FDA APPROVES LUMAKRAS® (SOTORASIB) IN COMBINATION WITH VECTIBIX® (PANITUMUMAB) FOR CHEMOREFRACTORY KRAS G12C-MUTATED METASTATIC COLORECTAL CANCER

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Pivotal Study Demonstrated the Combination More Than Doubled Progression-Free Survival Compared to Investigated SOC

THOUSAND OAKS, Calif., Jan. 17, 2025 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the U.S. Food and Drug Administration (FDA) has approved LUMAKRAS® (sotorasib) in combination with Vectibix® (panitumumab) for the treatment of adult patients with *KRAS* G12C-mutated metastatic colorectal cancer (mCRC), as determined by an FDA-approved test, who have received prior fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy. Approval is based on the pivotal Phase 3 CodeBreaK 300 study, which demonstrated that LUMAKRAS plus Vectibix is the first and only targeted treatment combination for chemorefractory *KRAS* G12C-mutated mCRC to show superior progression-free survival (PFS) compared to the investigated standard-of-care (SOC).[1*]

"Colorectal cancer is the third leading cause of cancer-related deaths in the United States, and fewer than one in five people diagnosed with metastatic disease survive beyond five years after diagnosis," said Jay Bradner, M.D., executive vice president of Research and Development at Amgen.[2] "LUMAKRAS plus Vectibix offers a targeted, biomarker-driven combination therapy that helps delay disease progression more effectively than the investigated standard of care. This new option validates our combination approach to improve outcomes for patients living with advanced *KRAS* G12C-mutated metastatic colorectal cancer."

The CodeBreaK 300 clinical trial compared LUMAKRAS at two different doses (960 mg daily or 240 mg daily) in combination with Vectibix to the investigator's choice of SOC (trifluridine and tipiracil or regorafenib) in patients with chemorefractory *KRAS* G12C-mutated mCRC. Study results demonstrated that LUMAKRAS 960 mg daily plus Vectibix (n=53) showed an improved median PFS of 5.6 months (4.2, 6.3) compared to 2 months (1.9, 3.9) on investigator's choice of care (n=54), with a hazard ratio (HR) of 0.48 (95% Confidence Interval [CI]: 0.3, 0.78) and a *p*-value of 0.005. The study demonstrated an improved overall response rate (ORR) of 26% (95% CI: 15, 40) compared to 0% with investigator's choice (95% CI: 0, 7). The study was not statistically powered for overall survival (OS). The median overall survival (mOS) for patients treated with LUMAKRAS plus Vectibix was not reached (NR) (8.6, NR), and mOS for patients treated with investigator's choice was 10.3 months (7, NR), with a HR of 0.7 (95% CI: 0.41, 1.18); the final analysis of OS was not statistically significant. Safety profiles were consistent with those historically observed for LUMAKRAS and Vectibix. The most common adverse reactions (≥20%) are rash (87%), dry skin (28%), diarrhea (28%), stomatitis (26%), fatigue (21%) and musculoskeletal pain (21%). PFS of LUMAKRAS 240 mg daily plus Vectibix (n=53) compared to investigator's choice was not statistically significant.

The *KRAS* G12C mutation is present in approximately 3-5% of colorectal cancers as determined by an FDA-approved biomarker test.[3-5] This emphasizes the important role of comprehensive biomarker testing in mCRC. By detecting an actionable mutation, eligible patients are now able to receive a corresponding targeted therapy that may lead to improved responses.

"In metastatic colorectal cancer, *KRAS* mutations are historically associated with worse mortality rates and inferior outcomes compared to non-mutated tumors, and standard treatment options have shown minimal benefit," said Marwan G. Fakih, M.D., primary study investigator and co-director of the Gastrointestinal Cancer Program, City of Hope.[3-6] "Designed for dual blockade of *KRAS* G12C and EGFR pathways, the combination of sotorasib plus panitumumab provides a needed new treatment option to better overcome cancer's escape mechanisms. The CodeBreaK 300 study showed superior progression-free survival compared to the investigated standard of care and represents a clinically meaningful benefit for patients with *KRAS* G12C-mutated metastatic colorectal cancer."

