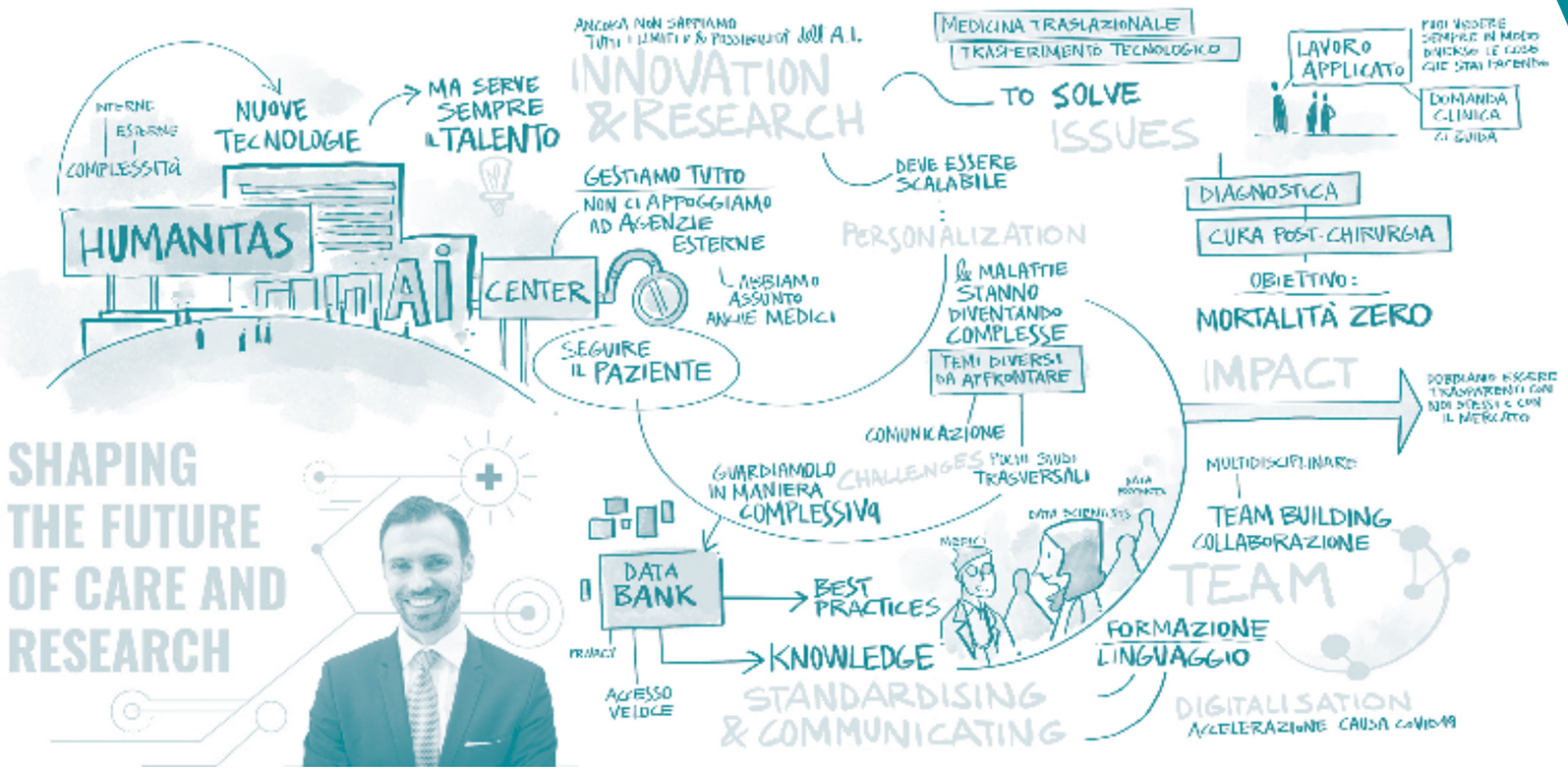
## OpenZone Talk

Sharing Ideas with
Victor Savevski

*Chief Innovation Officer - Humanitas Healthcare Group*

31 March 2021








# ZAMBON PHARMA



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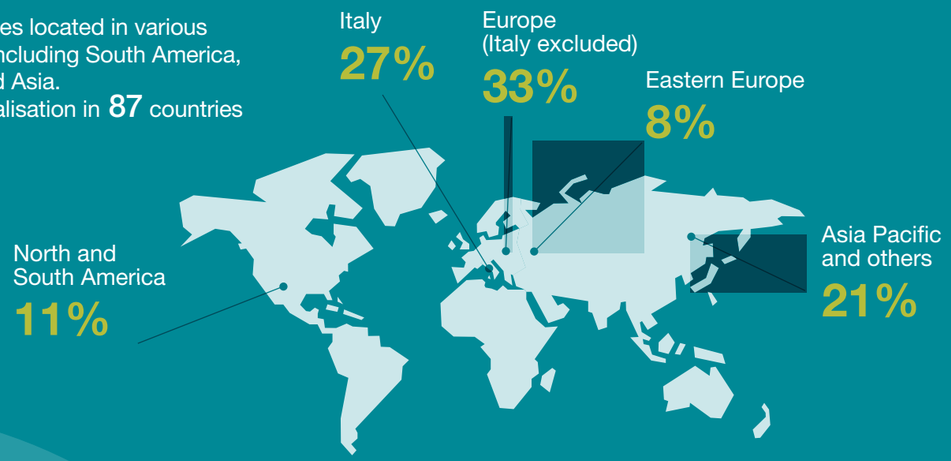
# BUSINESS RESULTS

## Sales by Geographical Area

**23** branches located in various countries including South America, Europe and Asia.
Commercialisation in **87** countries worldwide.




## People

Total
**2,398**

Production
**646**

Marketing
**1,266**

G&A
**296**

R&D/
Medical Affairs
**190**





**Revenues**
**638** Mio€

**EBITDA**
**115** Mio€

**Net Income**
**58** Mio€

## Therapeutic Areas

Diseases of the respiratory system
**46%**

Urinary tract infections
**18%**

Pain
**9%**

Neurological disorders
**8%**

Severe respiratory diseases
**4%**

Gastro
**8%**

Other
**7%**

# NEUROLOGICAL DISORDERS


Launch of Xadago® in the United Arab Emirates

SYNAPSES safety profile and tolerability study

Regulatory activities for the approval of *riluzole* in Europe





## PARKINSON'S DISEASE

Parkinson's Disease (PD) is one of the principal neurodegenerative diseases affecting the central nervous system. Its development is progressive: symptoms appear gradually and progress slowly. It is a debilitating condition that strongly impacts the quality of life of those who suffer from it. The disease's **motor symptoms**, such as tremor, rigidity and bradykinesia, occur alongside a series of **non-motor symptoms**, such as fatigue, depression and pain, which can begin to appear even before the motor symptoms do[1].

**1-2% of the population over the age of 60 suffers from PD**, a percentage that rises to 3-5% in the over-85 age group[1], and it is becoming increasingly widespread, due to the ageing of the population and associated health conditions. In 2020, **Covid-19** had a dramatic impact on people living with Parkinson's Disease: isolation, the inability to engage in physical activities and an increase in chronic stress led to a **worsening of motor and non-motor symptoms**[2].

