A Work Project, presented as part of the requirements for the Award of a Master's degree in Management from the Nova School of Business and Economics.

ProbiOxy: Redefining the Treatment Landscape of Inflammatory Bowel Disease

Probioxy: Redefining the Treatment Landscape of Inflammatory Bowel Disease - Operations and Key Assets

Steinar Litland (55906)

Work project carried out under the supervision of:

Nuno Arantes-Oliveira

20/12/2023

Group Part

Abstract: ProbiOxy, a biopharmaceutical start-up, is committed to developing the first probiotic treatment for Inflammatory Bowel Disease (IBD) to improve patients' quality of life. Our strategic approach involves securing initial funding, licensing intellectual property, advancing through pre-clinical and clinical trials, growing our patent portfolio, developing the product pipeline, and ultimately achieving acquisition by a prominent pharmaceutical entity. Central to our strategy is securing exclusive licensing of intellectual property from the Calouste Gulbenkian Foundation, allowing comprehensive ownership and strategic partnerships essential for market positioning. We prioritize protecting our intellectual property through patent filings and ongoing innovation to establish a robust portfolio, enhancing our competitiveness. Collaborations with Instituto Gulbenkian de Ciência and Contract Research Organizations accelerate research and clinical trials, ensuring regulatory compliance and market approval. Our diverse Board of Directors and Advisory Board drive innovation and strategic growth, while investor representatives align our strategic direction with market insights. Our financial strategy emphasizes securing venture capital investments to fuel research and development, ensuring prudent financial management aligned with operational milestones. ProbiOxy's dedication to compliance with regulatory standards, guided by partnerships with regulatory and legal experts underpins our commitment to safety and innovation in the probiotic sector. Through meticulous planning, strategic partnerships, and regulatory compliance, ProbiOxy aim to position itself as a leader in revolutionizing intestinal inflammation treatment with probiotics.

Keywords: Science-Based Entrepreneurship, ProbiOxy, Inflammatory Bowel Disease, Probiotic Treatment, ResistoBacterium, Research and Development, Business Plan, Key Resources, Operations

This work used infrastructure and resources funded by Fundação para a Ciência e a Tecnologia (UID/ECO/00124/2013, UID/ECO/00124/2019 and Social Sciences DataLab, Project 22209), POR Lisboa (LISBOA-01-0145-FEDER-007722 and Social Sciences DataLab, Project 22209) and POR Norte (Social Sciences DataLab, Project 22209).

Table of Contents

Executive Summary

Inflammatory Bowel Disease (IBD) affects ten million people globally, and its prevalence continues to rise. Existing treatments for IBD are not universally effective, leaving a significant number of patients with inadequate relief. This highlights an urgent need for innovative therapeutic approaches.

Our solution, ResistoBacterium, offers a novel approach to the treatment of IBD. It competes for nutrients with Escherichia coli AIEC, a common bacterial pathogen in IBD patients, enhancing colonisation resistance and effectively clearing the infection. ResistoBacterium, belonging to the Klebsiella family, is naturally present in human intestinal tracts, mouth, and nose.

ProbiOxy, our new venture, aims to exploit this market opportunity by introducing ResistoBacterium as our lead asset for treating IBD. Whether used as a complementary or standalone treatment, our goal is to increase the number of patients achieving and maintaining remission, thus reducing the frequency of acute episodes.

Our strategy encompasses several key stages: securing initial funding, licensing intellectual property, progressing through pre-clinical and clinical trials, expanding our patent portfolio, developing our product pipeline, and ultimately exiting via acquisition by an established pharmaceutical company.

ProbiOxy's assets include exclusive intellectual property rights from Calouste Gulbenkian Foundation (CGF) and a growing patent portfolio essential for developing probiotic treatments for IBD and related conditions. Partnering with Contract Research Organizations will enable efficient management of clinical trials, adhering to regulatory standards. ProbiOxy consists of a diverse and highly motivated team of six persons, with background from management, marketing, finance, operations, and science.

To fund clinical trials up to Phase II, we aim to raise approximately €27 million over three years through grants, venture capitalists, and corporate venture funding. This investment is projected to cover our expenses and position ProbiOxy as a compelling investment opportunity, thus increasing company value and reducing acquisition risk.

Our exit strategy involves selling ProbiOxy post-Phase II completion, targeting an estimated transaction value of $3.1 billion. This strategy aims to maximize Return on Investment for investors and founders. The biopharma acquisition market, fuelled by pharma companies' shift towards inorganic growth, presents ample opportunities for a strategic sale. Our target acquirers include firms like AbbVie and Amgen, chosen for their financial strength and strategic alignment. Our robust patent portfolio, offering access to innovative technologies and clinically successful drug candidates, forms the core of our value proposition.

While ProbiOxy will advance drug candidates for IBD through Phase II, the acquiring entity will assume responsibility for Phase III trials and subsequent commercialization upon successful completion and regulatory approval.

In summary, ProbiOxy is positioned to make a significant impact in the IBD treatment landscape, with a clear plan for development, funding, and strategic exit, offering promising solutions to patients and value to investors.

1 Introduction

Ten million people worldwide are suffering from Inflammatory Bowel Disease (IBD), and the global prevalence is rising (Hammer and Langholz 2020; Zhao et al. 2021). The two types of IBD are ulcerative colitis (UC) and Crohn's disease (CD). In these conditions, the immune system mistakenly attacks the gastrointestinal tract, leading to chronic inflammation. The symptoms of IBD can have a significant impact on a person's daily life. Medication can be taken to manage the symptoms and enter remission (Cleveland Clinic 2023). However, a significant portion of patients either do not react positively to existing treatments or experience a loss of response, necessitating the exploration of novel therapeutic strategies (Cai, Wang, and Li 2021).

The research about the probiotic Klebsiella strain ARO112 shows promising results in treating IBD. The bacterium is more efficient in clearing infections, accelerates the recovery of native gut microbiota, and helps prevent further inflammatory episodes (Cabral, Oliveira, and Xavier 2023a). Thus, we are launching ProbiOxy, a new venture created to seize the huge market opportunity for a new treatment for IBD.

Our vision is to develop the first probiotic medicine that effectively helps patients suffering from IBD and makes them experience a transformative shift in their quality of life. We aspire to be at the forefront of a new era in the field of intestinal inflammation, where next-generation probiotics redefine the treatment landscape for IBD and potentially other gastrointestinal disorders through a differentiated product pipeline.

The following report gives an overview of all the necessary components and attributes to put such a venture into practice.

Note: When the term "IBD" is used, it always refers to CD and UC.

2 The Problem

2.1 Inflammatory Bowel Disease

The cases of IBD are increasing worldwide, and understanding the disease relies on studying how the gut's immune system and its bacteria interact. Thanks to new technologies, we now have more data on gut microbes, and recent advances allow us to explore how these bacteria function and interact with the gut's immune system in more complex ways (Aden and Reindl 2019).

The two types of IBD are UC and CD, which cause chronic inflammation in the gut. Crohn's Disease is a chronic inflammatory bowel disease that can affect the entire gastrointestinal tract from the mouth to the anus, while Ulcerative Colitis affects the colon and rectum. The inflammation is closely related to the community of bacteria living in the gut. Generally, people with IBD have fewer types of bacteria and lower levels of certain substances called short-chain fatty acids (SCFAs) compared to those not affected by the disease, suggesting that the gut's microbial community, diet, and genetics play a role in causing anomalous immune responses that lead to IBD. (Ota and Sakuraba 2022)

The gut contains beneficial bacteria that guard against pathogenic invaders. These gut microbes are essential for getting nutrients, maintaining a robust immune system, and preventing harmful bacteria from taking over. Normally, people have a stable and diverse population of gut bacteria, but when they take medications like antibiotics, it damages both the beneficial and harmful microbes, increasing the person's susceptibility to bacterial infections. Thus, antibiotics disrupt the microbial community and weaken one’s defences against diseases. (Cabral 2023; Cabral, Oliveira, and Xavier 2023a)

The prevalence of these diseases is rising, and treatment options are constantly evolving. Medication, nutritional supplements, surgery, or a combination of these are among the therapy

possibilities. Some patients experience long periods of remission, even years where they are symptom-free. However, the symptoms generally recur several times over a person's life, even though some periods can be better.

2.2 Need

The common cyclic pattern in patients with IBD is characterised by episodes of intestinal inflammation, consequently leading to treatments that, in turn, may cause imbalances in the intestinal microbiota, making individuals more susceptible to infections. This imbalance means that pathobionts such as Escherichia coli AIEC (E. coli AIEC) - the most common bacterial pathogen in IBD patients – no longer must compete for nutrients and space, making colonisation much easier. This is most likely to lead to future infection, starting a cycle of gut inflammation that is again treated by antibiotics, which leads to AB-induced dysbiosis, consequently making the gut susceptible to infection again, creating a cycle of disease and treatment. Most patients with IBD are constantly in a disease-treatment cycle, and due to the loss of the gut's natural protection, they also become more susceptible to other negative symptoms, such as arthritis or dermatitis, further affecting their everyday lives. Consistently breaking this inflammation infection cycle represents one of the biggest challenges in the treatment of the disease and is now receiving a lot of attention from the scientific community and international financing. (Cabral 2023; Cabral, Oliveira, and Xavier 2023a)

Research shows that typically, initial therapy elicits a positive response in symptoms or inflammation levels for about 50% to 60% of patients. Among these responders, roughly 20% to 30% enter remission, and within the remission group, only half maintain remission over an extended period (Moss 2023). Moreover, due to high prescription costs, complex dosing regimens, and unpleasant delivery methods, non-adherence rates to treatment reach up to 60% in certain studies (Brown and Wiederrecht 2021).

2.3 Scope

According to the European Federation of Crohn's & Ulcerative Colitis Associations (EFCCA), there are now approximately 10 million people worldwide living with IBD.

Historically, IBD has been seen primarily in developed countries, with Europe and North America having the highest reported prevalence rates. Note that by prevalence it is meant all new and pre-existing cases, while the term incidence refers to the number of new cases. Recently, the incidence of IBD in North America and Europe is said to be stabilising or decreasing; however, the burden remains significant, with a prevalence of more than 0.3%. IBD's influence has increased in newly industrialised countries in Africa, Asia, and South America during the last 30 years. IBD patients appear to be more prevalent in urban than in rural areas, as well as in higher socioeconomic classes. This increase has been attributed to the significant increase in the modernisation and westernisation of the population. (Lawton 2019)

In Europe, the prevalence of CD ranges from 1.5 to 213 cases per 100,000, while those of UC range from 2.4 to 294 per 100,000. Overall, 0.3% of the European population is estimated to have been diagnosed with IBD, corresponding to a total estimation of 2.5–3 million people with a direct healthcare cost of 4.6–5.6 bn Euros/year and substantial indirect costs arising from work productivity or earning losses of approximately €1900 per patient yearly. (Hammer and Langholz 2020)

In the United States approximately 1.6 million people have CD or UC, and around 70,000 new cases of IBD are diagnosed each year with significantly higher costs per patient than in Europe. The annual direct cost of Crohn’s disease is estimated to be from $8,265 per patient to $18,963 per patient and the annual direct cost of ulcerative colitis is estimated to be from $5,066 per patient to $15,020 per patient. Based on this data and the current prevalence estimates of IBD, 780,000 cases of Crohn’s disease and 907,000 cases of ulcerative colitis, the total annual direct

costs for all patients with IBD in the United States falls between $11 billion to $28 billion. Based on a national health survey in 1999, indirect costs were as high as an estimate of $5,228 per patient, suggesting they are still relevant today. (Lawton 2019)

In North America, the prevalence of IBD has reached 0.5% of the population and is projected to affect approximately 4 million people by 2030 (Lawton 2019). Interesting research led by the Canadian Gastro-Intestinal Epidemiology Consortium (CanGIEC) demonstrated an average prevalence of IBD in Canada going from 400 per 100,000 in 2002 to 636 per 100,000 in 2014. The prevalence in 2023 is now estimated at 825 per 100,000, meaning that over 320,000 people in Canada are living with IBD. The prevalence is forecasted to rise even further with a rate of 2.44% per year such that 1.1% of the population, meaning that only in Canada there will be 470,000 people living with IBD by 2035. (Coward et al. 2023)

Moving to the other side of the world. In contrast to the Western regions, the occurrence of IBD is significantly lower in Asia. However, due to the rising incidence the number IBD patients in Asia is growing rapidly and the following data will show results from analysis in those countries. Between 2001 and 2015, the incidence CD and UC in Taiwan saw a rise from 0.6 and 2.1 to 3.9 and 12.8 per 100,000, respectively. In 2014, Hong Kong reported a prevalence of UC and CD at 24.5 and 18.6 per 100,000. In a survey study from Japan much higher prevalence rates were found for both UC and CD. The annual prevalence rates of UC and CD, per 100,000, were 172.9 and 55.6, respectively. Nearly a 10-fold increase compared to a previous survey performed 25 years earlier. (Hammer and Langholz 2020)

2.4 Causes

The origins and progression of IBD are believed to be significantly influenced by a myriad of factors, including genetic predispositions, environmental triggers, and the gut microbiome.

