



**University of Brighton**



**IP PRAGMATICS**

## DRAFT CLIENT REPORT

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**CLIENT:** UNIVERSITY OF BRIGHTON

**PROJECT TITLE:** BBSRC PATHFINDER - TECHNOLOGY MARKET ASSESSMENT AND PATENT LANDSCAPE ANALYSIS FOR USE OF TNF- $\alpha$  ANTAGONISTS IN THE MANAGEMENT OF CONSTIPATION IN THE ELDERLY

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## 1 EXECUTIVE SUMMARY

### BACKGROUND

Researchers at the University of Brighton have studied the underpinning biology and physiology of the ageing bowel which has implicated age-related changes in TNF- $\alpha$  expression as a cause of changes in faecal output in healthy older mice. Initial studies have shown that a marketed TNF- $\alpha$  antagonist, Etanercept (Pfizer and others) can reverse the effects of age-related constipation in this mouse model. This type of drug is currently prescribed for rheumatoid arthritis and ulcerative colitis, and is a biological molecule which is infused via injection and is expensive to manufacture. Although TNF- $\alpha$  antagonists are safe for chronic usage in elderly patients, the drug can suppress the immune system and these factors need to be taken into account when prescribing these drugs for the long-term treatment of the elderly.

Constipation is experienced by both humans and animals, so this opportunity is relevant to both human and animal health. It is not a well-defined disease entity, but a general collection of symptoms. Constipation is considered chronic if it is present for a total of at least 12 weeks (non-consecutively) in any one year period. Chronic constipation can significantly affect an individual's quality of life and may be associated with significant health care costs. The aetiology of constipation is usually multifactorial, and may include diet, structural issues, other disease conditions and medications. Primary forms also occur, but are less common. About 20% of the general population experiences problems with constipation during their life time, with elderly people and women being more commonly affected. Since many people self-treat, only a small number of patients seek medical help.

### MARKET CHARACTERISTICS – HUMAN HEALTH

The global constipation treatment market was estimated by BCC Research to be US\$12.58 billion in 2016, growing at a healthy CAGR of 7.1% to an estimated US\$22.93 billion by 2025. Within the overall market for constipation medication, the largest segment is for laxatives. Research and Markets suggest that over 65% of the \$1.89 billion chronic idiopathic constipation market is captured by OTC laxative drugs. Other treatment options are lifestyle changes (particularly diet, fluid intake and exercise), non-pharmacological consumer health market products and prescription pharmaceuticals. In the UK NICE advises diet and lifestyle changes initially, followed by drug treatment with different types of laxative. Of the prescription drugs, Linaclotide led sales in 2016, ending Amitiza's dominance of the market, which achieved sales of \$420million in 2016. Sodium picosulfate and lactulose achieved third and fourth place respectively. There is also a pipeline of new drugs, several of which are close to the market, with earlier stage development mainly focused on drugs which act on 5-HT<sub>4</sub>R.

### MARKET CHARACTERISTICS – ANIMAL HEALTH

Companion animals and horses are known to suffer from constipation and within species, prevalence is higher in certain breeds. The causes depend on the species and any underlying conditions that may be known to contribute to the condition.

According to an industry trade group, the global market for animal medicines is about one-fortieth of that spent on human medicines, but it has not been possible to find a breakdown of the market size for constipation treatments in animals. The rise in pet ownership is driving a rise in the companion animal pharmaceutical product market, with total U.S. pet industry expenditures projected by the American Pet Products Association to rise by almost \$3 billion to just over \$69 billion in 2017. As for humans, most treatments are focused on non-pharmacological approaches in the first instance, followed by laxatives and other medications depending on the exact type of gastric distress experienced. There is generally a lack of available products to treat chronic constipation and off-label use for drugs approved for humans are an option for vets. Chronic constipation that is unresponsive to medical management may be treated by surgical therapy with associated risks and significant cost implications.

