BioCentury
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PREPPING FOR PCSK9s

BY ERIN MCCALLISTER, SENIOR EDITOR

By securing Priority Review for Praluent alirocumab, Sanofi and Regeneron Pharmaceuticals Inc. deprived Amgen Inc. of what could have been a three-month head start with its competing PCSK9 inhibitor. But the partners also put themselves in the position of going first in what could be a game of chicken with payers.

Thanks to the use of a Priority Review voucher, the BLA for Sanofi and Regeneron's Praluent alirocumab to treat hypercholesterolemia has a July 24 PDUFA date. Amgen's PCSK9 inhibitor evolocumab has an Aug. 27 PDUFA date.

The proximity of the expected approvals, and the comparability of the published data on the two mAbs, together make the category ripe for a battle for exclusive formulary placement, with pricing and rebates as the only weapons.

While Sanofi and Regeneron will co-promote Praluent in the U.S., the pharma will lead commercialization. As the first mover, Sanofi has at least three options when it comes to setting the price: set the price for Praluent at the high end of the expected $7,000-$12,000 annual cost range with no rebates; set the price high but offer rebates at launch; or set a lower price and wait until Amgen's evolocumab is launched to start negotiations with payers.

In the first scenario, Sanofi would catch the ire of payers and gain little in the process as five weeks is not much time to build patient and prescriber preference for a new drug — especially with the prior authorization and step therapy requirements payers are planning to impose.

If Sanofi instead offers discounts from the start, it could be seen as a show of good will, resulting in more relaxed prior authorization or step therapy requirements. It would also put the onus on Amgen to offer similar or even greater discounts.

"AT LAUNCH, WE WILL HAVE A COMPREHENSIVE UTILIZATION MANAGEMENT STRATEGY, INCLUDING PRIOR AUTHORIZATION CRITERIA AND STEP THERAPY."

DAVID LASSEN, PRIME THERAPEUTICS

However, both that scenario and the third option, launching with a lower price, run the risk of leaving money on the table.

Three payers contacted by BioCentury said they would restrict access to only severely ill patients if the launch price is too high and unaccompanied by rebates, while one payer said it would consider giving Praluent exclusive formulary status if the rebates under the second scenario are large enough. Others have said they will wait until both drugs are on the market before wheeling and dealing for exclusive formulary status.

Sanofi wouldn't comment on how it will price Praluent or on what it has learned from recent commercial missteps with Zaltrap ziv-aflibercept and Lantus insulin glargine in the U.S.

The pharma had to give 50% rebates on cancer drug Zaltrap because the launch price was too high. And in 3Q14, the pharma revealed it was forced to give steep rebates for its diabetes product Lantus insulin glargine to maintain formulary access, resulting in a flat 2015 sales forecast for its diabetes franchise.

The pharma did say it will use its launch experience with Lantus and cardiovascular drug Plavix clopidogrel to help it build market share for Praluent among high-risk patients who either cannot tolerate statins or who need additional LDL control on top of available drugs.

Amgen said it will draw on its experience in bringing its osteoporosis biologic Prolia denosumab to a primary care market.

ON WATCH

Payers have been planning for Praluent and evolocumab because they would be the first biologics in a market dominated by small molecules and cheap generics — meaning they could translate into huge increases in drug costs.

In a February blog post in *Health Affairs*, CVS Health Corp. CMO Troyen Brennan and colleagues estimated that PCSK9s could cost about $7,000-$12,000 per year. He did not describe how he came up with the number and did not respond to BioCentury's request for clarification.

Praluent is under review for patients at high risk of cardiovascular events whose cholesterol can't be controlled with statins alone, or who cannot tolerate available therapies, or who have heterozygous familial hypercholesterolemia (heFH). Amgen wouldn't say what specific indications it is seeking; however, evolocumab's BLA includes data from trials in the same populations that Sanofi and Regeneron tested Praluent, as well as in patients with homozygous familial hypercholesterolemia (hoFH), an indication for which evolocumab has Orphan Drug designation. HoFH patients make up about 1% of the high-cholesterol population.

Jay Edelberg, head of the PCSK9 development and launch unit at Sanofi, estimates the size of the market in the U.S., EU and Japan to be about 24 million patients.

Brennan and colleagues estimated the total population in the U.S. could be about 15 million. Brennan estimated that annual costs in just the high-risk populations could be over $36 billion.

Amgen spokesperson Cuyler Mayer told BioCentury cost estimates like this "are exaggerated. The entire market for statins at its peak in the U.S. was $20 billion in a much larger eligible population."

Michael Sherman, CMO at regional insurer Harvard Pilgrim Health Care Inc., told BioCentury his organization has had some discussion with the manufacturers so the new drugs won't be a shock to the system.

"We've also had discussions already around what are the different populations that could benefit most, and will we restrict or will we not restrict with certain populations," he said.

He added he's not afraid to simply deny access if the costs are too high.

"If these are high cost, we will have the ability to block access immediately, and we are willing to play that card because these are really only a month apart. Now there might be a few people out there that are highly uncontrolled and need access immediately, and in these cases, we'd consider approving it; otherwise, we'd just wait," he said.

PBM Prime Therapeutics LLC also is preparing tactics to limit use.

"At launch, we will have a comprehensive utilization management strategy, including prior authorization criteria and step therapy," said David Lassen, chief clinical officer.

"We want to ensure that we have the right balance with prior authorization and utilization management to make sure that patients feel better and live well, but also that we can manage the total cost of care," he added.

Steve Miller, CMO at Express Scripts Holding Co., said because of their similar efficacy, PCSK9 inhibitors represent another opportunity to pit the companies against each other to extract discounts in exchange for exclusive or preferred formulary status.

Fifty two-week data from Phase III trials of the mAbs — the most comparable data sets available so far — showed LDL reductions up to 57% for Praluent and evolocumab. Praluent also reduced LDL by up to 52% after 24 weeks of treatment and evolocumab reduced LDL by up to 75% at 12 weeks.

SHOOTING HIGH

The price Sanofi sets for Praluent will set the tone for payer negotiations — and probably the ceiling for the market. For that reason, Roger Longman thinks Sanofi is better off coming out high and delaying rebates until Amgen is on the market.

