PRESS RELEASE

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Zambon Announces Publication of Phase 3 PROMIS I and II Study Results in The Lancet Respiratory Medicine Showing Efficacy Results of CMS I-neb in Patients with Non-Cystic Fibrosis Bronchiectasis Colonized with P. aeruginosa

- *Inhalation of colistimethate sodium via the I-neb® Adaptive Aerosol Delivery System (CMS I-neb) significantly reduced pulmonary exacerbations and improved quality of life in non-cystic fibrosis bronchiectasis (NCFB) patients colonized with P. aeruginosa*
- *Both trials showed that CMS I-neb was generally well tolerated, with no major safety concerns, and bronchospasm occurred in fewer than 5% of patients*
- *Zambon is continuing to work with regulatory authorities with the goal of making colistimethate sodium delivered via a customized inhalation device available to patients with bronchiectasis and P. aeruginosa chronic infection*

Zambon, a multinational pharmaceutical company focused on innovating cure and care to improve people's health and the quality of patients' lives, today announced the online publication of its Phase 3 PROMIS-I and PROMIS-II studies in *The Lancet Respiratory Medicine* journal. The PROMIS studies assessed the efficacy and safety of inhaled colistimethate sodium administered via the I-neb® Adaptive Aerosol Delivery System ("CMS I-neb") as a treatment to reduce the frequency of pulmonary exacerbations in patients with Non-Cystic Fibrosis Bronchiectasis (NCFB) chronically colonized with *P. aeruginosa* over 12 months, compared to placebo.

"The publication of these pivotal data in *The Lancet Respiratory Medicine* represents an important milestone in our commitment to developing innovative therapies for patients with severe respiratory diseases," said **Paola Castellani, Chief Medical Officer and R&D Head at Zambon**. "For patients with NCFB, a condition with no approved treatment options, the results from the PROMIS program highlight the potential of CMS I-neb to improve outcomes and quality of life. We look forward to working with regulatory authorities on a path to making this important treatment available to patients as quickly as possible."

Chronic infection with *P. aeruginosa* is associated with more severe disease, accelerated lung function decline, increased exacerbations, hospitalizations and a higher mortality rate.[i] The PROMIS trials represent the first large-scale, double-blind, placebo-controlled studies of inhaled colistimethate sodium, a widely used antibiotic in Europe for Cystic Fibrosis.

The published study results are based upon the two global Phase 3, multicenter, randomized, double-blind, placebo-controlled PROMIS-I and PROMIS-II trials in adult patients with bronchiectasis chronically colonized with *P. aeruginosa* with a history of at least two exacerbations requiring oral antibiotics or one requiring intravenous antibiotics in the previous year. Patients were randomized (377 in PROMIS-I and 287 in PROMIS-II) to receive inhaled colistimethate sodium or placebo via the I-neb device twice daily for up to 12 months. The primary efficacy endpoint was the annual pulmonary exacerbation rate. Key secondary efficacy endpoints were time to first exacerbation, quality of life, change in *P. aeruginosa*

density, severe exacerbation rate, and time to first severe exacerbation.

Key Findings from PROMIS-I and PROMIS-II:

- In the PROMIS-I trial, the primary endpoint of a significant reduction in annual pulmonary exacerbation rate was achieved, with a 39% reduction in exacerbations (rate ratio 0.61; 95% CI 0.46–0.82; p=0.0010) compared with placebo.
- Severe exacerbations were reduced by 59%, and patients treated with CMS I-neb experienced a clinically important[ii] improvement in quality of life, as measured by the St. George's Respiratory Questionnaire, and a reduction of *P. aeruginosa* density.
- The PROMIS-II study had to be stopped prematurely due to the COVID-19 pandemic and the results were not satisfactory. However, when a sub analysis of the PROMIS-II pre-pandemic period was done, the results were consistent with those obtained in the PROMIS-I trial.
- Both trials reported good tolerability, with no major safety issues identified. Bronchospasm was rare, occurring in less than 5% of patients.

"The results of the PROMIS program represent an important breakthrough for patients with NCFB, a population that has long suffered from chronic respiratory infections without any approved treatments. For the first time, we have robust evidence showing that CMS I-neb can significantly reduce exacerbations and improve quality of life in patients with NCFB and chronic *P. aeruginosa* infection, offering hope where there were previously limited options," said **Dr. Charles Haworth, Respiratory Physician at the Cambridge Centre for Lung Infection at Royal Papworth Hospital, and PROMIS trials Chief Investigator.**

"These findings underscore the importance of inhaled antibiotics, such as CMS I-neb, in reducing exacerbations and improving outcomes in patients with NCFB chronically infected with *P. aeruginosa.* Chronic bronchial infection plays a key role in driving inflammation and airway damage in bronchiectasis, and reducing exacerbations has been linked to better prognosis, quality of life and lung function," said **Professor James Chalmers, Professor of Respiratory Research at the University of Dundee and PROMIS Investigator.**

The PROMIS clinical program has received FDA Qualified Infectious Disease Product (QIDP), Fast Track and Breakthrough designations for the reduction in the incidence of pulmonary exacerbations in adult NCFB patients colonized with *P. aeruginosa*.

