NEWS RELEASE

Clinical and Immunological Results from Phase 1/2 Study of INO-3107 as a Treatment for Recurrent Respiratory Papillomatosis Published in Nature Communications

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Data shows that INO-3107 induced new populations of T cells in the blood that traveled to airway tissue and were associated with clinical benefit as measured by reduced need for surgeries

PLYMOUTH MEETING, Pa., Feb. 12, 2025 /PRNewswire/ -- INOVIO (NASDAQ: INO), a biotechnology company focused on developing and commercializing DNA medicines to help treat and protect people from HPV-related diseases, cancer, and infectious diseases, today announced that peer-reviewed data from its Phase 1/2 clinical trial with INO-3107 as a potential treatment for recurrent respiratory papillomatosis (RRP) were published online in Nature Communications under the title **DNA immunotherapy for recurrent respiratory papillomatosis (RRP): phase 1/2 study assessing efficacy, safety, and immunogenicity of INO-3107**. In the trial, treatment with INO-3107 induced new populations of T cells in the blood that traveled to the airway and papilloma tissue and were correlated with a reduction in the number of post-treatment surgeries. Of the 32 patients in the trial, 26 patients (81%) required fewer surgeries post-treatment when compared to the year prior to treatment. INO-3107 treatment was also well tolerated in the trial. INOVIO plans to submit its biologics license application (BLA) for INO-3107 in mid-2025 and request rolling submission and priority review under the FDA's accelerated approval program. If approved, INO-3107 would be the first DNA medicine approved for any indication in the United States.

The Phase 1/2 study showed the majority of participants experienced a reduced need for surgery, providing great hope for RRP patients who face both risk of vocal cord damage and immense impact on their daily lives with every surgery," said Dr. Peter Belafsky, Director of the Center for Voice & Swallowing at UC Davis Health and a principal investigator on the trial. "INO-3107 was designed with those patient needs in mind and has the potential to transform the treatment paradigm for RRP."

Dr. Matthew Morrow, INOVIO's Vice President of Translational Science stated, "The combination of the full clinical data set and the immunological evaluation described in this publication allows for a complete view of the immunological impact of INO-3107, which is a compelling story of a T cell-based mechanism of action that drives clinical benefit. The publication describes in detail how INO-3107 engaged both the innate and adaptive arms of the immune system of treated patients and directly points to the emergence of new T cell populations after treatment that traveled to infected tissue to fight RRP."

"These important data characterizing the cytotoxic T cell-based mechanism of action of INO-3107, in conjunction with our recently reported durability data showing that clinical benefit continued to improve through year two and into year three after initial treatment, with half of patients not requiring any surgeries in year two, are part of the growing body of evidence that INO-3107 has the potential to be the preferred product of choice for both patients and healthcare providers," said Dr. Jacqueline Shea, INOVIO's CEO and President. "The primary goal for RRP patients is to reduce or eliminate the need for surgery and INO-3107 has the potential to do just that for the majority of patients. Every surgery matters and a safe and effective therapeutic alternative to surgery would be truly life-changing for RRP patients and their caregivers."

Highlights from the Nature Communications Paper

- 81.3% (26/32) of patients had a decrease of at least one surgical intervention from the prior year (defined as the Overall Clinical Response Rate) after INO-3107 administration, including 28.1% (9/32) that required no surgical intervention (Complete Response) during or after the dosing window
    - The Overall Response Rate, which includes those patients who had either a Complete Response or a Partial Response (defined as ≥ 50% reduction in surgeries) was 72%
    - Patients in this trial were required to have ≥2 RRP surgical interventions in the year prior to initiating treatment
- INO-3107 was well tolerated in the 32 patients enrolled:
    - 41% (13/32) of patients reported a treatment-related Adverse Event (AE)
    - Most frequent treatment-related AEs reported were injection site pain (31%) and fatigue (9%)
    - No treatment-related AEs greater than Grade 2 severity were reported
- INO-3107 induced T cell responses specific to HPV-6 and HPV-11, including cytotoxic CD8+ T cells, which were still present at week 52, indicating the establishment of a memory response
- INO-3107 expanded clonal T cell populations in peripheral blood, including induction of new clonal T cell populations that traveled to airway and papilloma tissue
- INO-3107 induced inflammatory responses in papilloma and airway tissue associated with antiviral activity, including:

    - Interferon, cytokine and chemokine signaling
    - Adaptive and innate immune cell infiltration, with emphasis on T cells

- TCR sequencing provided direct evidence of increased overall T cell infiltration compared to pre-treatment
- Cytotoxic T cell signatures were observed in T cell infiltrated papilloma/airway tissue
- T cell infiltration in airway tissues of clinical responders were predominantly new T cell clonal populations not detectable prior to INO-3107 treatment
- Enhanced T cell responses were observed in all patients, but there were differences in the T cell responses between responders and non-responders that were associated with clinical benefit among the responders

About RRP

RRP is a debilitating and rare disease caused primarily by HPV-6 and/or HPV-11. RRP is characterized by the development of small, wart-like growths, or papillomas, in the respiratory tract. While papillomas are generally benign, they can cause severe, life-threatening airway obstruction and respiratory complications. RRP can also significantly affect quality of life for patients by affecting the voice box, limiting the ability to speak effectively. Surgery to remove papillomas is the standard of care for RRP; however, the papillomas often grow back. INOVIO's market research to date with patients and healthcare professionals indicates that a reduction of even one surgery matters, because every surgery poses a significant risk of causing permanent damage to the vocal cords. The most widely cited U.S. epidemiology data published in 1995 estimated that there were 14,000 active cases and about 1.8 per 100,000 new cases in adults each year.

