# Napo Therapeutics

## Spearheading European crofelemer growth

31st March 2022

**A proven and tested ethnobotanical drug crofelemer, the significant and growing market for Short Bowel Syndrome (SBS) patients, an established business platform and a strong, experienced management team combine to imply a robust investment case for Napo Therapeutics S.p.A. (Napo Therapeutics).**

**Napo Therapeutics will be the exclusive licensee and distributor of ethnobotanical anti-secretory drug crofelemer in Western, Central and parts of Eastern Europe (excluding Russia)**. Crofelemer is a proven drug which is actively marketed in the United States by Jaguar Health, Inc., under the trade name Mytesi® for the indication of non-infectious diarrhea in adults living with HIV/AIDS on anti-retroviral therapy, a specialty market indication which was fast-tracked by the FDA.

**Jaguar, which owns the majority of Napo Therapeutics, is currently completing a pivotal Phase 3 clinical trial for cancer therapy related diarrhea (CTD) with Mytesi® in the U.S.** Napo Therapeutics' mission is to provide access in the region to the drug for multiple patient populations and indications, with an initial focus on addressing the important rare/orphan disease indication of SBS and CDD (Congenital Diarrheal Disorders).

**Napo Therapeutics benefits from the potential to serve a sizable and growing market with the use of crofelemer to treat SBS.** Sufferers from SBS are frequently prone to acute cases of diarrhea, which has negative implications for both their ability to absorb nutrition and to avoid the inconvenience of frequent water stool output. This report argues that this debilitating disease can be treated effectively through the prescription of crofelemer, which may also reduce the quantity and time needed for parenteral nutrition.

**Despite being an early stage company, Napo Therapeutics as a business is built on solid foundations.** As part of a due diligence process, this report highlights the FDA approved status of the licensor's (Jaguar) drug Mytesi®, which has the same active ingredient of crofelemer but with a highly differentiated drug formulation.

**Napo Therapeutics' novel formulation of crofelemer is expected to be more appropriate and medically necessary for SBS patients.** In the fourth quarter of 2021, the European Medicines Agency (EMA) granted orphan-drug designation (ODD) for crofelemer for SBS following submission of Napo Therapeutics' ODD application. An additional patient case study has been submitted for publication, included epidemiological data for the incidence and prevalence of SBS, data on the pathophysiology of SBS, support for the mechanistic rationale for crofelemer for SBS, medical plausibility information for crofelemer for SBS, together with preclinical pharmacology and patient case studies.

**Crofelemer received ODD in the U.S. for SBS in 2017; and an additional patient case study has been submitted for publication.** Moreover, there is an established business structure in Europe as well as a clearly defined set of licences for the use of crofelemer by indication.

**Napo Therapeutics is run by an experienced and talented management team, which is based in Milan, Italy.** This management team, which has specific experience with rare disease business model and drug development, is supported by an international team of scientific advisors specifically tasked with the implementation of the licence from Jaguar Health, Inc. as well as a Board of Directors which includes Jaguar's CEO Lisa Conte.

**Description**

**Napo Therapeutics (a majority owned subsidiary of Jaguar Health, Inc.) has the mission to provide access to the proprietary first-in-class plant based medicine crofelemer in Europe** to address significant rare/orphan disease indications. The company plans initially to address the Short Bowel Syndrome market and the potential for crofelemer greatly to enhance the lifestyles of sufferers from that indication. Further ahead, crofelemer may be used to reduce the diarrhea among patients who are being prescribed cancer related treatments – notably chemotherapy, Inflammatory bowel disease, and other GI dysfunctions.

**Napo Therapeutics is headquartered in Milan, Italy**. The company's robust and experienced management team enjoys an open and interactive relationship with the Jaguar Health, Inc. (NASDAQ: JAGX) senior management.

**The transformative value driver is planned to occur in ~12-15 months**, which includes the completion and publication of a proof of concept investigator initiated trial (s), in support of expanded patient access program for the orphan designated indication of SBS, generating meaningful revenues for Napo Therapeutics in 2023.

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# Napo Therapeutics

## Valuation wake-up call

We highlight the current market valuations for publicly listed early stage and rapid growth pharmaceuticals companies – i.e. 8x market cap:sales revenue. Were crofelemer to break into the forecast market of US6.2bn for biosimilar teduglutide in 2027, the upside could arguably be substantial for investors in crofelemer. Please note the pre-requisite in the paragraph below.

## Jaguar Health Inc (NASDAQ: JAGX) shareholders

This report has been prepared from publicly available information and assumptions/analysis of the investment analyst. A full version of the report with financial models is available on request subject to signing of important non-disclosure agreement.

# Investment case

**The investment case for Napo Therapeutics is the company's ability to gain approval for and to market crofelemer across Europe and thus to grow sales revenue as the drug is prescribed to treat target indications.** Given crofelemer is already a proven and approved drug in the USA, where it is marketed under the brand name Mytesi® and includes a chronic indication, there is far less risk associated with crofelemer in Europe than other developmental drugs.

**Most drugs fail regulatory approval due to safety and/or manufacturing issues.** There is a full and proven supply chain in place to manufacture crofelemer and Jaguar, the licensor, has that obligation to supply crofelemer to Napo Therapeutics. In this report's opinion, crofelemer stands to make a significant difference to patients' lives.

**Napo Therapeutics offers investors a proven concept** which can generate early-revenue in the important target market of, initially, Short Bowel Syndrome (SBS). However, there is scope to grow the drug for additional indications beyond SBS both within its Tier A applications and in Tier B and Tier C, both of which we discuss in this report. The licensor's pursuit of these additional indications will continue to generate clinical and regulatory data that Napo Therapeutics is entitled to under the license agreement with Jaguar.**Overall, this report argues that there is a robust proof of concept for the business, meaningful and growing addressable markets, potential for a material due diligence process and a strong management team**

# Spearheading European crofelemer growth

This report is structured into four sections which cover the core crofelemer proof of concept (notably in modified form to address SBS and other orphan diseases), its addressable markets, an element of due diligence on the business itself and an assessment of the leadership team.

## Crofelemer - proof of concept

### Crofelemer and Mytesi® in a nutshell

Crofelemer is the active pharmaceutical ingredient (API) of the drug already FDA approved and marketed by Jaguar Health, Inc. in the USA, where it is sold under the brand name Mytesi®. Crofelemer has published clinical data for a number of diarrhea indications, including acute traveller's diarrhea, IBS, CTD, cholera, and HIV-related diarrhea, for which the product is currently FDA approved and marketed in the US. As stated earlier, Jaguar Health, Inc. owns a majority of Napo Therapeutics.

