LUMAKRAS™ (Sotorasib) Combined With Vectibix® (Panitumumab) Showed Encouraging Efficacy And Safety In Patients With KRAS G12C-Mutated Colorectal Cancer

September 16, 2021

New Data at ESMO 2021 Support Initiation of Phase 3 Trial of LUMAKRAS Plus Vectibix in Patients With 3L+ Colorectal Cancer

Amgen is Leading the Largest and Most Comprehensive Development Program in Patients with the KRAS G12C Mutation

THOUSAND OAKS, Calif., Sept. 16, 2021 /PRNewswire/ -- Amgen (NASDAQ: AMGN) today announced the first combination study results from the Phase 1b/2 CodeBreaK 101 study, the most comprehensive global clinical development program in patients with *KRAS* G12C-mutated advanced colorectal cancer (CRC). These new data show that combining LUMAKRAS™ (sotorasib) with Vectibix® (panitumumab), Amgen's monoclonal antibody epidermal growth factor receptor (EGFR) inhibitor, demonstrated encouraging efficacy and safety. Overall, the objective response rate (ORR) was 27% (confirmed and unconfirmed) among 26 patients in the efficacy analysis set (which included 5 patients who had progressed with prior sotorasib monotherapy). The disease control rate (DCR) was 81%. ORR and DCR were secondary endpoints. In the expansion cohort of sotorasib-naïve patients with refractory CRC (n=18), 33% of patients experienced a response (confirmed and unconfirmed). These data are being featured during the European Society of Medical Oncology 2021 (ESMO21) Virtual Congress.

"We are excited by these CodeBreaK 101 data, which show encouraging response rates that were much higher than the 9.7% response rate observed with LUMAKRAS monotherapy and highlight the importance of combination therapy for patients with *KRAS* G12C-mutated advanced colorectal cancer," said David M. Reese, M.D., executive vice president of Research and Development at Amgen. "Based on these results and the urgent need for new therapies, we are pleased to announce the initiation of a new Phase 3 trial with LUMAKRAS plus Vectibix in the third-line setting. This new trial, along with our doublet and triplet combination trials in colorectal cancer, demonstrates our commitment to delivering a new treatment option for metastatic CRC patients who harbor the *KRAS* G12C mutation."

In total, 31 patients with heavily pretreated (median of two prior lines of therapy; range 1-10) *KRAS* G12C-mutated metastatic CRC were enrolled in the dose exploration and dose expansion cohorts for the combination of LUMAKRAS and Vectibix. No patients experienced dose-limiting toxicities during the 28 days following initial treatment. The majority of treatment-related adverse events (TRAEs) were Grade 1-2 in severity, and no Grade 4 or fatal TRAEs were observed. The most common TRAEs (occurring in > 10% of patients) were consistent with known adverse events for LUMAKRAS and Vectibix and included dermatitis acneiform, dry skin, nausea, diarrhea, hypokalemia, hypomagnesemia, pruritus and rash. No new safety concerns were identified.

"With treatment response rates being as low as 2% in patients with colorectal cancer who progress in advanced stages, developing new treatment approaches for these patients is of critical interest," said Marwan G. Fakih, M.D., primary study investigator and co-director of the Gastrointestinal Cancer Program, City of Hope, Duarte, Calif. "Preclinical research has indicated that the addition of an EGFR inhibitor to $KRAS^{G12C}$ inhibition can be synergistic, and now we have the first clinical data indicating the combination of sotorasib and panitumumab has the potential to be a safe and effective treatment for patients with *KRAS* G12C-mutated advanced CRC."

Advancing Tarlatamab (formerly AMG 757) and AMG 404 in Small Cell Lung Cancer

In addition to the LUMAKRAS combination research, a presentation will detail the design of an ongoing study of half-life extended (HLE) bispecific T cell engager (BiTE®) molecule tarlatamab with anti-PD-1 antibody AMG 404 in patients with small cell lung cancer. The multicenter, open-label, Phase 1b study will evaluate the safety and tolerability of the combination and determine dosing as primary objectives, as well as examine preliminary antitumor activity and pharmacokinetics as secondary objectives.

Amgen to Webcast Investor Call at ESMO 2021

Amgen will host a webcast call for the investment community in conjunction with the European Society for Medical Oncology (ESMO) 2021 Congress. On Thursday, Sept. 16, 2021, at 8:30 a.m. ET, David M. Reese, M.D., executive vice president of Research and Development at Amgen, along with other members of Amgen's management team, will discuss clinical data being presented on the Company's $KRAS^{G12C}$ inhibitor LUMAKRAS™ (sotorasib) in combination with Vectibix® (panitumumab).

Live audio of the investor call will be broadcast over the internet simultaneously and will be available to members of the news media, investors and the general public.