## OUR **CONTRIBUTION**

Our commitment to the treatment of Parkinson's Disease **began in 2015**, when **Xadago®** ***(safinamide)*** was first introduced in Europe, followed by launches in North and South America and in Australia. *Safinamide*'s dual mechanism of action, which combines dopaminergic and non-dopaminergic action, works to treat the disease's motor and non-motor symptoms alike, improving patients' quality of life[3].

Throughout recent years of intense activity, Zambon has supported the scientific community, patients and healthcare providers. This multi-pronged commitment has allowed us to produce scientific evidence, conduct educational initiatives for clinicians and, first and foremost, provide support for patients, thanks to collaborations with associations for people affected by PD.

In 2020, Zambon Italy launched **MoveOn**, a web portal devoted to Parkinson's Disease and movement disorders. The content aggregator is intended for neurologists and its objective is to inform, educate and share tools that are easy to use and capable of improving patients' quality of life.

## OUR **PROSPECTS FOR GROWTH**

Launches of **Xadago®** ***(safinamide)*** continue around the world. Today it is available to clinicians and patients in **20 countries**. In 2020, it was introduced in the United Arab Emirates. The results of the **SYNAPSES study** have confirmed the medication's good safety profile and tolerability. This observational drug utilization study involved approximately 1,600 patients with PD, including subjects over 75 years of age as well as patients with psychiatric disorders or serious comorbidities. The study showed that there was an improvement in motor fluctuations, dyskinesia and motor symptoms after only 4 months of treatment[4].

2020 saw us continue our commitment to educational activities, working with academies and participating in virtual conferences focused on the importance of remote monitoring systems and on the adoption of a **multidisciplinary approach to treating PD**.

Xadago® recorded net revenues of 52.2 Mio€, a rise of 8.9% (4.3 Mio€) over the previous year, thanks to excellent performance in Spain (+9.4%) and Germany (+10.2%).

## AMYOTROPHIC LATERAL SCLEROSIS (**ALS**)

Amyotrophic lateral sclerosis (ALS) is a terminal neurodegenerative disease characterised by progressive muscular paralysis. It has a prevalence of approximately 5-7 cases per 100,000. There is no cure for ALS; treatment consists of symptomatic pharmacotherapy with drugs to slow the disease's progress in combination with physical exercise and home care, aimed to ensure the patient has the best possible quality of life.

During the course of the year—as a result of a 2019 agreement with **Aquestive**—studies and regulatory approval activities have moved forward to make a new *riluzole* oral film available on European market for the treatment of patients with ALS. As a matter of fact, our ambitious goal is to make this drug available to people suffering from this highly debilitating disease in the shortest possible period of time.

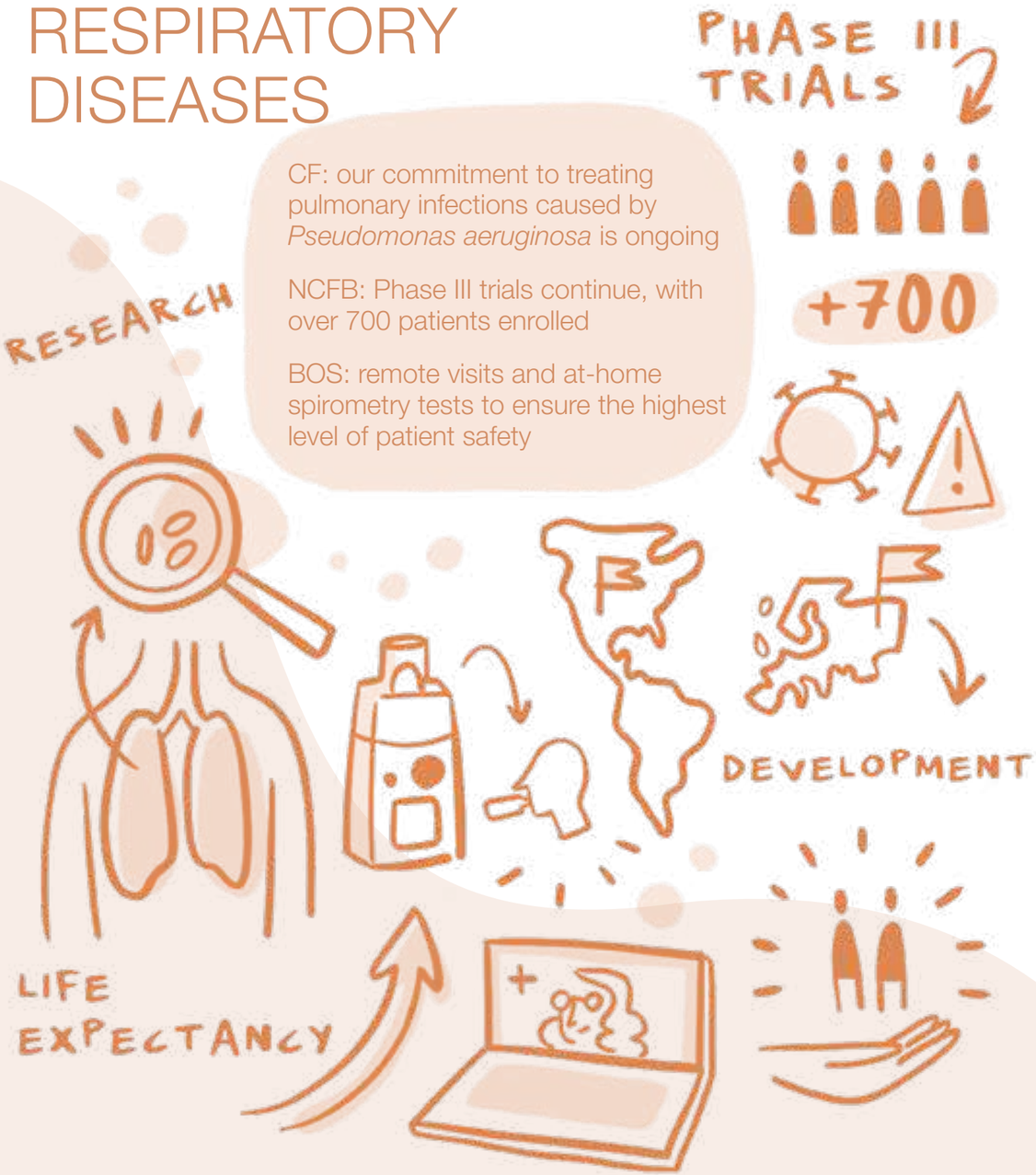
1. www.parkinson.it
2. Rick C. Helmich and Bastiaan R. Bloem Journal of Parkinson's Disease 10 (2020) 351–354
3. Muller T, Foley P (2017) Clinical pharmacokinetics and pharmacodynamics of safinamide. Clin Pharmacokinet 56, 251-261
4. Abbruzzese, Kulisevsky, Bergmans, & et al., 2021

# SEVERE RESPIRATORY DISEASES

CF: our commitment to treating pulmonary infections caused by *Pseudomonas aeruginosa* is ongoing

NCFB: Phase III trials continue, with over 700 patients enrolled

BOS: remote visits and at-home spirometry tests to ensure the highest level of patient safety








## SEVERE DISEASES OF THE **RESPIRATORY SYSTEM**

**Cystic fibrosis (CF)** is the most common of the **severe genetic diseases**, affecting approximately **70 thousand people worldwide**. It is characterised by chronic infections of the respiratory tract that cause a progressive decline in lung function, which has a serious impact on patients' quality of life. The life expectancy of people suffering from CF has increased considerably over the years. Thanks to scientific progress, a patient born in 2016 now has a life expectancy of 47.7 years, in comparison with 5 in the 1950s.