"There is an immense need for continued innovation and precision medicine to help address metastatic colorectal cancer," said Michael Sapienza, Chief Executive Officer of the Colorectal Cancer Alliance. "This new combination approach is an important breakthrough for patients with *KRAS* G12C-mutated metastatic colorectal cancer, offering a new beneficial treatment option for patients living with this devastating and challenging disease."

*****Investigator's choice for SOC included trifluridine/tipiracil or regorafenib.

About CodeBreaK 300

The CodeBreaK 300 trial enrolled 160 participants and compared LUMAKRAS® (sotorasib) at doses of 960 mg and 240 mg in combination with Vectibix® (panitumumab) to investigator's choice of standard of care (trifluridine/tipiracil or regorafenib) in patients with chemorefractory *KRAS* G12C-mutated metastatic colorectal cancer (mCRC). The study met its primary endpoint showing improved progression-free survival (PFS), and the key secondary endpoints of overall survival (OS) and overall response rate (ORR) also favored the combination.

About mCRC and the *KRAS* G12C Mutation

Colorectal cancer (CRC) is the second leading cause of cancer deaths worldwide, comprising 11% of all cancer diagnoses.[7] It is also the third most commonly diagnosed cancer globally.[8]

Patients with previously treated mCRC need more effective treatment options. For patients in the third-line setting, standard therapies yield median OS times of less than one year, and patients' response rates are less than 10%.[9]

KRAS mutations are among the most common genetic alterations in CRC, with the *KRAS* G12C mutation present in approximately 3-5% of CRC cases as determined by a U.S. Food and Drug Administration (FDA)-approved biomarker test.[3-5]

About LUMAKRAS® (sotorasib) in Combination with Vectibix® (panitumumab)

In the U.S., LUMAKRAS is now approved in combination with Vectibix® (panitumumab) for the treatment of adult patients with *KRAS* G12C-mutated mCRC, as determined by an FDA-approved test, who have received prior fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy. This

targeted therapy combines LUMAKRAS, a $KRAS^{G12C}$ inhibitor, with Vectibix, a monoclonal anti-EGFR antibody. The recommended dose of LUMAKRAS is 960 mg daily, and the recommended dose of Vectibix is 6 mg/kg IV q2 weeks.

About LUMAKRAS®/LUMYKRAS® (sotorasib)
LUMAKRAS received accelerated approval from the FDA on May 28, 2021. The FDA completed its review of Amgen's supplemental New Drug Application (sNDA) seeking full approval of LUMAKRAS on December 26, 2023, which resulted in a complete response letter. In addition, the FDA concluded that the dose comparison postmarketing requirement (PMR) issued at the time of LUMAKRAS accelerated approval, to compare the safety and efficacy of LUMAKRAS 960 mg daily dose versus a lower daily dose, has been fulfilled. The company said LUMAKRAS at 960 mg once-daily will remain the dose for patients with *KRAS* G12C-mutated non-small cell lung cancer (NSCLC) under accelerated approval. The FDA also issued a new PMR for an additional confirmatory study to support full approval that will be completed no later than February 2028.

About Vectibix® (panitumumab)
Vectibix is the first and only human monoclonal anti-EGFR antibody fully approved by the FDA for the treatment of mCRC. Vectibix was approved in the U.S. in September 2006 as a monotherapy for the treatment of patients with EGFR-expressing mCRC following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy.

In May 2014, the FDA approved Vectibix for use in combination with FOLFOX as first-line treatment in patients with wild-type *KRAS* (exon 2) mCRC. With this approval, Vectibix became the first-and-only anti-EGFR biologic therapy indicated for use with FOLFOX, one of the most commonly used chemotherapy regimens, in first-line treatment of mCRC for patients with wild-type *KRAS* mCRC.