The webcast, as with other selected presentations regarding developments in Amgen's business given at certain investor and medical conferences, can be accessed on Amgen's website, www.amgen.com, under Investors. Information regarding presentation times, webcast availability and webcast links are noted on Amgen's Investor Relations Events Calendar. The webcast will be archived and available for replay for at least 90 days after the event.

About LUMAKRAS™ (sotorasib)

Amgen took on one of the toughest challenges of the last 40 years in cancer research by developing LUMAKRAS, a $KRAS^{G12C}$ inhibitor.[1] LUMAKRAS has demonstrated a positive benefit-risk profile with rapid, deep and durable anticancer activity in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring the *KRAS* G12C mutation with a once daily oral formulation.[2]

In May 2021, LUMAKRAS was the first $KRAS^{G12C}$ inhibitor to receive regulatory approval anywhere in the world with its approval in the U.S., under accelerated approval. LUMAKRAS is also approved in the United Arab Emirates, and in Great Britain and Canada under Project Orbis.

Amgen is progressing the largest and broadest global $KRAS^{G12C}$ inhibitor development program with unparalleled speed and exploring more than 10 sotorasib combination regimens, including triplets, with clinical trial sites spanning five continents. To date, LUMAKRAS has treated almost 3,000 patients around the world through the clinical development program and commercial use.

In the U.S., LUMAKRAS was reviewed by the FDA under its Real-Time Oncology Review (RTOR), a pilot program that aims to explore a more efficient review process that ensures safe and effective treatments are made available to patients as early as possible. Amgen is participating in the FDA's Project Orbis initiative and through the initiative, has Marketing Authorization Applications (MAAs) for sotorasib in review in Australia and Brazil. Additionally, Amgen has submitted an MAA in the European Union, Japan, Switzerland, South Korea, Singapore, Israel, Turkey, Taiwan, Colombia, Thailand, Mexico and Hong Kong.

LUMAKRAS is also being studied in multiple other solid tumors.[1]

About CodeBreaK

The CodeBreaK clinical development program for Amgen's drug sotorasib is designed to treat patients with an advanced solid tumor with the *KRAS* G12C mutation and address the longstanding unmet medical need for these cancers. As the most advanced $KRAS^{G12C}$ inhibitor clinical development program, CodeBreaK has enrolled more than 800 patients across 13 tumor types since its inception.

CodeBreaK 100, the Phase 1 and 2, first-in-human, open-label multicenter study, enrolled patients with *KRAS* G12C-mutant solid tumors. Eligible patients must have received a prior line of systemic anticancer therapy, consistent with their tumor type and stage of disease. The primary endpoint for the Phase 2 study was centrally assessed objective response rate. The Phase 2 trial in NSCLC enrolled 126 patients, 124 of whom had centrally evaluable lesions by RECIST at baseline. The Phase 2 trial in colorectal cancer (CRC) is fully enrolled and results have been submitted for publication.

A global Phase 3 randomized active-controlled study comparing sotorasib to docetaxel in patients with *KRAS* G12C-mutated NSCLC (CodeBreaK 200) has completed enrollment. Amgen also has several Phase 1b studies investigating sotorasib monotherapy and sotorasib combination therapy across various advanced solid tumors (CodeBreaK 101) open for enrollment. A Phase 2 randomized study will evaluate sotorasib in patients with stage IV *KRAS* G12C-mutated NSCLC in need of first-line treatment (CodeBreaK 201).

For information, please visit www.hcp.codebreaktrials.com.

About Advanced Colorectal Cancer and the *KRAS* G12C Mutation

Colorectal cancer (CRC) is the second leading cause of cancer deaths worldwide, comprising 10% of all cancer diagnoses.[3] It is also the third most commonly diagnosed cancer globally.[4]

Patients with previously treated metastatic CRC need more effective treatment options, as standard therapies yield median PFS times of about two months and patients' response rates are less than 2%. [5,6]

KRAS mutations are among the most common genetic alterations in colorectal cancers, with the *KRAS* G12C mutation present in approximately 3-5% of colorectal cancers.[7,8,9]

About BiTE® Technology

BiTE® (bispecific T cell engager) technology is a targeted immuno-oncology platform that is designed to engage a patient's own T cells to any tumor-specific antigen, activating the cytotoxic potential of T cells to eliminate detectable cancer. The BiTE immuno-oncology platform has the potential to treat different tumor types through tumor-specific antigens. The BiTE platform has a goal of leading to off-the-shelf solutions, which have the potential to make innovative T cell treatment available to all providers when their patients need it. Amgen is advancing BiTE molecules across a broad range of hematologic malignancies and solid tumors and further investigating BiTE technology with the goal of enhancing patient experience and therapeutic potential.

LUMAKRAS™ (sotorasib) U.S. Indication

LUMAKRAS™ is indicated for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.

