician Sir Elton John and cricketer Ben Stokes, while numerous high-profile people from the world of healthcare were also recognized.

These included Dennis Gillings, founder of clinical research organisation Quintiles (now IQVIA), who received a knighthood for his services to the advancement of research into dementia and life sciences, including founding and leading the World Dementia Council.

OTHER HONOURS

Also knighted were NHS England's Simon Stevens, for services to the health service in England, and Jonathan Symonds, current chair of Genomics England and Deputy Group chairman of HSBC bank, and former chief financial officer of AstraZeneca, for services to UK Life Sciences and to finance.

Professor Dame Sally Davies, former chief medical officer for England, was awarded the Order of the Bath, for services to public health and to research.

Responding to the news, AstraZeneca's chief executive Pascal Soriot said: "Mene's knighthood is fitting recognition of his outstanding talent and commitment to UK science and drug discovery which is helping bring innovative new medicines to patients around the world."

Praising his transformation of drug discovery and development at the company he added that Pangalos was now accelerating efforts in the digital transformation of R&D.

Pangalos said: "I am truly humbled and immensely honored to receive this award and feel incredibly fortunate to have worked alongside so many talented colleagues and collaborators through my career. The UK is one of the best places in the world to do applied research, and life sciences clusters such as the one in Cambridge drive the convergence of scientific innovation and talent, enabling us to better turn science into life-changing medicines."

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APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Stephanie Fagan	Acadia Pharmaceuticals Inc	Chief Communications Officer and Senior Vice President, Corporate Affairs	bluebird bio Inc	Senior Vice President, Corporate Communications	18-Dec-19
Kristina Ingvar	BoneSupport AB	Executive Vice President, Quality Management and Regulatory Affairs	Novo Nordisk	Global Program Vice President, Regulatory Affairs	1-Apr-20
Kathryn Metcalfe	Bristol-Myers Squibb Co	Executive Vice President, Corporate Affairs	CVS Health	Chief Communications Officer	6-Jan-20
David Meek	FerGene	Chief Executive Officer and President	Ipsen Group	Chief Executive Officer	14-Jan-20
Joseph Horvat	Oncopeptides AB	President, North America	EMD Serono	Senior Vice President, Oncology Business Unit	2-Dec-19
Michael Frank	Revive Therapeutics Ltd	Chief Executive Officer and Chairman	Mifran Consulting	President	18-Dec-19

Click here for all appointments: https://bit.ly/2oHWRYn

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