Longman is CEO of reimbursement consultancy Real Endpoints LLC.

"They have to think about pricing not just at launch, but what's going to happen over the next two to four years. And what's going to happen to pricing is that it will have significant and inevitable downward pressure as the new entrants come in," he said.

Behind evolocumab, Pfizer Inc.'s PCSK9 inhibitor bococizumab is in Phase III testing. ETC-1002 from Esperion Therapeutics Inc. is in Phase II testing. ETC-1002 is a small molecule AMP-activated protein kinase (AMPK) activator and ATP citrate lyase (ACL) inhibitor, but it is targeted at the same populations likely to be treated with PCSK9s.

Longman thinks Sanofi should set the price of Praluent at the high end of the range payers are expecting, or about $11,000-$12,000. He thinks payers won't even consider exclusive formulary deals until Amgen's drug is available; therefore, offering rebates at launch would be premature because he doesn't think the pharma would gain anything.

"Under this scenario, they would assume that the price is going to go down over time as more drugs enter the market from Pfizer and Esperion, so maybe they could try to keep the price high, not do rebates at launch just like Gilead, and essentially self-restrict to only the sickest patients like those with familial hypercholesterolemia," Longman said.

Once Amgen enters the market, both companies could start to negotiate rebates and access with payers. However, Longman doesn't think the rebates should be too large, otherwise the companies risk creating a very rapid race to the bottom like in HCV (see "HCV Recap, ICYMI").

"Companies have to figure out an approach to pricing that allows them to discount more slowly and gradually than what happened in HCV. The only way to do that is by being much smarter about going after the niches in which you can provide the greatest value, the most obvious value," he said.

Longman suggested a rebate of about 10% once both drugs are launched would be reasonable, because the rebate will only increase once new entrants like bococizumab are launched.

REBATING EARLY

Ken Wong, associate professor in the school of pharmacy at Keck Graduate Institute, agrees that Sanofi will likely need to price at the high end of the range payers are expecting, but he said strictly following the Gilead model would only antagonize payers.

"There is a risk Sanofi carries in being too aggressive with their price if they aren't matching that with rebates or at least being engaged with and having an open dialogue with payers about their willingness to offer rebates once a competitor comes to the market," Wong said.

HCV RECAP, ICYMI

As new mAbs against PCSK9 are launched, payers and manufacturers alike will be working within a new pricing and reimbursement paradigm shaped in large part by the launches of HCV drugs by Gilead Sciences Inc. and AbbVie Inc. — but with some key differences.

To recap: payers were caught flat-footed when Gilead launched Sovaldi sofosbuvir in December 2013 at a WAC of $84,000 per 12-week course of therapy, with no rebates. Gilead's combo product, Harvoni ledipasvir/sofosbuvir, followed last October with a $96,000 WAC for a 12-week course.

Infuriated by the price for a drug in high demand for millions of patients and fearing the drug's budget impact, payers and PBMs restricted use to only the sickest patients and vowed to start a price war as soon as competition was available. As a result, AbbVie was able to launch Viekira Pak paritaprevir/ritonavir/ombitasvir/dasabuvir with an exclusive contract with Express Scripts Holding Co. by offering a steep rebate, sparking competition for contracts based on how low each company would go.

Gilead captured the lion's share of exclusive deals with private payers and PBMs, including Anthem Inc., Humana Inc., UnitedHealth Group Inc. and CVS Health Corp., but it came at a price. The biotech forecast that its average rebate for its HCV drugs in 2015 would be about 46%, up from 22% in 2014.

Gilead and Abbvie got co-exclusive placement with Prime Therapeutics LLC, and on its 4Q14 earnings call in January, AbbVie said it has reached exclusive deals "with a number of different regional" payers and PBMs, including Blue Shield of California. AbbVie hasn't disclosed its rebates.

The similarities with the PCSK9 inhibitors are that in both cases, the new drugs provide breakthroughs for patients who did not get enough efficacy or could not tolerate the side effects of much cheaper standard of care. Also in both cases, the efficacy between the competing drugs was indistinguishable to payers.

However, in HCV, the Gilead regimen was more convenient than AbbVie's, with once-daily dosing, and carried fewer contraindications.

In contrast, Praluent alirocumab from Sanofi and Regeneron Inc. and evolocumab from Amgen Inc. have identical dosing regimens and similar safety profiles, which makes picking one mAb over the other easier.

Also, Gilead had a one-year head start, while Sanofi and Regeneron probably will have just a five-week lead on Amgen, potentially allowing payers to negotiate rebates almost immediately and possibly before a single patient ever receives one of the new mAbs.

— ERIN MCCALLISTER

"WE TYPICALLY SEE QUICKER AND EARLIER ADOPTION WITH SPECIALISTS, AND WE ARE REALLY FOCUSING ON THESE HIGH-RISK PATIENT SEGMENTS."

VICTORIA CAREY, SANOFI

While he couldn't give an exact range that might be appropriate, he suggested 30% would be too high a jumping-off point given the expectation that rebates will increase as new entrants come in.

Wong was previously director of health economics and outcomes research at Bristol-Myers Squibb Co. and Novartis AG. Prior to that he led pharmacy departments at Cigna Corp. and CVS Caremark.

Sherman said if Sanofi set a high list price but offered an aggressive rebate that is good for a limited time, the pharma could lock up health plans even before evolocumab comes out. In fact, he said if the rebate were large enough, Harvard Pilgrim might consider an exclusive contract, though he declined to specify how high the rebate or low the final cost would need to be.

"In this case, they're negotiating against themselves, but there will be a choice in the near future and it might be a better alternative than getting into a bidding war," he said.

Prime's Lassen would not go so far. "With the close proximity at which they're both coming to market, it may be premature to say that the first company could land an exclusive deal out of the gate," he said.

MODERATE STANCE

Gary Cohen, executive director of the Specialty Pharmacy Certification Board, thinks Sanofi should come in with a more moderate price.

