PRESS RELEASE

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Zambon Presents Results from the Two Phase 3 PROMIS Studies of CMS I-neb in Patients with Non-Cystic Fibrosis Bronchiectasis at World Bronchiectasis Conference 2023

- Data show inhalation via the I-neb Adaptive Aerosol Delivery System of colistimethate sodium (CMS) results in reduction of pulmonary exacerbations in non-cystic fibrosis bronchiectasis (NCFB) patients compared to placebo
- The totality of the evidence from the Phase 3 PROMIS program supports a clinically meaningful benefit of CMS in reducing exacerbation frequency and improving quality of life in this very sick patient population with high unmet need for which there are no other approved treatments
- Treatment has been granted FDA QIDP, Fast Track and Breakthrough designations

MILAN, Italy and Boston, MA, July 18, 2023 — Zambon, a multinational pharmaceutical company focused on innovating cure and care to improve people's health and the quality of patients' lives, announced the final results from the Phase 3 PROMIS-I and PROMIS-II studies, which were presented today at the 2023 6th World Bronchiectasis Conference in New York, NY.

The studies, which examined the use of CMS powder for nebulizer solution, delivered by the I-neb AAD system (hereafter referred to as "CMS I-neb") for the reduction of the incidence of pulmonary exacerbations in adult patients with NCFB and *Pseudomonas aeruginosa* chronic infection, showed CMS I-neb reduced the annual rate of exacerbations. A significant reduction in *P. aeruginosa* density was consistently observed across all studies. The treatment was demonstrated to be generally well tolerated.

In patients with NCFB, lung infection with *P. aeruginosa* is associated with frequent pulmonary exacerbations and hospital admissions, reduced quality of life (QoL), and increased mortality[1]. Currently there is no approved therapy for the disease.

The data were presented at 21:30 CEST during the Management & Registry Updates session, and as Poster (abstract *"The Efficacy and Safety of Colistimethate Sodium Delivered Via the I-neb in Patients with Bronchiectasis and Pseudomonas aeruginosa Infection: the PROMIS-I and PROMIS-II Randomised Controlled Trials").*

The trials explored the effect of CMS I-neb on the frequency of pulmonary exacerbations in NCFB patients chronically infected with *P. aeruginosa*. PROMIS-I trial met its primary endpoint, demonstrating that use of CMS I-neb twice-daily resulted in a statistically significant reduction of pulmonary exacerbations over the course of the 12-month study. A total of 377 patients were randomized, 177 to CMS I-neb and 200 to placebo. The annual exacerbation rate (AER) was significantly lower in patients receiving CMS I-neb vs placebo (0.58 per patient per year vs 0.95,

rate ratio (RR) 0.61 95% CI 0.46-0.82, p=0.00101). The treatment effect was even larger in adherent subjects (43.5% reduction in exacerbations, p= 0.00080).

The trial also met important secondary endpoints, demonstrating improvements compared to placebo with prolonged time to first exacerbation in the CMS I-neb group (HR 0.59, 95% CI 0.43-0.81, p=0.00074). The frequency of severe exacerbations was also reduced (RR 0.41 95% CI 0.23-0.74, p=0.00300). QoL measured by the St. George's Respiratory Questionnaire (SGRQ) significantly improved in CMS I-neb arm with a 4.55 point difference vs placebo after 12 months of treatment (p=0.0055). After 28 days of treatment, P. aeruginosa density was significantly reduced in the treatment arm (p < 0.00001).

After consultation with FDA, PROMIS-II was prematurely terminated due to both the COVID-19 pandemic and the view of investigators that there was no longer equipoise after the strongly positive PROMIS-I results. The overall PROMIS-II study did not meet its primary endpoint, with AER of 0.89 for CMS vs 0.89 for placebo (RR: 1.00 [95% CI 0.75, 1.35] p=0.979). The reduction in P. aeruginosa sputum density observed in the CMS group was consistent with those obtained in PROMIS-I and the preceding Phase 2 trial, and statistically significant (LS mean treatment difference at Visit 3 -1.60, p<0.00001 and overall, -1.07, p<0.00001).

Rates of adverse events and severe adverse events were similar between treatment arms in both PROMIS-I and PROMIS-II trials.

As PROMIS-II was conducted predominantly during the COVID-19 pandemic, the impact of the pandemic was investigated in post hoc analyses. Pre-pandemic (before 11th March 2020, the date that the WHO declared the global pandemic), the AER in PROMIS-II was 0.92 in CMS I-neb vs 1.26 in placebo patients, RR 0.73 95% CI 0.49-1.08; whereas during the pandemic period, the AER was 0.87 in CMS I-neb vs 0.62 in placebo patients, RR 1.40 95% CI 0.93-2.13.
Data obtained in the pre-COVID-19 period of PROMIS-II are consistent with that observed in PROMIS-I, with a 27% reduction in annualized exacerbation rate for CMS vs placebo treated patients (AER RR: 0.73, 95% CI: 0.49, 1.08), which further supports the impact of CMS I-neb on exacerbation frequency outside of pandemic conditions.