About the PROMIS Development Program

The PROMIS-I and PROMIS-II are multicenter, randomized, double-blind, placebo-controlled trials investigating the efficacy and safety of inhaled colistimethate sodium administered via the I neb® Adaptive Aerosol Delivery System (CMS I-neb®) in adults with non-cystic fibrosis bronchiectasis chronically infected with *P. aeruginosa*. The primary objective of both trials was to investigate the annual rate of pulmonary exacerbations in patients receiving CMS I-neb® administered twice daily versus placebo.

Secondary endpoints included the time to first pulmonary exacerbation, the annual rate of severe pulmonary exacerbations, the time to first severe pulmonary exacerbation, quality of life measured by the St. George's Respiratory Questionnaire and the Quality of Life Questionnaire-Bronchiectasis (QOL-B), the number of exacerbation-free days, *P. aeruginosa* density and susceptibility, any developing resistance, and overall safety and tolerability.

The PROMIS-I trial enrolled 377 patients in 12 countries, including Australia, Belgium, Germany, Greece, Israel, Italy, Netherlands, New Zealand, Portugal, Spain, Switzerland, and the United Kingdom. The

PROMIS-II trial enrolled 287 patients in 12 countries, including Argentina, Australia, Canada, Germany, Greece, Israel, Italy, New Zealand, Poland, Portugal, France, and the United States.

About NCFB

Non-cystic fibrosis bronchiectasis (NCFB) is a chronic lung disease characterized by recurrent infection, inflammation, persistent cough, and production of sputum, and its prevalence is increasing worldwide.

NCFB has a progressive course primarily determined by the rate of exacerbations, many of which are related to *Pseudomonas aeruginosa*. Consequently, research efforts directed to treat infection by *P. aeruginosa* and its associated acute exacerbations remain a clinical priority.[iii]

The objectives of treatment in bronchiectasis are to prevent exacerbations, reduce symptoms, improve quality of life, and stop disease progression.

Cough and sputum production, along with breathlessness, are the most frequent symptoms, but rhinosinusitis, fatigue, hemoptysis, and thoracic pain are also common.

Over the last decade, the prevalence of NCFB has increased by 40% and is now estimated to be up to 566 per 100,000 people, making it the third most common chronic airways disease.[iv]

The incidence of NCFB appears to be rising too, particularly in women and older individuals.

About Colistimethate sodium (CMS)

Colistimethate sodium (CMS) is a pro-drug (the form used for inhalation therapy) of the antibiotic colistin.

Colistin is a polymyxin antibiotic derived from *Bacillus polymyxa var. colistinus.*

Polymyxin antibiotics are surface active agents that act by binding to and changing the permeability of the bacterial cell membrane, causing bacterial cell death.

Colistin is an active agent against aerobic Gram-negative pathogens that can cause life-threatening infections, such as *P. aeruginosa.*

Colistin remains one of the few active antimicrobial agents against multi-drug-resistant Gram-negative bacteria. It is currently considered one of the last therapeutic options for infections such as carbapenem-resistant *P. aeruginosa*.

About Zambon SpA

Zambon SpA is a multinational pharmaceutical company established in 1906 in Vicenza, whose history is founded on the values of an Italian family committed to innovating cure & care to improve patients' lives. It employs more than 2,500 people worldwide, is present in 23 countries in Europe, America and Asia, and has production facilities in Italy, Switzerland, China and Brazil. Thanks to its innovative, quality products commercialized in 87 countries, Zambon Spa reported a revenue of 843 million euros in 2023. Alongside the three historical therapeutic areas - diseases of the respiratory system, urinary tract infections and pain treatment – Zambon is focused on developing treatments for neurodegenerative diseases such as Parkinson's or rare diseases such as cystic fibrosis, BOS, to which is linked the major 2019 acquisition of Breath Therapeutics, and NCFB. For further information on Zambon please visit www.zambon.com.

For more information, please contact:
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[ii] McLeese RH, Spinou A, Alfahl Z, et al. Psychometrics of health-related quality of life questionnaires in bronchiectasis: a systematic review and meta-analysis. *Eur Respir J* 2021; 58: 2100025.

[iii] Severiche-Bueno D, Gamboa E, Reyes LF, Chotirmall SH. *Hot topics and current controversies in non-cystic fibrosis bronchiectasis.* Breathe 2019; 15: 286–295

[iv] Thornton, Christina S., Somayaji, Ranjani, Lim, Rachel K. Assessment of factors and interventions towards therapeutic adherence among persons with non-cystic fibrosis bronchiectasis. *ERJ Open Research*. 2022; 2022-10-01, 00340-2022. 10.1183/23120541.00340-2022. https://bit.ly/3TcvnqX