A principal attraction of crofelemer as a prescription drug includes the sourcing of its active pharmaceutical ingredient (API) which was developed through the science of ethnobotany. Jaguar, which is responsible for supply of crofelemer to Napo Therapeutics under the license agreement, sustainably harvests raw plant material (known as crude plant latex, CPL) in South America, transports it to India or Italy to be converted into an API, and has it then converted into finished product bottled in the US.

Importantly crofelemer is not an opioid. For mainstream diarrhea indications this contrasts the drug markedly with its main competitors. As might be expected, the use of opioids to treat diarrhea for long term indications can generate negative side effects. In particular, a common complaint is that such drugs halt diarrhea by effectively closing down the patient's gastrointestinal system which in turn can lead to constipation. Crofelemer works *with* the patient's body rather than *against* it.

### How crofelemer works

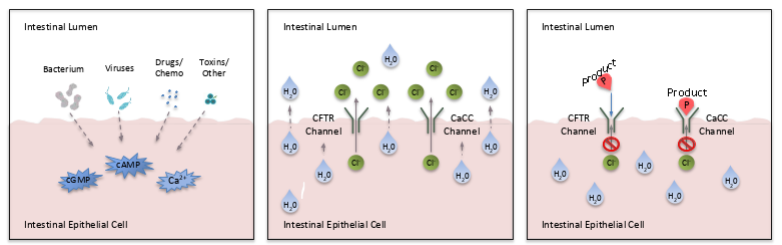
Crofelemer's unique quality is that it promotes the normalisation of a patient's intestinal contents as well as avoiding what effectively amounts to accompanied constipation. As a result, it contrasts markedly with anti-motility drugs (opioid-based over the counter and prescription medicines), which effectively constipate the

patient and arguably deliver few sustainable benefits. In addition, these antimotility drugs are not approved for use for chronic diarrhea relief and have not been specifically tested or approved in HIV, cancer, IbD, or SBS patient populations.

Where diarrhea may have been caused by insults associated with drugs, toxins and excess hormones rather than the common incidences of symptoms caused by contaminated food and drinks, there are clear medical benefits from what is effectively a restorative treatment. Indeed, the company states that in clinical trial studies approximately 98% of Mytesi® (crofelemer) patients reported no significant constipation due to taking the drug.

The essential workings of crofelemer are summarised in Figure 1. The drug acts at the last step in a physiological pathway, regardless of cause. It thus normalises defective chloride ion secretion and specifically mitigates dehydration through physiological correction leading to passage of formed stools. Importantly, the drug acts locally in the gut and has minimal oral absorption.

**Figure 1 – Crofelemer® - unique anti secretory mechanism of action**




*Source: Napo Pharmaceuticals Inc.*

## Crofelemer and SBS

Crofelemer is particularly pertinent in the potential treatment of Short Bowel Syndrome (SBS). While it should be noted that diarrhea as a condition on a medium to long term basis is neither desirable nor advisable, the severity of diarrhea for SBS patients can be exponential relative to normal sufferers, leading to extreme morbidity and even mortality in the disease management of these patients.

In addition to the discomfort caused, other negative symptoms include dehydration and loss of vital nutrients, which is clearly an added problem for patients already suffering from another prolonged ailment. The symptoms for sufferers from diarrhea with SBS can be significantly worse.

Crofelemer trials will aim to demonstrate both reduction of diarrhea and reduction in the time and quantity of parenteral nutrition, by allowing greater opportunity for the patient to naturally absorb essential nutrients.

SBS, which we discuss further in our “addressable market” section refers to catastrophic loss of bowel due either to surgical resection of diseased or necrotic bowel. Figure 4 compares a “before surgery” or “normal bowel” with one which is either post resection or diseased. The impact on bowel length can be to reduce it from a normal range of 460cm to 765cm to only around 150 cm or less (15-25 feet down to 5 feet or less).

As mentioned above, excessive bouts of diarrhea can lead to acute malnutrition as the body drains excessive fluid. As a result, may patients are subject to parenteral nutrition and other invasive disease management processes. A small percentage of patients may also be given teduglutide - an analogue of human glucagon-like peptide-2 (GLP-2) which preserves mucosal integrity by promoting growth and repair of the intestine - simultaneously with nutritional support.

**Hence, a naturally based SBS disease treatment such as crofelemer delivers significant benefits medically as well as reducing lifestyle disruption.**

## Orphan and early access competence

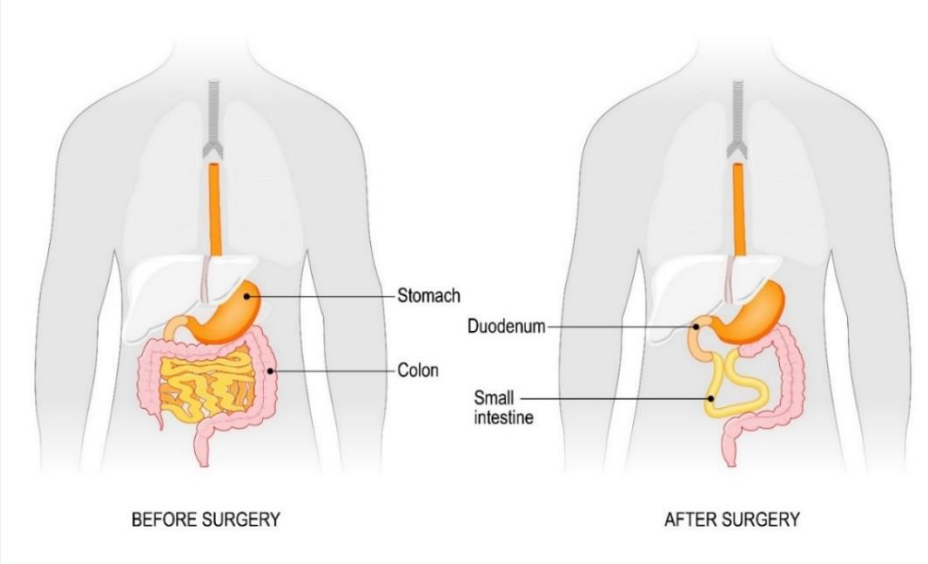
Napo Therapeutics boasts significant competence in orphan and early access drugs. An orphan drug is defined as a drug used to treat, prevent or diagnose an orphan disease – i.e. one which affects a small number of people. For example, in the US which at end-2020 had a population of 331 million persons the orphan threshold is currently 200,000 people. Orphan diseases are often serious or life threatening. (Sources: *www.cancer.gov* and *www.worldometers.info*)

Napo Therapeutics has been granted exclusive orphan status for crofelemer as a treatment drug for SBS - where it owns the exclusive perpetual license to the drug outright in the EU, Switzerland and the UK. Importantly, the company has a fully paid perpetual license. It is envisaged that as soon as April, hospital investigators within relevant jurisdictions will conduct clinical trials for crofelemer in relation to SBS.