### **COMPETITIVE POSITION**

Most healthcare organizations still consider standard laxatives as the first line of treatment for constipation as they are cheap and widely available. For example, a study comparing the costs of laxatives in Canada in 2014 revealed laxative costs of CA\$13-24/month, while prescription only medicines cost from \$80/month to \$240/month. In contrast, the cost of TNF-alpha antagonist Etanercept in the UK is between £328 - £715 per month, depending on the distributor and the type of injection delivery system.

Given the availability of low-cost, very safe, and relatively efficacious alternatives, a high-cost, injectable medicine with the potential for severe side effects and which causes a reduction in immune competence would rank very low down the list of treatment options for what is a distressing, but not life-threatening condition. We would therefore expect the market share for a treatment of this nature to be a very small segment of the overall market.

### **IP LANDSCAPE**

An examination of the patent landscape suggests that there is a fairly low interest in patents which address the treatment of chronic constipation in the elderly. The searches carried out have not identified any patents which relate to treatment of constipation directly with anti-TNF- $\alpha$  drugs. However, as constipation is a side-effect of conditions such as ulcerative colitis which is treated with anti-TNF- $\alpha$  drugs, this additional use of this class of drugs may have been considered obvious.

There may still be an opportunity for the team to develop an intellectual property position around novel compounds or novel delivery mechanisms targeting anti-TNF- $\alpha$  drugs for constipation. The patent literature suggests that investigation of treatments which combine TNF- $\alpha$  antagonism with targeted delivery mechanisms for constipation is not an active area of interest, either in the pharmaceutical companies or amongst academics. This suggests that this is not viewed as a commercially promising approach.

### **STAKEHOLDER FEEDBACK**

Primary research with clinicians and companies suggests that for human health, the treatment concept seems to fall between two different types of pharmaceutical intervention. Chronic constipation is generally seen as an indication that is not of high interest to the large prescription

medicine pharmaceutical companies, which view it as out of scope. It is of more interest to their consumer health divisions, but these are focused on over the counter remedies, and for these medicines injectable products with high cost would never be possible either from a market acceptance or a regulatory standpoint.

Limited clinical feedback suggests that there are existing treatments available or in the pipeline which are very safe and efficacious. Whilst the mechanistic concept was interesting, the costs and risks of infection were considered to rule out use of the existing anti-TNF drugs as a viable option for the elderly patient group.

There was a more open-minded attitude within animal health, where an injectable product was seen as less of a disadvantage, and there are clear unmet medical needs. However, the biggest problems (such as idiopathic megacolon in cats and ileus in horses) do not appear to be clearly linked to age, and so may be acting through a different mechanism from the one investigated by the team in their aged mouse model. Cost was consistently raised as an issue in animal health, particularly as the common treatments, such as laxatives, are very cheap and often efficacious.

**SWOT ANALYSIS**

STRENGTHS	WEAKNESSES
<ul style="list-style-type: none"> <li>• Novel approach, that does not appear to be actively researched by others</li> <li>• Potential to be curative, rather than just treat the symptoms</li> <li>• Large market for treatment of constipation</li> </ul>	<ul style="list-style-type: none"> <li>• Existing treatments are generally cheap, safe and efficacious</li> <li>• Exemplar treatment used by the team has drawbacks in terms of cost, route of administration and side effects</li> <li>• Early stage of development, and a new molecule is likely to be needed to enter this market</li> <li>• Regulatory hurdles for an OTC product are high</li> <li>• Little interest identified in pharmaceutical companies for new approaches to constipation</li> </ul>
OPPORTUNITIES	THREATS
<ul style="list-style-type: none"> <li>• Additional data on the effectiveness of etanercept compared with OTC laxatives in the Brighton mouse model could help to demonstrate superior activity for this approach</li> <li>• Identification of small molecule anti-TNF drugs would open up the potential for OTC drugs</li> </ul>	<ul style="list-style-type: none"> <li>• Lack of registered IP protection is likely to significantly impact on the ability to gain traction with pharmaceutical companies</li> </ul>