2.4.1 Environmental and Genetic Factors in IBD

IBD is thought to arise from a dysregulation of the gastrointestinal (GI) immune system in individuals who are genetically predisposed and exposed to certain environmental triggers. The "Hygiene Hypothesis" posits that improved sanitary conditions, resulting in reduced exposure to enteric pathogens during childhood, may lead to an inappropriate chronic immunological response upon encountering new antigens later in life. Furthermore, dietary habits, especially the consumption of sugars, sweeteners, and fats, have been implicated in elevating the risk of developing CD. Stress, both chronic and acute, has also been identified as a potential influencer of IBD, with chronic stress potentially exacerbating IBD by promoting damage to the inner lining of the intestinal tract. Additionally, geographic factors, such as the prevalence of IBD being higher in developed nations and increasing in developing countries as they industrialise, indicate a potential correlation between industrialisation and IBD incidence. The intricate interplay between genetic susceptibility and various environmental factors underscores the multifaceted aetiology of IBD (Kaplan, Molodecky, and Panaccione 2010).

2.4.2 The Role of the Gut Microbiome in IBD Pathogenesis

Delving deeper into the pathogenesis of IBD, the gut microbiome emerges as a pivotal factor, providing a new perspective on potential causes and contributors to the disease. Dysbiosis, characterised by an imbalance in the composition and function of microbial communities in the gut, is prominently observed in IBD. This phenomenon manifests as a reduction in microbial diversity, a decrease in beneficial bacteria, and an increase in potentially pathogenic bacteria. The relationship between dysbiosis and inflammation in IBD is complex and multifaceted, with microbial imbalances potentially acting as both a cause and a consequence of the intestinal inflammation observed in IBD. Furthermore, certain genetic mutations have been associated with modifications in the immune system, influencing the composition of the intestinal

microbiota and increasing vulnerability to intestinal pathogens (Aden and Reindl 2019).

2.5 Diagnosis

To identify IBD, it is necessary to assess the clinical symptoms associated with the condition. These symptoms include paediatric growth disorders, anaemia, abdominal pain, bloody diarrhoea, and arthritis. However, for a more accurate diagnosis of Crohn's disease and ulcerative colitis, a blend of lab tests and procedures is needed. The test and procedures focus on identifying clinical symptoms and pathogenic bacteria. The typical pathogenic bacteria responsible for IBD include Salmonella, Shigella, Yersinia, Campylobacter, Aeromonas, Clostridium difficile, E. coli, and tuberculosis. (Seyedian, Nokhostin, and Malamir 2019).

Lab tests include stool studies where the stool sample is tested on blood or organisms and tests for anaemia or infection. In endoscopic procedures, either the entire colon, parts of it, the stomach, small intestine, or other parts are examined with a tube. During a colonoscopy – the procedure where the entire colon is examined – a small sample of tissue may be taken to perform a biopsy to diagnose IBD and outline it from other infections. In addition, imaging procedures such as an X-ray of the abdominal area in case of severe symptoms, computerised tomography scans, or magnetic resonance imaging, may be performed (‘Inflammatory Bowel Disease (IBD) - Diagnosis and Treatment’, n.d.).

Recent research into the gut microbiome has opened new possibilities for diagnosing IBD in a non-invasive manner, potentially offering more accurate diagnoses and personalised treatment plans. A study from 2017 shed light on the dynamic changes within the gut microbiome in IBD patients, revealing distinct differences when compared to healthy individuals. The study, which analysed the gut microbiome from faecal samples over two years, found specific patterns that separated healthy individuals from those with various types of IBD. A new method, termed the 'healthy plane', was developed to track and compare microbiome variations in IBD patients,

showing the potential to diagnose the disease with even greater accuracy than some current methods (Halfvarson et al. 2017).

In another study, researchers examined the faecal microbiomes of IBD patients, focusing on distinguishing between UC and CD. The study found that CD was associated with a more unstable and altered gut microbiota compared to ulcerative colitis. An algorithm was developed capable of distinguishing between CD and other conditions, offering a new, non-invasive diagnostic tool (Pascal et al. 2017).

2.6 Treatment

As of now, there is no cure for IBD, but there are various treatments available (Crohn's & Colitis Foundation 2023). The primary objective in treating IBD is to diminish the inflammation responsible for causing symptoms. Ideally, it results in not only symptom alleviation but also the achievement of sustained remission and a decreased risk of complications. ('Inflammatory Bowel Disease (IBD) - Diagnosis and Treatment', n.d.) Remission means that patients no longer experience symptoms or the symptoms improve considerably and are no longer recurrent (Crohn's & Colitis Foundation 2023). Doctors first direct treatment to induce a remission that involves relief of symptoms and mucosal healing and then provide long-term treatment for the maintenance of the remission. Additionally, the previous response to medical treatment is crucial when treating recurrent symptoms (Gade et al., 2020).

The treatment of IBD varies depending on the particular type and the symptoms and the therapeutic need can change as time passes (Cleveland Clinic 2023; Crohn's & Colitis Foundation 2023). Traditional treatment approaches primarily focus on managing symptoms using pharmaceutical products as medication to provide symptom-free daily life to patients (Cai, Wang, and Li 2021). In case of medication no longer provides relief of symptoms, surgery may be necessary (Cleveland Clinic 2023). Nonetheless, a significant proportion of patients

exhibit either an initial lack of responsiveness or a decline in the efficacy of existing treatments, compelling the exploration of innovative therapeutic approaches (Cai, Wang, and Li 2021).

2.6.1 Pharmacotherapy

Prescription medications are the core of IBD treatments which may be combined with over-the-counter medications (Crohn's & Colitis Foundation 2023). The routes of administration include oral medication, topical medication, injections, and infusions (Walsh and Conmy n.d.). The objective of medical treatment is to initiate a state of remission using medications and subsequently continue with maintenance medications to prevent flare-ups of the disease. The conventional pharmaceutical products include the following five agents: aminosalicylates (5-ASAs), corticosteroids, immunomodulators, antibody agents, and antibiotics. (Gade, Douthit, and Townsley 2020)

Doctors often adopt a progressive approach to medication therapy, beginning with milder drugs and progressing to more potent options if the initial attempts fail to provide adequate relief (Seyedian, Nokhostin, and Malamir 2019). Gade, Douhit, and Townsley (2020) provide an overview of a rather complex system of treatment options according to the severity of Crohn's disease. For the management of mild to moderate symptoms of Crohn's disease Budesonide (a corticosteroid) and Sulfasalazine (a 5-ASAs) are used as the first approach for treatment. Depending on the success of achieving remission or not, the treatment with the same agent continues, antibiotics are added, or the treatment is switched to the treatment for moderate to severe CD. The treatment for moderate to severe CD includes systemic corticosteroids, immunosuppressants, and Anti-TNF agents. In case of no remission, surgery or biological agents are used next. Additionally, the previous response to medical treatment is crucial when treating recurrent symptoms (Gade, Douthit, and Townsley 2020).

According to Cabral (2023), the two most common types of medication are antibiotics

(antibacterials) and anti-inflammatory drugs. Aminosalicylates often serve as the initial treatment choice for addressing IBD (‘Inflammatory Bowel Disease Treatment Market Report 2030’ 2021). Examples are Humira, Asacol, and Prednisone (Grabos 2023). Antibiotics, on the other hand, manage bacterial infections by either eliminating or inhibiting the growth of bacteria. They achieve it by attacking the wall or coating surrounding bacteria, impeding the reproductive processes of bacteria, or halting the synthesis of proteins within bacteria. However, there is the risk of antibiotic resistance. (Healthline Medical Network 2023) Examples of antibiotics used to treat IBD are Ciprofloxacin, Metronidazole, or Rifaximin (Grabos 2023).

2.6.2 Surgery

If medication provides no longer relief of the symptoms in severe and/or sudden cases, patients with IBD may consider surgery (Gade, Douthit, and Townsley 2020). The surgery varies depending on the type.

70% of patients suffering from CD eventually need surgery. In a bowel resection, the diseased bowel sections are removed, and the two healthy ends are reconnected. After surgery, the remaining section of the intestine adjusts and operates in the same manner to its preoperative function. However, up to 60% of the patients getting a bowel section will have a recurrence within a decade and need a second bowel resection. (Cleveland Clinic 2023) Medication after the surgery can minimize the risk of a recurrence (‘Inflammatory Bowel Disease (IBD) - Diagnosis and Treatment’, n.d.).

On the other hand, 30% of the patients suffering from UC need surgery after living 30+ years with the condition. In the surgery either the colon (colectomy) or both the colon and the rectum (proctocolectomy) is removed, connecting the small intestine with the anus (Cleveland Clinic 2023).

2.6.3 Emerging Treatments

Novel therapeutic strategies include faecal microbiota transplantation, probiotics, and microbial metabolite inhibitors, among others (Higashiyama and Hokari 2023). Luo et al. (2022) state that while numerous innovative drugs, biological agents, and treatments have received approval for the treatment of IBD in the last decade, and ongoing efforts are dedicated to developing new therapies, the complex nature of IBD's pathology imposes significant limitations on the effectiveness of most of these approaches.

2.7 Patient Journey

Thanks to relevant knowledge provided by the Canadian Society of Intestinal Search (GI Society) and precious real-life insights provided by various interviews to individuals affected by IBD and interactions with specialized doctors; the long and full of ups and downs general patient journey can now be introduced.

Being a chronic disease, IBD represents a frightening diagnosis that is frequently difficult to treat and can be frustrating in terms of both symptoms and overall quality of life. Furthermore, as evidenced by various online sources and most importantly highlighted by the affected individuals we interviewed; the nature of the intestinal symptoms of IBD add a level of embarrassment to individuals affected making it particularly difficult to live with, discuss, and manage. The process from beginning to diagnosis to therapy for IBD, like that of many other inflammatory disorders, can be extensive, involving numerous appointments, analyses, misdiagnoses, and frustration. (GIS 2023)

The journey of a person with IBD often starts with symptoms. For some individuals, the symptoms are mild and may either stay the same or worsen gradually over time. However, for others, the symptoms may occur suddenly and become severe, causing extreme abdominal pain and up to twenty bowel movements per day. Diarrhoea, abdominal discomfort, bowel

urgency/incontinence, loss of appetite, weight loss, fever, exhaustion, and rectal bleeding are the most prevalent symptoms. Some people report nausea, vomiting, and constipation. In severe cases of Crohn's Disease also, ulcers, abscesses, and/or fistulas in the rectum and anus may occur, which can be extremely painful and frightening. Moreover, as highlighted by interviews, symptoms often extend outside of the digestive tract through episodes such as rashes, arthritis, anaemia, kidney stones, and eye inflammation, further impacting patients' quality of life. (GIS 2023)

Many individuals, especially those with mild symptoms, may delay seeking medical help due to various reasons such as attributing symptoms to dietary changes or stress. Some with more severe symptoms might postpone seeing a doctor, possibly out of embarrassment, until the situation becomes critical. However, regardless of the reason, visiting a doctor is a necessary next step in the process and the sooner it happens usually the better. (GIS 2023)

In some countries accessing medical care can be challenging, especially for people without a family doctor or with very long waiting times ahead. Occasionally these delays, especially in cases of more severe symptoms, lead the patients to emergency departments. Another relevant issue is that people encounter difficulties having their symptoms taken seriously by doctors, who may initially suggest lifestyle changes and dietary adjustments. This can result in setbacks for patients before convincing their doctor to investigate further or seek a more receptive healthcare provider. (GIS 2023)

Once the right physician or gastroenterologist is found, a thorough analysis of symptoms, medical history, and family history is conducted. Individuals with a first-degree relative diagnosed with IBD are more inclined to be affected. In case IBD, or another source of the symptoms, is suspected, the next step will be more accurate testing. If doctors strongly suspect you have IBD they usually prescribe medications such as a corticosteroid or 5-aminosalicylic

acid compounds (5-ASA), hoping these treatments will reduce symptoms. However, in case of misdiagnosis with a different disease, symptoms might worsen by taking the wrong medication. (GIS 2023) Both doctors and patients we interviewed stressed the paramount importance to have proper testing as soon as possible to ensure a correct diagnosis, to have the most suitable treatment plan.

Due to many conditions causing similar symptoms, it often takes a while for doctors to diagnose IBD. Testing usually starts with an examination in the doctor's office which might then order general blood tests to check for anaemia, infection, and the level of C-reactive protein, which is higher in case of inflammation in the body. Often, they also test for Celiac Disease. To continue, the analysis becomes more invasive and unpleasant for the patients as the most important tool in diagnosing IBD is endoscopy. It involves inserting a scope with a camera attached to it into your digestive system to look for any visible signs of inflammation or ulcerations. Depending on digestive tract affected location, it can be a gastroscopy, entering from the mouth, or a colonoscopy, entering via the anus; during an endoscopy, the doctors can even take a sample for microscopic testing. If inflammation is found, it probably highlights IBD; however, the testing and diagnosis will continue to establish if it is Crohn's disease, ulcerative colitis, or another type, as well as its location and severity, together with any related extra-intestinal manifestations. (GIS 2023)

Depending on the IBD type, its location and severity, which symptoms affect the individual, whether there are any complications, the age, and other factors; the proper treatment plan will be formulated. Medications focus on two main categories: medications to reduce the underlying inflammation responsible for your IBD and medications to help control the individual symptoms. (GIS 2023)

As evidenced in the above-mentioned treatment section; the main anti-inflammatory treatments

consist of 5-aminosalicylic acid compounds (5-ASA), corticosteroids, immunomodulators, and biologics. To support mucosal healing, bring patients into remission and help prevent future flare-ups, anti-inflammatory drugs will need to be taken even when feeling well. However, not all these medications have the same effect in each person, and sometimes a drug can work well for years and then lose its effectiveness (GIS 2023). More drug development research is needed to find more efficient longer-term solutions.