## Change of formulation for SBS patients

Importantly, crofelemer for SBS patients will be prescribed and distributed in a highly concentrated liquid and soluble powder formulation which is necessary to mitigate any insult to the intestinal tract of these kinds of highly ill patients. Mytesi® in the US is prescribed in bottles of tablets which are taken with water.

**Figure 2 – Short bowel syndrome (SBS) illustrated**




*Source: Napo Therapeutics presentation data*

Crofelemer the drug benefits from a unique anti-secretory mechanism of action which is shown in Figure 5. Put simply, crofelemer is a first-in-class, locally acting, chloride ion channel modulator, which normalises the increased volume of intestinal fluid and the imbalance of electrolytes in the gut that my result from inflammation and hypersecretion.

Furthermore, in patients with SBF-IF, a condition resulting from surgery to remove all or part of the intestine - who suffer severe malabsorption, crofelemer may help balance the secretion and reabsorption of fluids and facilitate better absorption of major nutrients (proteins, fats, carbohydrates and vitamins) and micro-nutrients (trace minerals) that support health and survival. Even a 20% reduction in the need for parenteral nutrition can be hugely beneficial to the patient's nutritional and health outcome, quality of life, and mitigation of complications.

**Figure 3 – Crofelemer unique anti-secretory mechanism of action**


*Source: Napo Therapeutics presentation data*

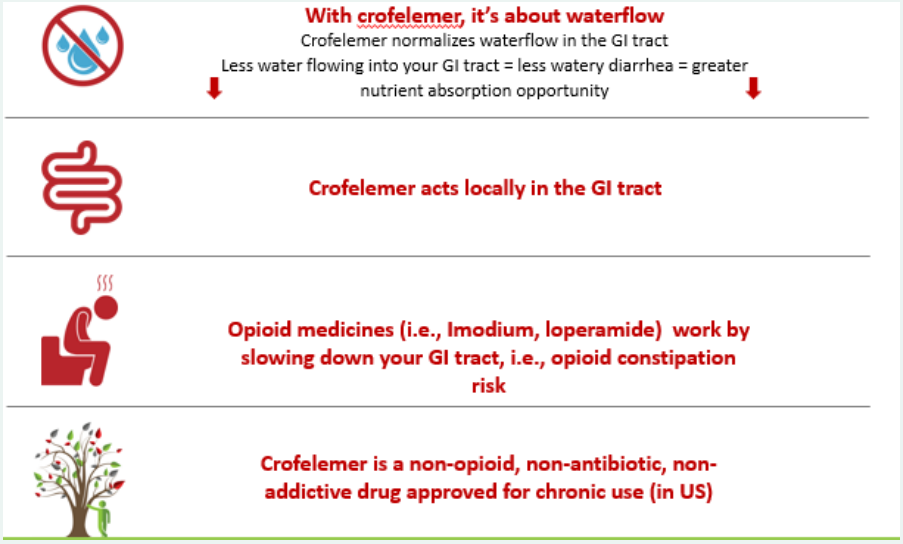
We note that for individuals with unaffected bowel function, Chloride ion (Cl) channels in the GI tract maintain a balance of salts—including chloride ions—and water that allows normal stool formation

In cases of **diarrhea or poor absorption in SBS-IF**, the smaller luminal surface area in a short gut leads to severe malabsorption of fluids and nutrients, and malnutrition.

**Crofelemer** works by regulating two chloride ion channels (CFTR and CaCC) in the GI tract, which normalizes the salt-water balance in intact bowel and leads to less hypersecretion and better resorption of fluids and nutrients in SBS-IF patients.

A supplementary illustration of how crofelemer works in more detail is given in Figure 4. As emphasised earlier in this report, crofelemer is a non-opioid that works differently from other treatments for GI dysfunction. The key points are that it prioritises, waterflow, acts locally in the GI tract, avoids constipation risk and is approved for chronic use in the US. Moreover, it is non-antibiotic and non-addictive.

**Figure 4 – How crofelemer works in more detail**




*Source: Napo Therapeutics presentation data*

## Crofelemer's sizable addressable markets in Europe

In this report's opinion, crofelemer addresses a number of sizable markets in Europe and should demonstrate superior performances to its key competitors and current practices when prescribed. An overview of these markets and their increasing market value is given in Figure 5.

**Figure 5 - Increasing market value**

**1 - Progression from supportive care to impact on outcome**

**2 - Cost of care to treatment modifying**

**3 - Global market for gastrointestinal agents (Rx & OTC) to reach US$21bn by 2025**

| Indication | Competitors | Market size/potential |
|---|---|---|
| HIV-D | 0 | Jaguar estimates peak US market sales revenue potential for Mytesi® to be US$50m to US$70m |
| Cancer Therapy Related | 0 | 1.8m cases in US in 2020. 1m undergo targeted therapy and/or chemo annually.<br>Rose 5% in past 2 years. Comp supportive care market may reach US$2.7bn by 2022. |
| SBS/Intestinal failure | 0 | 10,000 to 20,000 in US have SBS. |
| Congenital disorders | | Orphan drug designation provides potential accelerated approval. Estimated a<br>annual revenue for Gattex is US$0.5bn. Global SBS to reach US$4.6bn by 2027.<br>Gattex sales growth CAGR bn 2020 and 2027 estimated to be 26%. |
| Irritable bowel syndrome | 3 | 15% adult population. Most IBS products have est revenue potential of >US$1.0bn |
| Irritable bowel disorder | 0 | Estimated 1.2bn US residents have IBD |
| Covid-associated diarrhea | 0 | Assuming 25% poulation infected with COVID => above 50million in EU |
| Symptomatic relief of diarrhea from cholera | 0 | Priority review vouchers have sold for US$60m to US$350m |

*Source: CWIC Equity solutions estimates based on market information*

Napo Therapeutics' significant competence in orphan and early access drugs, which we describe above, is notably pertinent for France, Italy and the UK. Orphan drugs and early access drugs for rare diseases are actively encouraged by the French and Italian universal healthcare systems. France's government already released a "French National Plan for Rare Diseases 2018-2022 and Italy boasts the Italian National Rare Diseases Registry. Both reference points tend to confirm special publicly financed commitments to rare diseases. (Sources: *solidarites-sante.gouv.fr* and *www.iss.it*). Moreover, in the UK, the Early Access Medicines Scheme (EAMS) aims to give patients with life-threatening or seriously debilitating conditions access to pre-marketing authorisation drugs that fulfil a clear unmet medical need. (Source: *www.gov.uk* )

Some useful examples of early access programmes (EAPs) for orphan drugs in Europe are given in Figure 6. These include four drugs which were admitted into either the French or Italian EAPs and one which gained acceptance in the Middle East.

