Modernra Announces an Array of Clinical Advances and Outlines 2018 Priorities; 19 Development Candidates, including 10 Clinical Programs, Highlight Productivity of mRNA Platform

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Clinical advances include: planned phase 2 study for a VEGF mRNA therapeutic; a new cancer vaccine IND application; and initiation of two phase 1 studies of prophylactic vaccines for infectious diseases

Three new development candidates target liver expression of therapeutic human proteins and first antibody

2018 pipeline strategy focuses on new rare disease development candidates and advancing additional prophylactic vaccines development candidates in areas of high unmet need

Cambridge, Mass., January 8, 2018 — Moderna Therapeutics, a clinical stage biotechnology company that is pioneering messenger RNA (mRNA) therapeutics and vaccines to create a new generation of transformative medicines for high unmet medical needs in patients, today announced important advances in its mRNA development pipeline, demonstrating the increasing productivity of its platform, including its first mRNA program to enter phase 2, new infectious disease vaccine and oncology programs entered into Phase 1 clinical studies, and the ongoing expansion of its pipeline with several new development candidates (DCs). A leader in mRNA science and development, Moderna continues to make notable progress across its broad, diverse pipeline, which now includes 19 mRNA drug candidates spanning infectious diseases, immuno-oncology, rare diseases and cardiovascular diseases.

Moderna’s Chief Executive Officer Stéphane Bancel detailed company strategy and progress today at the 36th Annual J.P. Morgan Healthcare Conference in San Francisco.

The company today announced several new advances including:

- A Phase 2a study of mRNA AZD8601, a localized mRNA therapeutic encoding for vascular endothelial growth factor, VEGF-A, being developed in partnership with AstraZeneca. Information on the clinical study, including design and target indication, will be detailed in the coming weeks. Led by AstraZeneca, this will be Moderna’s first phase 2 study.
- A new development candidate, mRNA-3927, for a rare disease within the liver modality. mRNA-3927 directs liver expression of a deficient enzyme in patients with propionic acidemia (PA), a serious and potentially life-threatening rare disease, which is part of a family of disorders known as organic acidemias. There are no approved therapies or ongoing clinical trials for PA. In September, Moderna announced its first rare disease DC, mRNA-3704, to treat methylmalonic acidemia, or MMA, another serious and often deadly organic acidemia.
- The filing of an investigational new drug (IND) application for mRNA-5671, a KRAS cancer vaccine. KRAS is one of the most frequently mutated oncogenes in human cancer (approximately 30 percent of all cases). mRNA-5671 encodes for the four most commonly found KRAS mutations, which will cover most of the mutations that occur in non-small cell lung cancer, colorectal cancer and pancreatic cancer.
- The initiation of two phase 1 prophylactic vaccine studies for mRNA-1647, a cytomegalovirus (CMV) vaccine, and mRNA-1653, a human metapneumovirus and parainfluenza virus type 3 (HMPV+PIV3) combination vaccine. CMV is the most common cause of newborn disability and the most frequent viral disease in transplant recipients, often leading to transplant failure. mRNA-1647 is made of 6 mRNAs, one coding for the herpesvirus glycoprotein (gB) antigen and 5 coding for the pentamer. HMPV and PIV3 are the second and third most common causes, respectively, of lower respiratory hospitalizations in children, behind respiratory syncytial virus (RSV). Currently, there are no approved vaccines for CMV, HMPV or PIV3.
- A new development candidate, mRNA-1944, which directs liver expression of an antibody that can potentially neutralize chikungunya virus circulating in the blood. Moderna has a Phase 1 study underway for a prophylactic vaccine, mRNA-1388, to prevent infection from the chikungunya virus. An antibody approach would be more desirable in certain settings, such as in immuno-compromised populations, when rapid post-exposure treatment or prophylaxis is warranted, or when protection is needed only for short periods of time. This program is sponsored by DARPA.

“We are proud of the progress we have made over the past year as we continue to see real development pipeline momentum and productivity from our platform, and continue to deliver to the clinic important advances in mRNA science. We have achieved critical milestones in R&D, having gone from four clinical programs at the beginning of the year to now having 10 medicines in human testing, and our intention is to continue to rapidly advance our pipeline with an array of new development programs,” said Bancel. “2016 was the year of mRNA vaccines in the clinic. 2017 was the year of several mRNA therapeutics in the clinic. In 2018, we will continue to evolve our pipeline of mRNA therapeutics, specifically focusing on discovering new rare disease drug candidates, while remaining committed to advancing new vaccine development candidates to address serious unmet needs. We will also continue to work toward a summer 2018 opening and rolling scale-up of our GMP clinical mRNA manufacturing facility, which is a cornerstone of our long-term strategy to move multiple development programs simultaneously into and through phase 1, phase 2, and phase 3 clinical studies.”
As of today, nearly 700 subjects have been dosed across Moderna’s internally developed and partnered clinical programs with AstraZeneca and Merck. Moderna’s full pipeline can be found here.