"My advice to Sanofi would be to pick a price that is competitive so that they don't get in a situation where the PBM says: 'We don't want to reimburse at all, and when another drug comes out we'll exclude you,'" said Cohen, who is also the founder and former CEO of the National Association of Specialty Pharmacy.

Cohen thinks starting at a moderate price to win over payers and using the first year or so on the market to collect real-world evidence and outcomes data could allow the companies to avoid rebates in the first few years while they build the value case.

Data from ongoing CV outcomes trials of each mAb are expected by YE17.

"Be selective on your patients at the launch, do good outcomes studies to show what the savings are downstream with reductions in cardiovascular events and co-morbid conditions, and then start negotiations about greater access," Cohen said.

Access to larger populations usually equates to increased rebates, but Cohen said that wouldn't necessarily have to be the case if the companies can show significant benefits.

"If you're looking at the drug that is going to cost $7,000-$10,000 per year but you demonstrate that you can use pharmaceutical care to offset costs like hospitalizations or cardiovascular events that are very costly — just going to the hospital right now to do a CAT scan to detect blockage could be $8,000-$10,000 — the cost benefit from the drug could be tremendous," Cohen said.

Wong cautioned that if Sanofi leaves too much on the table by setting too low a launch price, it would be detrimental to the whole class. And even with a mid-range price at launch, Sanofi could leave the door open for Amgen to launch simultaneously with rebates and exclusive contracts.

"I wouldn't be surprised to see that happen with one of these drugs," Wong said.

Express Scripts' Miller said the PCSK9 market is already shaping up to be different from HCV, which could mean negotiations and discounts at launch or a mid-range price.

"The discussions we're having now with manufacturers suggest that they are very interested in bringing these products to market in a way that maximizes the value to patients while also being cognizant of the effect the new class will have on payers.

"That is not to say that we aren't going to work really hard to get the best price for our clients," Miller said.

Miller did not comment on whether the PBM would consider an exclusive deal for Praluent prior to the launch of evolocumab.

SANOFI'S PLAN

Sanofi would not discuss its pricing or rebate strategy this early in the game, but the company did say its launch strategy will start with cardiologists, with whom the pharma has not only established relationships, but also experience in launching first-in-class drugs.

"We're committed to establishing the appropriate price based on the value that Praluent has, and we are in the midst of doing a lot of different research about the value that our program brings to patients and payers," Victoria Carey told BioCentury.

Carey joined Sanofi last year as VP global/U.S. head of alirocumab. Previously, Carey was VP of global commercialization for cardiovascular products at BMS, and prior to that she was the U.S. commercial lead for BMS's melanoma drug Yervoy ipilimumab.

"If you look at other cardiovascular drugs, especially first-in-class, we typically see quicker and earlier adoption with the specialists, and we are really focusing on these high-risk patient segments," she said. "They are customers that are very well-known to us and have worked with our representatives and our teams for years."

Other first-in-class cardiovascular drugs on Sanofi's résumé include Plavix and Lovenox enoxaparin.

"BE SELECTIVE ON YOUR PATIENTS AT THE LAUNCH, DO GOOD OUTCOMES STUDIES TO SHOW WHAT THE SAVINGS ARE DOWNSTREAM WITH REDUCTIONS IN CARDIOVASCULAR EVENTS AND CO-MORBID CONDITIONS, AND THEN START NEGOTIATIONS ABOUT GREATER ACCESS."

GARY COHEN, SPECIALTY PHARMACY CERTIFICATION BOARD

Both drugs are now generic. However, Plavix was the first blood thinner in the class of purinergic receptor P2Y G protein-coupled 12 (P2RY12) antagonists and quickly became standard of care for multiple cardiovascular indications, including acute coronary syndrome (ACS). Lovenox is an injectable low-molecular weight heparin approved for multiple indications, including deep vein thrombosis (DVT) and venous thromboembolism (VTE).

Sanofi also expects to draw on its experience on the primary care side.

"We're the company that taught primary care doctors to prescribe insulin and teach patients how to inject themselves, and we will be taking that knowledge and incorporating it into the launch of Praluent," Carey said.

Both of the anti-PCSK9 mAbs are self-administered and the companies tested both monthly or bi-weekly injections in their clinical programs, but would not disclose which dosing regimens were being considered for approval.

Carey also said there is "lots that can be done," in the first five weeks before Amgen's drug is launched to build demand for Praluent, but she declined to elaborate.

She added that the pharma is doing pharmacoeconomic analysis that it plans to share with payers.

AMGEN'S PLAN

Amgen also said it is paying attention to payers' concerns about the potential high costs of the new PCSK9 inhibitors, but declined to discuss pricing or rebates.

"It is incumbent upon us to work with payers at the appropriate time and educate them on the unmet need for the significant portion of patients who, for a variety of reasons, cannot get to the LDL goal," Mayer said.

He added, "We are one of the few companies in the industry that has experience launching an injectable monoclonal antibody in both specialty and primary care settings."

The biotech launched Prolia, a mAb against RANKL, in 2010. Much like hypercholesterolemia, osteoporosis was dominated by cheaper small molecules and soon-to-be generics. Another similarity is that Prolia had greater efficacy than bisphosphonates in clinical trials. However, the mAb's label carried warnings about the risk of infection.

"It was the first biologic in this primary care area, and we recognized that it was a new paradigm, not just in the treatment of women with postmenopausal osteoporosis at high risk of fracture, but also for physicians in general, and that adoption would take time," said Mayer. bc

COMPANIES AND INSTITUTIONS MENTIONED

AbbVie Inc. (NYSE:ABBV), Abbott Park, Ill.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Anthem Inc. (NYSE:ANTM), Indianapolis, Ind.
Blue Shield of California, San Francisco, Calif.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Cigna Corp. (NYSE:CI), Bloomfield, Conn.
CVS Health Corp. (NYSE: CVS), Woonsocket, R.I.
Esperion Therapeutics Inc. (NASDAQ:ESPR), Plymouth, Mich.
Express Scripts Holding Co. (NASDAQ:ESRX), St. Louis, Mo.
Gilead Sciences Inc. (NASDAQ:GILD), Foster City, Calif.
Harvard Pilgrim Health Care Inc., Wellesley, Mass.
Humana Inc. (NYSE:HUM), Louisville, Ky.
Keck Graduate Institute, Claremont, Calif.
National Association of Specialty Pharmacy, Tampa, Fla.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Prime Therapeutics LLC, Eagan, Minn.
RealEndpoints LLC, Westport, Conn.
Regeneron Pharmaceuticals Inc. (NASDAQ:REGN), Tarrytown, N.Y.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Specialty Pharmacy Certification Board, Alexandria, Va.
UnitedHealth Group Inc. (NYSE:UNH), Minnetonka, Minn.

