GLOBAL COALITION FOR ADAPTIVE RESEARCH, AMGEN, AND EISAI ANNOUNCE FIRST PATIENT ENROLLED IN INTERNATIONAL COVID-19 TRIAL

AMGEN AND EISAI TO PARTICIPATE IN THE IMMUNE MODULATION DOMAIN OF REMAP-COVID, AN ADAPTIVE CLINICAL TRIAL TO TEST INTERVENTIONS FOR PATIENTS HOSPITALIZED WITH COVID-19

AMGEN'S APREMILAST AND EISAI'S ERITORAN TO BE EVALUATED ACROSS MULTIPLE INTERNATIONAL TRIAL SITES WITHIN THE REMAP NETWORK

October 27, 2020

(BUSINESS WIRE)--Global Coalition for Adaptive Research (LOS ANGELES, CA), Amgen (THOUSAND OAKS, CA), and Eisai Co., Ltd. (TOKYO, Japan "Eisai") -- The Global Coalition for Adaptive Research (GCAR) in collaboration with Amgen and Eisai, today announced enrollment of the first patient in the immune modulation domain of REMAP-COVID, a sub-study of REMAP-CAP (A Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia) that tests multiple interventions for the treatment of patients hospitalized with COVID-19. Amgen's *apremilast* and Eisai's investigational *eritoran* are being evaluated as potential therapeutic agents.

REMAP-CAP was developed to test treatments for severe pneumonia both in non-pandemic and pandemic settings. In February 2020, REMAP-CAP rapidly pivoted to its pandemic mode (the REMAP-COVID sub-study), as per its original intent, to incorporate additional potential treatment regimens specifically targeting COVID-19 and to expand enrollment to COVID-19 patients. This trial is a multicenter, randomized platform study, with treatments tested within groupings or "domains" based on pathway or mechanism of action.

The trial is being conducted in the multi-hospital UPMC (University of Pittsburgh Medical Center) health system along with over 20 hospitals in the United States. Additional global sites across the trial network will follow. University of Pittsburgh is serving as the U.S. Regional Coordinating Center.

"Partnering with the biopharmaceutical industry to be able to efficiently test well-understood targeted agents is critical to understanding treatment paradigms for COVID-19 patients," says Derek Angus, MD., MPH, FRCP, U.S. Principal Investigator of REMAP and Chief Healthcare Innovation Officer, UPMC Health System. "Today's announcement marks an important milestone in the collaboration between industry and the scientific and academic community to work collectively to evaluate potentially promising therapies to support patients hospitalized with COVID-19."

Amgen's *apremilast* is an oral drug which inhibits the activity of PDE4 (Phosphodiesterase 4), an enzyme found in inflammatory cells in the human body. By inhibiting PDE4, *apremilast* is thought to modulate the production of inflammatory cytokines and other mediators, which may prove helpful in inhibiting the inflammatory response associated with the signs, symptoms and pulmonary involvements observed in some COVID-19 patients. *Apremilast* is currently approved for use in more than 45 countries as an oral treatment for inflammatory diseases including moderate to severe plaque psoriasis, psoriatic arthritis and oral ulcers associated with Behcet's disease.

"Amgen believes that, based on its mechanism of action, *apremilast* might help prevent the respiratory distress seen in moderate to severe-stage adult COVID-19 patients," said David M. Reese, M.D., Executive Vice President of Research and Development at Amgen. "We are proud to be joining REMAP-COVID, which is an important and innovative effort utilizing a platform approach and has the

potential to rapidly identify whether *apremilast* may improve health outcomes for patients hospitalized with moderate to severe COVID-19."

Eritoran is Eisai's in-house discovered and developed investigational TLR4 (Toll-Like Receptor 4) antagonist created with natural product organic synthesis technology. It is a structural analogue of Lipid A, which is an activator of endotoxins of bacteria. It has been previously observed to be safe in 14 clinical studies including a large Phase 3 randomized trial in severe sepsis. It is expected to suppress inflammation and increasing in severity caused by COVID-19 by inhibiting the activation of TLR4, which is found in the most upstream of various cytokine gene expression signaling that causes the cytokine-storm.

"Eisai is pleased to participate in the groundbreaking REMAP-COVID effort, and we expect that this study will generate important insights about *eritoran's* potential to possibly improve health outcomes for patients with moderate and severe COVID-19," said Lynn Kramer, M.D., FAAN, Chief Clinical Officer, Neurology Business Group, Eisai "As part of our human health care mission, we are committed to making a difference for patients, their families and health care professionals across the globe."

GCAR is the U.S. Sponsor of REMAP-COVID and is guiding efforts to facilitate the inclusion of multiple pharma partners in REMAP-COVID globally.