Symptomatic medications can include things such as analgesics for pain, anti-diarrheal medications, laxatives in case of constipation, iron supplements in case of anaemia, oral nutritional supplements in case of unbalanced diet, and antibiotics to treat infections. This list could be even longer, as there are many different potential symptoms and complications, along with potential side effects from other medications, for which treatment might be needed. Some individuals might find a successful medication to control IBD quickly and easily; on the other hand, others might need to try many medications or combinations of medications before finding a treatment that enables remission. (GIS 2023) An upsetting aspect for IBD patients, also highlighted by doctors we interviewed, is that continuous monitoring to ensure the treatment plan's success will always be needed, involving frequent testing and eventual adjustments to medications.

In addition to medication, changes in diets or exercise routines are often recommended, and that is why a registered dietitian is also most often part of the ‘healthcare team’ of an IBD patient. When in remission, it is very important to stick to a healthy diet with plenty of nutrient-dense foods, fibre, protein, and healthy fats. But during a flare, switching to a very simplistic diet low in fibre and fats, or even a fully liquid diet, to let the bowel rest is key. (GIS 2023) Expert support is key for an efficient consideration of the different factors that play a role.

Unfortunately, even if a lot of people do not want to consider it, surgery remains often necessary

over the patient's lifetime. In this case the options can range from procedures to fix fistulas and fissures or drain abscesses to more complex surgeries such as bowel resection or stricturoplasty for CD, or different kinds of proctocolectomy for UC. (GIS 2023)

All the medications, surgeries, and other treatment methods we have nowadays are working toward remission of IBD. Patients might think to be in remission if symptoms are gone and feel well, however, IBD is a chronic disease, and they never are fully in the clear. It is therefore very important but at the same time challenging to always take the prescribed medications even when feeling great and continuously visit the expert practitioners to prevent and control any symptoms and complications from getting worse. The life of an IBD patient can be happy and thriving however, as it is now, will need constant medication and support and controls from a team of doctors ranging from a physician, gastroenterologist, dietitian, psychologist, and others.

2.8 Patient Persona

In the series of interviews with IBD patients we had the luck to speak with a very collaborative 56-year-old Italian CD Patient which provided us not only with very useful insights but also with her Day Hospital document. By Day Hospital it is meant a specific track record of every relevant step of the patient journey since the first symptoms or discovery of the disease. In the following Table 1, the most relevant and crucial moments of her patient journey are summarized. However, it is important to note that, it is even more complex and specific.

After several allergic reactions, and other complications such appendectomy, tonsillectomy and the diagnosis of Osteoporosis, the patient has been diagnosed with CD in 2011. After 5 years of flare-ups and different medications attempts, she underwent surgery in 2016. We see how even 2-3 years after the surgery unfortunately, negative side effects due to flare-ups and further hospitalization still occur. Since 2019 the situation has improved thanks to therapy with Infliximab and Ferinjet injections for iron deficiencies. However, in the interview the patient

highlighted how still the disease has influence in her everyday life through minor symptoms such as a more common diarrhea or abdominal pain compared to other people. Even if not officially in the Day Hospital yet the patient also mentioned taking Probiotics and Sodium-Butyrate supplementation to control the gut microbiota and maintain the low disease activity. And they are prescribed by a doctor after microbiota testing taken when needed to understand the specific deficiencies and suggest the right probiotics, showing how the market is already moving towards a more structured approach to the treatment of the disease.

The goal of including this Day Hospital in our work is to highlight the complexity of the IBD Patient Journey and how it goes beyond just gastrointestinal disorders, significantly impacting individuals' quality of life. It is key for specialized doctors to understand the specific patient conditions through appropriate testing to find the right cure.

Day Hospital - 56yo Chron Patient Patient Relevant Info: Allergy to Plasil and Aulin - previous appendectomy, tonsillectomy, adeinodectomy – Osteoporosis.	
2011	Chron Disease Diagnosis (Ileum-Colon) and oligo arthritis to be treated with steroid cycles over the years
2016	Surgery - 8cm Ileum resection
2016 - 2018	Therapies with Pentasa, Steroid and cycles of metronidazole and probiotics
01/2018	Regular anastomosis, erosions and ulcerations in the colon and rectum
08/2018	Arthralgia and ankle swelling with related treatment
09/2019	Hospitalization for exacerbation
09/2019	Post hospitalization started therapy with Infliximab, and Ferinject infusions for concomitant iron deficiency anemia. Significant clinical improvement and regression extra-intestinal inflammations

10/2020	Colonoscopy - Healing of previously highlighted ulcers
09/2022	Appearance of erythema after sun exposure - cured through Ferinject injection
Current Treatment Regime	Ferinject injection once a month - Adalimumab every 14 days - Folina 5 mg pd 10 days pm - Niferex 1cp 15 days pm - Flagyl 250 mg 2 pills per day in case of diarrhea - Zirtec in case of itching - Adequate saline dilation and supplementation

Table 1: Day Hospital.
Source: Own table

3 The Solution – ResistoBacterium

Conventional treatments focus on managing symptoms using pharmacotherapy. Nevertheless, a significant portion of patients either fails to respond to existing treatments or experiences a loss of response, prompting the exploration of novel therapeutic strategies (Cai, Wang, and Li 2021).

As described in chapter 2.2, the cyclical infection-inflammation cycle and traditional treatments such as antibiotics lead to imbalances in the microbiota bacterial diversity, causing pathobionts such as Escherichia coli (E.coli) AIEC no longer have to compete for nutrients and space, making colonization much easier (Cabral, Oliveira, and Xavier 2023a). On top of this, research highlighted the relevant issue that traditional probiotics may in some cases end up taking the space that could be used by bacteria to compete with E.coli AIEC, actually giving an advantage to the pathogen (Pickard et al. 2017).

The two experienced scientists Dr. Vitor Cabral and Dr. Rita Oliveira from the Gulbenkian Science Institute in Oerias, Portugal, have discovered a bacteria native to our gut's microbiome that directly competes with E.coli AIEC for nutrients, increasing the colonisation resistance against E.coli AIEC and therefore being more effective in clearing the infection. The bacterium is a part of the Klebsiella family and is naturally found in human intestinal tracts, mouth, and

nose. This strain of bacteria represents our company's main asset aimed at treating IBD patients and will be referred to and registered as the **ResistoBacterium.**

The research showed that ResistoBacterium provided colonisation resistance in the mice model after an antibiotic-induced dysbiosis and has also proven to be effective independent of colonisation order (Cabral, Oliveira, and Xavier 2023a), meaning it works both to treat E.Coli already present in the body but also prevents new ones from colonising.

From the first animal model testing on mice, three main competitive advantages against existing probiotics have been highlighted.

1. ResistoBacterium is more efficient in clearing infections compared to existing probiotics. As represented in the graph below, our probiotic treatment has been successful at clearing the infection (AIEC) from most subjects within 20 days. Only half of the subjects clear the infection with no treatment at all, while treatment with other probiotic bacteria led to prolonged infection. The crucial benefit of ResistoBacterium is that it cleared itself completely from most subjects within those 20 days allowing for a faster recovery of the native gut microbiota and subsequent natural protection, on the other hand, the other probiotic remains in the subjects taking space to other beneficial bacteria and not allowing for the recovery of the gut microbiota consequently leading to further infection. (Cabral, Oliveira, and Xavier 2023b)

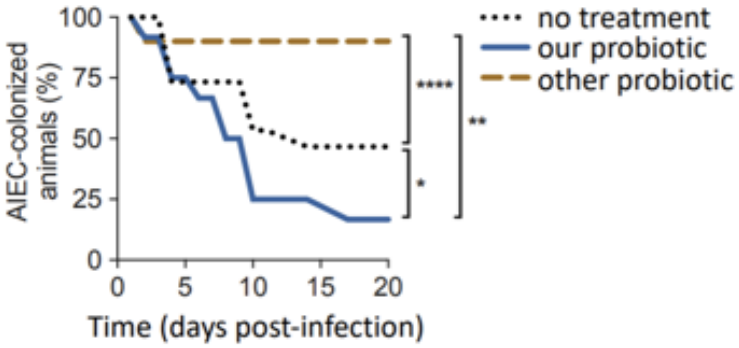

Figure 1: Efficiency of ResistoBacterium.
Source: (Cabral, Oliveira, and Xavier 2023b)

2. ResistoBacterium accelerates the recovery of native gut microbiota after imbalances caused by antibiotics. As shown in the graph below, our probiotic promotes faster recovery of the native gut microbiota, as it increases the number of butyrate producing bacteria slightly more than with no treatment approach but significantly more than other probiotics which does not affect this aspect. The significantly higher butyrate concentration in the feces of subjects who took ResistoBacterium support this fact. Butyrate levels are important for gut health as they represent the main source of energy for colonocytes and help prevent gut inflammation. Conversely, traditional probiotics prevent the recovery of microbiota and butyrate producing bacteria, leading to long-lasting depletion of intestinal butyrate levels. (Cabral, Oliveira, and Xavier 2023b)

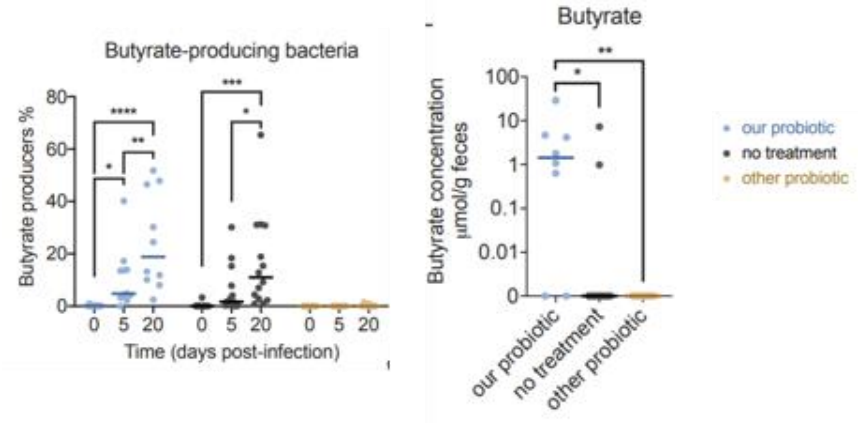

Figure 2: Increased butyrate with ResistoBacterium.
Source: (Cabral, Oliveira, and Xavier 2023b)

3. ResistoBacterium helps in preventing further inflammatory episodes thanks to the recovery of the native gut microbiota. As we see on the graph below the efficiency in preventing further inflammatory episodes up until 20 days post-infection is brilliant, especially compared to no treatment or other probiotic scenarios. The lack of treatment or the other probiotics leads to a transient or long-lasting inflammation increase leading to further of anti-inflammatory or antibiotic treatment. (Cabral, Oliveira, and Xavier 2023b)

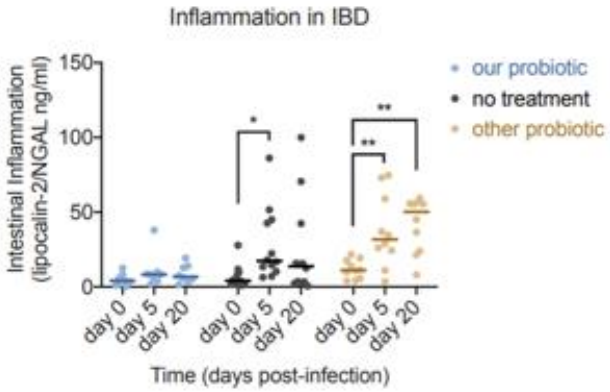

Figure 3: Efficiency of ResistoBacterium in preventing further inflammation episodes. Source: (Cabral, Oliveira, and Xavier 2023b)

ResistoBacterium is the main asset of our newly created venture: ProbiOxy. The venture will be introduced at a later stage.

4 The Market for Medical Treatment for IBD

4.1 Market Size

In 2021, the size of the worldwide market for drugs to treat inflammatory bowel disease reached $21 billion, and it is estimated to reach $34.5 billion by 2031, exhibiting a compound annual growth rate (CAGR) of 5.1% from 2022 to 2031 (‘Inflammatory Bowel Disease Drugs Market Report By 2031’, n.d.). The Medical Probiotics Market[1] is anticipated to achieve a value of approximately $6.54 billion by 2030, up from $3.84 billion in 2023, reflecting a compound annual growth rate (CAGR) of 7.9%. North America (38%) has again the biggest market share in 2023, followed by Asia Pacific (28.7%) and Europe (20%). (‘Medical Probiotics Market Size & Share Analysis - Industry Research Report - Growth Trends’ 2023) The estimated worth of the worldwide next-generation probiotics market in 2022 is approximately $168.1 million, and it is projected to demonstrate a compound annual growth rate (CAGR) of 11.2% to US$ 393.9

[1] The Medical Probiotics Market consists of probiotic ingredients, supplements, and foods specifically designed for therapeutic purposes, aimed at preventing and treating a wide range of medical conditions and diseases. (‘Medical Probiotics Market Size & Share Analysis - Industry Research Report - Growth Trends’ 2023)

million by 2030. North America is, with a market share of 37.8%, the market leader in terms of market share in 2022. (‘Next Generation Probiotics Market Size and Forecast to 2030’, n.d.)

