Generation Bio Announces Two Non-Viral Gene Therapy Milestone Achievements: Target Levels of Factor VIII Expression in Hemophilia A Mice and Translation of Expression from Mice to Non-Human Primates

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Data confirm delivery of closed-ended DNA to the liver via novel, cell-targeted lipid nanoparticles

Well tolerated at all dose levels in mice and non-human primates

Company on track to select development candidate for hemophilia A and begin IND-enabling studies this year, submit IND in 2022

Webcast and conference call to be held today at 8:00 a.m. EST

CAMBRIDGE, Mass., Jan. 04, 2021 (GLOBE NEWSWIRE) -- Generation Bio Co. (Nasdaq: GBIO), an innovative genetic medicines company creating a new class of non-viral gene therapy, announced data today from a study achieving tolerability and targeted factor VIII expression levels in hemophilia A mice with a single dose of closed-ended DNA (ceDNA) delivered via the company's novel, cell-targeted lipid nanoparticle (ctLNP) system. In this study, conducted with a ceDNA development construct, a dose response was observed across three cohorts, with the highest dose of 2.0 mg/kg yielding a mean human factor VIII expression of 23% of normal.

The company also announced data from studies conducted with a ceDNA research construct delivered via ctLNP demonstrating approximately 2:1 species translation from mice to non-human primates (NHPs). All doses in mice and NHPs were well-tolerated up to the highest dose of 2.0 mg/kg. These data confirm delivery of ceDNA to the liver via ctLNPs in higher species.

"Non-viral gene therapy has been an elusive goal for scientists for more than 40 years. Today's data are a significant step toward reaching that objective for the first time," said Matthew Stanton, Ph.D., chief scientific officer of Generation Bio. "Lipid nanoparticles have demonstrated remarkably predictable species translation from NHPs to patients across modalities such as RNAi and mRNA. We believe the high levels of factor VIII expression in mice using our ceDNA development construct and the demonstrated translation of expression from mice to NHP for our ctLNP delivery system are important proof points for our platform."

Generation Bio has previously demonstrated in immunocompetent mice that its ceDNA constructs with human factor IX achieved durable expression for months and that expression increased proportionately with redosing.

"These data are significant milestones as we create a new class of genetic medicine to overcome the limitations of viral gene therapy," said Geoff McDonough, M.D., president and chief executive officer of Generation Bio. "We have now demonstrated in preclinical studies the key features of our platform, including durability, titration and redosing and, importantly, translation of our novel, liver-directed ctLNPs. With predictable species translation and potent murine expression levels in line with our target product profile, we are on track to initiate IND-enabling studies for our hemophilia A program this year."

In parallel with hemophilia A, Generation Bio plans to advance programs in phenylketonuria (PKU) as well as in additional rare and prevalent diseases that are addressable using the company's liver-specific ctLNP delivery system and established, capsid-free manufacturing.

Summary of Key Company Data

Target levels of factor VIII expression and good tolerability in hemophilia A mice

A mean human factor VIII expression level of 23% of normal was observed in hemophilia A mice at day 10 following a single 2.0 mg/kg dose of a ceDNA development construct delivered systemically via a liver-directed ctLNP.

A dose-response relationship was demonstrated, with mean factor VIII expression of 16% of normal at 1.0 mg/kg, and 9% of normal at 0.5 mg/kg.

Doses of ceDNA-ctLNP were well tolerated through 2.0 mg/kg, the highest dose evaluated.

Tolerability and translation of expression from mice to non-human primates

Translation from mouse to NHP was established by delivering the same weight-adjusted dose of ceDNA-ctLNP in each species. Two separate studies were conducted. In the first study, a mean human factor VIII expression level of ~1% of normal was observed in mice at day 7 following a single dose of a ceDNA research construct delivered systemically via a liver-directed ctLNP at 1 mg/kg. This translated to a mean human factor VIII expression level of ~1% of normal in NHPs at day 5 using identical material and weight-adjusted dosing (1 mg/kg). In a second study employing a similar ctLNP, a mean human factor VIII expression level of ~3% of normal was observed in mice at day 5 following a single dose of a ceDNA research construct at 2 mg/kg. This translated to a mean factor VIII expression level of ~1% of normal in NHPs at day 5 using identical material and weight-adjusted dosing at 2 mg/kg.