This remarkable outcome is attributable to ongoing progress in the medical and pharmaceutical spheres, the use of antibiotic therapies to treat chronic infections, and improvements in diet[1].

## CONSTANTLY **INNOVATING** FOR PATIENTS

In 2020, Zambon strengthened its commitment to severe respiratory diseases.

### Cystic Fibrosis

The company has continued to work on ***colistimethate sodium* (Promixin®)** as a treatment for chronic pulmonary infections caused by *Pseudomonas aeruginosa* in patients with **cystic fibrosis**. In particular, Promixin® can be administered using the **I-neb® Adaptive Aerosol Delivery (AAD)** device jointly developed with Philips, which, thanks to third-generation AAD technology and the ability to monitor real adherence data, offers concrete support to healthcare providers and patients.

### Ongoing clinical trials focused on Non-cystic Fibrosis Bronchiectasis **(NCFB)**

2020 was a decisive year for Phase III trials of PROMIS 1 and PROMIS 2, involving patients with NCFB, an incurable pulmonary disease characterized by permanent bronchial dilation and inflammation, chronic productive cough and recurrent aggravation of infection. Bronchiectasis is viewed as the end result of a disease process involving a vicious cycle of inflammation, recurrent infections and damage to the bronchial walls that occurs due to a variety of primary causes, which can be infectious, genetic, inflammatory, environmental or allergenic in nature[2].

Despite the pandemic, the enrolment of patients for the PROMIS 1 study was completed in 2020, while a mitigation plan was put into effect for PROMIS 2 which ensured that enrolment could continue. The two Phase III trials, focused on the development of a treatment for NCFB, stand out for the number of clinical centres involved, how widely they were spread throughout the world (Europe, Australia, New Zealand, the U.S. and Latin America) and the number of patients enrolled: over 700 globally.

Our goal is to obtain, by 2023/24, an indication for *colistimethate sodium* in combination with I-neb® for the prevention of exacerbations in patients with NCFB and chronic *Pseudomonas aeruginosa* infection, both in Europe and the US.

### Ongoing clinical trials focused on Bronchiolitis Obliterans Syndrome **(BOS)**

Zambon renewed its commitment to patients with BOS, the most common form of chronic lung allograft dysfunction after lung transplantation. BOS is a rare and **rapidly progressive inflammatory disease** that irreversibly destroys the airways of the lungs, usually leading to respiratory insufficiency and death[3]. Although BOS commonly affects people following lung or stem cell transplant, it is also associated with autoimmune diseases or exposure to environmental contaminants. Currently, **there is no approved treatment** for BOS.[4]

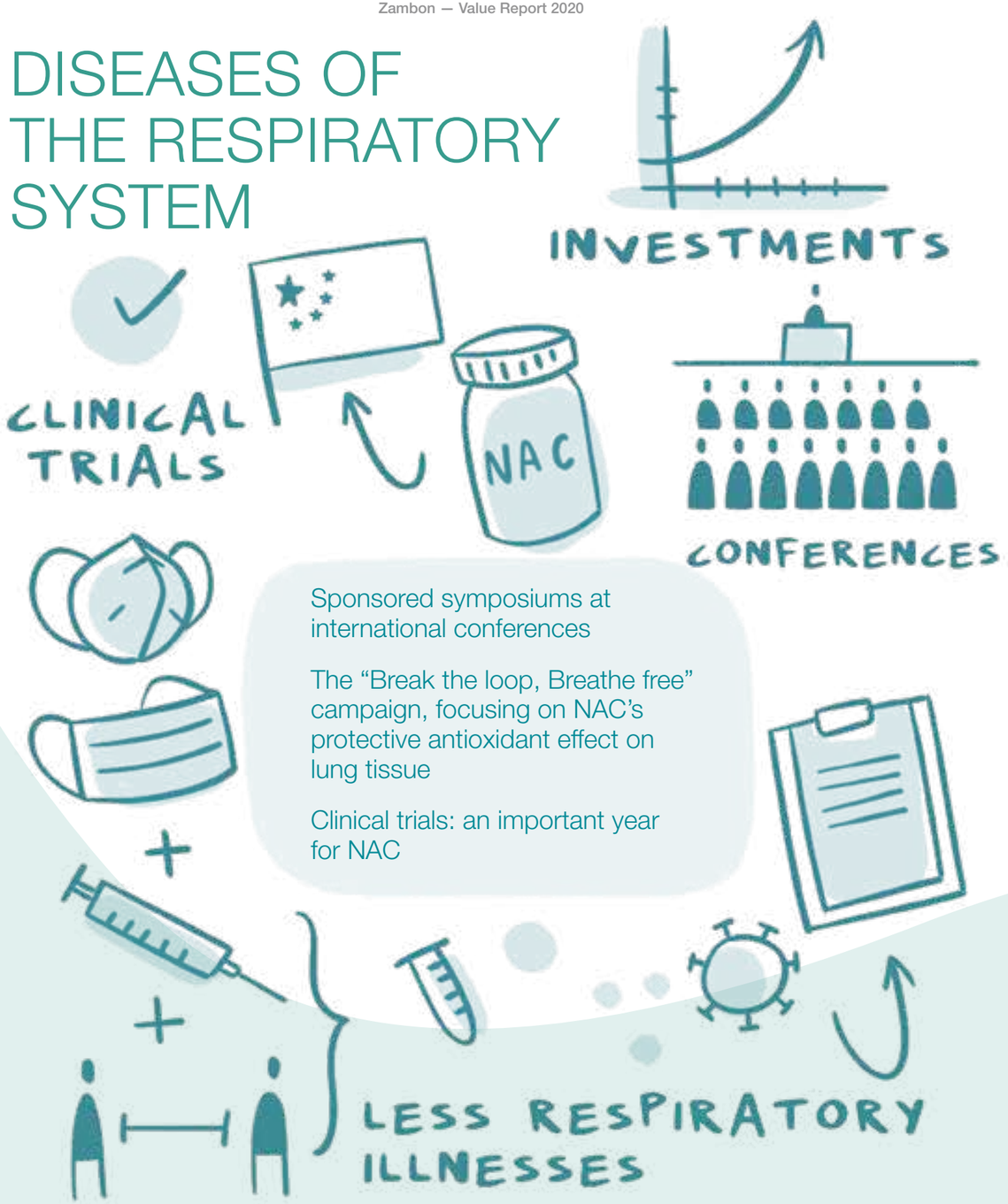
## MOVING TOWARDS **CONCRETE** OBJECTIVES

The **BOSTON development program** is evaluating *liposomal Cyclosporine-A* for inhalation (L-CsA-i) for the treatment of BOS. Cyclosporine-A is an immunosuppressive drug used in post-transplant treatments. The innovative L-CsA-i is encapsulated in liposomes, which distribute the medication **directly to the lungs** via a **drug-specific nebulisation system**.