4.2 Market Trends

Looking at articles, market reports, and other sources, we have concluded the following market trends to be important for our venture:

- Rise in global prevalence of IBD (Zhao et al. 2021).
- Increased understanding of the human gut microbiota and its role in health and diseases: increased interest in using next-generation probiotics (NGP) as a new approach towards prevention & treatment of diseases (‘Next Generation Probiotics Market Size and Forecast to 2030’, n.d.)
- Novel therapeutic strategies like faecal microbiota transplantation, probiotics, and microbial metabolite inhibitors (Higashiyama and Hokari 2023).
- Increasing adoption of biologics (‘Inflammatory Bowel Disease Treatment Market Report 2030’ 2021).
- The proliferation of prebiotics, postbiotics, and other supplements like vitamins, minerals, and omega-3 has intensified competition in the gut health market (‘Medical Probiotics Market Size & Share Analysis - Industry Research Report - Growth Trends’ 2023).
- Favourable regulatory framework: The Food and Drug Administration accepted the first probiotic as a medicine; VOWST (‘Our Products’, n.d.).
- Government funding and support for R&D related to the microbiome’s role in health also enables new innovations (Cabral 2023).
- R&D efforts and success of key players, for example Pfizer’s etrasimod (Pfizer 2022)

or approval of AbbVie's RINVOQ for the treatment of moderately to severely active CD by the European Commission (AbbVie 2023).

4.3 Competitive Landscape

The competitive landscape of medical treatment for IBD is characterised by a dynamic interplay between a few large, established pharmaceutical companies and a growing number of emerging players. These companies are constantly vying for market share by developing innovative therapies, expanding their product portfolios, and strengthening their presence in key markets.

At the forefront of the IBD treatment market stand AbbVie Inc., Johnson & Johnson, Takeda Pharmaceutical Company Limited, Pfizer Inc., Bristol Myers Squibb, Celgene Corporation, Merck & Co., Inc., AstraZeneca plc, Novartis AG, and UCB (IBD Treatment Market Report 2021). These companies have established themselves as industry leaders through their extensive research and development efforts, resulting in a wide range of effective therapies, including biologics, small-molecule drugs, and corticosteroids. Their dominance is further solidified by their strong brand recognition and established distribution networks.

However, the IBD treatment landscape is not without its disruptors. A wave of emerging companies is challenging the status quo by introducing novel therapeutic approaches that target different aspects of the disease and offer enhanced efficacy and reduced side effects compared to traditional treatments. Arena Pharmaceuticals, Galapagos NV, Sun Pharmaceutical Industries Ltd., Entyvio, and Salix Pharmaceuticals are among the notable players driving innovation in this space (IBD Treatment Market Report, 2021).

The increasing focus on biologics is a defining trend in the IBD treatment market. These protein-based therapies, derived from living organisms, have revolutionised IBD management due to their superior efficacy and reduced side effects compared to traditional corticosteroids. The success of biologics has propelled their adoption as the standard of care for IBD treatment

(IBD Treatment Market Report, 2021).

Alongside biologics, novel therapies are emerging, targeting specific molecular pathways and cellular processes involved in IBD pathogenesis. These therapies hold promise for more personalised and effective treatment strategies.

The competitive landscape is also being influenced by the increasing availability of generic IBD treatments. These generic versions of existing brand-name drugs offer similar efficacy at lower costs, putting downward pressure on prices and challenging the dominance of brand-name drug companies. This trend is particularly evident in the biologics segment, where generic versions of infliximab and adalimumab have gained significant market (‘IBD Treatment Market Report’ 2021).

The rising cost of IBD treatment is another pressing concern. The increasing use of biologics, coupled with the development of novel therapies, has driven up the overall cost of IBD management. This trend poses a significant challenge for patients, healthcare providers, and insurance companies, as it strains healthcare budgets and potentially limits access to treatment for some individuals (IBD Treatment Market Report, 2021).

In conclusion, the competitive landscape of medical treatment for IBD is characterized by a dynamic interplay between established players and emerging disruptors. The increasing focus on biologics, the development of novel therapies, the rise of generics, and the escalating cost of treatment are key trends shaping the market. Companies that can successfully navigate these challenges and deliver innovative, cost-effective, and patient-centric therapies will be well-positioned for long-term success in this evolving market.

4.4 Benchmarking

As stated above, some patients fail to enter remission or fail to sustain remission with the existing treatment options. Emerging therapies and drugs are interesting for us to analyse as

they might be able to provide an efficient solution in the future and thus might be our competitors. In the following, we present a few selected development-stage companies focused on the treatment of IBD.

1. **Microba – MAP315:** MAP 315 is an experimental live bacteria therapy consisting of bacteria that have been freeze-dried and encapsulated in a protective coating. This oral capsule is being studied as a potential treatment for ulcerative colitis. MAP 315 encourages the regeneration of the intestinal lining and the healing of the mucosal layers, which are crucial for long-lasting disease remission but not adequately addressed by current treatments. MAP315 has just started clinical trial 1 in June 2023. (Microba 2023)

2. **Telavant – RVT-3101:** Telavant's RVT-3101 is a unique antibody therapy that directly targets the TL1A protein, a key player in inflammatory processes. Telavant develops the solution to be the first-in-class subcutaneous therapy in UC and CD. RVT-3101 is in the Phase III of clinical trials for UC and in Phase II for CD. (Telavant 2023)

3. **Sanofi and Teva Pharmaceuticals – TEV'574:** TEV'574 is an Anti-TL1A which is classified as a novel biologic and is currently in Phase II of clinical trials for UC and CD. Teva Pharmaceuticals is an established company and an extensive innovative medicine and biosimilar pipeline. (Teva Pharmaceutivals 2023)

4. **Sitryx – SIT-033:** Sitryx regulates the cell metabolism to develop disease-modifying therapeutics. By intervening in cellular metabolism, it is possible to effectively address inflammation, reverse tissue damage, and ultimately improve patient outcomes. SIT-033, the program for IBD, is in the Lead Optimization phase, shortly before pre-clinical trials. (Sytrix 2023)

5. **Mozart Therapeutics – MTX-101:** Mozart Therapeutics is developing a pipeline of

> CD8 Treg modulators that are meant to restore durable immune balance. The lead program focuses on autoimmune mediated gastro-intestinal diseases and is the in pre-clinical stage. Mozart Therapeutics' innovative bispecific CD8 Treg modulator selectively interacts with inhibitory KIRs and regulatory CD8 T cell markers. (Mozart Therapeutics 2023)

As can be concluded from the descriptions above, the different companies use different approaches for the development of treatment for IBD, or gastro-intestinal diseases in general in the case of Mozart Therapeutics. What they all do, is to try to get an efficient solution for the treatment of IBD, respectively gastro-intestinal diseases. Microba positions itself clearly against current treatments: MAP315 "encourages the regeneration of the intestinal lining and the healing of the mucosal layers, which are crucial for long-lasting disease remission but not adequately addressed by current treatments." (Microba 2023)

In addition, they are in different stages of development. While most are also still in drug discovery and pre-clinical trials like us (ProbiOxy;), Telavant's RVT-3101 for UC is already in Phase III of clinical trials. The following illustration provides an overview. On the left side are the companies listed that develop the treatment solution. In the other columns, the name of the treatment solution with the specific development stage is shown.

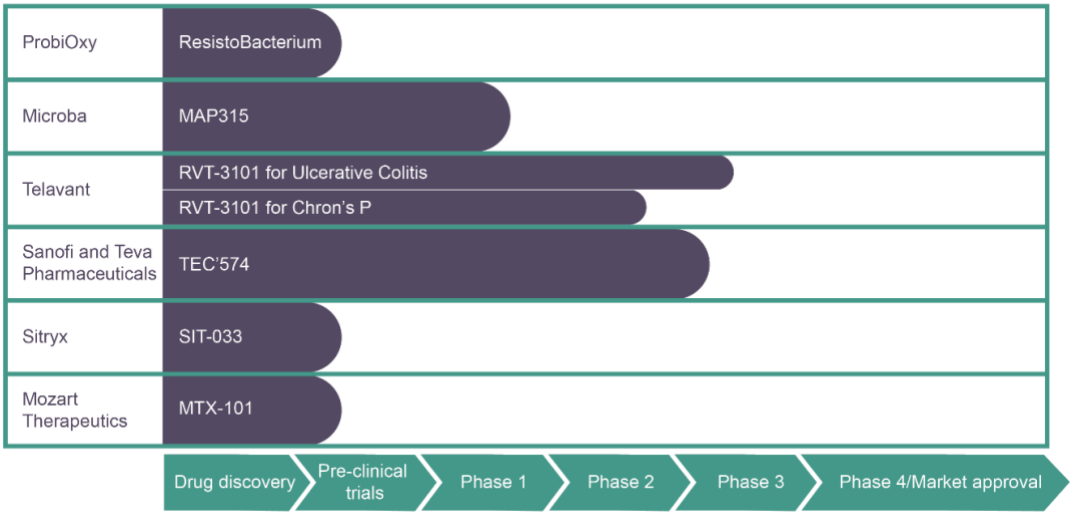

Figure 4: Overview of the development stages of emerging treatments for IBD
Source: Own illustration.

It is difficult to assess the strengths and weaknesses of the competitors as well as the competitive situation we will face at the start of the commercialisation since the competitive forces are likely to change. Some technologies will not make it through the (pre-)clinical trials while on the other hand, new efficient technologies may emerge.

When talking about benchmarking it is also worth talking about Seres Therapeutics' VOWST. The drug is already approved for the prevention of Clostridioides difficile infection after antibiotic treatment has been completed. It is not yet approved for the treatment of IBD. However, we can learn a lot from it as it is the first probiotic approved as a medicine by the FDA.

4.5 Where ResistoBacterium Fits into the Market

The market research, including the analysis of the competitive landscape, the benchmarking, as well as the existing treatment options, reveals the market gap: Conventional treatments focus on managing symptoms using pharmacotherapy. However, a significant portion of patients either fail to respond to existing treatments or experience a loss of response. Novel therapeutic strategies based on different approaches are being developed to get an efficient solution for the

treatment of IBD. As far as our knowledge, none of them is based on probiotics.

We are confident the added value of our asset will have significant benefits for IBD patients placing our ResistoBacterium among the “new conventional” treatments for IBD. The asset could potentially have even better effects in combination with other treatments. We will not necessarily substitute other treatments that have to be taken in acute disease situations, as our product is not scientifically fit for it, but we will enrich the landscape of possible treatments for IBD in the remission and maintenance phases. Thus, we position ResistoBacterium in the following way:

- **Probiotic Complementary Drug:**
    - Enhances the efficiency of existing IBD treatments.
- **Probiotic Stand-Alone Drug:**
    - Offers a standalone solution for patients with diverse disease and treatment journeys.

This widens our target group as patients with different disease journeys and treatment journeys can benefit from our solution. Our therapy is designed to rebalance the gut microbiota, reduce inflammation, and provide long-lasting relief to patients suffering from IBD and potentially many other forms of intestinal inflammation. Thus, **we provide a way to enter and maintain remission that supports a balanced microbiota, hence breaking the inflammation infection cycle.** ResistoBacterium decreases the flare-ups, increases the healthy periods of the gut, and breaks the inflammation-infection cycle thus significantly improving patients’ quality of life. Our goal is to have a significant impact and increase the number of people who enter and maintain remission, therefore significantly decreasing the number of people experiencing acute episodes of the disease.

The microbiota dysbiosis can change from individual to individual and can be affected by various factors; once the efficacy of our probiotic is proven and the final treatment approved, it will be the doctors and pharmacists that must analyse the patient's situation through different tests, such as the Microbiota testing, and eventually prescribe our treatment, being it complementary to another one or as a stand-alone treatment, or eventually another. Treatment differs a lot from patient to patient and needs a tailored approach. The following possible usages have been identified:

- **Low Disease Activity:**
    - ResistoBacterium is used in periods of low disease activity with minimal symptoms, to maintain low activity.

- **Remission Maintenance:**
    - ResistoBacterium is used in periods of remission, to maintain remission.
- **Acute Inflammation Support:**
    - As a complementary drug, ResistoBacterium aids in supporting remission during acute inflammation episodes.

ProbiOxy therefore positions its ResistoBacterium both as a complementary drug to existing treatments, potentially improving overall treatment effectiveness; but also, as a stand-alone drug with proven superior benefits compared to existing and emerging competitors.

Our probiotic will lower the incidence of flare-ups of both CD and UC globally, improving the patient’s quality of life and reducing society and healthcare costs associated with the disease, such as costs caused by absenteeism and hospitalization.

4.6 Demand Estimate

In anticipation of ProbiOxy's future entry into the treatment market (commercialisation), it is crucial to project the potential demand across different regions. By estimating the expected demand, we aim to offer a comprehensive understanding of the potential consumer base in various regions to provide future stakeholders with a clear perspective on the opportunities that lie ahead.

However, calculating the anticipated demand for ProbiOxy presents a unique challenge due to several factors inherent in the biopharmaceutical industry. Notably, ProbiOxy is poised to commence production and sales post the completion of extensive clinical trials, a timeline that spans several years into the future. While we acknowledge the escalating global prevalence of IBD and positive shifts in the regulatory framework, as discussed earlier, the market landscape is dynamic and subject to significant alterations. Moreover, the competitive arena is susceptible to profound transformations, with the emergence of new players and treatments potentially reshaping the entire landscape.

As the distribution channels will be determined by the acquiring entity, this estimation serves as a tool to illustrate the anticipated demand in distinct regions (Europe, North America, and Asia). For simplicity, we will focus on the US, Canada, Europe, and China since these show the opportunity in each region.