## 2 BACKGROUND

Through BBSRC funded research, researchers at the University of Brighton have studied the underpinning biology and physiology of the ageing bowel which has implicated age-related changes in TNF- $\alpha$  expression as a cause of changes in faecal output in healthy older mice. This provides a new model of constipation in elderly animals and humans which may be used to understand the underlying biology, leading eventually to novel methods of relieving this challenging condition. Initial studies using a marketed TNF- $\alpha$  antagonist, Etanercept (Pfizer and others), for treating ulcerative colitis (UC) and rheumatoid arthritis (RA) can reverse the effects of age-related constipation in this mouse model. Both UC and RA are chronic debilitating conditions that can affect older people and the drugs are safe in this age group, but as the drug can suppress the immune system the severity of the condition and how much it impacts on the life of the patient are clearly factors that need to be taken into account when prescribing these drugs for the long term treatment of the elderly.


To further quantify the market opportunity for effective management of age-related chronic constipation, the University successfully applied for BBSRC Pathfinder support to:

- Provide a detailed understanding of the current market and competitive landscape for the management of constipation in the elderly and in ageing companion animals, using secondary research and primary interviews with stakeholders from different market segments (animal health, consumer health, pharmaceuticals). This assessment will also include identification of competing products and treatment approaches, as well as regulatory constraints and hurdles
- Identify potential partners in the animal health/consumer health/pharmaceutical industries, and understanding their requirements through direct interviews
- Examine the IP landscape to identify technology developments in this market, in order to develop an appropriate IP strategy
- Identify a development plan that will provide proof-of-concept validation data required to attract the right partner to commercialise the technology
- Identify an appropriate route to commercialisation that may be supported by a full Follow on Fund application.

IP Pragmatics Limited (IPP) was appointed by the University to carry out this market and patent analysis work and this report summarises the findings from this study.

### 3 METHODOLOGY

In compiling this report IPPL used the following methods:

- Discussions with scientists and business managers at the University to gather background information on the technology, plans for its development and any existing commercialisation links with potential partners.
- Collation of secondary market information from published sources via Internet searches and via use of IPP's proprietary market report databases that it subscribes to from sources such as  Research, GlobalData, Frost & Sullivan, Marketline, Business Insights and Beauhurst (UKFunders).
- Patent database searches using open sources and proprietary Derwent Innovation patent analysis databases and software from Clarivate Analytics.
- Direct primary market information gathered from healthcare and veterinary professionals and companies and organisations operating in the field and within IPPL's personal business contact networks.

## 4 THE MARKET POTENTIAL AND OPPORTUNITIES

Chronic constipation not only affects humans but also affects a number of animal species.

### 4.1 THE MARKET FOR TREATING CONSTIPATION IN HUMANS

Constipation is not a well-defined disease entity, but a general term used to describe the difficulties that a subject experiences with moving their bowels. Diagnosis requires the collection of data such as family history, medications (especially those that are known to slow down the gastrointestinal transit) and comorbidities, together with a physical examination that includes digital rectal examination. In an effort to improve diagnosis of chronic constipation, an International group of experts proposed symptom-based criteria known as the Rome criteria<sup>1</sup>:

#### ROME III CRITERIA

1. A patient must have  $\geq 2$  of the following symptoms over the preceding 3 months:

- Straining during at least 25 % of defecations
- Lumpy or hard stools in at least 25 % of defecations
- Sensation of incomplete evacuation for at least 25 % of defecations
- Sensation of anorectal obstruction/blockage for at least 25 % of defecations
- Manual maneuvers to facilitate at least 25 % of defecations (e.g., digital evacuation, support of the pelvic floor)
- Fewer than three defecations per week

2. Loose stools are rarely present without the use of laxatives

3. There are insufficient criteria for irritable bowel syndrome

Constipation is considered chronic if it is present for at least 12 weeks (in total, not necessarily consecutively) during the previous year. Chronic constipation can significantly affect an individual's quality of life and may be associated with significant health care costs.<sup>2</sup>