2018 Strategic Priorities

During today’s presentation, Mr. Bancel outlined Moderna’s key strategic priorities for 2018 which include:

- Effective execution of the development pipeline by continuing to advance programs through clinical study and by moving additional development programs into the clinic;
- Emphasis on the discovery of new rare disease development candidates and new prophylactic vaccines to address high unmet medical needs;
- Continued investment in the evolution of the company’s mRNA platform, including exploring new modalities to expand the application of its technology in new therapeutic areas;
- Completion of construction of the company’s 200,000 square foot GMP mRNA clinical manufacturing facility in Norwood, Mass., with an anticipated opening in the summer of 2018 and subsequent rolling scale-up of the facility.

Detailed Q4 2017 Clinical and Development Program Updates

Moderna’s pipeline spans five modalities: prophylactic vaccines, therapeutic vaccines, intratumoral immuno-oncology therapeutics, localized therapeutics and liver therapeutics. Following are advances from across modalities since the company’s September business update:

Commercial Prophylactic Vaccines

- **Initiation of Phase 1 study of mRNA-1647, a cytomegalovirus (CMV) vaccine:** The Phase 1, placebo-controlled multi-center study of mRNA-1647 began dosing patients in November 2017, and will assess safety, tolerability and immunogenicity. [clinicaltrials.gov listing](https://clinicaltrials.gov). A complex vaccine, mRNA-1647 consists of six mRNAs, including five proteins (gH, gL, UL128, UL130 and UL131A) designed to express the pentamer complex, and another CMV antigen, the herpesvirus glycoprotein (gB) protein. CMV is the most common cause of newborn disability, leading to deafness, microcephaly (small, not fully developed heads and severe disabilities), vision loss and mental deficiencies, among other serious complications. It is also the most frequent viral disease in transplant recipients, often leading to transplant failure. Currently, there is no approved vaccine for CMV.

- **Initiation of Phase 1 study of mRNA-1653, a combination human metapneumovirus and parainfluenza virus type 3 (HMPV+PIV3) vaccine:** The placebo-controlled, multi-site Phase 1 study of mRNA-1653 began dosing patients in December 2017 and will assess for safety, tolerability, and immunogenicity. HMPV and PIV3 typically cause mild respiratory illness, but can become severe in young children, the elderly and other immunocompromised adults. HMPV and PIV3 are the second and third most common causes, respectively, of lower respiratory hospitalizations in children, behind RSV. Currently, there is no approved vaccine for either HMPV or PIV3.

- **Publications:** in September, Moderna announced a publication in the August issue of *Molecular Therapy* that provides mechanistic insights about its mRNA prophylactic vaccines. The research, led by Professor Karin Loré, Ph.D., and her group at the Karolinska Institutet in Stockholm, Sweden, characterizes how Moderna’s vaccines target key antigen-presenting cells, leading to both B cell and T cell activation, which yields a potent immune response. Two additional papers
based on Dr. Lore's work offer additional insights into the method of action of Moderna's vaccine technology. A paper published in November 2017 in Frontiers in Immunology demonstrates that Moderna vaccine technology is able to stimulate a type of B cell that makes high-quality, antigen-specific antibodies consistent with high seroconversion rates in humans. A second paper published in November in the Journal of Immunology, shows that Moderna's vaccine technology produces a desirable kinetic immune activation and subsequent suppression by myeloid derived suppressor cells (MDSCs), which are major regulators of T-cell responses.

Moderna also continues to advance vaccines in collaboration with government agencies and non-government organizations to address major public health issues. The company is furthering its efforts through its current contract with the Biomedical Advanced Research and Development Agency (BARDA) – part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services – to develop an mRNA Zika vaccine, now including a head-to-head comparison of two potential mRNA candidates (mRNA 1325 and mRNA 1893) through Phase 1, after which it will determine the best candidate for further clinical development to BLA submission for licensure.

**Therapeutic Vaccines**

- **Initiation of Phase 1 study of personalized cancer vaccine (PCV), mRNA-4157 (KEYNOTE-603):** In November, Moderna announced that it has initiated dosing for a Phase 1 study of its PCV. The Phase 1 open-label, dose escalation, multicenter study in the United States will assess the safety, tolerability and immunogenicity of mRNA-4157 alone in subjects with resected solid tumors and in combination with KEYTRUDA® (pembrolizumab), an anti-PD-1 therapy, marketed by Merck (known as MSD outside the U.S. and Canada) in subjects with unresectable solid tumors. Moderna has a strategic collaboration with Merck to develop PCVs in collaboration with KEYTRUDA®. Moderna first identifies neoepitopes present in a patient's tumor and then creates an mRNA-based PCV encoding for approximately 20 neoepitopes. When injected into the patient, the mRNA-based PCV directs the patient's cells to express the selected neoepitopes. In turn, this may help the patient's immune system better recognize cancer cells as foreign and eradicate them. mRNA-4157 also has the potential to enhance clinical outcomes associated with checkpoint inhibitor therapies. Leveraging its rapid cycle time, small-batch manufacturing technique and digital infrastructure, Moderna plans to manufacture and supply each individually tailored and manufactured PCV to patients within weeks.