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STRATEGY

PERSEVERING WITH PROSTVAC

BY STEPHEN HANSEN, ASSOCIATE EDITOR

After more than 20 years in clinical development, including over six years in the hands of Bavarian Nordic A/S, ProstVac rilimogene galvacirepvec found a potential commercial partner in Bristol-Myers Squibb Co.

Whether BMS exercises its option, and how much of the potential $975 million in deal value Bavarian Nordic gets, depends on how much of a survival benefit the prostate cancer vaccine can show in Phase III testing. But the real upside could lie in combining ProstVac with the pharma's pipeline of checkpoint inhibitors.

Last week, Bavarian Nordic granted BMS an exclusive option to ProstVac for $60 million up front, with the biotech eligible for an $80 million option exercise fee, clinical milestones starting at $50 million and ranging to over $230 million, $110 million in regulatory milestones and $495 million in sales milestones, plus tiered double-digit royalties.

Including all the milestones, the deal would be the largest reported option agreement for a Phase III compound.

BMS can exercise its option following review of data from the Phase III PROSPECT trial of ProstVac with or without GM-CSF vs. placebo in 1,298 patients with asymptomatic or minimally symptomatic chemotherapy-naïve metastatic castration-resistant prostate cancer (CRPC).

The clinical milestones are triggered if the median OS benefit in PROSPECT exceeds the 8.5-month OS benefit seen in Phase II. Robert Ang, SVP of business development at Bavarian Nordic, said the milestones are not capped. In other words, the larger the median OS benefit compared with the Phase II result, the larger the payment.

The structure of the deal allows BMS to hedge against the all-too-common scenario that Phase III results are not as good as Phase II, while also allowing Bavarian Nordic to participate in the upside if the results are even better.

"We both recognized that the value for ProstVac increases based on the magnitude of efficacy seen in the Phase III trial," said Ang.

The stakes are perhaps higher in this case than in many, because ProstVac has not yet been tested against standard of care. At least seven new drugs have been approved to treat CRPC while ProstVac was in the clinic, including two approved in the last five years that have extended OS to a median of 32-35 months in trials and are now standard of care.

PROSTVAC'S LONG ROAD

ProstVac first entered the clinic in 1994 for metastatic CRPC, and has been tested in 11 clinical studies, including PROSPECT. The long development road had a lot to do with the fact that ProstVac is a first-generation cancer vaccine that entered development well before the mechanisms of immune system responses to cancer were understood (see "ProstVac in Time," page 8).

Therion Biologics Corp. began developing ProstVac and a pancreatic cancer vaccine using the same technology under a CRADA with the National Cancer Institute.

The technology is a poxvirus-based immunotherapy that delivers a cancer antigen combined with three costimulatory molecules known as the Tricom triad — CD58 (LFA-3), intercellular adhesion molecule-1 (ICAM-1; CD54) and CD80 (B7-1). The Tricom triad enhances the immune response against the antigen.

> "WE BOTH RECOGNIZED THAT THE VALUE FOR PROSTVAC INCREASES BASED ON THE MAGNITUDE OF EFFICACY SEEN IN THE PHASE III TRIAL."
>
> ROBERT ANG, BAVARIAN NORDIC

ProstVac is composed of two different viral vectors, vaccinia and fowlpox, that encode the PSA antigen and the Tricom triad. When PSA is presented to immune cells, it triggers the generation of cytotoxic T lymphocytes (CTLs) that then kill PSA-expressing cancer cells.

Ang said two viral vectors are used because although vaccinia is highly immunogenic, it is also known to cause a neutralizing antibody response if administered repeatedly, whereas the fowlpox vector does not. Ang said the advantage of using both together prevents the immune system from mounting a response against the vectors and instead focuses the response on the PSA antigen.

James Breitmeyer, EVP and president of cancer immunotherapy at Bavarian Nordic, said early on Therion had to work out how to optimize ProstVac's dosing and formulation.

ProstVac did show early signs of efficacy, as Phase I data showed PSA stabilization lasting 11-25 months in nine patients. Early Phase II data showed the vaccine delayed PSA progression in patients with rising PSA levels but no disease.

But Breitmeyer said Therion made two mistakes with the platform technology. First, in a 125-patient Phase II trial for advanced CRPC, Therion went after progression-free survival (PFS) as the primary endpoint rather than OS. In fact, one of the lessons from the first-generation cancer vaccine companies as a class is that short-term endpoints like PFS are not

suitable because the vaccines prolong survival by slowing tumor growth, rather than by shrinking tumors.

The second mistake — for a similar reason — was staking the company's future on PanVac-VF by accelerating it into Phase III.

"Pancreatic cancer moves too fast for immunotherapy to work," Breitmeyer noted. "In their study, they only had a 13-week average survival, and that's just not long enough to retrain the immune system."

These mistakes could not have been predicted based on the understanding of immuno-oncology at the time, but they became apparent in mid-2006, when both products failed trials, dashing Therion's hopes of selling itself in conjunction with a BLA filing for PanVac.

Data from the ProstVac Phase II trial showed the vaccine plus GM-CSF missed the primary endpoint of PFS. There was a trend toward an improvement in OS, but those data were not yet mature.

Less than a month later, PanVac-VF missed the primary endpoint of two-month improvement in OS in a Phase III trial to treat metastatic pancreatic cancer.

Therion went bankrupt in 2006.

Bavarian Nordic scooped up the program from NCI in August 2008, and Breitmeyer said development of ProstVac "has been surprisingly straightforward" since then.