For people with BOS, Covid-19 is challenging because of their immunocompromised status. To ensure the safety of the patients enrolled, their continuous treatment and the integrity of the data collected, Zambon implemented a contingency plan including remote visits and at-home spirometry tests.

1. Natalie E. West, Patrick A. Flume. Unmet needs in cystic fibrosis: the next steps in improving outcomes, Expert Rev Respir Med. 2018 July; 12(7): 585–593
2. D. Weycker et al., Prevalence and incidence of Non cystic fibrosis bronchiectasis among US adults in 2013, Chronic Respiratory Disease 2017, Vol. 14(4) 377–384
3. Chambers DC, et al. J Heart Lung Transplant. 2018;37(10):1169–1183.
4. Verleden GM, et al. J Heart Lung Transplant. 2019; 38(5):493-503.

# DISEASES OF THE RESPIRATORY SYSTEM




Sponsored symposiums at international conferences

The “Break the loop, Breathe free” campaign, focusing on NAC’s protective antioxidant effect on lung tissue

Clinical trials: an important year for NAC





## RESPIRATORY DISEASES

Respiratory diseases encompass a broad spectrum of conditions, which range from relatively basic acute seasonal disorders, such as cough, flu and acute bronchitis, to chronic progressive illnesses, such as chronic obstructive pulmonary disease (COPD) and bronchiectasis.

In 2020, the measures implemented to fight Covid-19, such as social distancing, mask wearing and the use of flu vaccines, deterred acute respiratory illnesses, the flu first and foremost among them, from manifesting in many countries, and also limiting the number of exacerbations of chronic conditions[1].

## **OUR COMMITMENT** TO THE SCIENTIFIC COMMUNITY

Although Fluimucil® (*N-Acetylcysteine, NAC*) is one of Zambon’s historic products, scientific **investments into this molecule are ongoing**.

In 2020, the company focused on understanding the role of *NAC* in continuous administration. A symposium was organised for the scientific community, “*Which Target to Protect and Preserve Lung Health*”, during the European Respiratory Society (ERS) International Meeting. A new communication campaign was also launched, “*Break the Loop, Breathe Free*”, which aimed to highlight the drug’s protective antioxidant effect on lung tissue.

## MOVING TOWARDS IMPORTANT **GOALS**

2020 was a significant year for NAC, when it comes to clinical trials. In China, Phase I and III studies related to the registration of intravenous NAC in patients with mucosal hypersecretion have been completed. The results represent a step forward in the approval process for the use of NAC IV for the treatment of COPD in the market.

Lastly, 2020 saw the launch of a number of investor initiated trials (IITs) involving the use of NAC in the treatment of Covid-19. Despite the negative impact the pandemic has had on the market for drugs to combat respiratory diseases, Zambon’s revenues stood at 291.8 Mio€, a 14.9% (51.1 million euro) decrease in comparison with 2019, a fall in line with market trends.

1. https://www.medrxiv.org/content/10.1101/2020.03.30.20047993v2.full.pdf
https://www.medrxiv.org/content/10.1101/2020.09.18.20189647v2
https://www.theatlantic.com/science/archive/2021/02/covid-19-flu-season/617924/
https://www.sciencedirect.com/science/article/pii/S2589537021000699
https://thorax.bmj.com/content/76/Suppl_1/A102.1.abstract

# PAIN

Results in line with expectations, despite the challenging market context

An additional focus on the needs of doctors and patients to offer increasingly targeted solutions

A reaffirmed growth strategy






## **PAIN**: TYPES OF PAIN

93% of the world's population has experienced a headache or physical pain at least once during the past year. A headache, which affects 84% of the world's population, is the most common type of pain, followed by muscle pain (83%), joint pain (73%), menstrual pain (67%) and toothache (60%)[1].

Severe pain (mild and moderate) often has an impact on social relationships and on the emotional sphere, so much so that 65% of the world's population believe that pain interferes with their ability to fully enjoy their professional and personal lives[2].

## ZAMBON'S **ANSWER** TO PAIN

Spidifen® **is a non-steroidal anti-inflammatory drug containing *ibuprofen and arginine salt*** that offers a front-line treatment solution for mild-to-moderate severe pain.

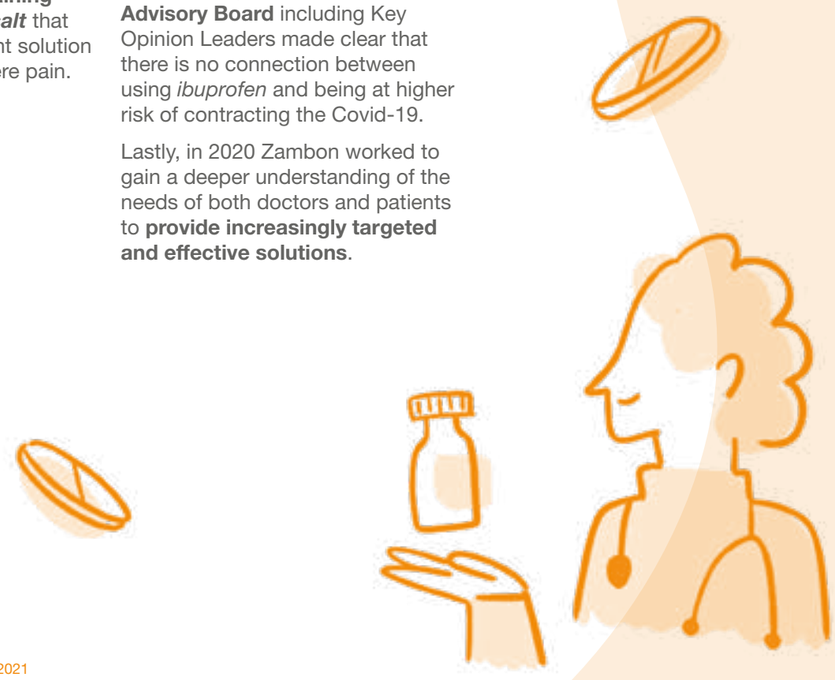
## A **CONSOLIDATED** STRATEGY

In 2020, thanks to its **presence in 54 countries**, **Spidifen®** earned revenues in the amount of 52.5 Mio€, despite an extremely complex market context.

**Spidifen®'s mid-term strategy continues to be based on two key elements**: **growth in the OTC sector** and updating **communications that target healthcare providers** using content created with the support of important names in the scientific community. In particular, we published a **scientific monograph** entitled "*Nonsteroidal anti-inflammatory drugs, ibuprofen and ibuprofen-arginate*", by Prof. Patrono, which highlights the distinct mechanisms of action of different NSAIDs.

