Prime Medicine Announces Recent Progress and Highlights 2023 Strategic Priorities

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-- New preclinical data in Friedrich's ataxia and cystic fibrosis provided further proof-of-concept for Prime Editing's ability to achieve restoration of genetic function --
-- New preliminary safety analyses demonstrated no detected off-target activity in Prime Edited Wilson's disease cells --
-- New data leveraging PASSIGE technology demonstrated ability to integrate kilobase-sized DNA in human T cells --
-- Additional LNP and AAV delivery data demonstrated efficient in vivo delivery of Prime Editing to various target tissues in rodents --
-- Multiple catalysts expected in 2023, including first development candidate nomination in 1Q and additional in vivo data in 2H --
-- Strong corporate position, with robust intellectual property position and cash to fund operations into 2025 --

CAMBRIDGE, Mass., Jan. 09, 2023 (GLOBE NEWSWIRE) -- Prime Medicine, Inc. (Nasdaq: PRME), a biotechnology company committed to delivering a new class of differentiated one-time curative genetic therapies, today provided an update on recent advancements of its Prime Editing technology and progress across its initial pipeline of eighteen programs, and outlined its strategic priorities and expected milestones for 2023.

"Since our inception, we have focused on building the necessary foundation to maximize Prime Editing's therapeutic potential, identifying and progressing a diverse initial pipeline, introducing optimizations to extend the reach of our Prime Editing technology, and investing in the CMC and delivery capabilities that will ultimately be required to deliver our investigational therapies to patients," said Keith Gottesdiener, M.D., President and Chief Executive Officer of Prime Medicine. "Today, we are pleased to announce accomplishments across our portfolio and platform, including new preclinical proof-of-concept data in Friedrich's ataxia and cystic fibrosis showing restoration of genetic function; new safety analyses detecting no off-target editing in Prime Edited Wilson's disease cells; the first presentation of our ability to use PASSIGE technology to precisely insert a whole gene into human T cells; and further optimization of our lipid nanoparticle and adeno-associated virus delivery platforms. Together, these updates reinforce our belief in Prime Editing as an extremely powerful, differentiated technology, with the potential to deliver one-time, curative genetic therapies to address a wide spectrum of diseases. As we enter 2023, we look forward to progressing our most advanced programs toward the clinic, while continuing to optimize our technology and build the internal organization, culture and expertise necessary to meet our ambitious goals."

Recent Business Updates

Pipeline

Prime Medicine is advancing a strategic pipeline of eighteen programs. The company is initially focused on indications with the opportunity for the fastest, most direct path to the clinic and technical success in humans, as well as indications that cannot be treated using other gene editing approaches. *In vivo* studies are progressing across Prime Medicine's portfolio and, in recent months, the company has established preclinical proof-of-concept and expanded safety data in a variety of target tissues and indications. Today, Prime Medicine is announcing new preclinical data for several programs:

- **Friedrich's Ataxia** (FRDA), a multisystem, autosomal recessive neurodegenerative disorder affecting the central and peripheral nervous systems, as well as the heart and other organs. FRDA is caused by GAA-repeat nucleotide sequence expansions in intron 1 of the *FXN* gene encoding the frataxin protein, which plays important roles in mitochondria. In preclinical studies, Prime Medicine is using its technology to precisely remove the GAA pathological repeats at the *FXN* gene, restoring Frataxin protein expression and sensory neuron function in patient dorsal root ganglia.
    - Today, Prime Medicine announced new preclinical data demonstrating that Prime Editing-mediated removal of pathological repeats *in vitro* results in correction of hypermethylation at the *FXN* gene, restoring genetic function back to wild-type levels. The company believes these data also support the evaluation of Prime Editing for the potential treatment of other repeat expansion diseases, many of which exhibit hypermethylation as a key feature of the underlying pathogenesis.

- **Cystic Fibrosis** (CF), a progressive lung disease characterized by the production of thick mucus lung secretions, which block patients' airways, leading to inflammation, lung infection and, ultimately, lung failure. CF is caused by loss of function mutations in the *CFTR* gene, which reduces chloride and bicarbonate transport to the epithelial lumen, resulting in thickened secretions, blocked ducts and bronchioles and secondary infections. F508del and mutations at seven additional hotspots, including G542X, are found in 98 percent of patients.
    - Today, Prime Medicine shared initial preclinical data showing greater than 70 percent precise editing of the G542X mutational hotspot *in vitro*, as well as functional restoration of swelling and CFTR function in patient-derived intestinal organoids. The G542X mutation is not addressed by currently marketed therapies. The company believes these data demonstrate that precise genetic correction by Prime Editing has the potential to achieve complete phenotypic rescue.

- **Off-target Safety Data:** Prime Medicine is progressing a comprehensive suite of assays to evaluate the potential off-target activity of its Prime Editors. Because it does not create double-stranded breaks and requires three "edit checks," or places where there must be a match between the editor and target DNA in order to complete an edit, Prime Editing occurs with high specificity, low indel rates and minimal to no off-target activity, resulting in potentially greatly improved safety and

tolerability. Today, Prime Medicine shared preclinical safety analyses from two programs – new data in Wilson's disease (WD) and an incremental update on previously reported data in Chronic Granulomatous Disease (CGD) – which together further support Prime Editing as a highly specific and predictable gene editing tool.