About INO-3107

INO-3107 is an investigational DNA medicine designed to elicit an antigen-specific T cell response against both HPV-6 and HPV-11 proteins. These targeted T cells seek out and kill HPV-6 and HPV-11 infected cells, with the aim of potentially preventing or slowing the growth of new papillomas. In a Phase 1/2 clinical trial conducted with INO-3107 in patients requiring ≥2 RRP surgical interventions in the year prior to initiating treatment, 81.3% (26/32) of patients had a decrease in surgical interventions in the year after INO-3107 administration compared to the prior year, including 28.1% (9/32) that required no surgical intervention (Complete Response) during or after the dosing window. Patients in the trial had a median range of 4 surgeries (2-8) in the year prior to dosing. After dosing, there was a median decrease of 3 surgical interventions (95% confidence interval -3, -2). At the outset of the trial (Day 0), patients had a clinically warranted procedure to have RRP tissue surgically removed, but any surgery performed after Day 0 during the dosing window was counted against the efficacy endpoint. Treatment with INO-3107 generated a strong immune response in the trial, inducing activated CD4 T cells and activated CD8 T cells with lytic potential. T cell responses were also observed at Week 52, indicating a persistent cellular memory response. INO-3107 was well tolerated, with trial participants experiencing mostly low-grade (Grade 1) treatment-emergent adverse effects such as injection site pain and fatigue. Like other DNA medicines, INO-3107 has shown the ability to generate antigen-specific T cells that is not affected by anti-vector immunity impacting immunogenicity, either

before administration or after the first dose unlike other T cell generating platforms such as viral vectors. This feature of DNA medicines is anticipated to allow INO-3107 to maintain T cell response and overall efficacy, which could make it an important therapeutic option for a majority of RRP patients.

The FDA previously granted INO-3107 Orphan Drug designation and Breakthrough Therapy designation and has advised INOVIO that it can submit a biologics license application under the FDA's accelerated approval program using data from INOVIO's already completed Phase 1/2 trial. The European Commission granted INO-3107 Orphan Drug designation. In addition, INOVIO has CE-marked its CELLECTRA® delivery device in the EU, which allows INOVIO to commercialize the device in the EU and other geographies that recognize CE-marking. The United Kingdom awarded INO-3107 the Innovation Passport. This designation serves as the entry point to the Innovative Licensing and Access Pathway (ILAP), which aims to accelerate time to market and facilitate patient access to medicines.

About INOVIO's DNA Medicines Platform

INOVIO's DNA medicines platform has two innovative components: precisely designed DNA plasmids, delivered by INOVIO's proprietary investigational medical device, CELLECTRA®. INOVIO uses proprietary technology to design its DNA plasmids, which are small circular DNA molecules that work like software the body's cells can download to produce specific proteins to target and fight disease. INOVIO's proprietary CELLECTRA® delivery devices are designed to optimally deliver its DNA medicines to the body's cells without requiring chemical adjuvants or lipid nanoparticles and without the risk of the anti-vector response historically seen with viral vector platforms.

About INOVIO

INOVIO is a biotechnology company focused on developing and commercializing DNA medicines to help treat and protect people from HPV-related diseases, cancer, and infectious diseases. INOVIO's technology optimizes the design and delivery of innovative DNA medicines that teach the body to manufacture its own disease-fighting tools. For more information, visit **www.inovio.com**.

Forward-Looking Statements

This press release contains certain forward-looking statements relating to our business, including the planned submission of a BLA in mid-2025 and plan to request rolling submission and priority review under the FDA's accelerated approval program, and the potential clinical benefit of INO-3107 if approved. Actual events or results may differ from the expectations set forth herein as a result of a number of factors, including uncertainties inherent in pre-clinical studies, clinical trials, product development programs and commercialization activities and outcomes, the availability of funding to support continuing research and studies in an effort to prove safety and efficacy of electroporation technology as a delivery mechanism or develop viable DNA medicines, our ability to support our pipeline of DNA medicine products, the ability of our collaborators to attain development and

commercial milestones for products we license and product sales that will enable us to receive future payments and royalties, the adequacy of our capital resources, the availability or potential availability of alternative therapies or treatments for the conditions targeted by us or collaborators, including alternatives that may be more efficacious or cost effective than any therapy or treatment that we and our collaborators hope to develop, issues involving product liability, issues involving patents and whether they or licenses to them will provide us with meaningful protection from others using the covered technologies, whether such proprietary rights are enforceable or defensible or infringe or allegedly infringe on rights of others or can withstand claims of invalidity and whether we can finance or devote other significant resources that may be necessary to prosecute, protect or defend them, the level of corporate expenditures, assessments of our technology by potential corporate or other partners or collaborators, capital market conditions, the impact of government healthcare proposals and other factors set forth in our Annual Report on Form 10-K for the year ended December 31, 2023, our Quarterly Report on Form 10-Q for the quarter ended September 30, 2024, and other filings we make from time to time with the Securities and Exchange Commission. There can be no assurance that any product candidate in our pipeline will be successfully developed, manufactured, or commercialized, that the results of clinical trials will be supportive of regulatory approvals required to market products, or that any of the forward-looking information provided herein will be proven accurate. Forward-looking statements speak only as of the date of this release, and we undertake no obligation to update or revise these statements, except as may be required by law.

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