That October, it reported four-year follow-up data from the Phase II trial showing ProstVac plus GM-CSF led to a statistically significant OS benefit of 8.5 months vs. placebo (25.1 vs. 16.6 months).

But Bavarian did face investor concerns over its ability to partner the vaccine, which it had hoped to do before Phase III. In March 2011, the stock fell 40% after Bavarian said it was considering a rights offering to fund PROSPECT independently while it continued to search for a partner. The company raised $131.1 million in a May 2011 rights offering and started the trial that year.

COMPETING IN CRPC

The final analysis of PROSPECT's primary endpoint of OS will occur at 534 deaths. Breitmeyer said the statistical analysis plan includes multiple interim analyses, the first of which could come before year end.

However, he said the company has low expectations about meeting the OS endpoint at that time. He called the analysis a "major Hail Mary that is mainly in place as a futility check to make sure there isn't a safety issue."

Ang said the trial could be completed as early as 2017.

The benchmark for competitiveness will likely be set by two of the drugs approved while ProstVac has been in the clinic, which have become SOC for chemotherapy-naïve CRPC: Zytiga abiraterone acetate from Johnson & Johnson, and Xtandi enzalutamide from Medivation Inc. and Astellas Pharma Inc.

In 2012, Zytiga was approved for chemo-naïve CRPC patients based on an OS advantage of 35.3 months vs. 30.1 months vs. placebo.

Xtandi was approved last year, based on data from the Phase III PREVAIL trial that showed Xtandi improved OS to 32.4 months vs. 30.2 months for placebo.

Ang said Bavarian Nordic also has data showing synergistic improvements in OS when ProstVac is combined with first-generation antitestosterone therapies like nilutamide — suggesting that ProstVac could complement Zytiga or Xtandi, both of which inhibit the effects of androgens on tumor growth.

COMBO POTENTIAL

The greatest long-term upside for ProstVac may be in the deal's co-development component, which will explore combinations of ProstVac and compounds in Bristol-Myers' immuno-oncology pipeline.

A Phase II study to combine BMS's Yervoy ipilimumab and ProstVac is in the planning stages. Yervoy is a human mAb against CTLA-4 receptor that is approved to treat melanoma.

Breitmeyer said a better understanding of how the tumor dampens the immune response using the checkpoint system points toward a synergistic effect when a cancer vaccine is used in combination with checkpoint inhibitors. BMS markets Opdivo nivolumab, an inhibitor of the checkpoint protein PD-1, to treat metastatic melanoma and metastatic squamous non-small cell lung cancer (NSCLC).

Breitmeyer said Bavarian has shown treatment with ProstVac "induces a very substantial up-regulation of PD-L1 in the tumor" and thus prostate cancer patients with little or no PD-L1 expression would "be the perfect population for treating with a combination like ProstVac and a checkpoint inhibitor."

Data reported in February from a Phase I trial of ProstVac plus escalating doses of Yervoy in 30 CRPC patients led to a median OS for all dose cohorts of 31.3 months, and 37.2 months for patients receiving 10 mg/kg of Yervoy. The predicted median OS would have been 18.5 months. In the 10 mg/kg Yervoy plus ProstVac arm, 20% of the patients remained alive at 80 months.

Breitmeyer said preclinical data point toward even greater efficacy when multiple checkpoint inhibitors are combined with a cancer vaccine like ProstVac. bc

COMPANIES AND INSTITUTIONS MENTIONED

Astellas Pharma Inc. (Tokyo:4503), Tokyo, Japan
Bavarian Nordic A/S (CSE:BAVA), Kvistgaard, Denmark
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Dana-Farber Cancer Institute, Boston, Mass.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Medivation Inc. (NASDAQ:MDVN), San Francisco, Calif.
National Cancer Institute (NCI), Bethesda, Md.

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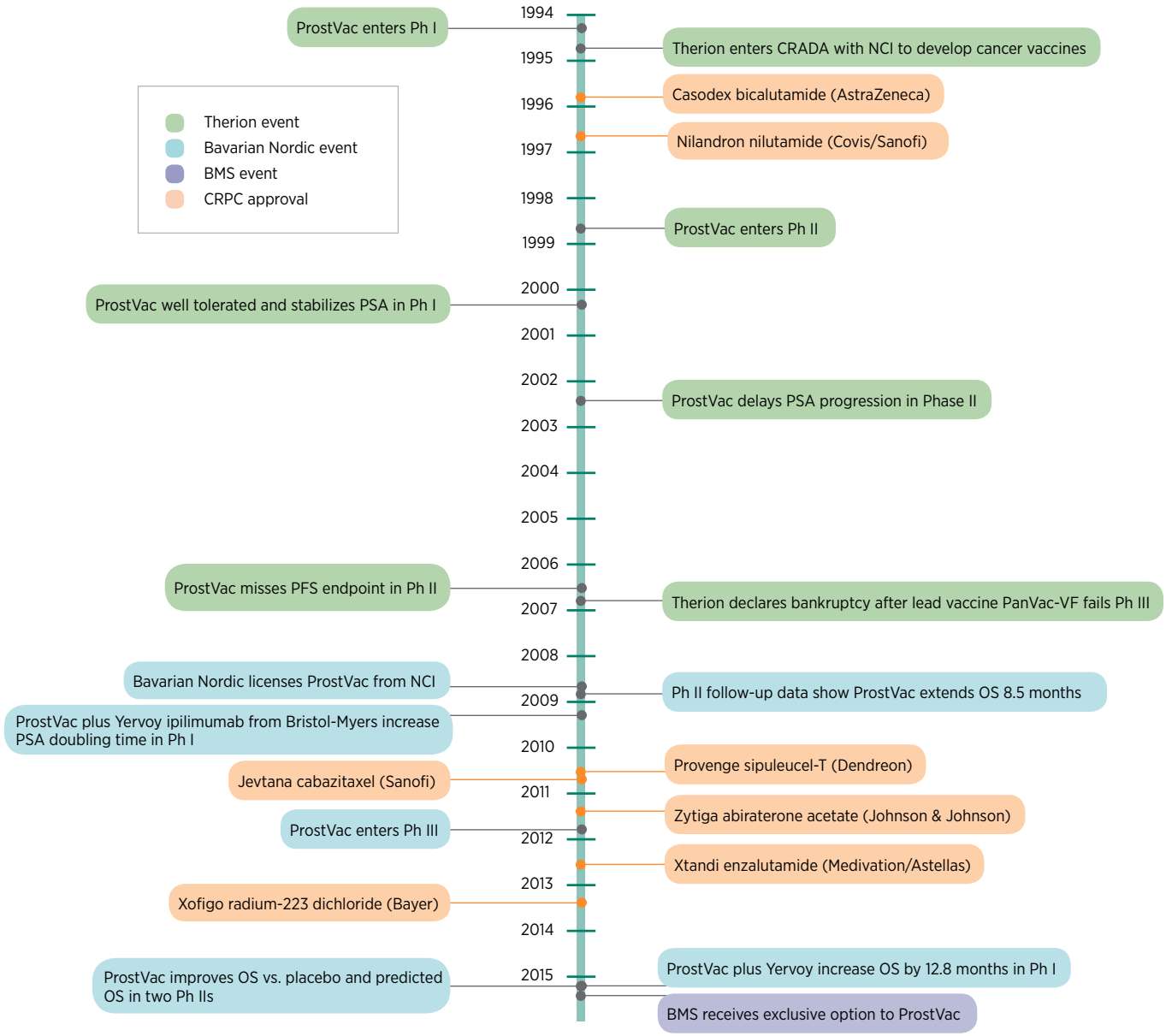
PROSTVAC IN TIME