**Figure 6 - Early access to orphan drugs in Europe**

| Drug | Indication | Company | EAPs |
|---|---|---|---|
| Cystadrops® (cysteamine) | A cystine depleting agent idicated for the treatment of corneal cystien crystal deposits in adults and children with cystinosis | Recordati rare diseases | France, Italy, Middle East |
| Oriadeyo® (berotraisat) | Oral therapy used to prevent swelling attacks in people with hereditary angioedema (HAE) | BioCryst Pharmaceuticals | France |
| Orkambi® (lumacaftor/ivacaftor) | Cystic fibrosis (CF) | Vertex Pharmaceuticals | France |
| Translarna® (ataluren) | Duchene muscular dystrophy (DMD) | PTC Therapeutics | Italy |

*Sources: Company website data*

Furthermore, unmet medical needs for crofelemer outside Europe should expand the potential clinical trial population for the drug. The Middle East is a region – potentially due to congenital predisposition to SBS – which has recently shown interest in the potential for crofelemer to be accessed by patients in the region under investigator-initiated trials.

For example, Investigator Initiated Trials (IITs) and Proof of Concept studies have been requested by Sheikh Khalifa Medical Medical City in Abu Dhabi, UAE. Moreover, the World Congress of Gastroenterology (WCOG) will be held in partnership with the Emirates Gastroenterology and Hepatology Society between 12th and 14th December 2022 in Dubai, UAE.

## SBS – an expanding global opportunity

Napo Therapeutics makes a strong claim that SBS is an expanding global opportunity. The key market mathematics tend to support that positive view. Treatment options are currently limited for SBS. Despite that limited offer, the market was estimated to be worth US$0.6bn in 2019 with the potential to grow to $4bn by 2027 – i.e. at a 30% compound annual growth rate (Source: *www.mynewsdesk.com*).

The estimated population size for SBS is around 20,000 in Europe, where it is growing dramatically with a similar 20,000 estimated for the US. Our own assumptions thus appear conservative at closer to 18,000.

## Parenteral nutrition avoidance

Crofelemer's potential ability to eliminate the time during which patients to have parenteral nutrition represents major healthcare system cost and patient welfare advantages. Parenteral nutrition is defined as a form of nutrition that is delivered into a vein. Parenteral nutrition does not use the digestive system. It may be given to people who are unable to absorb nutrients through the intestinal tract because of vomiting that won't stop, severe diarrhea ,or intestinal disease. But it is an arguably inconvenient and visibly expensive solution.

The purpose of parenteral nutrition is to give all of the protein, fats, carbohydrates, vitamins and minerals (the "nutrients of life") a person needs using intravenous (IV) administration, since there is not sufficient

length of the intestinal tract to appropriately absorb vital nutrients. Parenteral nutrition can be administered for up to 7 days a week, 20 hours a day. Importantly, this type of parenteral nutritional support is rarely administered without complications. (Source: *www.cancer.gov* )

Parenteral nutrition is costly to administer. Estimated reimbursement costs incurred by universal healthcare providers in Europe are hard to quantify precisely given the potential for complications. It is well known that the administration of parenteral nutrition is rarely straightforward.

Data from the United States suggest that total costs of parenteral nutrition in the 16.5 days ahead of an operation might be of the order of US$3,500 to US$4,000 – i.e. around US$250 per day. Were this to be extrapolated to an SBS patient requiring full-time parenteral nutrition the number could be inferred to be closer to US$90,000. Moreover, that would be without any complications. (Source: *pubmed.ncbi.nlm.nih.gov*).

## SBS and IF – Crofelemer to reduce patient mortality and morbidity

**SBS** is a complex condition characterized by severe **malabsorption of fluids and nutrients** due to surgical resection of bowel segments, congenital anomalies or disease-associated loss of absorption requiring parenteral nutritional support for survival. SBS patients suffer from **malnutrition, dehydration, imbalances of fluids and salts,** excessive intestinal fluid output and **risk of organ failure.**

**Intestinal failure (IF)** is defined as the reduction of intestine function to the extent that that fluids and nutrients given by the enteral/parenteral route are required to maintain health.

Importantly, sufferers from both SBS and IF face serious challenges to their ability to carry out normal activities associated with daily living. In particular, the ability to participate in academic activities and workplaces is severely compromised by the frequency and persistency of encountering incidences of acute diarrhea, and the disruption to the life of required parenteral nutrition requirements. Moreover, there are frequent health and expensive complications associated with lifelong parenteral nutrition. Hence, we stress the negative impact on life quality in this report.

(Sources: *Managing the Adult Patient With Short Bowel Syndrome, Carol Rees Parrish, MS, RD and John K. DiBaise, MD* and *www.medicinejournal.co.uk* ).

## Increasing market value

This report believes strongly in crofelemer's key deliverables. The company argues for the progression from supportive care, such as symptomatically managing diarrhea in specific patient population, to a direct impact on outcome. It is arguably important to allow patients to improve their outcomes and to some extent thrive during their disease intervention (i.e. parenteral nutrition intervention in SBS;cancer therapy for CTD.

Put simply, the **gastrointestinal tract is arguably the body's second line of defence of the immune system after the skin.** Normal functioning of the small intestine is crucial to optimize a patient's absorption of fluids and nutrients to support life.

## Cancer therapy related diarrhea (CTD)

Cancer therapy related diarrhea is clearly a massive market and one which we believe crofelemer is in a strong position to address. For example, around 1.8m new cancer cases were diagnosed in the US in 2020 with the estimated number in the UK being around 0.4m.

In both countries around half of one percent of the population can expect to be diagnosed with a cancer each year. Clearly, with ageing populations this number is likely to increase as reflected in the greater propensity for healthcare systems to screen older people for common cancers such as breast and bowel.

Worldwide, the number of newly diagnosed cases of cancer is estimated to be around 18 million annually. More importantly for Napo Therapeutics and the opportunity for crofelemer is that around 9.8 million people are currently estimated to be receiving chemotherapy. Diarrhea can be an adverse side effect of chemotherapy and other cancer therapies, such as targeted treatment options.