To calculate the estimated demand for ProbiOxy, it is imperative to delineate the addressable markets for each region. After researching from various sources, we compiled data reflecting the estimated number of IBD cases in each region. It is worth noting that due to variations in data availability, the estimates encompass different years, with China, for instance, providing projections for 2025, as it can be seen in Table 2.

USA	Canada	China	Europe
2020	2023	2025	2020
2 390 000	320 000	1 500 000	2 500 000

Table 2: Number of IBD cases per region.
Source: Own illustration based (D. Lewis et al. 2023) for American data; Coward et al. 2023 for Canadian data; He et al. 2023 for Chinese data; Hammer and Langholz 2023 for European data

To homogenize the data for projection purposes, we adopted a Compound Annual Growth Rate (CAGR) of 6.1% according to , calculated between 2022 and 2030. To simplify the estimation process, we assume this growth rate is applicable uniformly from 2020 to 2037. With this approach, we were able to align the diverse datasets to establish a cohesive foundation for projecting the demand for ProbiOxy, which we anticipate will enter the market in 2032, after concluding phase III clinical trials.

	USA	Canada	China	Europe
2032	4 836 876	545 241	2 270 382	5 087 737

Table 3: Total estimated addressable market per region (number of patients), 2032
Source: Own illustration based on previous table

After delineating the total addressable market for each region, the next step involved assuming penetration rates specific to each market. We assumed a penetration rate of 8% for the USA and 6% for the remaining regions and this penetration rates already considers the fact that our products are not targeted at anyone with IBD (for example we do not expect patients with severe cases of IBD who need surgery to require our probiotic). The choice of a 6% penetration rate reflects a cautious approach, so as not to overestimate demand. The higher 8% penetration rate for the USA is justified by the country's well-established probiotic market, high consumer awareness, and recent approval of a probiotic as a treatment option. Additionally, we considered an annual adoption rate growth of 5% for the initial 5 years of ProbiOxy's operations. This allows for a comparative analysis between the estimated demand for 2032 and 2037, providing insights into the projected growth trajectory during the initial years of ProbiOxy's market presence. With these considerations, we computed the anticipated demand for each region, as

illustrated in Table 3.

	USA	Canada	China	Europe
2032	408 566	34 350	143 034	320 527
2037	599 365	50 392	209 831	470 213

Table 4: Expected demand per region (number of patients)
Source: Own illustration based on previous table

As evident from the table, **the United States and Europe emerge as pivotal regions for ProbiOxy**. The USA, with the highest demand, becomes a strategic cornerstone due to its well-established probiotic market. Meanwhile, China showcases emerging market potential of Asia, emphasizing the importance of getting the approval of local regulatory agencies in the future. Overall, this data emphasizes the substantial revenue-generating potential of ProbiOxy, and the opportunity associated with each market.

5 Our patients

5.1 Segmentation and Targeting

The target market for the ResistoBacterium is diverse, encompassing individuals of all ages, genders, and nationalities who suffer from IBD. The emphasis, however, lies in a shared commitment to proactive health management through comprehensive testing. The key to effective targeting revolves around the understanding that the efficacy of ResistoBacterium is maximised when tailored to an individual's unique microbiota composition. As already mentioned before in section 4.5 our probiotic will be fit for people seeking both a complementary or a stand-alone treatment and both to maintain or induce remission. However, the most precise target market is going to be all individuals with a dedicated gastroenterologist committed to undergoing microbiota testing and with specialised treatment based on microbiota analysis.

To have a coherent targeting strategy for our probiotic and pave the way to market for the acquiring company we will be dedicated to collaborating with gastroenterologists. Both to promote the significance of microbiota testing in IBD management and as well to provide educational resources to related professionals on the benefits of ResistoBacterium as a solution to treat IBD. Our primary message centres around the necessity of microbiota testing, facilitated by gastroenterologists, to ascertain the most effective treatment. We will tailor our marketing efforts to this commitment to personalised treatment and highlight the importance of understanding the unique microbiota composition for optimal IBD management.

5.2 Client Personas

It is difficult to set a typical IBD patient profile as the demographics and individuals' circumstances can be of any type. Varying in age, attitudes, life habits, extra complications, and treatment regimens the common aspect of patients that will benefit from our probiotic is that

they have a dedicated personal gastroenterologist who will be able to provide the right treatment at the right time, knowing the personal situations and the essential microbiota tests results of the individuals. With our probiotic, gastroenterologists and other dedicated specialists will have a new and efficient probiotic, among the already existing treatments, to use depending on the individual's circumstances. Figure 5 illustrates potential client personas of ProbiOxy.

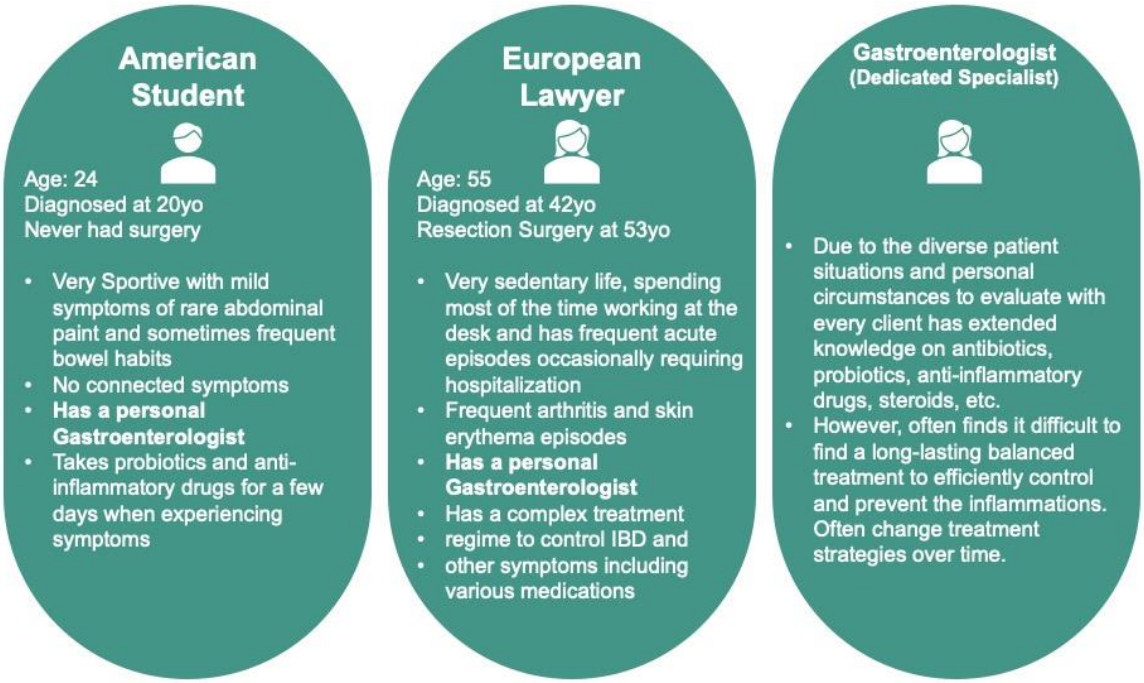

Figure 5: Our Client Personas
Source: Own illustration

5.3 The Purchase Process of Patients for IBD Treatment

When an individual experiences symptom and a lack of physical well-being, the first step is to visit a healthcare professional, in most cases a doctor in a clinic (gastroenterologist), to talk about the symptoms, needs, and possible treatment options.

After consultation and joint decision-making between the patient and the healthcare professional, the healthcare professional prescribes a treatment for IBD. Healthcare professionals personalise treatment plans to address the unique needs of each individual, considering the type and severity of their symptoms. Medications may be administered in

different quantities, formulations, and timeframes. (Crohn's & Colitis Foundation 2023) According to Davari et al. (2018) the following factors affect the prescribing decision of doctors: personal attributes of the doctor, treatment costs, patient preference, the pharmaceutical industries' marketing, promotion strategies, department heads, and co-workers, expectations of patients or their families, and clinical condition of the patient.

The purchase process depends on the type of medication and, thus, indirectly on the severity of symptoms (for more details, see Chapter 2.6). Severe cases of IBD may require hospitalisation, where patients receive intravenous medications, surgery, and other treatments. Other IBD medications (mostly biologics) are administered through outpatient infusion centres – as part of a hospital or an independent centre. In those two cases, the purchase process is administered via the treating institution, e.g., hospitals or outpatient infusion centres. Possible distribution points for prescription drugs can be specialized gastroenterologists, hospitals, medical centres, and hospital, retail, or online pharmacies. Hospital pharmacies captured the highest percentage of revenue (44%) in the global IBD treatment market. The position of the market leader of the hospital pharmacy segment is linked to an increase in the prevalence of IBD and thus increase in hospital admissions, the hospital's infrastructure, and the accessibility of treatment in hospitals. ('Inflammatory Bowel Disease Treatment Market Report 2030' 2021)

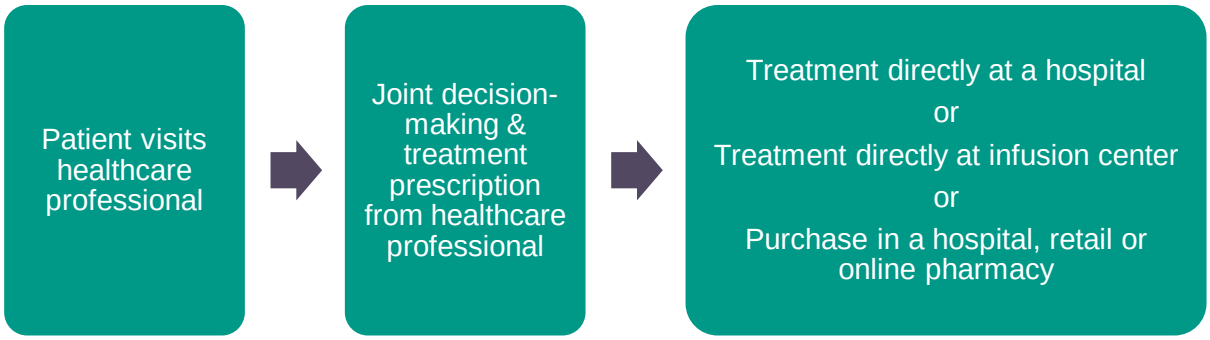

Figure 6: Purchase process of patients for treatment for IBD
Source: Own illustration

6 Key Resources

6.1 Patent

6.1.1 Acquiring the Intellectual Property

Calouste Gulbenkian Foundation are the owners of IGC and their intellectual property (IP), and ProbiOxy will secure an exclusive license with CGF for their ground-breaking invention. This license will grant ProbiOxy comprehensive ownership of all IP associated with the project, including the patent, upon its approval. As part of this exclusive licensing agreement, ProbiOxy will have the right to sublicense the IP to third-party entities, which could prove advantageous as an intermediate step towards commercialising the invention or as an alternative to outright selling the company.

ProbiOxy will pay CGF through a milestone agreement stating which stages CGF will receive payments for the license. The milestone payments are pivotal, as they will be methodically dispersed upon achieving significant developmental benchmarks, such as the successful completion of each clinical trial phase or upon reaching key investment milestones. This system ensures that ProbiOxy's financial commitments are aligned with its developmental progress, reflecting the increasing value of the venture as it moves closer to its ultimate goal of acquisition.

ProbiOxy's exclusive licensing agreement strengthens its market position and ensures a competitive edge, emphasizing its strategic significance to potential acquirers and investors.

6.1.2 Protecting the IP

For an R&D company like ProbiOxy, protecting our IP is one of our priorities. A patent gives us ownership and the opportunity to develop and later sell our invention and, therefore, a critical part of our business. The patent process is costly and takes time, but it is a necessity.

In July 2023, the scientists from IGC submitted a patent to the European Patent Office. It comprises 15 claims related to probiotic compositions and their specific application areas. In general, when filing a patent, one expects some of the claims to be rejected and, therefore, have several claims that differ in various extent, like how specific or broad they are.

We are aware that other researchers are also researching the K. oxycota bacteria and have filed patents and are therefore prepared that some of our claims might be rejected if they are found to conflict with theirs. However, this group does not test any disease model and is focused on the displacement of the invading bacterium K. pneumoniae (Osbelt et al. 2021) and hence does not know or show if it would recover the microbiota or inflammation, which is of the main capabilities of our invention.

6.1.3 Patent Portfolio

ProbiOxy will stay committed to continuously filing for new patents as a part of our ongoing development efforts. Through our dedicated research, we will explore and discover new possibilities for our probiotics and will strive to develop a portfolio of patents that will make ProbiOxy less reliant on IGC and the original license. This will result in increased value for ProbiOxy's shareholders, as IGC will be entitled to a smaller portion of the final sales sum when the license from them becomes less important.

Having a strong patent portfolio can help ProbiOxy stay ahead of its competitors. As our research on the probiotic product continues, we expect to identify more areas where it can be used effectively and discover new combinations that will increase its overall value. Although we have already listed some potential uses in our product pipeline (6.3), we anticipate identifying more in the future. We will include any new discoveries in our patent filings to expand and solidify our patent portfolio. This will make it difficult for competitors to replicate the unique properties and benefits of ProbiOxy.

6.2 Partnerships

6.2.1 Instituto Gulbenkian de Ciência

Our closest partner is Instituto Gulbenkian de Ciência. The institute shows a great willingness and motivation to cooperate on this project and to allow us to work with their scientists and research. This partnership will be the foundation of the project. We are thrilled that IGC, Dr. Cabral and his team share our vision. Early in the communication, IGC welcomed us on the inside of their walls, so we gain a more comprehensive understanding of the project and its potential before signing the final agreement of partnership.