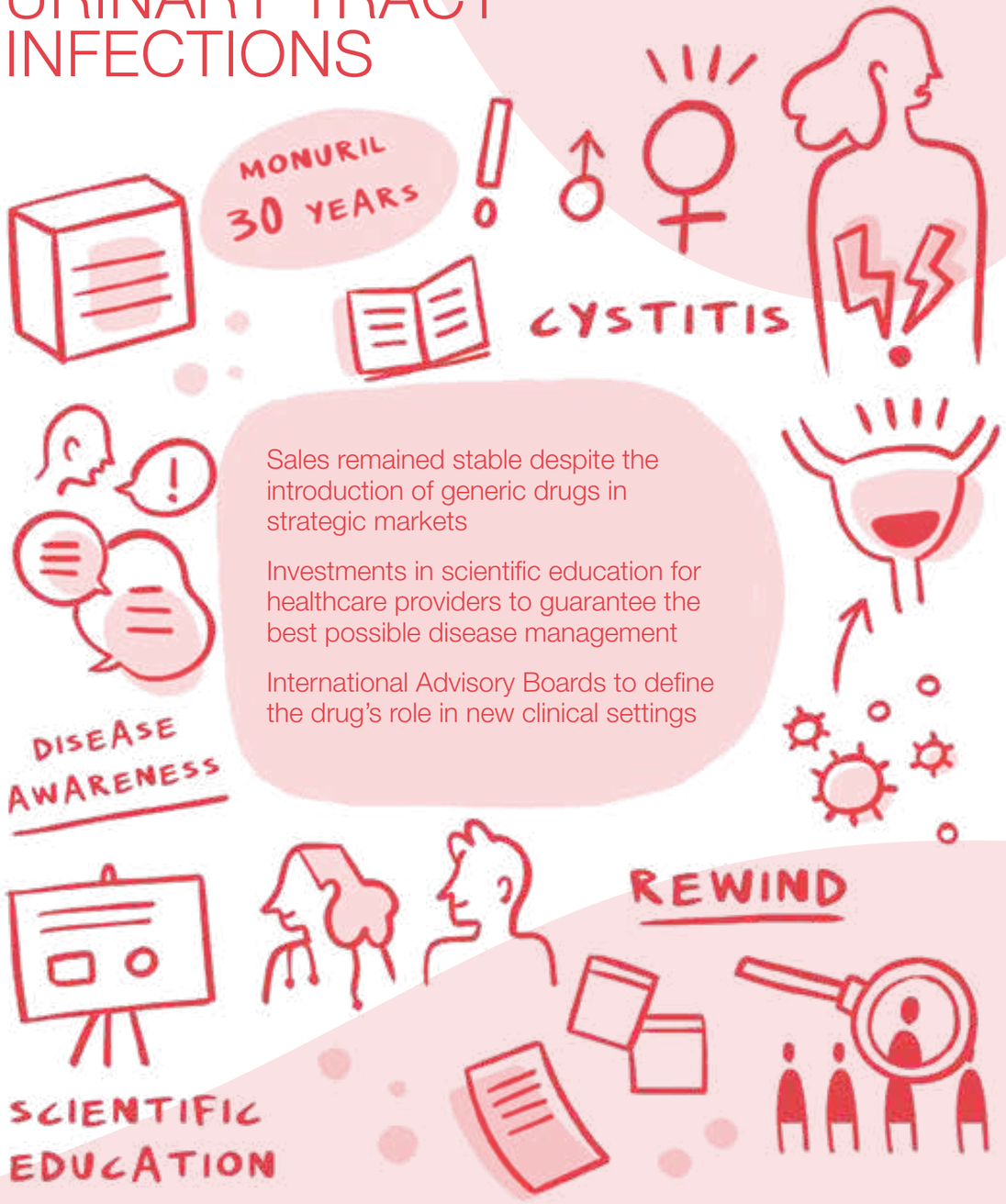
Furthermore, an **International Advisory Board** including Key Opinion Leaders made clear that there is no connection between using *ibuprofen* and being at higher risk of contracting the Covid-19.

Lastly, in 2020 Zambon worked to gain a deeper understanding of the needs of both doctors and patients to **provide increasingly targeted and effective solutions**.



1. Global Pain Index Report 2020
2. Spidifen Customer Centric Model 2021

# URINARY TRACT INFECTIONS




Sales remained stable despite the introduction of generic drugs in strategic markets

Investments in scientific education for healthcare providers to guarantee the best possible disease management

International Advisory Boards to define the drug's role in new clinical settings





## A **FREQUENT** OCCURRENCE

Urinary tract infections (UTIs) are a frequent occurrence that largely affects the female population. It is estimated that one in two women suffers from a urinary tract infection during her life, with an annual incidence of 12.6%[1]. Recurrences are common: 27% of women experiencing UTIs have a recurrence within 6 months from the first episode[2].

The pathogen that most frequently causes this type of infections is *Escherichia coli*, even if, less frequently, other bacteria, viruses or fungi can also be responsible[3].

Urinary tract infections can also affect men, especially during invasive diagnostic investigations such as prostatic transrectal biopsy and, because of this, Zambon is currently conducting a Phase I clinical study that analyzes the prostatic penetration of fosfomycin trometamol in healthy male volunteers, with the aim of assessing whether a prophylactic use during diagnostic investigations can be valid. The study will conclude by the end of 2021.

## OUR ADDED **VALUE**

**Monuril® (*fosfomycin trometamol*) has been available to women across the world for over 30 years**. A single dose is recommended, as a first-choice treatment for uncomplicated acute urinary infections, by the **European Association of Urology (EAU)** and two doses for antibiotic prophylaxis in men undergoing transrectal prostate biopsy posology (before and after surgery)[4].

In this regard, we mention "REWIND" (Real World International Database) a clinical practice study that has analyzed data from over 50 thousand patients (Italy, Belgium, Russia and Brazil). Despite the use of different methods for the study of data and sources, fosfomycin trometamol was found to be the most used antibiotic in all four countries considered.

The "SURF" study (SUsceptibility and Resistance of uropathogens to Fosfomycin in comparison with other antimicrobial agents) also came to a conclusion in 2020, with the aim of demonstrating once again the susceptibility of *Escherichia coli* (the most responsible pathogen for cystitis) to *fosfomycin trometamol* in recent times.

In 2020 we kept on with our **commitment to providing scientific information** to healthcare providers through **educational activities** and **disease awareness** campaigns to disseminate the most recent recommendations based on international guidelines. We are in fact convinced that patients can be guaranteed the best possible treatment only through a correct scientific update.

