PRESS RELEASE

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Positive Results from Phase 3 PROMIS-I Study of CMS I-neb® in Patients with Non-Cystic Fibrosis Bronchiectasis Presented at European Respiratory Society (ERS) Annual Meeting

- Data shows 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 primary endpoint was met, the annual rate of exacerbations 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)
- Treatment has been granted FDA QIDP and Fast Track designations

Zambon, a pharmaceutical company on a mission to innovate cure & care to make patients' lives better, is pleased to announce the final results from the Phase 3 PROMIS-I study, which were presented at the European Respiratory Society Congress today.

The study, 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 prevention of pulmonary exacerbations in patients with NCFB, showed CMS I-neb® significantly reduced the annual rate of exacerbations and severe exacerbations in patients with NCFB and *Pseudomonas aeruginosa* chronic infection and prolonged the time to first exacerbation compared to placebo, also improving Quality of Life (QoL). The treatment was demonstrated to be well tolerated.

In patients with non-cystic fibrosis bronchiectasis, lung infection with *P. aeruginosa* is associated with frequent pulmonary exacerbations and admission to hospital for treatment, reduced quality of life, and increased mortality[1]. Currently there is no approved therapy for the disease.

The data were presented at the 9.30am CEST clinical trials session, ALERT: bronchiectasis and COVID' under the abstract *31109/3979:The efficacy and safety of colistimethate sodium delivered via the I-neb® in bronchiectasis: the PROMIS-I randomized controlled trial*.

The trial explored the effect of CMS I-neb® on the frequency of pulmonary exacerbations in NCFB patients chronically infected with *P. aeruginosa*. The 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 rate of exacerbations 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). Quality of life measured by the St. George's Respiratory Questionnaire (SGRQ) significantly improved in CMS I-neb® arm with 4.55 point difference *vs* placebo after 12 months treatment (p=0.0055). After 28 days treatment, *P. aeruginosa* density was significantly reduced in the treatment arm, p < 0.00001). The percentage of patients with adverse events was similar between groups. Bronchospasm and antibiotic resistance were infrequently observed (2.8% and 1% respectively).

"*The PROMIS-I data show that CMS taken twice daily through the I-neb® reduces exacerbation frequency and improves quality of life in people with bronchiectasis and chronic P. aeruginosa infection,"* said **Dr. Charles Haworth, Respiratory Physician at the Cambridge Centre for Lung Infection at Royal Papworth Hospital**, and PROMIS-I Chief Investigator. "*The data also demonstrate that 12 months treatment is well tolerated. These results are encouraging for patients as there is currently no approved drug treatment for this indication.*"

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].

"*We would like to extend our sincere gratitude to all of the patients and study centers for their collaboration throughout PROMIS-I,"* said **Paola Castellani, CMO and R&D Head** at Zambon. "*We are delighted to see that the hard work and commitment from all parties has paid off and provided us with encouraging data. We hope that these data will prove to be an important step as we seek a much-needed treatment to manage NCFB.*"

The PROMIS clinical program has received FDA Qualified Infectious Disease Product (QIDP) and Fast Track designation for the prevention of pulmonary exacerbations in adult NCFB patients with *P. aeruginosa*.

"At Zambon, we are committed to developing treatments for severe respiratory diseases with limited treatment options," said **Roberto Tascione, CEO** at Zambon. *"This trial is testament to our growing credibility in this area, representative of our drive for innovation and creates a strong foundation upon which we can continue to grow and provide needed medicines to improve patients' lives. With a number of our other mid- and late-stage trials in respiratory diseases ongoing, we are encouraged by the positive data of PROMIS-I which we hope is the first of many successes."*

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, in order to make the drug approved across the globe.

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

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About the PROMIS-I Study
PROMIS-I is a double-blind, placebo-controlled, multi-centre, clinical trial to investigate the efficacy and safety of 12 months of therapy with inhaled colistimethate sodium (CMS) in the treatment of subjects with non-cystic fibrosis bronchiectasis (NCFB) chronically infected with *Pseudomonas aeruginosa.* The study involved a total of 377 patient enrolled in the following 12 Countries: Australia, Belgium, Germany, Greece, Israel, Italy, Netherlands, New Zealand, Portugal, Spain, Switzerland, United Kingdom.

The primary objective of PROMIS-I trial was to investigate the effect on the frequency of pulmonary exacerbations of the use of inhaled CMS, administered twice daily via the I-neb® Adaptive Aerosol Delivery System for 12 months, compared to placebo in patients with non-cystic fibrosis bronchiectasis (NCFB) chronically infected with *P. aeruginosa.*

Secondary objectives included time to the first NCFB pulmonary exacerbation, number of severe NCFB pulmonary exacerbations, time to the first NFCB severe pulmonary exacerbation, quality of Life, *P. aeruginosa* density and resistance, number of exacerbation-free days, overall safety and tolerability.

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 is a pharmaceutical multinational company committed to innovating cure & care to improve patients' lives. With ambitious plans for growth, its goal is to improve people's health through the development of innovative and quality medicines.

Zambon products are commercialized in 87 countries. The company has 23 subsidiaries in three different continents – Europe, America and Asia – and owns manufacturing units in Italy, Switzerland, China and Brazil.

The company has taken now a new role in the industry On top of the diseases of the respiratory system, the urological system and Pain, Zambon is establishing a global pipeline and introducing important treatments for serious illness such as Parkinson's Disease, Cystic Fibrosis, BOS and NCFB.

Zambon was established in 1906 in Italy and today counts around 2,398 employees all over the world.

For further information please visit www.zambon.com