**Crofelemer has potential to "enable" innovation:** In fields such as targeted cancer therapies (such as TKIs and EGFRs) should also be noted. For example, **patients with cancer-therapy related diarrhea (CTD) were 40% more likely to discontinue chemotherapy or targeted cancer therapy than patients without CTD.** (Source: *www.meetinglibrary.asco.org* ). As a result, the use of crofelemer to prevent or better control CTD may enable patients to complete their course of therapy with their ideal cancer treatments at recommended doses. Patients with CTD used significantly more healthcare resources, increasing the overall cost of cancer care by nearly 3 times..(Source: *www.meetinglibrary.asco.org* ).

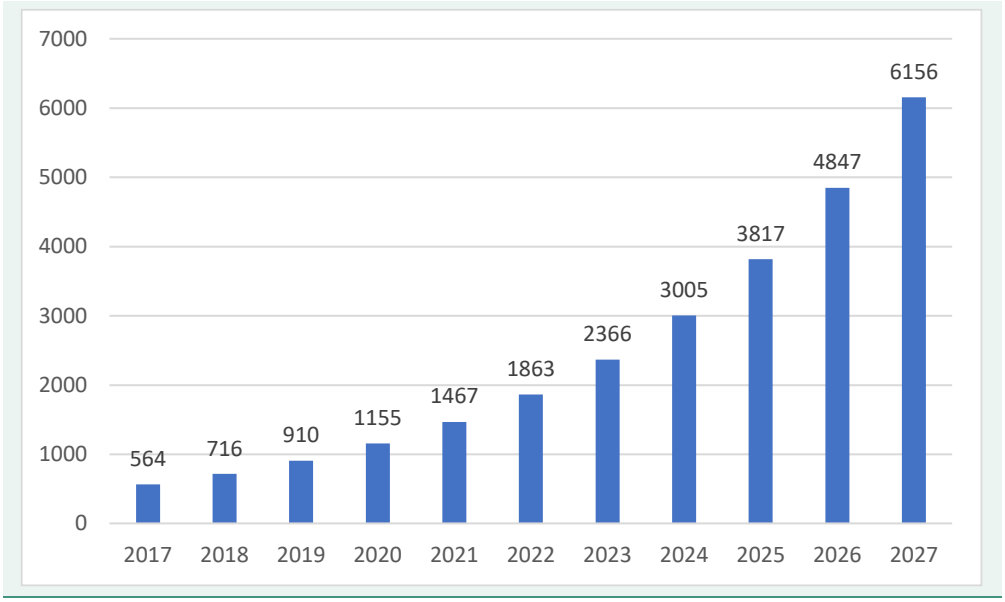
## Teduglutide – the opportunity to grab market share

Teduglutide is the dominant drug currently on offer for SBS patients. Two manufacturer brands currently serve the market for teduglutide. These are Revestive and GATTEX® both of which are distributed by Takeda.

Teduglutide is a glucagon-like peptide-2 analog (GLP-2 analog) that is used for the treatment of short bowel syndrome. It works by promoting mucosal growth and possibly restoring gastric emptying and secretion, and was approved with an endpoint of reducing the duration required for parenteral nutrition. These studies did not indicate an improvement in quality of life measures, which have limited teduglutide's reimbursement opportunity in several European countries.

Estimated market size and growth for teduglutide is summarized in Figure 7 which uses www.biospace.com data. Biospace estimated that in 2018 the global market size for teduglutide and biosimilars was US$564m. However, their expectation was for phenomenal compound growth of the order of 27% annually. If correct, the implied market size for teduglutide and biosimilars would be in excess of US$6bn well ahead of the end of the current decade. This market estimate did not include the possibility of a crofelemer/anti-secretory mechanism of action.

**Figure 7 – Teduglutide projected growth in US$m**




*Source: www.biospace.com*

## Teduglutide – assessing the limitations

A number of side effects and limitations are associated with teduglutide. It is interesting that both the US FDA and EMA granted orphan status to crofelemer, recognizing the unmet need in the SBS marketplace served by biosimilars to GLP-2 analogs... "Good but by no means perfect" is arguably an accurate description of the drug or associated treatment. A number of the drug's shortcomings are not shared by crofelemer. It is estimated that teduglitide currently has ~2.7% market share of the SBS market place, and is limited in the target patient population relative to the expectations for crofelemer to be tested in clinical trial design: broader enrollment criteria post surgical adaptation time and endpoint definition including quality of life.

Additionally, teduglutide should not be prescribed to patients chronically. Typically courses of teduglutide are limited to between 3 and 4 months, in contrast to crofelemer which can be prescribed on a continuous basis.

Using www.mayoclinic.org as a source, a number of other arguably unwelcome side effects can be identified from subcutaneous injection of teduglutide. These include but are not necessarily limited to the following:-

- Decrease in the amount of urine
- excess air or gas in the stomach or bowels
- fast heartbeat
- fever
- full or bloated feeling
- hives, itching, skin rash
- hoarseness
- irritation

- joint pain, stiffness, or swelling
- noisy, rattling breathing
- pressure in the stomach
- redness of the skin
- stomach pain
- swelling of the abdominal or stomach area
- swelling of the eyelids, face, lips, hands, or feet
- tightness in the chest
- troubled breathing at rest
- troubled breathing or swallowing
- weight gain

In addition, some patients may be expected to encounter indigestion as well as severe nausea and vomiting. Based on the experience with Mytesi® taken in tablet form in the US, crofelemer is less likely to cause so many adverse side effects in our view.

## A closer look at Napo Therapeutics

Despite being at a relatively early stage, Napo Therapeutics gives the impression of being a well-grounded business with strong business partnerships, a clear competence in orphan and early access programmes, a near term transformative value enhancing event (EAP revenue generation), and the substantial benefits of its close association with its majority owner Jaguar Health, Inc. in the USA. Napo Therapeutics has indicated its intention to seek a liquidity event in the next 12-15 months, consistent with the completion of its planned POC IIT trials in support of EAP.

We look at each of these items in turn as well as commenting in more detail on the current competitive backdrop and Napo Therapeutics' robust IP protection.

### Strong partnerships

#### *Outsourced manufacturing*

Napo Therapeutics benefits from a number of strong business partnerships, which arguably belie the company's early-stage status. In our view, the most important of these is its outsourced manufacturing platform where partners include Indena, Glenmark and Patheon.

**Indena** is based in Milan, Italy and prides itself on being a 100-year old leading global research, development and global manufacturer of pharmaceuticals and botanical extracts. The company has capacity at its industrial facility to produce 50 tons of crofelemer active pharmaceutical ingredient (API) annually.