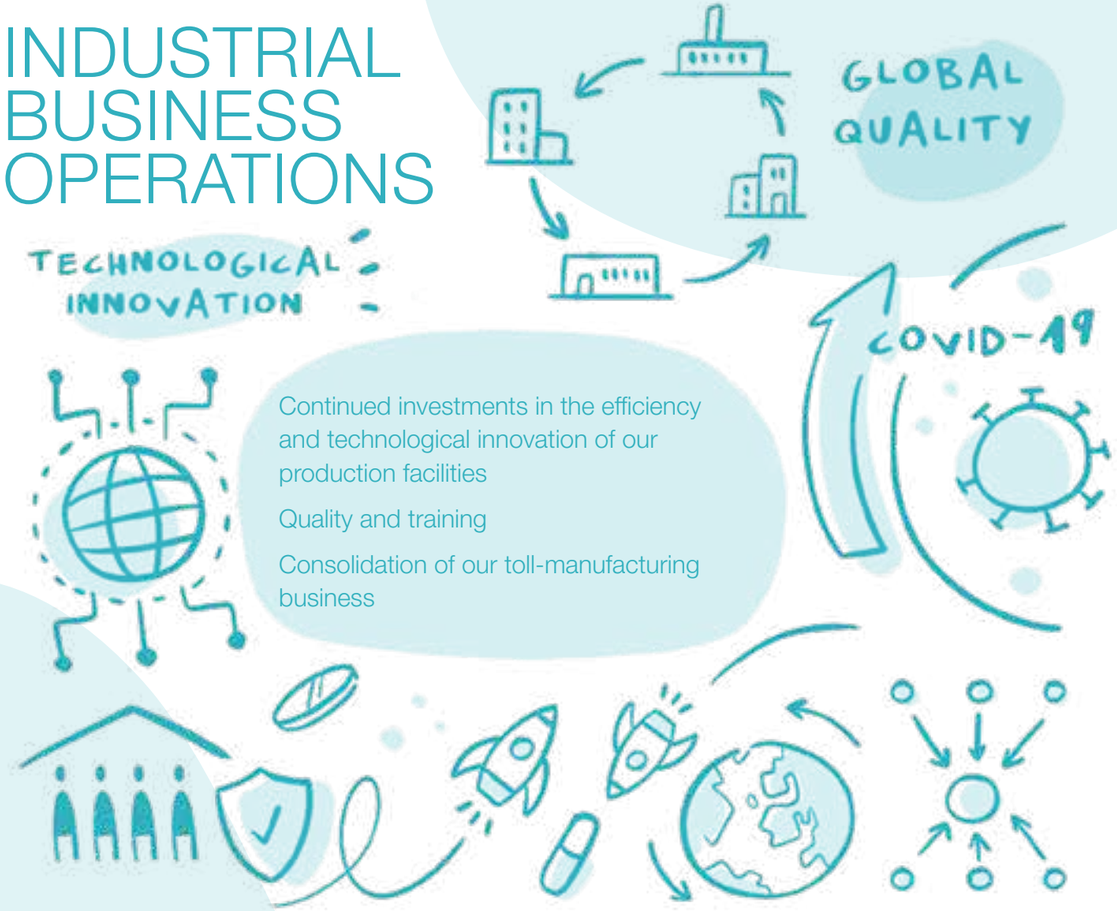
Finally, we conducted **two** (virtual) **Advisory Boards** with seven international Key Opinion Leaders (United States, Canada, Russia, United Kingdom and Switzerland) in the fields of urology, microbiology and gynaecology, with the aim of clearly defining the role of Monuril® in different clinical settings in light of new scientific findings.

## A PATH **WELL LAID**

In 2020, sales of Monuril® remained stable, coming in at 91.3 Mio€ (-1.0% in comparison with 2019). These results are significant, considering the introduction of generic drugs in the Central/ Southern European and US markets.

1. Foxman, B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. *Dis Mon* **49**, 53–70 (2003).
2. Medina, M. & Castillo-Pino, E. An introduction to the epidemiology and burden of urinary tract infections. *Therapeutic Advances in Urology* **11**, 1756287219832172 (2019).
3. Chambers, ST. Cystitis and Urethral Syndromes. in *Infectious Diseases* (Mosby, 2004).
4. Bonkat, G. et al. EAU Guidelines on Urological Infections 2021. (2021).

# INDUSTRIAL BUSINESS OPERATIONS




Continued investments in the efficiency and technological innovation of our production facilities

Quality and training

Consolidation of our toll-manufacturing business

## Cadempino Switzerland

**69** Mio
(million units produced)

third parties and generics manufacturers of carbapenems

**19** Mio

## Vicenza Italy

**63** Mio
(million units produced)

demonstrate the site's extraordinary complexity

**240** SKU

## São Paulo Brazil

**3,3** Mio
(million units produced)

## Haikou China

**13** Mio
(million units produced)

## Virtual plant

**10** Mio
units sold (including Xadago® for 700k and Promixin® 200k boxes)

**132** Mio€
sales in the world (including Xadago® and Proximin®)





## INNOVATION, FLEXIBILITY AND EFFICIENCY TO ALWAYS BE MORE COMPETITIVE

2020 was one of the **most challenging years in the history of Zambon's production facilities**. The Covid-19 pandemic had a strong impact on all four of our industrial facilities, **but our timely intervention putting special procedures into place**, first in our Haikou plant and then in all of the Group's other facilities, allowed us to proactively manage the waves of the pandemic in China, Europe and South America.

We are truly proud of having implemented a **series of processes capable of guaranteeing the safety of our people** and, at the same time, **ensuring the uninterrupted supply of necessary drugs to our suppliers, clinics, doctors and patients.**

The pandemic forced us to **act rapidly** and **respond flexibly** to **market** volatility. During the first six months of 2020, we reached a peak in production, that we were able to maintain thanks to our organisational system and investments made in prior years: streamlining initiatives and technological innovation and digitalisation projects were fundamental to our ability to deliver **156 million pieces** and supply every market.

It is important to point out that in 2020, in line with our strategic objectives, we also **invested 36.7 Mio€** for the purpose of **continuing to improve efficiency and technological innovation at our production facilities**.

In chronological terms, our Chinese plant in **Haikou** was the first to feel the impact of the pandemic. Despite the difficulties that existed at that time, we installed a number of new pieces of machinery and production equipment, in line with the actions laid out in our strategic plan. Thanks to work carried out in synergy with our Corporate departments, we were able to validate the new processes and get the new systems up and running, allowing us to increase efficiency and production capacity to be ready for future challenges.

In our plant in **Vicenza** (Italy), many actions were taken to prevent the virus from spreading internally and provide continuity to the business. We concentrated on re-engineering processes and activities and adhered to our plans for the construction of the **new Marco Polo facility**, destined for the production of 300 mg vials of Fluimucil® for the Chinese market.

It is also important to point out that we recorded no accidents or injuries in 2020, a truly noteworthy outcome generated by our long history of effort put into training and investments in safety.

In **Cadempino**, in Switzerland, we invested in training and in process optimisation, in particular the "automated maintenance" project, put into action through e-learning platforms.

From a production standpoint, we consolidated our toll-manufacturing business by launching new production activities and guaranteed our biggest customers larger-than-predicted volumes.

At our **Barueri plant (São Paulo)** in Brazil, which opened in 2019, investments continued to guarantee insourcing of Zambon products currently being manufactured by third parties. Moreover, additional SKUs (Stock Keeping Units) were approved, expanding the product portfolio for the Brazilian market.

Overall, it was an intense and busy year for **Global Quality** as well, which ran virtual audits and implemented internal systems for sharing information and policies remotely in all four of the production facilities and all of the Group's subsidiaries.

The coronavirus pandemic caused delays and other serious problems in businesses' global supply chains, highlighting how vulnerable many supply chains are to sudden interruptions. At Zambon, we were able to contain this problem thanks to the efforts of our supply chain and to our pool of suppliers, who proved themselves to be solid and reliable.