- In WD, a devastating rare disease of the liver, Prime Medicine announced the results of a preliminary off-target analysis in induced pluripotent stem cell (iPSC)-derived hepatocytes, which detected no guide-dependent Prime Editing activity across 170 identified potential off-target sites.
- In CGD, a rare disease that causes recurrent, debilitating infections in children, Prime Medicine shared the results of a preliminary off-target analysis in CD34+ cells, which detected no guide-dependent Prime Editing activity across 550 identified potential off-target sites.

Prime Editing Platform

Since it was first described in 2019, Prime Medicine's platform team has continued to optimize its PASSIGE (**P**rime **A**ssisted **S**ite-**S**pecific **I**ntegrase **G**ene **E**diting) technology. PASSIGE combines Prime Editing with an integrase or site-specific recombinase enzyme to enable the introduction of large-sized cargo into the genome as a potential one-time therapy. This approach further increases the versatility of Prime Editing and broadens the range of permanent genomic edits that Prime Editing can make to potentially treat disease, including the ability to insert, delete or invert gene-sized pieces of DNA.

- Today, Prime Medicine announced new preclinical data utilizing PASSIGE in a one-step, non-viral process, which resulted in an approximately 60 percent precise insertion of a 3.5 kilobase transgene at a single targeted site in primary human T cells.

CMC and Delivery

Prime Medicine is investing in internal chemistry, manufacturing, and controls (CMC) development and delivery capabilities in order to build the foundational competencies necessary to deliver its pipeline programs to patients as the company prepares to enter the clinic. In recent months, Prime Medicine has continued to advance its lipid nanoparticle (LNP) and adeno-associated virus (AAV) delivery platforms, demonstrating and disclosing for the first time today:

- Additional proof-of-concept data for LNP delivery of Prime Editors to rodent liver, including the first *in vivo* demonstration of the introduction of a precisely edited stop codon in the *PCSK9* gene, resulting in greater than 40 percent editing and greater than 90 percent reduction in serum PCSK9 protein. Prime Medicine is using PCSK9 as a model system for developing its modular LNP delivery platform to the liver.
- New data demonstrating that dual AAV delivery to the central nervous system achieves high efficiency transduction in murine models, with a high level of precise editing in transduced cells. Specifically, using intracerebroventricular delivery, Prime Editing precisely edited approximately 90 percent of transduced cortical cells and, utilizing local administration, Prime Editing precisely edited approximately 80 percent of transduced neurons.

Anticipated Upcoming Milestones

Prime Medicine expects the following activities and next steps to drive the Prime Editing platform forward:

Pipeline

- Nominate first development candidate for CGD in 1Q 2023.
- Initiate investigational new drug (IND)-enabling studies in CGD in 2023.
- Expand preclinical proof-of-concept *in vivo*, including sharing data from *in vivo* rodent studies and large animal studies in several programs in 2H 2023.
- Share *in vitro* preclinical data in additional liver, eye and neuromuscular programs.
- First IND filing expected as early as 2024 and additional IND filings anticipated in 2025.

Platform

- Continue to develop and optimize non-viral and viral delivery systems and share additional proof-of-concept data from *in vivo* rodent and large animal studies in 2H 2023.
- Further demonstrate superior "off-target" profiles for Prime Editing programs.
- Expand Prime Editing using proprietary recombinase and/or retrotransposon technologies for new and existing programs.

Financial Guidance

Based on its current operating plans, Prime Medicine expects that its cash, cash equivalents and short-term investments as of September 30, 2022, together with the approximately $200 million in gross proceeds raised through its initial public offering in October 2022, will be sufficient to fund its anticipated operating expenses and capital expenditure requirements into 2025.

About Prime Medicine

Prime Medicine is a biotechnology company committed to delivering a new class of differentiated, one-time, curative genetic therapies to address the widest spectrum of diseases. The company is deploying Prime Editing technology, a versatile, precise, efficient and broad gene editing technology,

which is designed to make only the right edit at the right position within a gene. With the potential to repair approximately 90 percent of known disease-causing genetic mutations across many organs and cell types, medicines based on Prime Editing could offer a one-time curative genetic therapeutic option to a broad set of patients.

Cautionary Note Regarding Forward Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, implied and express statements about Prime Medicine's beliefs and expectations regarding: the initiation, timing, progress and results of its research and development programs, preclinical studies and future clinical trials; its ability to demonstrate, and the timing of, preclinical proof-of-concept in vivo for multiple programs; its ability to advance any product candidates that Prime Medicine may identify and successfully complete any clinical studies, including the manufacture of any such product candidates; its ability to quickly leverage programs within its initial target indications and to progress additional programs to further develop its pipeline; the timing of its regulatory filings, including its investigational new drug applications submissions; the implementation of its strategic plans for its business, programs and technology; and our estimates of our expenses, capital requirements, and needs for additional financing as well as our cash runway into 2025. The words "may," "might," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" and similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, risks associated with: uncertainties related to the authorization, initiation and conduct of preclinical and other development requirements for potential product candidates, including uncertainties related to regulatory approvals; risks related to the results of preclinical studies or clinical studies not being predictive of future results in connection with future studies; the scope of protection Prime Medicine is able to establish and maintain for intellectual property rights covering its Prime Editing technology; Prime Medicine's ability to identify and enter into future license agreements and collaborations; and general economic, industry and market conditions, including rising interest rates and inflation. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in Prime Medicine's most recent Quarterly Report on Form 10-Q, as well as any subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent Prime Medicine's views only as of today and should not be relied upon as representing its views as of any subsequent date. Prime Medicine explicitly disclaims any obligation to update any forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

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