The aetiology of constipation is usually multifactorial and a component of a wider complex clinical picture (secondary constipation). However, primary forms (idiopathic, functional) are also diagnosed:

#### PRIMARY FORMS

There are 3 types of primary constipation:

1. Slow transit constipation (STC): characterized by infrequent bowel movements where altered colonic motility plays a major role. It may also be associated with several endocrine

<sup>1</sup> Schuster, B. Constipation in older adults. Can. Fam. Physician (2015)

<sup>2</sup> <https://emedicine.medscape.com/article/184704-overview#a2>



and metabolic disorders such as hypothyroidism, hypercalcemia, porphyria or diabetes mellitus. STC is seen more frequently in female patients.

2. Pelvic floor dysfunction: characterized by a lack of coordination between abdominal muscles contraction and pelvic floor muscle relaxation on straining.
3. Normal transit constipation (NTC): characterized by difficulty in evacuating bowels. Patients sometimes meet the criteria for IBS with constipation (IBS-C). The primary difference between chronic constipation and IBS-C is the prominence of abdominal pain or discomfort in IBS. Patients with NTC usually have a normal physical examination. NTC is the most common subtype.

## SECONDARY FORMS

Secondary forms of constipation can be caused by a variety of issues. The most common causes of secondary constipation are<sup>3</sup>

Category	Examples
<b>Diet</b>	<p>Inadequate water intake</p> <p>Inadequate fibre intake</p> <p>Over consumption of coffee, tea or alcohol</p> <p>Ignoring the urge defecate</p> <p>Reduced levels of exercise</p>
<b>Structural</b>	<p>Anal fissures</p> <p>Thrombosed haemorrhoids</p> <p>Colonic strictures</p> <p>Obstructing tumours</p> <p>Volvulus</p> <p>Idiopathic megarectum</p>
<b>Systemic conditions</b>	<p><b>Endocrinologic and metabolic disorders:</b> Hypercalcemia, hyperparathyroidism, hypokalemia, hypothyroidism, pregnancy, and diabetes mellitus (constipation is the most common gastrointestinal problem affecting the diabetic population)</p> <p><b>Neurologic disorders:</b> Stroke, Hirschsprung disease, Parkinson's disease, multiple sclerosis, diabetic autonomic neuropathy, spinal cord lesion, head injury, cerebrovascular accident, dementia, Chagas disease, and familial dysautonomia</p> <p><b>Connective-tissue disorders:</b> Scleroderma, amyloidosis, and mixed connective-tissue disease</p>
<b>Other disorders</b>	<p>Depression</p> <p>Eating disorders</p>

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<b>Medicines</b>	Medications that may contribute to constipation include: Anabolic steroids Antacids containing aluminium and calcium Anticholinergics (eg, benzotropine and trihexyphenidyl) Anticonvulsants Antidepressants (eg, tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs)) Antihistamines Anti-Parkinsonian drugs (eg, dopaminergic drugs) Calcium channel blockers (eg, verapamil) Cholestyramine and stimulant laxatives (long-term use) - Although laxatives are frequently used to treat constipation, chronic laxative use becomes habituating and may lead to the development of a dilated atonic laxative colon, which necessitates increasing laxative use with decreasing efficacy Diuretics (e.g, furosemide, hydrochlorothiazide) Inadequate thyroid hormone supplementation Metals (eg, iron and bismuth) Nonsteroidal anti-inflammatory drugs (NSAIDs; eg, ibuprofen and diclofenac) Opioids (eg, codeine and morphine) Psychotropic drugs <sup>3</sup> Sympathomimetics (eg, pseudoephedrine)
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#### 4.1.1 MARKET SIZE

About 20% of the general population experiences problems with constipation during their life time<sup>4</sup> with elderly people and women (M/F ratio: 1:2-3) being mostly affected.

In North America alone, chronic constipation affects approximately 63 million people. Worldwide, approximately 12% of people suffer from self-defined constipation. People in the Americas and the Asian Pacific suffer twice as much as their European counterparts.