Dr. Cabral and Dr. Oliveira are the ones who discovered the probiotic and will join ProbiOxy to develop the drug further. Dr. Cabral and Dr. Oliveira will act as co-founders and researchers in our company. Hence, they will have equity in ProbiOxy and are also to be paid fair compensation for their dedicated research hours.

6.2.2 Partnerships with pharma companies

Partnering with a major pharmacy company early in ProbiOxy's development can offer significant advantages. Such a partnership provides access to resources like research and development support and financial backing, essential for technological advancement and maintaining stability without immediate profitability pressure. It also offers guidance in navigating the biopharma industry, including market dynamics and regulatory compliance, leveraging the experience of established companies.

The relationship-building aspect of these partnerships is equally critical. By aligning early with potential acquirers, ProbiOxy can position itself strategically within the interests of these larger entities, enhancing its appeal as an acquisition target. (In Chapter **Error! Reference source not found.** Potential Acquirers, we will discuss specific companies in more detail). However, there are potential drawbacks. Close alignment might lead to a loss of independence and decision-

making autonomy. There's a risk of strategic goals diverging, leading to conflicts, and ProbiOxy's innovations might be overshadowed by the larger partner's product portfolio.

In conclusion, partnering with a big pharmacy company presents ProbiOxy with growth and acquisition opportunities but requires balancing to maintain its strategic direction and core objectives. Managed effectively, this strategy can establish ProbiOxy as a significant player in the biopharma industry.

6.2.3 Contract Research Organizations

In pharmaceutical research and development, Contract Research Organizations (CROs) like IQVIA are crucial, offering specialized services to streamline clinical trials. IQVIA, a multinational company, provides a comprehensive suite of services, including clinical trial design, patient recruitment, regulatory submissions, and data analysis (‘Protocol Design’, n.d.). They stand out as a trusted partner for companies seeking to expedite the development of life-changing therapies and stick out as a highly interesting partner for ProbiOxy.

IQVIA's expertise in protocol design ensures clinical trials are scientifically sound and comply with ethical and regulatory standards (‘About us’ n.d.). In Phase I trials, they help monitor side effects and assess the safety profile of new treatments, like our probiotic formulation (‘Gut Feeling’ n.d.). Moving to Phase II, IQVIA's capabilities in trial design enable effective evaluation of our probiotic's efficacy and optimal dosage in patients with intestinal inflammation (‘Phase IIb/III Trials’, n.d.).

IQVIA's clinical trial management platform streamlines research from protocol design to data analysis and regulatory submissions. Their proficiency in navigating regulatory pathways expedites market approval, and their data analytics offer valuable insights into the efficacy and safety of our probiotic (‘IQVIA About us’ n.d.)

Collaborating with IQVIA will accelerate our R&D, enhancing the development of our next-

generation probiotic for patients with intestinal inflammation. Their global reach and commitment to quality are pivotal in achieving our goal of a safe and effective therapeutic option.

6.2.4 Regulatory and Legal experts

PTR Pharma Consulting

PTR Pharma Consulting, a subsidiary of the German company regenold GmbH, founded in 1994, has established itself as a leader in regulatory consulting, offering a comprehensive suite of services spanning the entire lifecycle of pharmaceutical and biotechnological products. Since its inception in 2006, PTR has been instrumental in aiding numerous clients to navigate the intricacies of international regulatory frameworks, ensuring that products are not only compliant but also primed for market access and success. Their expertise encompasses development, international regulatory affairs, pharmacovigilance, and market access, making them a multifaceted partner in the highly regulated pharmaceutical landscape (‘PTR Pharma Consulting - About Us’, n.d.).

6.3 Board of Directors

ProbiOxy's Board of Directors consist of a diverse and dynamic team steering the company towards ground breaking achievements in the field of probiotics. Our executive members, led by CEO Giorgio Brizio Falletti Di Castellazzo, bring a wealth of experience from various sectors, including finance, marketing, and operations, ensuring strategic guidance and effective management. Our non-executive members, Dr. Vitor Cabral, and Dr. Rita Oliveira, enrich our board with their profound academic insights and research expertise, particularly in microbiology and genetics. Together, this blend of executive acumen and scientific prowess positions ProbiOxy at the forefront of innovation and excellence in probiotic research and development.

6.3.1 Executives

Giorgio Brizio Falletti di Castellazzo

Giorgio Brizio Falletti Di Castellazzo, as the Chief Executive Officer (CEO) of ProbiOxy, brings his dynamic background consisting of significant work experiences, quality education, and a proven track record of impactful contributions. Giorgio, with a background as a Circular Economy Analyst and relevant experience in corporate banking as an ESG analysis at Intesa Sanpaolo, excelled in navigating sustainability issues across industries and in the development of tools for understanding circular economy principles. His role encompassed technical and soft skills, including relationship management and effective teamwork, with past colleagues highlighting his adaptability and open-mindedness.

In summary, Giorgio's comprehensive skill set, encompassing the financial world, a commitment to social responsibility, and adeptness at navigating challenges positions him perfectly to guide ProbiOxy toward continued success.

Miguel Seca Reis Pelayo de Sousa

As Chief Financial Officer (CFO) at ProbiOxy, Miguel oversees the global financial operations of the company. He brings a strong academic background, Miguel is currently pursuing a Master's in Management at Nova School of Business and Economics, complemented by his Bachelor's degree in Economics from the Faculty of Economics at the University of Porto. Miguel also gained valuable hands-on experience at FEP Junior Consulting, showcasing his dedication to applying financial resourcefulness in practical business settings.

In joining Probioxy, Miguel leverages his diverse background and education to contribute to the company's financial success. He is committed to driving strategic financial initiatives and ensuring fiscal responsibility within the organisation.

Anna Katharina Schneider

Anna Schneider is pursuing a Master's in Management at Nova School of Business and Economics, specialising in Entrepreneurship. In addition, she is a Project Leader at Klima-Allianz Schweiz, working part-time. Anna has gained valuable insights into marketing during the development of a marketing strategy for Isantin GmbH, a science-based company and during the development of a marketing activation plan for the “ClimateActions”-App designed by MYBLUEPLANET to engage the Swiss population in climate protection.

With her strong educational background and practical experience, Anna is a great fit for the Chief Marketing Officer (CMO) position. Her expertise in strategic management, marketing, and analytics, along with her hands-on experience, will be instrumental in driving the exit strategy and marketing strategies and initiatives of the company.

Steinar Litland

Steinar Litland's position as Chief Operating Officer (COO) draws strength from his diverse roles at Bønes Virik and Emerchandise, his academic credentials, and his leadership in student organizations. During his tenure as Head of Business Relations in BI Student Organization, he learned how to establish and maintain key partnerships. As an executive researcher at Bønes Virik, he honed his skills in strategic planning and research, which are essential for R&D operations. At Emerchandise, his involvement in production processes provided him with valuable insights into product development, crucial for turning research into market-ready products.

Steinar’s Master's degree in Management and Bachelor's degree in International Management provide him with a solid foundation in business strategy and innovation. In summary, Steinar’s versatile skill set, from project management to production knowledge, equips him to oversee ProbiOxy's operations effectively.

6.3.2 Non-Executives

Dr. Vitor Cabral

Dr. Cabral embarked on his academic journey at the Universidade de Coimbra Faculdade de Ciencias e Tecnologia, where he completed his Licenciatura em Biologia - Ramo Científico in 2008. He further honed his expertise by earning a PhD in Eukaryote and Prokaryote Microbiology in 2012 at the prestigious Institut Pasteur and Université Paris Diderot, under the mentorship of Professor Christophe d'Enfert.

Postdoctoral fellowships at globally recognised institutions like the Albert Einstein College of Medicine and Columbia University have enriched Dr. Cabral's research experience. His current role as a Postdoctoral Fellow at Instituto Gulbenkian de Ciência underscores his dedication to advancing the field of microbiology, particularly in the realm of natural sciences.

Dr. Cabral's career is distinguished by his commitment to mentorship and education, having guided numerous students across various levels, including Medical, MD/PhD, and PhD candidates and postdoctoral researchers. His scholarly contributions include 12 peer-reviewed journal articles and a book chapter, alongside organising five significant academic events. His work has been recognised with prestigious awards and honours, reflecting his impact and dedication to the scientific community.

Dr. Cabral's addition to our team is not just a testament to his illustrious career but also aligns with our mission to pioneer ground-breaking research in probiotics. His expertise will undoubtedly drive our endeavours to develop innovative solutions for gut health and related areas.

Dr. Rita Oliveira

Dr. Rita Oliveira is a distinguished member of our research team. She has a robust academic

background and a wealth of research experience that she brings to our team, particularly in the field of microbiota research.

Dr. Oliveira's academic journey is rooted in a solid foundation in Genetics and Molecular Biology, from which she received her bachelor's degree in 2009. She advanced her studies with a Master’s degree in Evolution and Developmental Biology in 2011, both from the Faculty of Science at Lisbon University in Portugal. Her master's research focused on the differentiation of human stem cells.

After completing her master's degree, Dr. Oliveira's passion for research led her to the Gulbenkian Institute of Science. Working in Dr. Karina Xavier’s laboratory, she delved into the study of quorum sensing and its manipulation of the gut microbiota. This work was part of her engagement with the Integrative Biology and Biomedicine program, where she commenced her PhD studies. Dr. Oliveira completed her PhD in 2020, focusing on Interspecies interactions in recovery from microbiota dysbiosis.

Dr. Oliveira's academic and professional journey reflects her commitment to scientific discovery and her ability to make significant contributions to our understanding of the microbiota and its critical role in human health.

6.4 Advisory Board

Nuno Arantes-Oliveira

Nuno Arantes-Oliveira brings a wealth of experience in entrepreneurship, investment, and academia in Life Sciences and Healthcare. His career, which started with groundbreaking genetics research at UCSF, encompasses founding and leading companies in Europe and the U.S., focusing on technology transfer, drug development, and healthcare services. Nuno's expertise in guiding clinical-stage biotech and MedTech enterprises is evident from his time at Clinical Research Ventures. His roles, including President of Portugal’s Biotechnology

Industry Organization and on the board of Health Cluster Portugal, highlight his global influence. At ProbiOxy, Nuno's strategic vision, business acumen, and extensive network will significantly influence scientific innovation, entrepreneurial initiatives, and industry partnerships, underscoring our commitment to biotechnological excellence and transformative impact.

Pedro Henriques

Pedro Henriques brings unparalleled expertise to Probioxy with his extensive background in intellectual property. A Portuguese chartered patent attorney since May 17, 2000, Mr Henriques boasts an impressive 30 years of experience in this field.

Mr. Henriques earned a Dipl. Ing. degree from Oporto University (FEUP). Post-graduation, and with nearly one year of industry experience, he commenced his journey into intellectual property by joining an Oporto-based IP firm with a storied legacy dating back to 1930 (Arlindo de Sousa Marcas e Patentes Lda).

In the biotech sector, Mr. Henriques has played a pivotal role in handling national and international patents for Portuguese companies and universities. His expertise spans various areas, including notable contributions to patents related to yeasts in the wine sector. Moreover, he has dealt with the validation in Portugal of euro-PCT patents, in particular on behalf of the Government of the United States of America, as represented by the Secretary of the Department of Health and Human Services.

Investor Representatives

ProbiOxy plans to include representatives from future venture capital partners on its advisory board. This move is aimed at aligning our company's strategic direction with the insights of experienced investors who have a vested interest in our success. Having venture capital members on our advisory board will provide a wealth of experience in market dynamics,

investment strategies, and corporate governance. Their involvement will ensure that ProbiOxy benefits from a broader perspective on industry trends, financial management, and strategic networking opportunities. This synergy will help us make better decisions and achieve our goals more effectively.

6.5 Financial Capital

Financial capital stands as a cornerstone for ProbiOxy's journey from a promising start-up to a market leader in the biopharmaceutical industry. It fuels every aspect of the company's operations, from research and development to securing intellectual property and navigating the complex pathways of clinical trials. ProbiOxy’s financial strategy, detailed in the chapter on finances, revolves around a robust plan to secure funding primarily through venture capital investments. This approach not only underpins our immediate research needs but also strategically positions us for future growth and scalability. By aligning our financing strategy with our operational milestones, ProbiOxy ensures a steady flow of capital, which is essential for maintaining momentum in our innovative endeavours and achieving long-term objectives. The financial framework, therefore, is not just about securing funds but also about judicious allocation and management, ensuring that every dollar is a step towards revolutionising IBD treatment.

For a detailed exploration of our financial strategy and how we plan to utilise these funds effectively, refer to the comprehensive analysis in the chapter about finances.

6.6 Facilities

Research Facilities

ProbiOxy is set to make significant progress by partnering with IGC to conduct the remaining pre-clinical trials at their facilities. This collaboration will be a pivotal phase in our project, providing access to advanced resources and expertise required for thorough testing and

validation of our probiotic products. It is a crucial step forward that will help us achieve our goals with greater confidence.

Under this forthcoming agreement, ProbiOxy will benefit from a cost-effective arrangement, agreeing to pay only the cost-price for the use of IGC's facilities and consumables. This approach is designed to optimise our financial resources and foster a collaborative environment conducive to scientific innovation. The costs incurred will be meticulously documented and are planned to be integrated into future milestone payments, ensuring transparency and accountability in our financial planning.

Offices

ProbiOxy is dedicated to sustaining an efficient and flexible work environment alongside our research at IGC. We continue to conduct most non-research activities remotely, leveraging the benefits of cost-effectiveness, productivity, and work-life balance for our team. Regular online team meetings on digital platforms ensure seamless communication and collaboration, maintaining efficiency and engagement.