In June 2017, the FDA approved a refined indication for Vectibix for use in patients with wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS* as determined by an FDA-approved test for this use) mCRC, specifically as first-line therapy in combination with FOLFOX and as monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy.

LUMAKRAS® (sotorasib) in Combination with Vectibix® (panitumumab) U.S. Indication
Vectibix® in combination with sotorasib, is indicated for the treatment of adult patients with *KRAS G12C*-mutated mCRC, as determined by an FDA-approved test, who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

LIMITATIONS OF USE
Vectibix® is not indicated for the treatment of patients with *RAS*-mutant mCRC unless used in combination with sotorasib in *KRAS* G12C-mutated mCRC. Vectibix® is not indicated for the treatment of patients with mCRC for whom *RAS* mutation status is unknown.

IMPORTANT SAFETY INFORMATION FOR LUMAKRAS® (SOTORASIB)
Hepatotoxicity

- LUMAKRAS® can cause hepatotoxicity and increased ALT or AST which may lead to drug-induced liver injury and hepatitis.
- In the pooled safety population of NSCLC patients who received single agent LUMAKRAS® 960 mg hepatotoxicity occurred in 27% of patients, of which 16% were Grade ≥ 3. Among patients with hepatotoxicity who required dosage modifications, 64% required treatment with corticosteroids.
- In this pooled safety population of NSCLC patients who received single agent LUMAKRAS® 960 mg, 17% of patients who received LUMAKRAS® had increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST); of which 9% were Grade ≥ 3. The median time to first onset of increased ALT/AST was 6.3 weeks (range: 0.4 to 42). Increased ALT/AST leading to dose interruption or reduction occurred in 9% of patients treated with LUMAKRAS®. LUMAKRAS® was permanently discontinued due to increased ALT/AST in 2.7% of patients. Drug-induced liver injury occurred in 1.6% (all grades) including 1.3% (Grade ≥ 3).
- In this pooled safety population of NSCLC patients who received single agent LUMAKRAS® 960 mg, a total of 40% patients with recent (≤ 3 months) immunotherapy prior to starting LUMAKRAS® had an event of hepatotoxicity. An event of hepatotoxicity was observed in 18% of patients who started LUMAKRAS® more than 3 months after last dose of immunotherapy and in 17% of those who never received immunotherapy. Regardless of time from prior immunotherapy, 94% of hepatotoxicity events improved or resolved with dosage modification of LUMAKRAS®, with or without corticosteroid treatment.
- Monitor liver function tests (ALT, AST, alkaline phosphatase and total bilirubin) prior to the start of LUMAKRAS®, every 3 weeks for the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop transaminase and/or bilirubin elevations. Withhold, reduce the dose or permanently discontinue LUMAKRAS® based on severity of the adverse reaction. Consider administering systemic corticosteroids for the management of hepatotoxicity.

Interstitial Lung Disease (ILD)/Pneumonitis

- LUMAKRAS® can cause ILD/pneumonitis that can be fatal.
- In the pooled safety population of NSCLC patients who received single agent LUMAKRAS® 960 mg ILD/pneumonitis occurred in 2.2% of patients, of which 1.1% were Grade ≥ 3, and 1 case was fatal. The median time to first onset for ILD/pneumonitis was 8.6 weeks (range: 2.1 to 36.7 weeks). LUMAKRAS® was permanently discontinued due to ILD/pneumonitis in 1.3% of LUMAKRAS®-treated patients. Monitor patients for new or worsening pulmonary symptoms

indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold LUMAKRAS® in patients with suspected ILD/pneumonitis and permanently discontinue LUMAKRAS® if no other potential causes of ILD/pneumonitis are identified.

Most Common Adverse Reactions

- The most common adverse reactions ≥ 20% were diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough.

Drug Interactions

- Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, dietary and herbal products.
- Inform patients to avoid proton pump inhibitors and H2 receptor antagonists while taking LUMAKRAS®.
- If coadministration with an acid-reducing agent cannot be avoided, inform patients to take LUMAKRAS® 4 hours before or 10 hours after a locally acting antacid.