Indena's operations are substantial and lend significant feasibility to the Napo Therapeutics project in Europe. In addition, its status as a leader in pharmaceuticals from botanical extracts makes it an ideal partner with which to work with crofelemer as Jaguar Health, Inc. has already proved with Mytesi®.

The company employs more than 800 staff who work across its R&D Centre, 5 production sites and 5 international branches. It sells into 7 different countries. Indena produces drug substances under cGMP EMA and FDA guidelines.

**Glenmark Pharma** is an innovative pharmaceuticals research company which aims to explore the unparalleled possibilities of science and innovation to create breakthrough therapies for the global patient population. Its sustained investment in research and development helps the company identify and advance promising treatments that benefit millions of patients globally while maintaining high ECG credentials

Glemark Pharma claims to be home to some of the best global scientific talent that continuously challenges treatment paradigms and builds on the success of established franchises. At present, its portfolio of differentiated medicines in respiratory, dermatology and oncology is acclaimed as breakthrough solutions for a wide range of diseases.

**Patheon** is a service brand within Thermo Fisher Scientific's brand portfolio. Contract development and manufacturing organization (CDMO) services offered under the Patheon brand include small molecule API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics and commercial manufacturing and packaging. In 2017, Patheon was acquired by Thermo Fisher Scientific to form its Pharma Services business.

### *Research & Development*

Napo Therapeutics works with multiple Clinical Research Organizations which offer a complete range of clinical development and consulting services to pharmaceutical, biotechnology and medical companies.

### *Other services*

Other service providers into Napo Therapeutics include Syneos Health and Alira Halth for market research, Granzer for regulatory consulting and services, Carter & Benson for management recruitment, Willkie Farr & Gallagher LLP for legal services and E&Y for accounting based business services and SecNewGate for Corporate Communication and Social Media. Overall, the partnerships represent in our view an important endorsement of any due diligence process for Napo Therapeutics. They are summarized in Figure 8.

**Figure 8 – Napo Therapeutics partnerships**

*Source: Napo Therapeutics presentation data*

## Jaguar Health, Inc.

Napo Therapeutics' business outlook is significantly underpinned by its relationship with majority owner Jaguar Health, Inc. who developed crofelemer into Mytesi® in the US. As we discuss in our next section on Management & Strategy, Jaguar Health, Inc. will have an important steering role in the future management of Napo Therapeutics.

However, it should be noted that both the formulation of crofelemer in Europe and the indications for which the drug is prescribed – i.e. the markets which it will address - are markedly different.

Crofelemer will be distributed in Europe as a new brand with a new highly concentrated liquid formulation in contrast to Mytesi® in the US which is prescribed in bottles of pills. This difference is important medically for administration to SBS patients, which received the classification as an orphan drug in Europe.

Overall, Napo Therapeutics adds a significant skillset in orphan drugs to Jaguar Health, Inc.'s existing capabilities, which supports the argument that the relationship is value enhancing. Crofelemer will address new markets in fresh jurisdictions but with the backing of an established company with an approved drug based on similar ethnobotanical credentials.

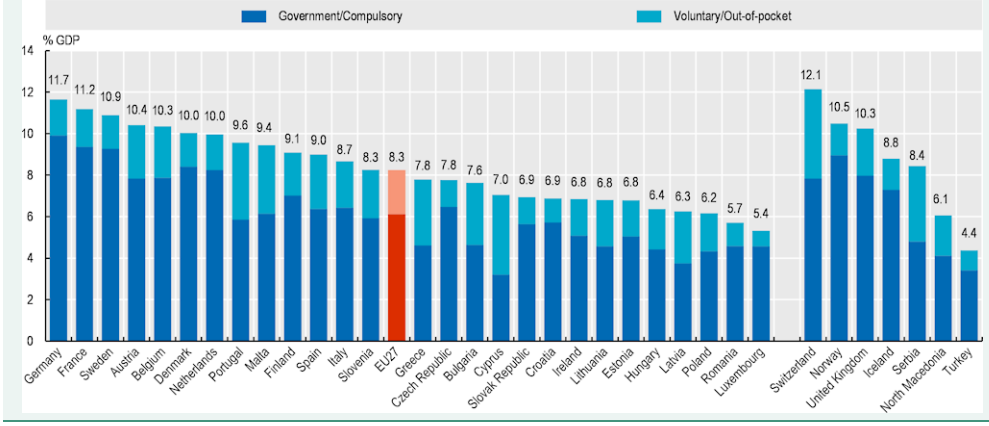
## The European advantage

This report notes the importance of targeting France, Italy and the UK for rare diseases. Such countries have proven, stated objectives in combatting rare diseases through designated vehicles within their health systems as stated earlier in this report.

However, investors should also note the preponderance of universal – i.e. taxpayer or mandatory insurance scheme funded – healthcare systems within the European Union and the UK. As a result, when assessing relative healthcare expenditure as a portion of GDP investors should in our view be aware that such expenditure is typically being incurred by single-entity government funded organizations.

In 2019, the unweighted average expenditure by EU countries on healthcare was 8.3% of GDP. However, this statistic through being unweighted masquerades the larger portions of GDP which are expensed by the more sizable EU economies – notably Germany at 12% and France at 11%. Outside the EU, the larger economies of Switzerland and the UK spent 12% and 10% respectively. These comparisons are illustraded in Figure 9.

**Figure 9 – Health expenditure as % GDP in 2019**




*Source: www.oecd-ilibrary.org*

## Current treatment profiles – teduglutide in more detail

Crofelemer in this report's view has no direct competitor given its potential exclusivity and orphan status. However, it is worth noting some particulars of the drug which it is likely to replace.

As mentioned above, a small percentage of SBS patients are sometimes treated with teduglutide which is delivered in powdered form and injected via a canular into the patient. Examples of branded, approved teduglutide drugs include Gattex® (USA) and Revestive® (Europe).

A disadvantage of teduglutide is that for some patients there are a number of observable side effects (Source: *www.mayoclinic.org* ) as well as the any inconveniences associated with subcutaneous delivery of the drug. In addition, it can be argued that teduglutide delivers limited quality of life benefits which contrasts markedly with crofelemer's ability reduce incidences of diarrhea.

But a clear positive message from the administration of teduglutide in its key branded forms is that health authorities are willing to reimburse substantial sums of money for the drug. This sends a clear positive message in this report's opinion for crofelemer when sold in powdered form to treat SBS patients. In Figure 10 we include our estimates for teduglutide/Revesitve® reimbursement costs in major European jurisdictions.