Once again, as in previous years, our **Virtual Plant** (our organisational model for the centralised management of contract production of Zambon products) played an integral part in programmes to optimise synergies between the different facilities in a streamlined and increasingly integrated fashion.

# BUSINESS DEVELOPMENT

Scouting for new molecules in synergy with the Group's strategies continues

New local agreements were struck and existing partnerships strengthened

The new Next Generation Pharma Assets department identifies new potential future assets






In 2020, Zambon's Business Development team continued working on building the pipeline of future development. We **continued to scout and evaluate new opportunities** with the goal to discover assets in synergy with those currently in our portfolio and in line with the Group's strategies.

Over the course of the year, the business development activities were focused on the field of neurological disorders, this after having consolidated its commitment in the field of Severe Respiratory Diseases in 2019 with the acquisition of Breath Therapeutics. This move allowed Zambon to take an important step forward in the US market.

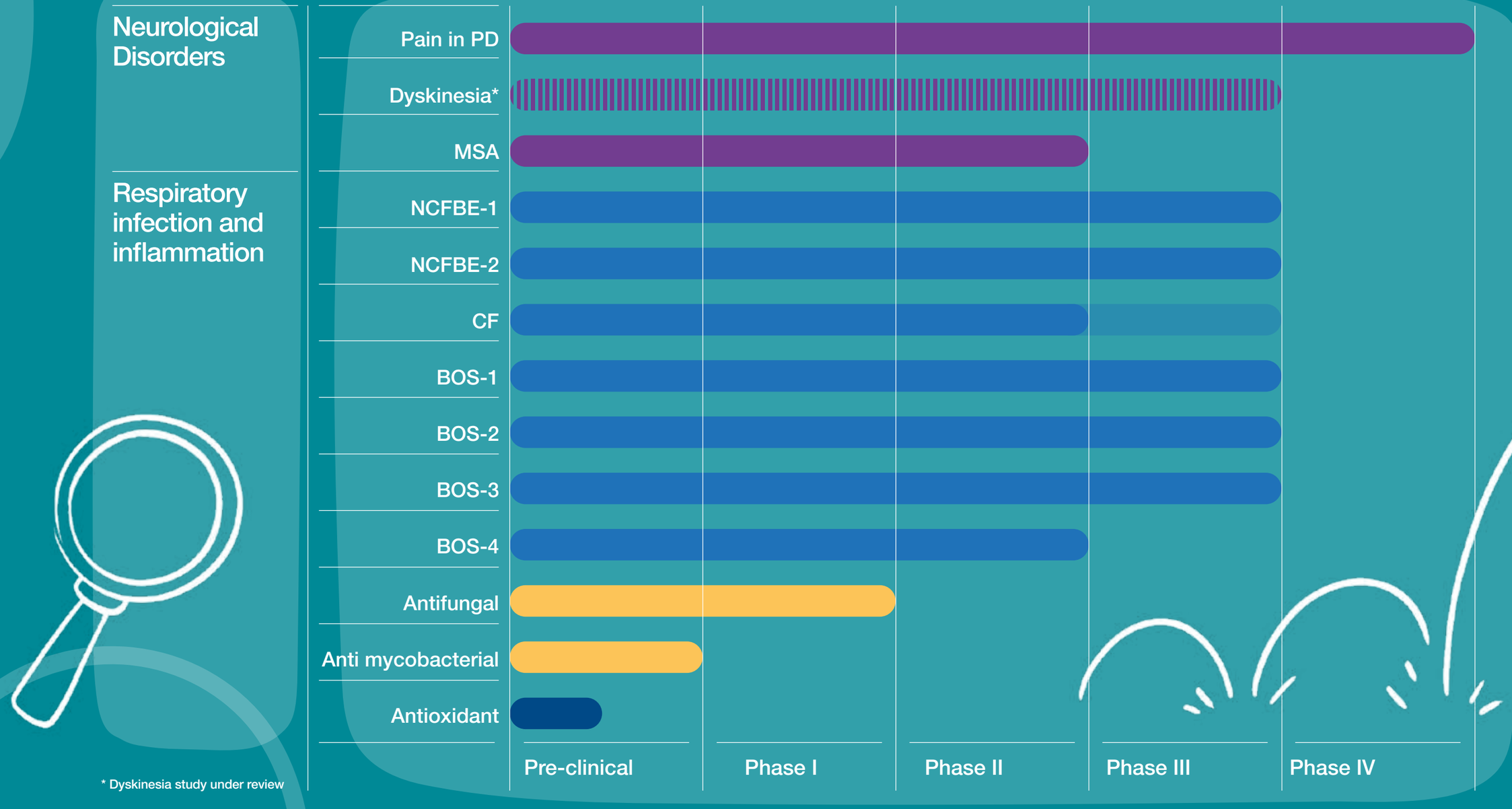
In 2020, the activities of the Global Team, which were concentrated on seeking out opportunities for the mid-term, took place alongside a series of important local initiatives focused on signing agreements with shorter timeframes and strengthening existing partnerships.

In addition, more long-term scouting activities were conducted in 2020 by **Next Generation Pharma Assets**, a department created within Global Business Operations with the aim of identifying opportunities and assets to fuel Zambon's growth in coming years.

Activities also continued in 2020 to move towards EMA approval **for *riluzole* oral film** for patients with amyotrophic lateral sclerosis (ALS). In 2019, following an agreement with **Aquestive Therapeutics**, the company acquired the European commercialization rights for this special formulation.

The efforts of the Corporate Business Development once more proved to be essential to the success of Zambon's growth strategy, and in coming years will continue to focus on rare diseases, neurological disorders and severe respiratory diseases.

# PIPELINE




* Dyskinesia study under review

# GOOD SCIENCE

In 2020 Zambon reaffirms its focus on severe respiratory diseases and neurological disorders. Despite the pandemic, the company achieved progress in Research and Development and strengthened its partnerships within the international scientific community.

## **NEURODEGENERATIVE** DISEASES

Research into the **unique mechanism of action of *safinamide*** (Xadago®) led to the publication of **three articles in scientific journals** in collaboration with research centres.

The Phase IIa investigation trial on the potential of *safinamide* in MSA (Multiple System Atrophy), a rare neurodegenerative disease with pathological features similar to Parkinson's Disease, has been completed with results coming by the first half of 2021.

A **Phase IIIb trial** focusing on ***Levodopa*-induced dyskinesia (PD-LID)** was redefined, and all of the related **preparatory activities** have been **successfully completed**.

Lastly, despite some pandemic-related delays, the **Phase IV trial focusing on pain related to Parkinson's Disease** completed its patient enrolment. It is expected to be **completed and its results analysed during 2021**.

## **RESPIRATORY** INFECTIONS AND INFLAMMATIONS

### COLISTIMETHATE SODIUM (PROMIXIN®) VIA I-NEB®

Despite difficulties arising from Covid-19, **important progress** was made in the international program dedicated to the potential treatment of pulmonary infections caused by gram-negative *Pseudomonas aeruginosa* bacteria in patients suffering from Non-cystic fibrosis bronchiectasis (NCFB) using *colistimethate sodium* administered by inhalation through the use of the I-neb® nebuliser.