"*We would like to extend our sincere gratitude to all of the patients and study centers for their collaboration throughout the PROMIS trials program,"* said **Paola Castellani, CMO and R&D Head** at Zambon. "R*esults of PROMIS-II were unexpected in light of the positive data seen in PROMIS-I and the Phase 2 trial. Unfortunately, PROMIS-II was predominantly conducted during the COVID-19 pandemic, with more than 50 percent of the visits during the pandemic period, in contrast to PROMIS-I which was performed almost completely before the pandemic. The unprecedented COVID-19 pandemic fundamentally changed the environment in which the trial was conducted, with marked changes in patient behavior, the significant drop of background rate of exacerbations and trial conduct. The post-hoc analyses provided helpful insights into the possible underlying causes for the inconsistent results and demonstrated that, pre-pandemic, the benefit of CMS on annualized exacerbation rate was consistent with PROMIS-I".*

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*.

"In my view PROMIS-II was a fundamentally different clinical trial in the pre-COVID and COVID periods. For that reason I think it is important to look at the efficacy of CMS I-neb during the pre-COVID and COVID periods separately," said **Dr. Charles Haworth, Respiratory Physician at**

the Cambridge Centre for Lung Infection at Royal Papworth Hospital, and PROMIS trials Chief Investigator.

"When we look at the totality of the evidence gathered outside of pandemic conditions, what is striking is that we see a highly consistent beneficial effect of CMS I-neb on exacerbations, the most important clinically relevant endpoint for people with bronchiectasis," said ***Professor James Chalmers, Professor of Respiratory Research at the University of Dundee and PROMIS investigator****.*

NCFB has a progressive course primarily determined by the rate of exacerbations, many of which are related to *P. aeruginosa*. Consequently, research efforts directed to treat infection by *P. aeruginosa* and its associated acute exacerbations remain a clinical priority[2].

"With no approved drugs for patients with NCFB colonized by P. aeruginosa anywhere in the world, the completion of the Phase 3 PROMIS clinical trial program marks an important step forward in support of our mission to develop and provide treatment options for people with rare and severe respiratory diseases, " said **Ilaria Villa, CEO at Zambon.** *"We look forward to working with the FDA over the coming months with the hope of bringing much needed benefit to patients whose lives are severely impacted by this disease."*

There are no approved inhaled treatments currently available for patients with bronchiectasis and *P. aeruginosa* infection. Zambon, together with its long-standing partner **Xellia**, will continue to actively work in strict collaboration, to make the drug approved across the globe.

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, annual rate of severe pulmonary exacerbations, 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), 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 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.

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.

The **prevalence of NCFB** varies among populations, with studies reporting an overall prevalence ranging from 486 to 1,106 per 100,000 persons, with higher prevalence being reported in females. Prevalence was also shown to increase with age and peaked at ages 80–84 years.

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.*

The polymyxin antibiotics are surface active agents and 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, an example being *P. aeruginosa.*

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

About I-neb
The I-neb is a third-generation nebulizer for Adaptive Aerosol Delivery (AAD).

The I-neb is a small, battery powered, lightweight and silent drug delivery device, delivering a precise, reproducible dose of the drug.

The AAD technology ensures optimal drug delivery by only delivering medication when the patient inhales, (not continuously as in other nebulizers). This gives the medication the best opportunity to reach deep into the lungs and greatly reduces waste to the environment. AAD delivers the right amount of medication, regardless of breath size or breathing pattern.

I-neb generates a fine-particle low-velocity aerosol, by forcing the liquid medication through a fine mesh. Faster than conventional jet or ultrasonic nebulizers, I-neb support shorter treatment times (usually 3 to 4 minutes) and precise drug delivery.

About Zambon S.p.A.

Zambon SpA is a modern 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 2,474 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 765 million euros in 2022. 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

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1. Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. *A Comprehensive Analysis of the Impact of Pseudomonas aeruginosa Colonization on Prognosis in Adult Bronchiectasis.* Ann Am Thorac Soc Vol 12, No 11, pp 1602–1611, Nov 2015
2. Severiche-Bueno D, Gamboa E, Reyes LF, Chotirmall SH. *Hot topics and current controversies in non-cystic fibrosis bronchiectasis.* Breathe 2019; 15: 286–295