Please see accompanying LUMAKRAS® full Prescribing Information.

IMPORTANT SAFETY INFORMATION FOR VECTIBIX® (PANITUMUMAB)
BOXED WARNING: DERMATOLOGIC TOXICITY
Dermatologic Toxicity: Dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC Grade 3 and higher) in 15% of patients receiving Vectibix® monotherapy

- Vectibix® can cause dermatologic toxicity, which may be severe. Clinical manifestations included, but were not limited to, acneiform dermatitis, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures.
- Among 229 patients who received Vectibix® as monotherapy, dermatologic toxicity occurred in 90% including Grade 3 (15%). Among 585 patients who received Vectibix® in combination with FOLFOX, dermatologic toxicity occurred in 96% including Grade 4 (1%) and Grade 3 (32%). In 126 patients receiving Vectibix® in combination with sotorasib across clinical studies, dermatologic toxicities occurred in 94%, including Grade 3 (16%) of patients.
- Monitor patients who develop dermatologic or soft tissue toxicities while receiving Vectibix® for the development of inflammatory or infectious sequelae. Life-threatening and fatal infectious complications including necrotizing fasciitis, abscesses, and sepsis have been observed in patients treated with Vectibix®. Life-threatening and fatal bullous mucocutaneous disease with blisters, erosions, and skin sloughing has also been observed in patients treated with Vectibix®. It could not be determined whether these mucocutaneous adverse reactions were directly related to EGFR inhibition or to idiosyncratic immune-related effects (eg, Stevens Johnson syndrome or toxic epidermal necrolysis). Withhold or discontinue Vectibix® for dermatologic or soft tissue toxicity associated with severe or life-threatening inflammatory or infectious complications. Dose modifications for Vectibix® concerning dermatologic toxicity are provided
- Vectibix® monotherapy or in combination with oxaliplatin-based chemotherapy is not indicated for the treatment of patients with colorectal cancer that harbor somatic *RAS* mutations in exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) of either *KRAS* or *NRAS* and hereafter is referred to as "*RAS*."
- Retrospective subset analyses across several randomized clinical trials were conducted to investigate the role of *RAS* mutations on the clinical effects of anti-EGFR-directed monoclonal antibodies (panitumumab or cetuximab). Anti-EGFR antibodies in patients with tumors containing *RAS* mutations resulted in exposing those patients to anti-EGFR related adverse reactions without clinical benefit from these agents. Additionally, in Study 20050203, 272 patients with *RAS*-mutant mCRC tumors received Vectibix® in combination with FOLFOX and 276 patients received FOLFOX alone. In an exploratory subgroup analysis, OS was shorter (HR = 1.21, 95% CI: 1.01-1.45) in patients with *RAS*-mutant mCRC who received Vectibix® and FOLFOX versus FOLFOX alone.
- Vectibix® can cause progressively decreasing serum magnesium levels leading to severe (Grade 3 or 4) hypomagnesemia. Among 229 patients who received Vectibix® as monotherapy, hypomagnesemia occurred in 38% including Grade 4 (1.3%) and Grade 3 (2.6%). Among 585 patients who received Vectibix® in combination with FOLFOX, hypomagnesemia occurred in 51% including Grade 4 (5%) and Grade 3 (6%). In 126 patients receiving Vectibix® in combination with sotorasib across clinical studies, decreased magnesium occurred in 69%, including Grade 4 (2.4%) and Grade 3 (14%).
- Monitor patients for hypomagnesemia and hypocalcemia prior to initiating Vectibix® treatment, periodically during Vectibix® treatment, and for up to 8 weeks after the completion of treatment. Other electrolyte disturbances, including hypokalemia, have also been observed. Replete magnesium and other electrolytes as appropriate.
- In Study 20020408, 4% of patients experienced infusion reactions and 1% of patients experienced severe infusion reactions (NCI-CTC Grade 3-4). Infusion reactions, manifesting as fever, chills, dyspnea, bronchospasm, and hypotension, can occur following Vectibix® administration. Fatal infusion reactions occurred in postmarketing experience. Terminate the infusion for severe infusion reactions.
- Severe diarrhea and dehydration, leading to acute renal failure and other complications, have been observed in patients