A recalculation of the number of patients needed for the PROMIS 1 trial to have the statistical validity allowed to achieve its recruitment goals without any impact on the quality of the study. The report on this trial is due in 2021.





The impact of the pandemic on the **PROMIS 2** trial was mitigated by actions aimed to ensure recruitment that was completed in 2021. In any event, the "Fast Track" designation received from the US FDA (Food and Drug Administration) means that data will be sent continuously.

### A LIPOSOMAL FORMULATION OF CYCLOSPORINE-A FOR INHALATION (**L-CSA-I**) VIA EFLOW®

**Bronchiolitis Obliterans Syndrome** (BOS) is a progressive inflammatory and fibrotic disease of the respiratory system that commonly develops in patients who have undergone a lung transplant. **L-CsA-i is an innovative liposomal formulation of the** immunosuppressant **drug *Cyclosporine-A*** and created for use via inhalation utilizing a specially designed version of the **eFlow® Technology nebulizer system** (PARI Pharma GmbH). *Cyclosporine-A* is currently administered systemically, but this innovative drug-device combination was designed to deliver L-CsA-i locally, thereby reducing systemic exposure.

Specifically, two **Phase III trials are currently ongoing (BOSTON-1 and BOSTON-2)**, involving patients suffering from BOS following lung transplantation. Patients who complete the treatment period in the BOSTON-1 or BOSTON-2 studies will, if eligible, be recruited for the **BOSTON-3** trial, an observational study to gather long-term efficacy and safety data for the drug. A **Phase II clinical trial (BOSTON-4)** to evaluate the safety of L-CsA-i for the treatment of adult patients suffering from BOS following allogeneic haematopoietic stem cell transplantation is also underway.

### ADDITIONAL PROJECTS IN **CLINICAL PHASE**

In 2020 **a Phase I** three part, single ascending dose (SAD), multiple ascending dose (MAD) & Cross-Over Study in healthy and asthmatic subjects has been carried out to test the safety and pharmacokinetics of a new dry powder inhaled formulation of the **fungicide *Voriconazole* produced using proprietary E-dry® technology.**

The project's goal is to obtain a new inhalable formulation of *Voriconazole* to use as a new treatment for *Allergic Bronchopulmonary Aspergillosis* (ABPA), a hypersensitive reaction to *Aspergillus fumigatus* in asthmatic patients.

### PROJECTS IN THE **PRECLINICAL PHASE**

**E-dry® technology** is at the basis of **two other projects coming down the pipeline in preclinical phase**.

The first envisions the development of an inhalable formulation of a **drug to treat pulmonary infections caused by atypical mycobacteria**, a condition that significantly complicates the clinical condition of patients suffering from severe diseases of the respiratory system, such as bronchiectasis or cystic fibrosis. In 2020 the necessary experiments were planned to advance the process of developing the candidate for clinical development.

The second project involves a **new inhalable formulation of an antioxidant** recommended for prophylactic treatment for exposure to particles and chemical substances that are toxic to the organism. In 2020, we concentrated on the preliminary activities necessary for subsequent planning of formulative research.

### THE CENTRAL NERVOUS SYSTEM (**CNS**)

In 2020, despite the pandemic, Zambon continued to present **data about *Safinamide* (Xadago®)**, to the international scientific community with a **symposium at the Movement Disorders Society (MDS) Virtual Congress** and a poster at the **European Academy of Neurology Virtual Congress**. Furthermore, **two new articles on the effectiveness of Xadago®** for treating pain and cognitive impairment in patients with Parkinson's Disease were published in the *Journal of Neural Transmission*.

In 2020 the approval from EMA (European Agency for Medicines) of the clinical study report for the **Phase IV observational study "Synapses**" was obtained; meanwhile, the **Phase IV European observational study "*Success*"** and the **Phase III study "*Xindi*"** for the registration of the drug in **China** are currently ongoing. Finally, we have 11 investigator-initiated trials (IITs) assessing the effectiveness of *safinamide* to treat non-motor symptoms, cognitive impairment, freezing of gait, apathy and chronic pain in Parkinson's Disease. And finally, we received fast-track authorisation for the registration of *safinamide* in Turkey.

# OUR MATURE DRUGS PORTFOLIO AND "GOOD SCIENCE" ACTIVITIES

## **RESPIRATORY** DISEASES

Once again in 2020, Fluimucil® (*N-acetylcysteine, NAC)*, one of the company's historic drugs, was the **focus of a series of scientific dissemination activities**.

The results of the International Expert Panel Meeting held in 2019 were published in the Current Neuropharmacology journal in the article "The Multifaceted Therapeutic Role of N-Acetylcysteine (NAC) in Disorders Characterized by Oxidative Stress". The purpose of the meeting and, consequently, of the article was to clarify the benefits of using Fluimucil® in different clinical settings. A study was also published in *Drug Safety* entitled "Safety of N-acetylcysteine at High Doses in Respiratory Diseases: A Review", which confirms the tolerability of Fluimucil® when administered off-label at high doses.

In September, at the ERS (European Respiratory Society) International Congress, Zambon sponsored a virtual symposium on the role of Fluimucil® in the treatment of chronic respiratory diseases.

In China, Phase I and III pivotal trials involving approximately 350 patients were completed for the use of intravenous *N-acetylcysteine* in patients with mucus hypersecretion. The results of a Phase I trial conducted on healthy Chinese and Caucasian volunteers were also significant. This study showed the same safety and pharmacokinetics results for both groups. The study was published in *Advances in Therapy* under the title "Pharmacokinetics and Safety of Single and Multiple Doses of Oral N-Acetylcysteine in Healthy Chinese and Caucasian Volunteers: An Open-Label, Phase I Clinical Study".

Lastly, an extension phase study on the use of Fluimucil® in patients with retinitis pigmentosa—a rare and serious orphan disease, genetic in nature, which affects the retinal pigment epithelium and the retina, leading to gradual and progressive vision loss—is currently ongoing in the United States.

## **URINARY TRACT** INFECTIONS

Monuril® (*fosfomycin trometamol*) has also been the focus of numerous scientific activities. In particular, we are awaiting the publication of data from the **international SURF study**, aimed at assessing the rate of antibiotic resistance to *fosfomycin trometamol* and other antibiotics commonly used in urinary tract infections. Zambon is working with the EMA to conduct a **Phase I pharmacokinetic/pharmacodynamic study**, which will conclude at the end of 2021. Finally, 2020 saw the organisation of **two virtual Advisory Boards** on the role of *fosfomycin trometamol* in different clinical contexts; these involved international KOLs from the United States, Canada, Russia, the United Kingdom and Switzerland.

## PAIN

Spidifen® (*ibuprofen and salt of l-arginine*) was also the focus of important activities, such as the publication of the **scientific monograph** entitled "Nonsteroidal anti-inflammatory drugs, ibuprofen and ibuprofen-arginate", by Professor Patrono, which aims to highlight the distinct mechanisms of action of different NSAIDs.

A scientific Advisory Board was held on the interaction between ibuprofen and Covid-19, with the objective to clear that no connection has been demonstrated between ibuprofen use and a higher risk of being infected by Covid-19.