This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

LUMAKRAS™ (sotorasib) Important Safety Information

Hepatotoxicity

- LUMAKRAS™ can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis.
- Among 357 patients who received LUMAKRAS™ in CodeBreaK 100, hepatotoxicity occurred in 1.7% (all grades) and 1.4% (Grade 3). A total of 18% of patients who received LUMAKRAS™ had increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST); 6% were Grade 3 and 0.6% were Grade 4. In addition to dose interruption or reduction, 5% of patients received corticosteroids for the treatment of hepatotoxicity.
- Monitor liver function tests (ALT, AST 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, dose reduce or permanently discontinue LUMAKRAS™ based on severity of adverse reaction.

Interstitial Lung Disease (ILD)/Pneumonitis

- LUMAKRAS™ can cause ILD/pneumonitis that can be fatal. Among 357 patients who received LUMAKRAS™ in CodeBreaK 100, ILD/pneumonitis occurred in 0.8% of patients, all cases were Grade 3 or 4 at onset, and 1 case was fatal. LUMAKRAS™ was discontinued due to ILD/pneumonitis in 0.6% of 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 H_2 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 LUMAKRAS™ full Prescribing Information.

About Vectibix® (panitumumab)

Vectibix is the first fully human monoclonal anti-EGFR antibody 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 after 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 biologic therapy indicated for use with FOLFOX, one of the most commonly used chemotherapy regimens, in the 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 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.

INDICATION AND LIMITATION OF USE

Vectibix® is indicated for the treatment of patients with wild-type *RAS* (defined as wild-type in both *KRAS* and *NRAS* as determined by an FDA-approved test for this use) metastatic colorectal cancer (mCRC): as first-line therapy in combination with FOLFOX, and as monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy.

Limitation of Use: Vectibix® is not indicated for the treatment of patients with *RAS* mutant mCRC or for whom *RAS* mutation status is unknown.

IMPORTANT SAFETY INFORMATION

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 *[see Dosage and Administration (2.3), Warnings and Precautions (5.1), and Adverse Reactions (6.1)].*

- In Study 20020408, dermatologic toxicities occurred in 90% of patients and were severe (NCI-CTC grade 3 and higher) in 15% of patients with mCRC receiving Vectibix®. The clinical manifestations included, but were not limited to, acneiform dermatitis, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures.
- 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 (e.g., 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 in the product labeling.
- Vectibix® 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.

- Progressively decreasing serum magnesium levels leading to severe (grade 3-4) hypomagnesemia occurred in up to 7% (in Study 20080763) of patients across clinical trials. 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® in combination with chemotherapy.
- 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®. 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®.
- Keratitis and serious cases of keratitis, ulcerative keratitis, known risk factors for and corneal perforation, have occurrred with Vectibix use. 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.
- Vectibix® can cause fetal harm when administered to a pregnant woman. Advise pregnant women and females of reproductive potential of the potential risk to a 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. The most common serious adverse reactions (≥ 2% difference between treatment arms) were diarrhea and dehydration.

To see the Vectibix® Prescribing Information, including Boxed Warning visit www.vectibix.com.

About Amgen Oncology
At Amgen Oncology, our mission to serve patients drives all that we do. That's why we're relentlessly focused on accelerating the delivery of medicines that have the potential to empower all angles of care and transform lives of people with cancer.

For the last four decades, we have been dedicated to discovering the firsts that matter in oncology and to finding ways to reduce the burden of cancer. Building on our heritage, Amgen continues to advance the largest pipeline in the Company's history, moving with great speed to advance those innovations for the patients who need them.

At Amgen, we're advancing oncology at the speed of life™.

For more information, follow us on www.twitter.com/amgenoncology.

About Amgen
Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. This approach begins by using tools like advanced human genetics to unravel the complexities of disease

and understand the fundamentals of human biology.

Amgen focuses on areas of high unmet medical need and leverages its expertise to strive for solutions that improve health outcomes and dramatically improve people's lives. A biotechnology pioneer since 1980, Amgen has grown to be one of the world's leading independent biotechnology companies, has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

For more information, visit www.amgen.com and follow us on www.twitter.com/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., Kyowa-Kirin Co., Ltd., or any collaboration to manufacture therapeutic antibodies against COVID-19), the performance of Otezla® (apremilast) (including anticipated Otezla sales growth and the timing of non-GAAP EPS accretion), or the Five Prime Therapeutics, Inc. acquisition, 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 such as the ongoing COVID-19 pandemic on our business, outcomes, progress, or effects relating to studies of Otezla as a potential treatment for COVID-19, 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. A breakdown, cyberattack or information security breach 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. 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.

The scientific information discussed in this news release related to our product candidates is preliminary and investigative. Such product candidates are not approved by the U.S. Food and Drug Administration, and no conclusions can or should be drawn regarding the safety or effectiveness of the product candidates. Further, any scientific information discussed in this news release relating to new indications for our products is preliminary and investigative and is not part of the labeling approved by the U.S. Food and Drug Administration for the products. The products are not approved for the investigational use(s) discussed in this news release, and no conclusions can or should be drawn regarding the safety or effectiveness of the products for these uses.

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