**Figure 10 – European competitive landscape - pricing & reimbursement**

| Healthcare system | Annual price | Reimbursement |
|---|---|---|
| Germany | €255,000 to €265,000 | Yes |
| France | €220,000 to €230,000 | Yes |
| Italy | €195,000 to €205,000 | Yes |
| Spain | €220,000 to €230,000 | Yes |
| Ireland | €225,000 to €235,000 | Yes |
| Sweden | €210,000 to €220,000 | Yes |
| United Kingdom (Scotland) | n/a (confidential) | ongoing/(yes) |

*Sources: CWIC Equity Solutions Ltd estimates*

Teduglutide treatments typically generate reimbursement payments from universal health providers in Europe typically of the order of €195,000 to €265,000 per patient. Given the potential for add-ons, the higher numbers seem reasonable assumptions for potential revenue per patient, according to Napo Therapeutics' own business research.

Based on observable reimbursement costs and the number of potential SBS patients which we include in our financial forecasts, we believe the value proposition from crofelemer for SBS sufferers is arguably clear.

## Robust IP protection

Currently, Jaguar Health through Napo Pharmaceuticals, Inc., a wholly-owned subsidiary of Jaguar Health, holds around 145 patents, of which the majority do not expire until 2027-2031 and has 42 patents pending.

As a result of its botanical guidance protection, there is no generic pathway which might devalue the ownership of crofelemer as an orphan drug to treat SBS patients in the near term.

# Management and strategy

## Strategy

The central strategy of Napo Therapeutics is to develop its identity as a rare disease business model, and to develop, market and distribute crofelemer in a highly concentrated liquid administration (powered formulation to be reconstituted) in Europe to address the important and likely growing number of SBS indications in the region. This report's view is that the company is correct in its opinion that SBS sufferers are not well served by the current range of treatments include the requirement of parenteral nutrition.

Napo Therapeutics is set to deliver a drug that makes a meaningful difference to the quality of its patients' lives over the long term. Moreover, the business dynamics given likely pricing and a sizable addressable market make clear sense.

Napo Therapeutics' near term goals are outlined in Figure 11. What the company plans to do is achieve its synopsis pivotal clinical trial by the end of March 2022 and move swiftly towards EMA scientific advice approval by the end of the year. A heavy schedule of submissions and clinical evidence generation as well as the start of both the early access programmes and pivotal clinical trials are expected to occur in the first half of 2023.

**Figure 11 - Near term goals**

| Date | Objective |
|---|---|
| Mar-22 | Synopsis pivotal clinical trial |
| Apr-22 | Start POC study, communication plan readiness |
| May-22 | KOLs engagement |
| Jun-22 | Brand positioning, new website, social media |
| Jul-22 | MSLs disease awareness |
| Aug-22 | |
| Sep-22 | Scientific advice submission request, PDCO meeting |
| Oct-22 | |
| Nov-22 | End POC study |
| Dec-22 | EMA scientific advice approval |
| Jan-Mar 23 | CTA submission in Europe |
| | POC clinical outcome evidence |
| | Scientific publication |
| April-June 23 | Start early access programmes |
| | Start pivotal clinical trial |

*Source: Napo Therapeutics presentation data*

These near term goals can be summarized more succinctly as the milestones and deadlines which appear in Figure 12. There is a clear message in terms of both moving quickly and covering of key areas of study results, scientific advice, early access programmes and clinical trials which all argue in favour of Napo Therapeutics moving towards the kind of revenue generation which we include in our forecasts.

**Figure 12 - Milestones and deadlines**

| Milestones | Deadline |
|---|---|
| POC Study results | Q4 2022 |
| EMA Scientific advice | Q4 2022 |
| Start Early access programmes | Q2 2023 |
| Start Pivotal clinical trial | Q2 2023 |

*Source: Napo Therapeutics presentation data*

## Management team

The Napo Therapeutics management team is led by Massimo Mineo in his role of General Manager and Managing Director. He is backed up by Chief Regulatory Officer Annabella Amatulli and Chief Medical Officer Martire Particco, MD. There is a Joint Steering Committee for Napo Therapeutics with Jaguar and Napo Pharma management. We summarize the management team in Figure 13 with key biographical details in the paragraphs beneath.

**Figure 13 - Napo Therapeutics Management**

| Officer | Role |
|---|---|
| Massimo Mineo | General Manager and Managing Director |
| Annabella Amatulli | Chief Regulatory Officer |
| Martire Particco | Chief Medical Officer |

*Source: Napo Therapeutics*

**Massimo Mineo** is a veteran of Europe's pharmaceutical industry for 20+ years, is responsible and accountable for the strategy, planning and implementation of all Napo Therapeutics' commercial and operational activities within Europe. His success will be defined by bringing crofelemer to market for target indications, beginning with SBS-IF. Importantly, Massimo has a rare disease focus.

**Annabella Amatulli** is a recognized expert in global regulatory affairs, is responsible for both high-level strategic planning and hands-on support for Napo Therapeutics' development programs and licensed products from the regulatory standpoint. She serves as the primary liaison between Napo Therapeutics and European health authorities.

**Martire Particco, MD** is a physician with 30+ years of experience in Europe's pharmaceutical industry and in clinical practice leads Napo Therapeutics' clinical programmes. These programmes are intended to support marketing authorization in Europe for crofelemer, beginning with the SBS-IF and CDD target indications.

Napo Therapeutics' management team is backed up by three additional layers of business and pharmaceutical expertise. These include the Scientific Advisors to Napo Therapeutics as part of the License from Jaguar, the Napo Therapeutics Board of Directors and the Jaguar/Napo Pharma Joint Steering Committee. The three bodies are summarised in Figures 14, 15 and 16 with accompanying biographies beneath each figure.

**Figure 14 - Advisors to Napo Therapeutics as part of licence from Jaguar**

| Advisor | Key attributes |
|---|---|
| Corey A Siegel | Section chief of gastroenterology and hepatology |
| Wolfgang Fischbach | Gastroenterologist and oncologist |
| Mohammed Miqdady | Pediatric gastroenterology, hepatology and nutrition expertise |

Note: Discussions are in place with key opinion leaders in France and Italy

*Source: Napo Therapeutics*

**Corey A. Siegel, MD, MS:** Section Chief of Gastroenterology and Hepatology and the Co-Director of the Inflammatory Bowel Disease (IBD) Center at the Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire. He is a Professor of Medicine and of The Dartmouth Institute for Health Policy and Clinical Practice at the Geisel School of Medicine at Dartmouth.