It took more than 20 years for ProstVac rilimogene galvacirepvec to go from the start of a Phase I trial to finding a potential commercial partner in **Bristol-Myers Squibb Co.** (NYSE:BMY). If the pharma exercises the option it obtained last week from **Bavarian Nordic A/S** (CSE:BAVA), it would be the third company to participate in getting the prostate cancer vaccine to market. Bavarian Nordic licensed the candidate from **NCI** after its original developer, Therion Biologics Corp., went bankrupt. Therion closed its doors in 2006 after ProstVac and pancreatic cancer vaccine PanVac-VF each failed in clinical trials.

ProstVac has since had encouraging data including showing an overall survival benefit in Phase II when combined with BMS's Yervoy ipilimumab. A placebo-controlled Phase III trial is expected to read out around 2017. However, it has not been tested against standard of care, as at least seven new drugs have been approved for castration-resistant prostate cancer (CRPC) during the time ProstVac has been in the clinic, including two that were approved after the Phase III had begun.

The timeline shows selected milestones during ProstVac's development. *Sources: BCIQ: BioCentury Online Intelligence, ClinicalTrials.gov, company press releases*



EMERGING COMPANY PROFILE

AAVs FOR THE CNS

BY JENNIFER RHODES, STAFF WRITER

Voyager Therapeutics Inc. has a pipeline of adeno-associated viral vector-based gene therapies and is developing novel vectors that are optimized for better distribution in the CNS, among other qualities.

Third Rock Ventures launched Voyager about a year ago. The newco has one program in the clinic and four programs in preclinical development. All but one are optioned to Genzyme Corp. under a February deal.

Voyager's lead, VY-AADC01, is an AAV serotype 2 vector encoding dopa decarboxylase (DDC; AADC) that is delivered to the posterior putamen using image-guided, convection-enhanced delivery (CED) to treat Parkinson's disease (PD). PD is caused by the loss of dopamine-producing neurons, which causes motor symptoms including tremor. AADC converts levodopa into dopamine in the brain.

According to Steven Paul, a venture partner at Third Rock and Voyager's president and CEO, the posterior putamen is the region with the most dopamine deficiency in PD patients and where dopamine replenishment via levodopa counteracts motor symptoms.

VY-AADC01 is in an open-label Phase Ib trial sponsored by the University of California San Francisco, where Voyager co-founder Krystof Bankiewicz is a professor. Preliminary data from the first cohort are expected in 3Q15.

The trial is evaluating higher doses than those used in a Phase I trial Bankiewicz conducted of a prior version of the product. Paul said it had good safety and "some encouraging hints of efficacy," but it "wasn't fully optimized" and was administered via an intrastriatal infusion. That version was partnered with Genzyme, but the Sanofi unit discontinued it in 2013 citing strategic considerations. Voyager has a license to data from that study, but VY-AADC01 is the company's own.

Oxford BioMedica plc is developing a different approach to stimulating dopamine production in the putamen via gene therapy, but Paul declined to comment on how it may compare to VY-AADC01.

OXB-102 is a lentiviral vector-based therapy that is in preclinical development. It is a more potent formulation of Oxford's ProSavin, which encodes tyrosine hydroxylase, AADC and a cofactor and has completed a Phase I/II trial. Oxford Biomedica believes expression of the three genes in non-dopaminergic cells will lead to local dopamine production in the putamen.

Bankiewicz is also collaborating with uniQure N.V. on a gene therapy that delivers a different gene to treat PD that is in Phase I testing. AAV2-GDNF is an AAV vector encoding glial cell-derived neurotrophic factor (GDNF). According to the company, GDNF may protect and strengthen dopamine-producing brain cells.

Voyager's three disclosed preclinical programs are for progressive neuromuscular diseases. VY-FXN01 replaces the defective frataxin (FXN; FRDA) gene, which causes Friedreich's ataxia.

The other two knock down mutant genes responsible for disease: VY-SOD101 knocks down superoxide dismutase 1 (SOD1) for amyotrophic lateral sclerosis (ALS); and VY-HTT01 knocks down expression of the damaged Huntingtin (HTT) protein for Huntington's disease. Voyager plans to move the three into the clinic over the next two years.

VOYAGER THERAPEUTICS INC.
Cambridge, Mass.

Technology: Adeno-associated virus (AAV)-based gene therapies for CNS disorders

Disease focus: Neurology, gene/cell therapy

Clinical status: Phase I

Founded: 2014 by Third Rock Ventures, Krystof Bankiewicz, Guangping Gao, Mark Kay and Phillip Zamore

University collaborators: University of California San Francisco, University of Massachusetts Medical School

Corporate partners: Genzyme Corp.