- **Investigational new drug (IND) application filed for mRNA-5671, a KRAS cancer vaccine:** KRAS is one of the most frequently mutated oncogenes in human cancer (approximately 30% of all cases). KRAS mutations are found principally in non-small cell lung cancer (NSCLC), colorectal cancer and pancreatic cancer, and are associated with worse outcomes. Hotspots of KRAS mutations are found in different tumor types and can serve as tumor rejection epitopes. Presentation of these epitopes to the immune system may elicit a robust anti-tumor response. mRNA-5671 encodes for the four most commonly found KRAS mutations, which will cover most of the mutations that occur in NSCLC, colorectal cancer and pancreatic cancer.

- **National Cancer Institute (NCI) to study mRNA-based PCV:** In collaboration with Moderna, the Surgery Branch of the NCI’s Center for Cancer Research plans to sponsor a Phase 1/2 study to investigate the safety and immunogenicity of mRNA-based PCVs for patients under the direction of Steven A. Rosenberg, M.D., Ph.D., Chief of Surgery, NCI. As part of this collaboration, Moderna will manufacture mRNA-based personalized cancer vaccines (NCI-4650) for up to 12 patients with advanced-stage, metastatic cancers.

**Localized Therapeutics**

- **Phase 2a study of mRNA AZD-8601:** Phase 2a study of mRNA AZD8601: Dosing of patients is anticipated for early in the first quarter of 2018 for the Phase 2a study of mRNA AZD8601, a localized mRNA therapeutic encoding for vascular endothelial growth factor, VEGF-A. The mRNA AZD8601 program is led by AstraZeneca. Data from a Phase 1 randomized, double-blind, placebo-controlled, single ascending dose study that assessed the safety, tolerability and pharmacokinetics (PK) of mRNA AZD8601 after single dose administration in male patients with Type 2 diabetes mellitus are expected to be presented at a scientific congress and published in 2018.

**Liver Therapeutics**

- **Naming of pre-clinical development candidate mRNA-3927, encoding an intracellular enzyme to treat Propionic Acidemia (PA):** PA is a rare, autosomal recessive organic acidemia/aciduria caused by a mitochondrial enzyme deficiency in propionyl-CoA carboxylase (PCC) due to mutations in PCCA (PA type I) or PCCB (PA type II). mRNA-3927 combines mRNA-encoded proteins for both the PCCA and PCCB enzyme components with the goal of addressing all PA subtypes. PA is a natural follow-on to the MMA program, as both are organic acidemias with defective enzymes along the same metabolic pathway. PA is a rare disease with no approved therapy. The disorder typically impacts newborn children, and patients with PA often present acutely with metabolic acidosis, cardiac arrhythmias and hyperammonemia causing severe central nervous system dysfunction.

- **Naming of pre-clinical development candidate mRNA-1944, encoding an antibody against the chikungunya virus:** mRNA-1944 encodes for an antibody that can neutralize the chikungunya virus circulating in the blood. Moderna has a Phase 1 study underway for a prophylactic mRNA vaccine (mRNA-1388) to prevent infection from chikungunya virus. However, in certain situations, such as in immuno-compromised populations, when rapid post-exposure treatment or...
prophylaxis is warranted, or when protection is needed only for short periods (three to six months), an antibody approach is desirable. Chikungunya typically causes mild fever and transient joint pain. In approximately 15 percent of infected patients, it can cause long-term, severe arthritis. Chikungunya historically has been limited to warmer climates in Asia and Africa, but recent cases have been identified in the Americas and Europe. There is no approved vaccine or treatment for chikungunya.

- **Collaboration for mRNA AZD-7970, encoding the secreted protein relaxin to treat heart failure**: In November, Moderna and AstraZeneca announced a new strategic agreement to co-develop and co-commercialize mRNA AZD-7970, which is designed to instruct cells in the body to produce and express relaxin, a secreted protein with systemic effect. Heart failure occurs when the heart is weakened and cannot pump enough blood to meet the body's needs. Biologic functions for relaxin suggest that expression of the hormone may directly impact underlying conditions that exacerbate heart failure, leading to the regrowth of heart tissue, controlling inflammation, reordering the extracellular matrix, improving renal function, and relieving hepatic portal pressure.