While valuing remote work, we also recognise the importance of face-to-face interactions. We plan to organise occasional in-person meetings at convenient locations for team building and strategic discussions. As our financial situation improves, we will explore securing our physical office space.

7 Operations

7.1 Research and Development

The figure below shows the drug development process. The first step has already been taken by IGC by discovering the asset, and according to our business plan, ProbiOxy will continue

the development to the end of Phase II.

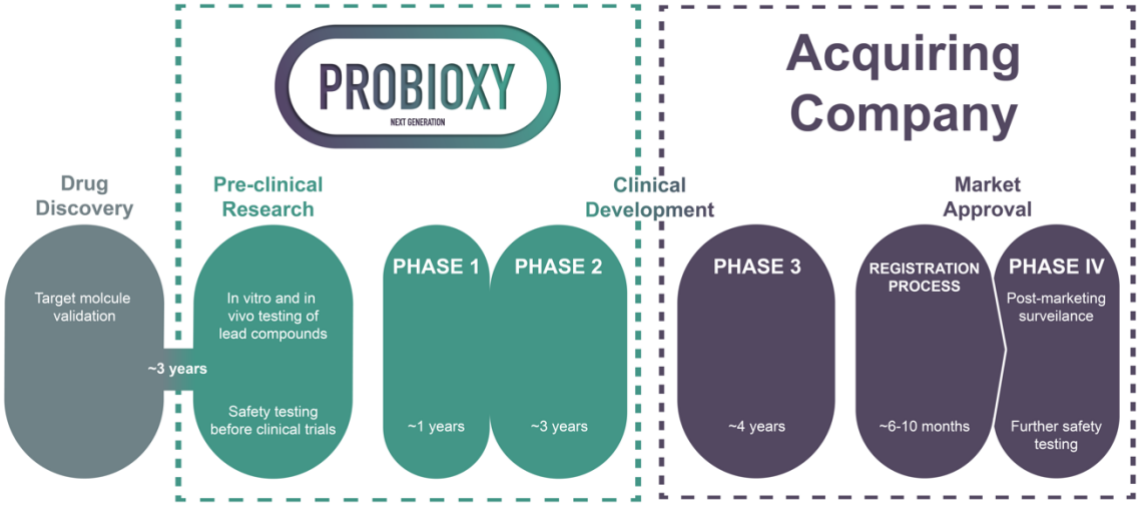

Figure 7: Drug Development Timeline
Source: Own illustration

7.1.1 Pre-Clinical Trials

Building upon the diligent efforts of Dr. Cabral and Dr. Oliveira, ProbiOxy will keep a high standard while conducting the remaining pre-clinical safety assessments for our product. Our immediate focus will be on three critical areas based on Dr. Cabral's evaluations:

1. **Presence of Antibiotic Resistance Genes**: Although preliminary tests have been completed, we recognise the need for a broader investigation. We will expand the spectrum of antibiotics tested to ensure our product does not harbour genes that could contribute to the pressing issue of antibiotic resistance.
2. **Resistance to Host Defence Mechanisms**: As a staple in safety assessments, this trial is essential. We are committed to demonstrating that our product does not interfere with or resist the natural immune responses of the host, maintaining a harmonious balance within the microbiome.
3. **Presence of Virulence Genes and Toxic Metabolites**: Thus far, only computational analyses have been performed in this domain. To supplement these findings, we will

conduct empirical testing to rigorously verify that our product is free from virulent properties and harmful metabolites.

Additionally, we are contemplating further assessments that are not commonly required but may enhance our safety profile:

- **Hemolysis**: Given its rarity in probiotics, this test will be considered on a case-by-case basis, especially if our product has the potential to interact with blood components in any capacity.
- **Presence of Macrocapsules**: While not a standard component of safety assessments, examining the macrocapsules could provide valuable insights into the delivery and release mechanisms of our product. This test will be evaluated for its relevance to our product's specific application and intended use.

ProbiOxy is fully invested in the meticulous continuation of these pre-clinical trials. Our aim is not just to comply with regulatory requirements but to exceed them, ensuring that our product stands as a paragon of safety and reliability in its market.

7.1.2 Clinical Trials

7.1.2.1 Phase I

In Phase I trials, the first step is creating a clinical trial protocol, detailing study objectives, participant criteria, duration, dosage, and methods to limit bias. It also explains data collection and analysis methods, serving as the trial's blueprint.

Phase I trials typically involve 20 to 80 volunteers, focusing on safety and monitoring the probiotic's interaction with the human body, including dosage levels and acute side effects (Commissioner 2019). Adjustments are made based on preclinical data and observations to optimise safety and benefits.

Prior to the trial, an Investigational New Drug (IND) application must be submitted to

regulatory bodies like the FDA or EMA, including animal study data, toxicity data, manufacturing information, the protocol, prior human research data, and investigator information. This is a crucial regulatory step for participant safety and meaningful data.

The regulatory body, like the FDA, has 30 days to review the IND application. They may approve the trial's commencement or place a clinical hold if there are significant concerns about risks or trial adequacy. This process ensures volunteer safety and trial quality.

Conducting a Phase I clinical trial for our probiotic requires detailed scientific planning, rigorous safety assessments, and strict adherence to regulatory requirements. Each step, from preclinical research to regulatory approval, ensures the probiotic's safety and sets the stage for further efficacy studies in Phase II.

7.1.2.2 Phase II

This phase is a pivotal stage in the development of our new probiotic, where we expand our testing to include a larger group, typically several hundred participants. These individuals will be persons with IBD. Our plan for this phase, which we anticipate will last from several months to two years, is not just to further assess the safety, established in Phase I, but also to evaluate efficacy (Commissioner 2019).

We will employ a randomised study design to objectively compare our probiotic's effectiveness against standard treatments or a placebo. Randomisation ensures that observed effects are attributable solely to the probiotic.

IQVIA will assist in developing robust research protocols covering participant selection and data collection methods. Their data analysts will manage and analyse trial data, refining our product and strategy. IQVIA, along with PTR, will ensure compliance with industry guidelines and government regulations, crucial for ethical considerations and market approval.

Completing Phase II successfully lowers market risk for potential ProbiOxy buyers. The insights from this phase will guide Phase III trials, providing a solid foundation for these final studies.

7.1.3 R&D for Portfolio Expansion

The R&D initiatives at ProbiOxy are closely connected to our strategic expansion of the product pipeline, which is outlined in chapter **Error! Reference source not found.**. We aim to continuously innovate and broaden our range of probiotic treatments, ensuring that ProbiOxy stays at the forefront of biopharmaceutical advancements. Our commitment to expanding our product pipeline involves a multi-faceted approach, which includes cutting-edge research, strategic collaborations, and a keen insight into emerging therapeutic needs and opportunities.

Although our focus is developing the probiotic treatment for IBD patients, we will also dedicate a significant portion of our R&D resources to exploring new formulations and treatment methodologies that can enhance the efficacy and safety profiles of our existing products. R&D activities on different target patients will in many cases crossroads and one find can be used for several products.

Furthermore, our R&D strategy is deeply aligned with our long-term vision. We conduct a rigorous assessment of market trends, patient needs, and technological advancements, ensuring that our product pipeline development is both responsive and proactive. By integrating these insights into our R&D processes, ProbiOxy aims to expand its product pipeline and ensure that each new development is strategically positioned to meet the evolving demands of the overall intestinal inflammation landscape.

Through this dynamic and forward-thinking approach to R&D, ProbiOxy aims to solidify its position as a leader in the biopharmaceutical sector, continuously pushing the boundaries of what is possible in treatment and care with probiotics.

7.2 Compliance

Our aim is that our probiotic will be used as a medical treatment, which has the potential to significantly improve the quality of life for individuals with IBD. Although we will not be the ones applying for official approvals to become a medical treatment, it is crucial for us to contribute to making the final road to approval as smooth as possible. Therefore, we are conducting pre-clinical trials with extreme care, complying strictly with guidelines, and utilizing regulatory experts.

We will adhere to the ICH S7 Safety Pharmacology Studies guidelines by the EMA, focusing on safety pharmacology studies to assess the probiotic's impact on vital body functions. Emphasising data quality and integrity is key for due diligence and negotiations with potential buyers. Our risk assessment and mitigation strategy, along with securing strategic partnerships and protecting intellectual property, enhance our product's appeal and company valuation. Regular communication with regulatory bodies ensures compliance with the evolving regulatory landscape. Our market analysis and financial planning aim to establish our company as a leader in safety and innovation in the probiotic sector.

Incorporating PTR Pharma Consulting aligns our development with pharmaceutical industry standards, ensuring compliance with global authorities like the FDA and EMA. PTR's expertise in foreseeing regulatory challenges and offering strategic solutions accelerates the approval process. This partnership bolsters our credibility and optimises our resources, allowing us to focus on innovation while navigating regulatory complexities. This approach positions our company as a prime acquisition candidate, promising profitability, and market success.

8 Post Exit

While ProbiOxy will focus on advancing drug candidates through pre-clinical trials, Phase I and II clinical trials, the acquirer of ProbiOxy will be responsible for undertaking Phase III trials. These trials are pivotal for obtaining approval from regulatory bodies. For our business plan to be successful, we aim to make the last steps of the journey as feasible as possible.

8.1 Clinical Trial Phase III

Upon successful completion of Phase II, our drug candidates will be poised for the critical Phase III trials. This phase is designed to solidify the efficacy and safety profile of the drug on a larger scale. Our acquirer will be tasked with conducting these extensive trials, which are both resource-intensive and crucial for regulatory approval.

Objectives of Phase III Trials

1. **Confirming Efficacy and Safety**: Phase III trials aim to confirm the results obtained from earlier phases by testing the drug in a larger population. This phase is essential for verifying that the drug effectively treats the targeted condition without unacceptable side effects.
2. **Comparative Analysis**: Often, Phase III trials involve comparing the new drug with standard treatments. This comparison is vital to establish the drug's relative effectiveness and safety.
3. **Long-term Effects**: These trials are longer in duration, allowing for the observation of long-term effects and the identification of any rare side effects.

The design of Phase III trials is a meticulous process, building upon the data and insights gained from Phase I and II. Key considerations include:

- **Participant Selection**: Criteria for participant selection are more stringent, focusing on the target demographic for the drug.

- **Trial Duration and Size**: These trials involve a larger number of participants and can last several years.
- **Control Groups and Blinding**: To ensure unbiased results, control groups and blinding methods are often employed.
- **Data Collection and Analysis**: Rigorous data collection and statistical analysis are crucial to validate the trial outcomes.

Before embarking on Phase III trials, our acquirers must submit a detailed Investigational NDA to regulatory authorities. This application includes comprehensive data from previous trials, manufacturing information, and the proposed study protocols. The regulatory bodies will review the application to ensure the safety and integrity of the trial. Successful completion of Phase III trials is a prerequisite for submitting a marketing application to the FDA or EMA.

8.2 Market Approval

The journey from Phase III clinical trials to market approval for a drug involves securing approval from the FDA and the EMA, along with other agencies in markets the acquirer might decide to pursue. After Phase III, a thorough analysis of data covering efficacy, safety, and risk-benefit balance is essential. This information forms the core of the Marketing Authorization Application (MAA) for the EMA and the NDA for the FDA. These applications contain all development data, including clinical results, manufacturing details, and marketing plans, demonstrating adherence to quality, safety, and efficacy standards. (‘New Drug Application (NDA) | FDA’ 2022; ‘From Laboratory to Patient - the Journey of a Medicine Assessed by EMA’, n.d.) The FDA and EMA validate these applications, followed by an expert review to assess the drug's risk-benefit profile. This may involve additional information requests and, for complex treatments, advisory committee consultations. A crucial part of the process is the inspection of manufacturing facilities to ensure Good Manufacturing Practices compliance and quality control. The final decision ranges from full approval to potential rejection. If approved,

negotiations on labelling and patient information precede marketing. The process does not end there; post-marketing surveillance, including Phase IV trials, is vital for long-term safety monitoring.

Navigating FDA and EMA market approval is complex, demanding thorough regulatory knowledge, planning, and proactive regulatory body communication. Successful completion signifies a drug's potential for significant healthcare impact, offering new treatment options.

9 References

AbbVie. 2023. ‘AbbVie Announces European Commission Approval of RINVOQ® (Upadacitinib) for the Treatment of Moderately to Severely Active Crohn’s Disease’. April 2023. https://www.prnewswire.com/news-releases/abbvie-announces-european-commission-approval-of-rinvoq-upadacitinib-for-the-treatment-of-moderately-to-severely-active-crohns-disease-301798397.html.

Aden, Konrad, and Wolfgang Reindl. 2019. ‘The Gut Microbiome in Inflammatory Bowel Diseases: Diagnostic and Therapeutic Implications’. *Visceral Medicine* 35 (6): 332–37. https://doi.org/10.1159/000504148.

Brown, Noël, and Greg Wiederrecht. 2021. ‘Biotech and Big Pharma: Blueprint for Successful Partnership’. October 2021. https://www.rbccm.com/en/gib/biopharma/story.page.

Cabral, Vitor. 2023. Interviews about the break through innovation.

Cabral, Vitor, Rita A. Oliveira, and Karina B. Xavier. 2023a. Bacterial composition. Provisional European Patent Application EP23184673, filed 2023, and issued 2023.

———. 2023b. ‘NOVA SBE Support Material’. Gulbenkian Ciência.