**Prof. Dr. med. Wolfgang Fischbach:** German gastroenterologist and oncologist. 2007 and yearly since 2010: FOCUS list of Germany´s best gastroenterologists & oncologists. Since 1992: Principal investigator of the German multicentre studies on gastrointestinal lymphomas, supported by continuous grants of the German Cancer Society. 2003: President of the German Society of Gastroenterology. 1995: Professor of medicine at the university of Würzburg. 1993-2018: Head of Dept. of Medicine, Klinikum Aschaffenburg, academic teaching hospital of the university of Würzburg.

**Mohammed Miqdady, MD:** Division Chief of the Pediatric Gastroenterology, Hepatology & Nutrition Division at Sheikh Khalifa Medical City in the United Arab Emirates. American Board certified in Pediatric Gastroenterology, Hepatology and Nutrition. Also serves as an Adjunct Staff at the Cleveland Clinic in Ohio, US.

**Figure 15 - Napo Therapeutics Board of Directors**

| Board Members | Role |
|---|---|
| Lisa Conte | Board member |
| Joshua Mailman | Board member |
| Dr Niccolo Caderni | Board member |
| Gianmaria Conti | Board member |
| John Micek III | Board member |
| Jonathan B Siegel | Board member |

*Source: Napo Therapeutics*

**Lisa Conte** is the founder, president & CEO of Jaguar Health, Inc.. 30+ years of industry experience. Obtained first oral anti-secretory human product FDA approval under botanical guidance from the FDA Board of directors of Healing Forest Conservancy. Life Science Leader, Editorial Advisory Board. Raised over $400m.

**Joshua Mailman** is a New York City based impact investor; co-founded Social Venture Network (now Social Venture Circle) in 1987; founded Threshold Foundation in 1981; founded Business for Social Responsibility in 1992. Founded Serious Change L.P., a $100M privately held impact fund, in 2006;

founding investor in GonoPhone (Grameen Telecom) - only cell phone 40% owned by a social enterprise, current market cap $4bn. Founding investor in Global Telesystems with George Soros and Alan Slifka - grew to $5B market cap; founding investor in Stoneyfield Farms yoghurt company - sold to Danone SA,

**Dr Niccolo Caderni** Former European Space Agency Fellow at University of Cambridge, UK. Former VP of M&A at Bankers Trust International; former chairman of Webiz, the private equity fund of the Italian utility giant; former chairman of RAFT, a leading research institute in field of regenerative medicine

**Gianmaria Conti** is a founding partner of CPAssociati, a chartered accountant's professional firm in Italy. He has extensive experience providing advisory services to national and international companies in the areas of corporate governance, finance transactions, M&A operations, and tax.

**John Micek III** is a member of Jaguar's board of directors. Board member and CEO/CFO of Enova Systems. Former managing director of Silicon Prairie Partners venture fund. Managing partner of Verdant Ventures, a merchant bank dedicated to sourcing and funding university and corporate lab spinouts in areas including pharmaceuticals and cleantech. Practising California attorney specializing in financial services.

**Jonathan B Siegel** is a life sciences industry veteran with 21+ years experience investing and transacting in healthcare. CEO/Board Chairman of OPY Acquisition Corp. I, a publicly traded blank-check company that went public in Oct 2021. CEO/Founder of JBS Healthcare Ventures, a firm he founded in 2017 to focus on developing cost-effective solutions to improve healthcare outcomes. Left Kingdon Capital Management in 2017, where he was principal of the firm, a member of the executive committee, and the sector head for healthcare. Portfolio manager for healthcare with SAC Capital Advisors from 2005–2011.

**Figure 16 - Jaguar/Napo joint steering committee**

| Committee member | Role |
|---|---|
| Lisa Conte | CEO |
| Steven King | Chief Sustainable Supply, Ethnobotanical Research & IP Officer |
| Pravin Chaturvedi | Chief Scientific Officer, Chair of Scientific Advisory Board |
| Darlene Horton | Chief Medical Officer |
| David Sesin | Chief Manufacturing Officer |
| Ian H Wendt | Chief Commercial Officer |

*Source: Napo Therapeutics*

**Lisa Conte**. Please refer to biographical detail in previous section.

**Steven King, PhD.** Served as head of sustainable supply, ethnobotanical research & IP: 1989-2020. Board of Directors of Healing Forest Conservancy

**Pravin Chaturvedi, PhD.** 25+ years drug development experience. Co-Founded Scion, IndUS and Oceanyx Pharmaceuticals. Successfully developed Mytesi® (first pivotal adaptive design) and 7 pharmaceutical products.

**Darlene Horton, MD.** Biopharmaceutical veteran and leading clinical development expert. 25 years experience in development of investigational and commercialized biopharmaceutical and drug-device combination products. Experienced in design of SBS clinical programs.

**David Sesin, PhD.** Pharmaceutical scientist with experience from drug discovery through manufacturing. Developed crofelemer manufacturing process.

**Ian H. Wendt, MBA.** Has held commercial leadership roles across sales, marketing and operations at some of the largest brands in the pharmaceutical industry over past 25 years.

## Valuation

The observable multiple of sales (29th March 2022) for comparable pharmaceutical companies is around 8x market capitalisation to net revenue, which is summarised in Figure 17.

**Figure 17 – Comparable market cap: sales revenue valuations**

| | Market cap (US$m)* | Revenue (US$m)* | cap/revenue x |
|---|---|---|---|
| Amphastar Pharmaceuticals, Inc. (NasdaqGS: AMPH) | 1,730 | 469 | 3.7 |
| Avadel Pharmaceuticals plc (NasdaqGS: AVDL) | 413 | 54 | 7.6 |
| Enanta Pharmaceuticals, Inc. (NasdaqGS: ENTA) | 1,440 | 91 | 15.8 |
| Exelixis, Inc. (NasdaqGS: EXEL) | 7,020 | 1591 | 4.4 |
| Horizon Therapeutics (NasdaqGS: HZNP) | 24,050 | 3972 | 6.1 |
| Innoviva, Inc. (NasdaqGM: INVA) | 1,370 | 335 | 4.1 |
| Ironwood Pharmaceuticals, Inc. (NasdaqGS: IRWD) | 2,050 | 434 | 4.7 |
| Relief Therapeutics (SWX:RLF) | 273 | 20 | 13.7 |
| Supernus Pharmaceuticals, Inc. (NasdaqGM: SUPN) | 1,730 | 677 | 2.6 |
| **Average** | | | **7.8** |

**Notes**
Revenue numbers are most recent one year forward estimate
US market caps at close 29th March 2022
European market cap at 1100 30th March 2022

*Source: www.marketscreener.com*

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