treated with Vectibix®. Among 229 patients who received Vectibix® as monotherapy, acute renal failure occurred in 2% including Grades 3 or 4 (2%). Among 585 patients who received Vectibix® in combination with FOLFOX, acute renal failure occurred in 2% including Grade 3 or 4 (2%). In 126 patients receiving Vectibix® in combination with sotorasib across clinical studies, acute renal failure occurred in 3.2%, including Grade 3 (0.8%). Monitor patients for diarrhea and dehydration, provide supportive care (including anti-emetic or anti-diarrheal therapy) as needed, and withhold Vectibix® if necessary.

- Fatal and nonfatal cases of interstitial lung disease (ILD) (1%) and pulmonary fibrosis have been observed in patients treated with Vectibix®. Pulmonary fibrosis occurred in less than 1% (2/1467) of patients enrolled in clinical studies of Vectibix®. Grade 1 ILD/pneumonitis occurred in 0.8% (1/126) of patients enrolled in clinical studies of Vectibix® in combination with sotorasib. In the event of acute onset or worsening of pulmonary symptoms interrupt Vectibix® therapy. Discontinue Vectibix® therapy if ILD is confirmed.
- In patients with a history of interstitial pneumonitis or pulmonary fibrosis, or evidence of interstitial pneumonitis or pulmonary fibrosis, the benefits of therapy with Vectibix® versus the risk of pulmonary complications must be carefully considered.
- Exposure to sunlight can exacerbate dermatologic toxicity. Advise patients to wear sunscreen and hats and limit sun exposure while receiving Vectibix®.
- Serious cases of keratitis, ulcerative keratitis, and corneal perforation have occurred with Vectibix® use. Among 585 patients who received Vectibix® in combination with FOLFOX, keratitis occurred in 0.3%. In 126 patients receiving Vectibix® in combination with sotorasib across clinical studies, keratitis occurred in 1.6%, ulcerative keratitis occurred in 0.8%, and vernal keratoconjunctivitis in 0.8% (all were Grade 1-2). Monitor for evidence of keratitis, ulcerative keratitis, or corneal perforation. Interrupt or discontinue Vectibix® therapy for acute or worsening keratitis, ulcerative keratitis, or corneal perforation.
- In an interim analysis of an open-label, multicenter, randomized clinical trial in the first-line setting in patients with mCRC, the addition of Vectibix® to the combination of bevacizumab and chemotherapy resulted in decreased OS and increased incidence of NCI-CTC Grade 3-5 (87% vs 72%) adverse reactions. NCI-CTC Grade 3-4 adverse reactions occurring at a higher rate in Vectibix®-treated patients included rash/acneiform dermatitis (26% vs 1%), diarrhea (23% vs 12%), dehydration (16% vs 5%), primarily occurring in patients with diarrhea, hypokalemia (10% vs 4%), stomatitis/mucositis (4% vs <1%), and hypomagnesemia (4% vs 0). NCI-CTC Grade 3-5 pulmonary embolism occurred at a higher rate in Vectibix®-treated patients (7% vs 3%) and included fatal events in three (< 1%) Vectibix® -treated patients.
- As a result of the toxicities experienced, patients randomized to Vectibix®, bevacizumab, and chemotherapy received a lower mean relative dose intensity of each chemotherapeutic agent (oxaliplatin, irinotecan, bolus 5-FU, and/or infusional 5-FU) over the first 24 weeks on study compared with those randomized to bevacizumab and chemotherapy.
- Based on data from animal studies and its mechanism of action, Vectibix® can cause fetal harm when administered to a pregnant woman. When given during organogenesis, panitumumab administration resulted in embryolethality in cynomolgus monkeys at exposures approximately 1.25 to 5 times the recommended human dose. Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females of reproductive potential to use effective contraception during treatment, and for at least 2 months after the last dose of Vectibix®.
- In monotherapy, the most commonly reported adverse reactions (≥ 20%) in patients with Vectibix® were skin rash with variable presentations, paronychia, fatigue, nausea, and diarrhea.
- The most commonly reported adverse reactions (≥ 20%) with Vectibix® + FOLFOX were diarrhea, stomatitis, mucosal inflammation, asthenia, paronychia, anorexia, hypomagnesemia, hypokalemia, rash, acneiform dermatitis, pruritus, and dry skin. Serious adverse reactions (≥ 2% difference between treatment arms) were diarrhea and dehydration.
- The most common adverse reactions (≥ 20%) in patients receiving Vectibix® in combination with sotorasib 960 mg were rash, dry skin, diarrhea, stomatitis, fatigue and musculoskeletal pain.