- **Publications**: In December, Moderna announced the publication of preclinical data supporting its first rare disease development program, mRNA-3704, a therapeutic for methylmalonic acidemia (MMA), a serious and often life-threatening organic acidemia disorder. The data, published in the journal *Cell Reports*, demonstrate that intravenous (IV) administration of an mRNA therapeutic encoding for human methylmalonyl-CoA mutase (hMUT), the enzyme most frequently mutated in MMA, enabled liver expression of hMUT in MMA mouse models, leading to a significant reduction in methylmalonic acid and complete survival of treated mice versus control group with a dramatic improvement in weight gain. Repeat IV dosing did not increase markers of liver toxicity or inflammation. The study was conducted in partnership with researchers at the Medical Genomics and Metabolic Genetics Branch of the National Human Genome Research Institute at the National Institutes of Health.

**Q4 2017 AND RECENT BUSINESS/FINANCIAL UPDATES**

**Board of Directors and Organizational Updates**

- **John Mendlein joined Moderna as President, Corporate and Product Strategy**: Earlier this month, Moderna announced that John Mendlein, Ph.D., joined the company as President, Corporate and Product Strategy. In this role, Dr. Mendlein will be responsible for corporate strategy, product advancement and strategy, partnering and product protection. He will serve on Moderna’s Executive Committee and report to Chief Executive Officer Stéphane Bancel. Dr. Mendlein has helped start and lead numerous innovative life sciences companies. He is Vice Chairman of the Board and a founder of Fate Therapeutics, Inc., and holds board positions with Editas Medicine, Inc., and Axcella Health, Inc. He also serves on the Biotechnology Industry Organization (“BIO”) emerging companies board. Dr. Mendlein previously served as the Chief Executive Officer of aTyr Pharma, and Fate Therapeutics, as well as Adnexus Therapeutics, Inc., (acquired by BMS). Before that, he served as Chairman and Chief Executive Officer of Affinium Pharmaceuticals, Ltd. (acquired by Debiopharm Group), and as a board member, General Counsel and Chief Knowledge Officer at Aurora Bioscience Corporation (acquired by Vertex Pharmaceuticals). 

- **Stephen Berenson appointed to Board of Directors**: In October, Moderna announced that Stephen Berenson was joining the company’s Board of Directors. Mr. Berenson, who joined Flagship Pioneering in June of 2017, previously served for 12 years as the Vice Chairman of Investment Banking at J.P. Morgan, and focused on providing high-touch strategic advice and complex transaction execution to leading companies across all industries globally. In total, Mr. Berenson spent more than 33 years with J.P. Morgan as an investment banker, where he worked across all major geographies, product areas and industry groups. He played key roles in building J.P. Morgan's M&A, equities and technology investment banking businesses.

- **Continued growth across organization**: In 2016, Moderna expanded its headcount from approximately 500 to nearly 600 team members.

- **Continued strong cash position**: Moderna maintained a strong cash position in 2017. As of December 31, 2017, the company had approximately $910 million in cash, as compared to $1.306 billion in cash as of December 31, 2016.

- **2017 cash inflows**: From reimbursement, product milestones and investment income was approximately $55 million.

- **Significant investments in the business**: Moderna's cash operating expense and capital expenditures in 2017 totaled approximately $455 million.

**About Moderna Therapeutics**

Moderna pioneers the discovery and development of messenger RNA (mRNA) therapeutics and vaccines, an entirely new class of medicines that directs the body’s cells to produce intracellular or secreted proteins that can have a therapeutic or preventive benefit for both patients and healthy individuals. With its breakthrough platform, Moderna is creating mRNA medicines for a wide range of diseases and conditions, in many cases by addressing currently undruggable targets or underserved areas of medical need. Moderna is developing its innovative mRNA medicines for infectious diseases, immuno-oncology, rare diseases, and cardiovascular diseases, through solely controlled programs and collaborations with strategic partners.

Headquartered in Cambridge, Mass., privately held Moderna currently has strategic relationships with AstraZeneca, Plc. (AZ), Merck, Inc (MRK) and Vertex Pharmaceuticals (VRTX), as well as the Defense Advanced Research Projects Agency (DARPA), an agency of the U.S. Department of
Defense; the Biomedical Advanced Research and Development Authority (BARDA), a division of the Office of the Assistant Secretary for Preparedness and Response (ASPR) within the U.S. Department of Health and Human Services (HHS); and the Bill & Melinda Gates Foundation. In 2017 Moderna was ranked a top biopharma industry employer by Science Magazine and a Top Places to Work by the Boston Globe. To learn more, visit www.modernatx.com.

Moderna Contacts

Investors:
Lorence Kim
617-209-5849
lorence.kim@modernatx.com

Media:
media@modernatx.com