"GCAR is delighted to utilize our expertise in implementing and overseeing innovative trials to collaborate on this important effort," shared Meredith Buxton, PhD, Chief Executive Officer of GCAR. "We are committed to working closely with pharma and the REMAP Network to identify new effective treatments for patients with COVID-19 by serving as U.S. sponsor of this important and innovative platform trial."

About REMAP-CAP
REMAP-CAP is led by world experts in critical care, clinical trials, pandemic and infectious disease outbreaks, virology, immunology, emergency medicine, and Bayesian statistics. REMAP-CAP has enrolled over 2000 patients at 263 sites across 19 countries. This vital research is being conducted in collaboration with Berry Consultants, leaders in statistical design for adaptive platform trials, and is being supported by governments and non-profits worldwide.

To learn more about REMAP-CAP and the REMAP-COVID sub-study, please visit www.remapcap.org and follow @remap_cap

About Otezla® (apremilast)
Otezla® (apremilast) is an oral small-molecule inhibitor of phosphodiesterase 4 (PDE4) specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels, which is thought to indirectly modulate the production of inflammatory mediators. The specific mechanism(s) by which Otezla exerts its therapeutic action in patients is not well defined.

By inhibiting PDE4, Otezla is thought to modulate the production of inflammatory cytokines and other mediators, which may prove helpful in inhibiting the inflammatory response associated with the signs, symptoms and pulmonary involvements observed in some COVID-19 patients. Amgen plans to collaborate with platform trials to investigate Otezla in treatment of hospitalized COVID-19 patients.

Otezla® (apremilast) U.S. INDICATIONS
Otezla® (apremilast) is indicated for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

Otezla is indicated for the treatment of adult patients with active psoriatic arthritis.

Otezla is indicated for the treatment of adult patients with oral ulcers associated with Behçet's Disease.

Otezla® (apremilast) U.S. IMPORTANT SAFETY INFORMATION

Contraindications

- Otezla® (apremilast) is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation

Warnings and Precautions

- Diarrhea, Nausea, and Vomiting: Cases of severe diarrhea, nausea, and vomiting were associated with the use of Otezla. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting; advise patients to contact their healthcare provider. Consider Otezla dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting
- Depression: Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on Otezla. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and they should contact their healthcare provider if such changes occur
    - Psoriasis: Treatment with Otezla is associated with an increase in depression. During clinical trials, 1.3% (12/920) of patients reported depression compared to 0.4% (2/506) on placebo. Depression was reported as serious in 0.1% (1/1308) of patients exposed to Otezla, compared to none in placebo-treated patients (0/506). Suicidal behavior was observed in 0.1% (1/1308) of patients on Otezla, compared to 0.2% (1/506) on placebo. One patient treated with Otezla attempted suicide; one patient on placebo committed suicide
    - Psoriatic Arthritis: Treatment with Otezla is associated with an increase in depression. During clinical trials, 1.0% (10/998) reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. Suicidal ideation and behavior was observed in 0.2% (3/1441) of patients on Otezla, compared to none in placebo-treated patients. Depression was reported as serious in 0.2% (3/1441) of patients exposed to Otezla, compared to none in placebo-treated patients (0/495). Two patients who received placebo committed suicide compared to none on Otezla
    - Behcet's Disease: Treatment with Otezla is associated with an increase in depression. During the phase 3 clinical trial, 1% (1/104) reported depression or depressed mood compared to 1% (1/103) treated with placebo. No instances of suicidal ideation or behavior were reported in patients treated with Otezla or treated with placebo
- Weight Decrease: Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla
    - Psoriasis: During the clinical trials, body weight loss of 5-10% occurred in 12% (96/784) of patients treated with Otezla and in 5% (19/382) of patients treated with placebo. Body weight loss of ≥10% occurred in 2% (16/784) of patients treated with Otezla compared to 1% (3/382) of patients treated with placebo
    - Psoriatic Arthritis: During the clinical trials, body weight loss of 5-10% was reported in 10% (49/497) of patients taking Otezla and in 3.3% (16/495) of patients taking placebo

    - Behçet's Disease: During the clinical trials, body weight loss of >5% was reported in 4.9% (5/103) of patients taking Otezla and in 3.9% (4/102) of patients taking placebo
- Drug Interactions: Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended

Adverse Reactions

- Psoriasis: Adverse reactions reported in ≥5% of patients were (Otezla%, placebo%): diarrhea (17, 6), nausea (17, 7), upper respiratory tract infection (9, 6), tension headache (8, 4), and headache (6, 4)
- Psoriatic Arthritis: Adverse reactions reported in at least 2% of patients taking Otezla, that occurred at a frequency at least 1% higher than that observed in patients taking placebo, for up to 16 weeks (after the initial 5-day titration), were (Otezla%, placebo%): diarrhea (7.7, 1.6); nausea (8.9, 3.1); headache (5.9, 2.2); upper respiratory tract infection (3.9, 1.8); vomiting (3.2, 0.4); nasopharyngitis (2.6, 1.6); upper abdominal pain (2.0, 0.2)
- Behçet's Disease: Adverse reactions reported in at least ≥5% of patients taking Otezla, that occurred at a frequency at least 1% higher than that observed in patients taking placebo, for up to 12 weeks, were (Otezla%, placebo%): diarrhea (41.3, 20.4); nausea (19.2, 10.7); headache (14.4, 10.7); upper respiratory tract infection (11.5, 4.9); upper abdominal pain (8.7, 1.9); vomiting (8.7, 1.9); back pain (7.7, 5.8); viral upper respiratory tract infection (6.7, 4.9); arthralgia (5.8, 2.9)

Use in Specific Populations

- Pregnancy: Otezla has not been studied in pregnant women. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Otezla during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/otezla/
- Lactation: There are no data on the presence of apremilast or its metabolites in human milk, the effects of apremilast on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Otezla and any potential adverse effects on the breastfed child from Otezla or from the underlying maternal condition
- Renal Impairment: Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min) for details, see Dosage and Administration, Section 2, in the Full Prescribing Information

Please click here for Otezla® Full Prescribing Information.

About Eritoran (E5564)

Eritoran is Eisai's in-house discovered and developed investigational TLR4 (Toll-Like Receptor 4) antagonist created with natural product organic synthesis technology. It is a structural analogue of Lipid A which is an activator of endotoxins of bacteria. It has been previously observed to be safe in 14 clinical studies including a large Phase 3 randomized trial in severe sepsis. It is expected to suppress inflammation and increasing in severity caused by COVID-19 by inhibiting the activation of TLR4, which is found in the most upstream of various cytokine gene expression signaling that causes the cytokine-storm.

About Global Coalition for Adaptive Research (GCAR)
The Global Coalition for Adaptive Research (GCAR) is a 501(c)(3) nonprofit organization uniting physicians, clinical researchers, advocacy and philanthropic organizations, biopharma, health authorities, and other key stakeholders in healthcare to expedite the discovery and development of treatments for patients with rare and deadly diseases by serving as Sponsor of innovative and complex trials including master protocols and platform trials. In this effort, GCAR is serving as U.S. Trial Sponsor of REMAP-CAP.

To learn more about GCAR, visit www.gcaresearch.org and follow us: @GCAResearch and www.facebook.com/GCAResearch.

About UPMC (University of Pittsburgh Medical Center)
Pittsburgh-based UPMC is inventing new models of patient-centered, cost-effective, accountable care. UPMC integrates more than 90,000 employees, 40 hospitals, 700 doctors' offices and outpatient sites. *U.S. News & World Report* consistently ranks UPMC Presbyterian Shadyside on its annual Honor Roll of America's Best Hospitals and ranks UPMC Children's Hospital of Pittsburgh on its Honor Roll of America's Best Children's Hospitals. For more information, go to UPMC.com.

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 biologics manufacturing 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 the world's largest independent biotechnology company, 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.

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 any collaboration or potential collaboration in pursuit of therapeutic antibodies against COVID-19 (including statements regarding such collaboration's, or our own, ability to discover and develop fully-human neutralizing antibodies targeting SARS-CoV-2 or antibodies against targets other than the SARS-CoV-2 receptor binding domain, to potentially prevent or treat COVID-19), or the Otezla® (apremilast) acquisition (including anticipated Otezla sales growth and the timing of non-GAAP EPS accretion), 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 Amgen's 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 its 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 Amgen projects. 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.

The scientific information discussed in this news release related to Amgen's 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 Amgen's 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.

About Eisai Co., Ltd.
Eisai Co., Ltd. is a leading global research and development-based pharmaceutical company headquartered in Japan. We define our corporate mission as "giving first thought to patients and their families and to increasing the benefits health care provides," which we call our *human health care* (*hhc*) philosophy. With approximately 10,000 employees working across our global network of R&D facilities, manufacturing sites and marketing subsidiaries, we strive to realize our *hhc* philosophy by delivering innovative products to address unmet medical needs, with a particular focus in our strategic areas of Neurology and Oncology. As a global pharmaceutical company, our mission extends to patients around the world through our investment and participation in partnership-based initiatives to improve access to medicines in developing and emerging countries. For more information about Eisai Co., Ltd., please visit www.eisai.com.

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