Please see full Prescribing Information, including **Boxed WARNING.**

About Amgen

Amgen discovers, develops, manufactures and delivers innovative medicines to help millions of patients in their fight against some of the world's toughest diseases. More than 40 years ago, Amgen helped to establish the biotechnology industry and remains on the cutting-edge of innovation, using technology and human genetic data to push beyond what's known today. Amgen is advancing a broad and deep pipeline that builds on its existing portfolio of medicines to treat cancer, heart disease, osteoporosis, inflammatory diseases and rare diseases.

In 2024, Amgen was named one of the "World's Most Innovative Companies" by Fast Company and one of "America's Best Large Employers" by Forbes, among other external recognitions. Amgen is one of the 30 companies that comprise the Dow Jones Industrial Average®, and it is also part of the Nasdaq-100 Index®, which includes the largest and most innovative non-financial companies listed on the Nasdaq Stock Market based on market capitalization.

For more information, visit Amgen.com and follow Amgen on X, LinkedIn, Instagram, TikTok, YouTube and Threads.

Amgen Forward-Looking Statements

This news release contains forward-looking statements that are based on the current expectations and beliefs of Amgen. All statements, other than statements of historical fact, are statements that could be deemed forward-looking statements, including any statements on the outcome, benefits and synergies of collaborations, or potential collaborations, with any other company (including BeiGene, Ltd. or Kyowa Kirin Co., Ltd.), the performance of Otezla® (apremilast) (including anticipated Otezla sales growth and the timing of non-GAAP EPS accretion), our acquisitions of Teneobio, Inc., ChemoCentryx, Inc., or Horizon Therapeutics plc (including the prospective performance and outlook of Horizon's business, performance and opportunities, any potential strategic benefits, synergies or opportunities expected as a result of such acquisition, and any projected impacts from the Horizon acquisition on our acquisition-related expenses going forward), as well as estimates of revenues, operating margins, capital expenditures, cash, other financial metrics, expected legal, arbitration, political, regulatory or clinical results or practices, customer and prescriber patterns or practices, reimbursement activities and outcomes, effects of pandemics or other widespread health problems on our business, outcomes, progress, and other such estimates and results. Forward-looking statements involve significant risks and uncertainties, including those discussed below and more fully described in the Securities and Exchange Commission reports filed by Amgen, including our most recent annual report on Form 10-K and any subsequent periodic reports on Form 10-Q and current reports on Form 8-K. Unless otherwise noted, Amgen is providing this information as of the date of this news release and does not undertake any obligation to update any forward-looking statements contained in this document as a result of new information, future events or otherwise.