Cai, Zhaobei, Shu Wang, and Jiannan Li. 2021. ‘Treatment of Inflammatory Bowel Disease: A Comprehensive Review’. *Frontiers in Medicine* 8 (December): 765474. https://doi.org/10.3389/fmed.2021.765474.

Cleveland Clinic. 2023. ‘Inflammatory Bowel Disease (Overview)’. Cleveland Clinic. 9 October 2023. https://my.clevelandclinic.org/health/diseases/15587-inflammatory-bowel-disease-overview.

Commissioner, Office of the. 2019. ‘Step 3: Clinical Research’. *FDA*, April.

https://www.fda.gov/patients/drug-development-process/step-3-clinical-research.

Coward, Stephanie, Eric I Benchimol, M Ellen Kuenzig, Joseph W Windsor, Charles N Bernstein, Alain Bitton, Jennifer L Jones, Kate Lee, and Sanjay K Murthy. 2023. 'The 2023 Impact of Inflammatory Bowel Disease in Canada: Epidemiology of IBD'. *2023 Sep 5*, 7 December 2023. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10478802/#:~:text=The%20prevalence%20in%202023%20is,live%20with%20IBD%20by%202035.

Crohn's & Colitis Foundation. 2023. 'Understanding IBD Medications and Side Effects'. https://www.crohnscolitisfoundation.org/sites/default/files/2023-10/understanding-ibd-medications-brochure-FINAL%2010.23_0.pdf.

D. Lewis, James, Lauren E. Parlett, Michele L. Jonsson Funk, Douglas E. Schaubel, Andres Hurtado-Lorenzo, and Michael David Kappelman. 2023. 'Incidence, Prevalence, and Racial and Ethnic Distribution of Inflammatory Bowel Disease in the United States'. *July 20, 2023*, December.

Davari, Majid, Elahe Khorasani, and Bereket Molla Tigabu. 2018. 'Factors Influencing Prescribing Decisions of Physicians: A Review'. *Ethiopian Journal of Health Sciences* 28 (6): 795–804. https://doi.org/10.4314/ejhs.v28i6.15.

'From Laboratory to Patient - the Journey of a Medicine Assessed by EMA'. n.d.

Gade, Ajay K, Nathan T Douthit, and Erin Townsley. 2020. 'Medical Management of Crohn's Disease'. *Cureus*, May. https://doi.org/10.7759/cureus.8351.

GIS. 2023. 'IBD Patient Journey'. *Gastrointestinal Society* (blog). January 2023. https://badgut.org/information-centre/patient-journeys/ibd-patient-journey/.

Grabos, Katarzyna. 2023. Interview about the medications for IBD currently sold in

Switzerland.

Halfvarson, Jonas, Colin J. Brislawn, Regina Lamendella, Yoshiki Vázquez-Baeza, William A. Walters, Lisa M. Bramer, Mauro D'Amato, et al. 2017. 'Dynamics of the Human Gut Microbiome in Inflammatory Bowel Disease'. *Nature Microbiology* 2 (5): 1–7. https://doi.org/10.1038/nmicrobiol.2017.4.

Hammer, Turid, and Ebbe Langholz. 2020. 'The Epidemiology of Inflammatory Bowel Disease: Balance between East and West? A Narrative Review'. *30 December 2020*, 30 December 2020, Vol 3 edition.

He, Dandan, Lanzhen He, Yijuan Yuan, Lingli Huang, Qi Xiao, Xinmei Ye, and Jun-E Zhang. n.d. 'Stigma and Its Correlates among Patients with Crohn's Disease: A Cross-Sectional Study in China'. *21 June 2023*.

Healthline Medical Network. 2023. 'How Do Antibiotics Work?' Healthline. 2023. https://www.healthline.com/health/how-do-antibiotics-work.

Higashiyama, Masaaki, and Ryota Hokari. 2023. 'New and Emerging Treatments for Inflammatory Bowel Disease'. *Digestion* 104 (1): 74–81. https://doi.org/10.1159/000527422.

'IBD Treatment Market Report'. 2021. 2021. https://www.thebrainyinsights.com/report/inflammatory-bowel-disease-treatment-market-12607.

'Inflammatory Bowel Disease Drugs Market Report By 2031'. n.d. Allied Market Research. Accessed 10 November 2023. https://www.alliedmarketresearch.com/inflammatory-bowel-disease-drugs-market.

'Inflammatory Bowel Disease (IBD) - Diagnosis and Treatment'. n.d. Mayo Clinic. Accessed

17 November 2023. https://www.mayoclinic.org/diseases-conditions/inflammatory-bowel-disease/diagnosis-treatment/drc-20353320.

'Inflammatory Bowel Disease Treatment Market Report 2030'. 2021. The Brainy Insights. November 2021. https://www.thebrainyinsights.com/report/inflammatory-bowel-disease-treatment-market-12607.

'Inflammatory Bowel Disease Treatment Market Size to Surpass USD 40.8 BN by 2030'. 2022. 7 November 2022.

'IQVIA, About Us'. n.d. Accessed 1 December 2023. https://www.iqvia.com/about-us.

Kaplan, Gilaad G., Natalie Molodecky, and Remo Panaccione. 2010. 'Environmental Triggers of IBD.' *Inflammatory Bowel Disease Monitor* 11 (2): 49–56.

Lawton, Tracy. 2019. 'Inflammatory Bowel Disease Insight Report: Current Therapies, Drug Pipeline and Outlook'. BioSpace. 19 November 2019. https://www.biospace.com/article/inflammatory-bowel-disease-insight-report-current-therapies-drug-pipeline-and-outlook/.

Luo, Hua, Guiqing Cao, Chun Luo, Dechao Tan, Chi Teng Vong, Yinyue Xu, Sicen Wang, Haitao Lu, Yitao Wang, and Wanghui Jing. 2022. 'Emerging Pharmacotherapy for Inflammatory Bowel Diseases'. *Pharmacological Research* 178 (April): 106146. https://doi.org/10.1016/j.phrs.2022.106146.

'Medical Probiotics Market Size & Share Analysis - Industry Research Report - Growth Trends'. 2023. November 2023. https://www.coherentmarketinsights.com/industry-reports/medical-probiotics-market.

Microba. 2023. 'Microba Commences Phase I Clinical Trial for IBD Therapeutic'. Microba Life Sciences. 29 June 2023. https://microba.com/news/microba-commences-phase-i-

clinical-trial-for-ibd-therapeutic/.

Moss, Robby. 2023. ‘UPMC Enterprises Invests in Mozart Therapeutics to Support the Development of Treatments for Autoimmune and Inflammatory Diseases’. UPMC Enterprises. 9 June 2023. https://enterprises.upmc.com/blog/mozart-investment/.

Mozart Therapeutics. 2023. ‘Development Pipeline | KIR CD8 Treg Modulator’. 2023. https://www.mozart-tx.com/pipeline/#pipeline.

‘New Drug Application (NDA) | FDA’. 2022. 2022. https://www.fda.gov/drugs/types-applications/new-drug-application-nda.

‘Next Generation Probiotics Market Size and Forecast to 2030’. n.d. Accessed 19 October 2023. https://www.coherentmarketinsights.com/market-insight/next-generation-probiotics-market-5468.

Osbelt, Lisa, Marie Wende, Éva Almási, Elisabeth Derksen, Uthayakumar Muthukumarasamy, Till R. Lesker, Eric J.C. Galvez, et al. 2021. ‘Klebsiella Oxytoca Causes Colonization Resistance against Multidrug-Resistant K. Pneumoniae in the Gut via Cooperative Carbohydrate Competition’. *Cell Host & Microbe* 29 (11): 1663-1679.e7. https://doi.org/10.1016/j.chom.2021.09.003.

Ota, Shinji, and Hirotake Sakuraba. 2022. ‘Uptake and Advanced Therapy of Butyrate in Inflammatory Bowel Disease’. *Immuno* 2 (4): 692–702. https://doi.org/10.3390/immuno2040042.

‘Our Products’. n.d. Seres Therapeutics. Accessed 19 November 2023. https://www.serestherapeutics.com/our-products/.

Pascal, Victoria, Marta Pozuelo, Natalia Borruel, Francesc Casellas, David Campos, Alba Santiago, Xavier Martinez, et al. 2017. ‘A Microbial Signature for Crohn’s Disease’.

Gut 66 (5): 813–22. https://doi.org/10.1136/gutjnl-2016-313235.

Pfizer. 2022. 'Pfizer Announces FDA and EMA Acceptance of Etrasimod Regulatory Submissions for Ulcerative Colitis'. December 2022. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-fda-and-ema-acceptance-etrasimod.

'Phase IIb/III Trials'. n.d. Accessed 1 December 2023. https://www.iqvia.com/solutions/research-and-development/clinical-trials/phase-iibiii-trials.

Pickard, Joseph M., Melody Y. Zeng, Roberta Caruso, and Gabriel Núñez. 2017. 'Gut Microbiota: Role in Pathogen Colonization, Immune Responses, and Inflammatory Disease'. *Immunological Reviews* 279 (1): 70–89. https://doi.org/10.1111/imr.12567.

'Protocol Design'. n.d. Accessed 1 December 2023. https://www.iqvia.com/solutions/research-and-development/clinical-trials/protocol-design.

'PTR Pharma Consulting - About Us'. n.d. Accessed 13 November 2023. https://www.ptrconsulting.pt/about.html.

Seyedian, Seyed Saeid, Forogh Nokhostin, and Mehrdad Dargahi Malamir. 2019. 'A Review of the Diagnosis, Prevention, and Treatment Methods of Inflammatory Bowel Disease'. *Journal of Medicine and Life* 12 (2): 113–22. https://doi.org/10.25122/jml-2018-0075.

Sytrix. 2023. 'The Science'. 2023. https://www.sitryx.com/science#different-diseases-targeted-through-specific-cell-types.

Telavant. 2023. 'Pipeline'. 2023. https://www.telavanttx.com/pipeline.

Teva Pharmaceutivals. 2023. ‘Teva Innovative Medicine & Biosimilar Project Pipeline’. November 2023. https://www.tevapharm.com/product-focus/research/pipeline/.

Walsh, Cathy, and Caroline Conmy. n.d. ‘Understanding Medication in Inflammatory Bowel Disease (IBD)’.

Zhao, Mirabella, Lóránt Gönczi, Peter L Lakatos, and Johan Burisch. 2021. ‘The Burden of Inflammatory Bowel Disease in Europe in 2020’. *Journal of Crohn’s and Colitis* 15 (9): 1573–87. https://doi.org/10.1093/ecco-jcc/jjab029.

10 Appendix

Table of Abbreviations

5-ASAs	Aminosalicylates
CAGR	Compound Annual Growth Rate
CanGIEC	Canadian Gastro-Intestinal Epidemiology Consortium
CD	Crohn's Disease
CEO	Chief Executive Officer
CFO	Chief Financial Officer
CGF	Calouste Gulbenkian Foundation
CMO	Chief Marketing Officer
COO	Chief Operating Officer
CRO	Contract Research Organisation
E. coli AIEC	Escherichia coli AIEC
EFCCA	European Federation of Crohn's & Ulcerative Colitis Associations

Group Part

EMA	European Medicines Agency
FDA	Food and Drug Administration
GACD	Global Alliance for Chronic Disease
GI	Gastrointestinal
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
IGC	Instituto Gulbenkian de Ciência
IM	Information Memorandum
IND	Investigational New Drug
IP	Intellectual Property
IPO	Initial Public Offering
M&A	Mergers and Acquisitions
MAA	Marketing Authorization Application
NBO	Non-binding Offer
NDA	Non-Disclosure Agreement
NGP	Next-Generation Probiotics
PCT	Patent Cooperation Treaty
R&D	Research and Development
POC	Proof of Concept
ROI	Return on Investment

Group Part	
SCFAs	Short-Chain Fatty Acids
SPA	Sales and Purchase Agreement
UC	Ulcerative colitis
VC	Venture Capitalist
WHO	World Health Organization

Index of Figures and Tables

List of interviews and interview partners

Date	*Name*	*Position*	*Topic*
26.09.2023	Vitor Cabral	Researcher at IGC	Kick-off meeting
17.10.2023	Vitor Cabral	Researcher at IGC	Clarify questions about the break-through innovation
24.10.2023	4 individuals (anonymous)	Have been diagnosed with IBD	Survey to find out about their path of the diseases and treatment.
26.10.2023	Katarzyna Grabos	Pharmacist at the “Apotheke in Gossau” in Switzerland	Treatment options for IBD that are currently sold in Switzerland
28.10.2023	Viviana Triolo	Affected by IBD since 2011	Provided various key insights on Patient Journery and IBD
08.11.23	Marta Ribeiro	Head of Innovation at IGC	Innovation at IGC
08.11.23	Vitor Cabral	Researcher at IGC	Clarify questions about the break-through innovation
28.11.23	Etta	Specialist in dietetics and	Considerations and insights

	Finocchiaro	clinical nutrition at Fooderapy – Torino, Italy	about probiotic's current use and their potential in treating IBD
02.12.23	Pedro Henriques	Patent Attorney	Understanding the Mechanisms of PCT Patents
06.12.23	Cédric Schöllhorn	M&A Consultant at Business Transaction AG	Exit Strategy
06.12.23	Male (25yo)	Chron's Patient	Patient Journey
09.12.23	Pedro Henriques	Patent Attorney	PCT Official Fees

Table 5: List of Interview partners and interviews.
Source: Own illustration