Number of employees: 38

Funds raised: $75 million

Investors: Third Rock Ventures, Genzyme Corp.

CEO: Steven Paul

Patents: None issued

The Genzyme deal included options to license ex-U.S. rights to VY-AADC01, VY-FXN01 and VY-HTT01 after human proof-of-concept trials. Genzyme also has an option to co-commercialize VY-HTT01 in the U.S. and an option to worldwide rights to an undisclosed CNS program. Voyager received $65 million and a $35 million equity investment up front and is eligible for $745 million in milestones plus royalties. The deal excludes VY-SOD101.

VY-AADC01 uses a standard AAV2 vector, but vectors have not been selected for the preclinical programs. Voyager is working to engineer and optimize AAV vectors and has deals for vectors.

The deals include an exclusive license from the University of Massachusetts Medical School covering novel AAV variants and an option to license novel AAV variants from Stanford University. The company also has a non-exclusive, worldwide license from RegenxBio Inc. to use NAV vectors for ALS, Friedreich's and Huntington's. NAVs are new serotypes with improved transduction efficiency, durability and manufacturability.

Voyager also hired five scientists with expertise in AAV production methods, including Robert Kotin, a co-inventor of the baculovirus-based AAV production system. Paul said the baculovirus-based manufacturing process can be scaled to produce larger quantities for indications where larger volumes are needed. A cGMP facility Voyager is setting up with UMass will produce clinical-grade vector by year end.

Voyager has filed for patents related to process development, production and vector engineering. bc

COMPANIES AND INSTITUTIONS MENTIONED

Genzyme Corp., Cambridge, Mass.
RegenxBio Inc., Washington, D.C.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Stanford University, Stanford, Calif.
uniQure N.V. (NASDAQ:QURE), Amsterdam, the Netherlands
University of California San Francisco, San Francisco, Calif.
University of Massachusetts Medical School, Worcester, Mass.
Voyager Therapeutics Inc., Cambridge, Mass.

"WHILE EMA HAS RELEASED CLEAR GUIDANCE THAT PROVIDES A DEVELOPMENT PATHWAY FOR A PATHOGEN-FOCUSED INDICATION, FDA APPEARS CONSTRAINED BY ITS EXISTING RULES."

YOSHINORI YAMANO, SHIONOGI

COMMENTARY

SWIFT ACTION FOR MDR BUGS

BY YOSHINORI YAMANO, VP, DISCOVERY RESEARCH LABORATORY FOR CORE THERAPEUTIC AREAS, SHIONOGI & CO. LTD.

Medical societies such as the Infectious Diseases Society of America, governmental regulatory agencies such as FDA and EMA, and politicians agree that the normal process for new drug approval is too lengthy and costly to meet the urgent need for new agents to treat serious infections caused by multi-drug resistant pathogens. However, while EMA has released clear guidance that provides a development pathway for a pathogen-focused indication, FDA appears constrained by its existing rules.

FDA has made some progress in re-evaluating the clinical requirements for approval of new antibacterial agents, but it has not yet clarified the pathway for pathogen-focused development programs.

During a meeting on Dec. 4-5, 2014, FDA's Anti-Infective Drugs Advisory Committee discussed issues related to clinical development programs and trial designs for antibacterial products to treat patients with serious bacterial infections for which there are limited or no therapeutic options. Edward Cox, director of FDA's Office of Antimicrobial Products, said, "We're talking about more streamlined programs, so there will be greater uncertainty around safety and efficacy. But if we think about the need here, it's important for patients who don't have options to be able to balance those benefits and risks."

But none of the FDA proposals presented directly addressed circumstances unique to pathogen-specific infections, and it remains unclear how much and what kind of data would be needed. The committee noted the agency should have flexibility regarding the amount of data required for different indications where there is unmet need, but also said, "the standard for demonstrating the efficacy and safety of drugs should remain the same."

The committee also discussed the NDA for Avycaz ceftazidime/avibactam from Actavis plc and AstraZeneca plc. The FDA proposed, and the committee recommended, approval of Avycaz only for specific infection sites — not for the treatment of infections caused by MDR bacteria at multiple sites for which it was developed. In the end, the committee did not provide much clarity regarding how to develop a new antibiotic for a pathogen-focused indication.

Clarification of the pathway is crucial for pharmaceutical companies still investing significant financial and human resources into the development of new agents to address the threat of multi-drug resistant (MDR) bacteria, in particular Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and Enterobacteriaceae.

Shionogi would like FDA to actively pursue the creation of a pathogen-based development pathway similar to that which is already supported by EMA, such that the U.S. and EU regulatory systems would be aligned in their approach to accelerating the development of new antibacterials that can treat infections caused by MDR bacteria.

We believe FDA needs new statutory guidance to allow the agency the flexibility to pursue and implement such a new pathway, and thereby appropriately accelerate the approval of new agents which are appropriately labeled to treat limited patient populations with high unmet medical need.

A FEASIBLE PATH

In October 2013, EMA released an addendum to its Guideline on the Evaluation of Medicinal Products Indicated for the Treatment of Bacterial Infections. The guidance recommends a pathogen-focused treatment indication, without reference to a specific infection site, as a new approach to facilitate the development of new antibacterials targeting multi-drug resistant infections for which there are limited therapeutic options. EMA

has reinforced this new approach during subsequent communications with pharmaceutical companies.

FDA also recognized the need for a pathogen-focused approach in its draft guidance on Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases, which was released in July 2013.

During the December advisory committee meeting, FDA presented only two options for the design of pivotal clinical studies in streamlined development programs. One was a non-inferiority trial of infections at a single body site, using larger-than-usual non-inferiority margins. The other was a superiority trial, with pooling across different body sites of infection, where the control group for statistical inferential testing would be the best available therapy (BAT). Given these limited options, it is essentially not feasible to pursue a streamlined, pathogen-focused approval for a drug targeting MDR pathogens at different infection sites.