No forward-looking statement can be guaranteed and actual results may differ materially from those we project. Discovery or identification of new product candidates or development of new indications for existing products cannot be guaranteed and movement from concept to product is uncertain; consequently, there can be no guarantee that any particular product candidate or development of a new indication for an existing product will be successful and become a commercial product. Further, preclinical results do not guarantee safe and effective performance of product candidates in humans. The complexity of the human body cannot be perfectly, or sometimes, even adequately modeled by computer or cell culture systems or animal models. The length of time that it takes for us to complete clinical trials and obtain regulatory approval for product marketing has in the past varied and we expect similar variability in the future.

Even when clinical trials are successful, regulatory authorities may question the sufficiency for approval of the trial endpoints we have selected. We develop product candidates internally and through licensing collaborations, partnerships and joint ventures. Product candidates that are derived from relationships may be subject to disputes between the parties or may prove to be not as effective or as safe as we may have believed at the time of entering into such relationship. Also, we or others could identify safety, side effects or manufacturing problems with our products, including our devices, after they are on the market.

Our results may be affected by our ability to successfully market both new and existing products domestically and internationally, clinical and regulatory developments involving current and future products, sales growth of recently launched products, competition from other products including biosimilars, difficulties or delays in manufacturing our products and global economic conditions. In addition, sales of our products are affected by pricing pressure, political and public scrutiny and reimbursement policies imposed by third-party payers, including governments, private insurance plans and managed care providers and may be affected by regulatory, clinical and guideline developments and domestic and international trends toward managed care and healthcare cost containment. Furthermore, our research, testing, pricing, marketing and other operations are subject to extensive regulation by domestic and foreign government regulatory authorities. Our business may be impacted by government investigations, litigation and product liability claims. In addition, our business may be impacted by the adoption of new tax legislation or exposure to additional tax liabilities. If we fail to meet the compliance obligations in the corporate integrity agreement between us and the U.S. government, we could become subject to significant sanctions. Further, while we routinely obtain patents for our products and technology, the protection offered by our patents and patent applications may be challenged, invalidated or circumvented by our competitors, or we may fail to prevail in present and future intellectual property litigation. We perform a substantial amount of our commercial manufacturing activities at a few key facilities, including in Puerto Rico, and also depend on third parties for a portion of our manufacturing activities, and limits on supply may constrain sales of certain of our current products and product candidate development. An outbreak of disease or similar public health threat, such as COVID-19, and the public and governmental effort to mitigate against the spread of such disease, could have a significant adverse effect on the supply of materials for our manufacturing activities, the distribution of our products, the commercialization of our product candidates, and our clinical trial operations, and any such events may have a material adverse effect on our product development, product sales, business and results of operations. We rely on collaborations with third parties for the development of some of our product candidates and for the commercialization and sales of some of our commercial products. In addition, we compete with other companies with respect to many of our marketed products as well as for the discovery and development of new products. Further, some raw materials, medical devices and component parts for our products are supplied by sole third-party suppliers. Certain of our distributors, customers and payers have substantial purchasing leverage in their dealings with us. The discovery of significant problems with a product similar to one of our products that implicate an entire class of products could have a material adverse effect on sales of the affected products and on our business and results of operations. Our efforts to collaborate with or acquire other companies, products or technology, and to integrate the operations of companies or to support the products or technology we have acquired, may not be successful. There can be no guarantee that we will be able to realize any of the strategic benefits, synergies or opportunities arising from the Horizon acquisition, and such benefits, synergies or opportunities may take longer to realize than expected. We may not be able to successfully integrate Horizon, and such integration may take longer, be more difficult or cost more than expected. A breakdown, cyberattack or information security breach of our information technology systems could compromise the confidentiality, integrity and availability of our systems and our data. Our stock price is volatile and may be affected by a number of events. Our business and operations may be negatively affected by the failure, or perceived failure, of achieving our environmental, social and governance objectives. The effects of global climate change and related natural disasters could negatively affect our business and operations. Global economic conditions may magnify certain risks that affect our business. Our business performance could affect or limit the ability of our Board of Directors to declare a dividend or our ability to pay a dividend or repurchase our common stock. We may not be able to access the capital and credit markets on terms that are favorable to us, or at all.

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