In totality, the ~2:1 expression ratio from mice to NHPs is similar to that observed across other modalities delivered via LNPs, including RNAi and mRNA, and establishes a basis for final development candidate selection. The expression levels in mice using a ceDNA development construct, coupled with the ~2:1 expression ratio from mice to NHPs and expected 1:1 translation from NHPs to humans, support selection of a final hemophilia A clinical development candidate this year. The observed expression levels in mice with a ceDNA development construct may correspond to or exceed the 5% of normal threshold in humans that has been clinically proven to prevent serious bleeds in patients.

Doses of ceDNA-ctLNP in both mice and NHPs were well tolerated up to 2 mg/kg, the highest dose evaluated. There were no adverse clinical observations, changes in clinical pathology, or histopathology findings including in the liver and spleen in NHPs.

Generation Bio's ctLNP employs N-acetyl galactosamine, or GalNAc, as the ligand for targeting of liver cells via the asialoglycoprotein receptor, or ASGPr. GalNAc-ASGPr is a well-validated, selective ligand-receptor pair for systemic delivery to hepatocytes.

Durable expression

In previously released data from a study in immunocompetent mice, a single intravenous dose of ceDNA formulated in an LNP yielded long-term expression in the liver for months using the reporter protein luciferase and human factor IX.

Redosable and titratable

LNP delivery does not stimulate an antibody response, thereby enabling redosing and overcoming a major limitation of viral gene therapy. Generation Bio has previously released data showing that ceDNA delivered in an LNP does not induce neutralizing antibodies and can be redosed in mice with normal immune systems.

Redosing five weeks after the initial dose proportionately increased expression using both the reporter protein luciferase and human factor IX in mice. After the first administration of a factor IX ceDNA research construct in an LNP, mice demonstrated 5% to 10% activity levels of factor IX protein in the blood. After repeat administration at the same dose, the activity levels rose to 10% to 20%.

These results support the potential of Generation Bio's non-viral gene therapy platform to safely titrate patients to the desired level of protein expression and to enable repeat dosing if needed to maintain expression over a lifetime.

Conference Call Information

Generation Bio will host a conference call and webcast today, Jan. 4, at 8:00 a.m. EST. The live webcast can be accessed on the investor page of the company's website at investors.generationbio.com. A replay of the webcast will be available on Generation Bio's website approximately two hours after the completion of the event and will be archived for up to 90 days.

Investors may listen to the call by dialing (833) 693-0530 from locations in the United States or +1 (786) 857-9397 from outside the United States. Please refer to conference ID number 9249849.

About Generation Bio

Generation Bio is an innovative genetic medicines company focused on creating a new class of non-viral gene therapy to provide durable, redosable treatments for people living with rare and prevalent diseases. The company's non-viral platform incorporates a proprietary, high-capacity DNA construct called closed-ended DNA, or ceDNA; a cell-targeted lipid nanoparticle delivery system, or ctLNP; and an established, scalable capsid-free manufacturing process. The platform is designed to enable multi-year durability from a single dose of ceDNA and to allow titration and redosing if needed. The ctLNP is designed to deliver large genetic payloads, including multiple genes, to specific tissues to address a wide range of indications. The company's efficient, scalable manufacturing process supports Generation Bio's mission to extend the reach of gene therapy to more people, living with more diseases, in more places around the world.

For more information, please visit www.generationbio.com.

Forward-Looking Statements

Any statements in this press release about future expectations, plans and prospects for the Company, including statements about our strategic plans or objectives, our technology platforms, our research and clinical development plans, and other statements containing the words "believes," "anticipates," "plans," "expects," and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: uncertainties inherent in the identification and development of product candidates, including the conduct of research activities, the initiation and completion of preclinical studies and clinical trials and clinical development of the Company's product candidates; whether results from preclinical studies such as the ones referred to above will be predictive of the results of later preclinical studies and clinical trials, including whether levels of expression in one species will translate to expected levels of expression in another species; expectations for regulatory approvals to conduct trials or to market products; challenges in the manufacture of genetic medicine products; the Company's ability to obtain sufficient cash resources to fund the Company's foreseeable and unforeseeable operating expenses and capital expenditure requirements; and the impact of the COVID-19 pandemic on the Company's business and operations; as well as the other risks and uncertainties set forth in the "Risk Factors" section of our most recent quarterly report on Form 10-Q, which is on file with the Securities and Exchange Commission, and in subsequent filings the Company may make with the Securities and Exchange Commission. In addition, the forward-looking statements included in this press release represent the Company's views as of the date hereof. The Company anticipates that subsequent events and developments will cause the Company's views to change. However, while the Company may elect to update these forward-looking statements at some point in the future, the Company specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the Company's views as of any date subsequent to the date on which they were made.

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