A pathogen-focused superiority study could potentially show evidence of effectiveness against infections caused by MDR bacteria at multiple infection sites; however, as much as one may want to show superiority, it remains unattainable using currently accepted endpoints (e.g., mortality). For example, in hospital-acquired/ventilator-associated pneumonia (HAP/VAP), only a small proportion of all-cause mortality can be attributed to the infection, and hence a superiority study with mortality as the primary endpoint is not realistic.

To resolve this challenging and ambiguous situation, Shionogi believes there should be another option: a pathogen-focused study that includes infections at different body sites caused by MDR bacteria, with assessment of efficacy based on meaningful clinical and microbiological endpoints analyzed with descriptive statistics. Inferential testing using non-inferiority, rather than superiority, would be applied to specific subsets of patients, e.g., HAP/VAP with the mortality endpoint. While this design requires agreement on a less robust test for non-inferiority, it would still confirm that the drug is effective. We must accept that there will be greater uncertainty around safety and efficacy in order to develop agents that treat small populations where enrollment is a challenge and the unmet need is high.

Recently, FDA approved a new antibiotic, Zerbaxa ceftolozane/tazobactam from Cubist Pharmaceuticals Inc. (now part of Merck & Co. Inc.), for the indications of complicated intra-abdominal infections (cIAIs) and complicated urinary tract infections (cUTIs). Avycaz was approved last month for the indications of cIAIs and cUTIs where limited or no alternative treatments are available. Although these two antibiotics have good microbiological activity against certain MDR Gram-negative bacteria, the clinical studies supporting approval were standard clinical studies for cIAIs and cUTIs and did not focus on MDR bacteria. Consequently, these clinical trials did not provide sufficient evidence that these antibiotics were in fact clinically effective against infections caused by MDR bacteria. In particular, there was no clinical efficacy data in patients with HAP, which is the area of greatest unmet medical need.

FDA's current position that it will only grant approval for new antibiotics for site-specific indications results in a high risk of inappropriate or off-label use, since the approved indications do not address either the most clinically important sites of infection or the specific MDR pathogen classes against which the new drug is effective. Based on FDA's current rules on product labeling, information not directly linked to the approved indications cannot be included, which leaves prescribing physicians uninformed and searching for alternative sources of information as to how new agents should best be used in the most critical infections they encounter.

Furthermore, the originating companies are tightly constrained by the product labeling in their ability to provide information to physicians. This lack of focused labeling creates a conflict with the tenets of antibiotic stewardship, which would restrict the use of these drugs to second- or third-line therapy in patients with limited treatment options; in other words, for infections with MDR organisms.

"WE MUST ACCEPT THAT THERE WILL BE GREATER UNCERTAINTY AROUND SAFETY AND EFFICACY IN ORDER TO DEVELOP AGENTS THAT TREAT SMALL POPULATIONS WHERE ENROLLMENT IS A CHALLENGE AND THE UNMET NEED IS HIGH."

YOSHINORI YAMANO, SHIONOGI

Shionogi strongly believes that the development process and the resulting product label should clearly reflect the core rationale for rapid development of new agents active against MDR organisms, namely an MDR-pathogen-focused indication for patients with limited treatment options. The product indication should clearly reflect how the drug should be used once marketed; in other words, its use should be restricted to patients with multi-drug resistant infections. This approach would benefit both the patients with MDR infections, as well as prescribing physicians, who would have more pathogen-specific information available in the product's label.

LEGISLATIVE BACKING

Legislators appear to have recognized that FDA is constrained by existing regulations in taking new approaches such as those proposed herein, and that there is a need for new statutory authority to allow the pursuit of non-traditional approval pathways for antibiotics focused on problematic pathogens.

The Antibiotic Development to Advance Patient Treatment (ADAPT) Act proposed in December 2013 specifically focuses on refining FDA's pathway for the approval of limited-population antibacterial drugs (LPADs), in addition to providing incentives for investment and innovation. More recently, the Promise for Antibiotics and Therapeutics for Health (PATH) Act proposed in December 2014 also aims to create a pathway for limited population-focused development and approval.

COVER STORY

NIXING ANTIBODY AGGREGATION

Newco Solvanix's technology can reduce the aggregation of mAbs by introducing as few as two mutations, without affecting binding or immunogenicity.

STRATEGY

CARDIO REBOOT

Cardiologist Philip Sager says the current thinking on preclinical cardiovascular safety involves new ways of looking at ion conductance to replace QT, and might enable or rescue many compounds.

ADDING UP FOR AD

NIH's meeting with G7 health leaders coincided with three announcements about AD funding, and stakeholders are optimistic the field is starting to get some much-needed attention.

TOOLS

T AS IN TRANSPLANTS

A T cell-based fingerprint in the plasma of kidney transplant recipients could identify patients who will develop tolerance and not need immunosuppressive therapy.

DISTILLERY

This week in therapeutics

This week in therapeutics includes important research findings on targets and compounds, grouped first by disease class and then alphabetically by indication.

This week in techniques

This week in techniques includes findings about research tools, disease models and manufacturing processes that have the potential to enable or improve all stages of drug discovery and development.

Meanwhile, the Strategies to Address Antimicrobial Resistance (STAAR) Act proposed in April 2014 would establish an Antimicrobial Resistance Office in HHS, with a requirement for FDA to consult the office on pending applications.

Reimbursement issues are also under discussion; for example, the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act proposed in March 2014 would allow for enhanced reimbursement for qualifying medicines in Medicare Part A. In addition, the President's Council of Advisors on Science and Technology (PCAST) Report on Antibiotic Resistance published in September 2014 recommends the development of new regulatory pathways to evaluate urgently needed antibiotics.

We join with physicians, patients and other research-driven pharmaceutical companies in the hope that the House of Representatives, the Senate, and the president quickly move to approve new legislation that would allow FDA to better facilitate the approval of new antibiotics with the potential to treat MDR bacterial infections. bc

COMPANIES AND INSTITUTIONS MENTIONED

Actavis plc (NYSE:ACT), Dublin, Ireland
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K
European Medicines Agency (EMA), London, U.K.
Infectious Diseases Society of America (IDSA), Arlington, Va.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Shionogi & Co. Ltd. (Tokyo:4507), Osaka, Japan
U.S. Department of Health & Human Services (HHS), Washington, D.C.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

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