The prevalence of constipation increases with age; studies have suggested that 30-40% of adults in the US over 65 years of age have cited constipation as a problem. In population studies of this age group, 26% of women compared to 16% of men considered themselves to be constipated, while in an 84 year-old subgroup of patients, the proportion of sufferers increased to 34% in women and 26% in men<sup>1</sup>. Since many people self-treat, only a small number of patients seek medical help.

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<sup>3</sup> Uher R et al, Adverse reactions to antidepressants (2009) British Journal of Psychiatry

<sup>4</sup> BCC Report: GI Therapeutics and Diagnostics: Technologies and Global Markets (PHM046C Sept 2016)

The global constipation treatment market was worth an estimated US\$12.58 billion in 2016, with the US market worth \$5.84 billion in 2017. The global constipation treatment market to forecast exhibit a healthy CAGR of 7.1%, estimating it to reach an overall valuation of US\$22.93 billion by 2025<sup>5</sup>.

Within the total market, the largest market segment is for laxatives. The prescription laxative market is predicted to hit almost \$2.0 billion in 2021 according to BCC Research. This represents a 21.1% CAGR from the \$753.2 million estimated for 2016. During the forecast period, the U.S. market is expected to grow significantly. In 2021, the U.S. market is forecast to reach almost \$1.7 billion, for a five-year CAGR of 23.1% from 2016:

**GLOBAL PRESCRIPTION LAXATIVE MARKET, BY REGION, THROUGH 2021  
(\$ MILLIONS)**

Region	2015	2016	2021	CAGR% 2016-2021
U.S.	325.3	598.5	1,691.5	23.1
Europe	112.5	140.0	250.0	12.3
ROW	12.8	14.7	22.0	8.4
Total	450.6	753.2	1,963.5	21.1

Source: BCC Research

#### 4.1.2 GEOGRAPHICAL DISTRIBUTION

Geographically, North America is the leading market for constipation treatments, for all disease segments as well as in functional/idiopathic constipation. The North America constipation market is estimated to be worth \$9.98 billion by the end of 2025. Europe follows as the second largest market currently. Growth regions include Asia Pacific with Japan, India, and China identified as three emerging markets for constipation treatment. Mexico and Brazil are considered high potential growth markets in Latin America because of improvement of medical infrastructure.<sup>6</sup>

#### 4.1.3 MARKET OPPORTUNITIES

##### CHRONIC IDIOPATHIC CONSTIPATION

Where the cause of constipation is unknown or unclear it is classed as idiopathic constipation. The global chronic idiopathic constipation (CIC) treatment market is expected to reach \$2.86 billion by 2025 from \$1.89 billion in 2017 according to Research and Markets. Their research suggests that over 65% of the CIC market is captured by the OTC drugs segment while a Transparency Market Research report estimates that only 12% are medically diagnosed with idiopathic constipation.

<sup>5</sup> Transparency Market Research: Global Constipation Treatment Market, 2017

<sup>6</sup> Transparency Market Research Report: Chronic Idiopathic Constipation (CIC) Treatment Market - Global Industry Analysis, Size, Share, Growth, Trends, and Forecast 2016 – 2024

In the elderly, chronic constipation is a frequently reported bowel symptom with considerable impact on quality of life and health expenses. Constipation is not a physiologic consequence of normal aging, but medications, underlying diseases, and rectal sensory-motor dysfunction may all contribute to its increased prevalence in older adults. Furthermore, there are psychosocial and behavioral factors that may predispose the elderly to develop constipation, such as decreased mobility and inadequate calorific intake. Therefore in the elderly there is usually more than one etiologic mechanism, requiring a multifactorial treatment approach<sup>7</sup>.

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## OPIOID INDUCED CONSTIPATION

The number of patients suffering from opioid induced constipation is increasing across the globe as the number of people consuming opioid drugs increases; around 40% of patients are thought to experience opioid-induced constipation. According to the American Academy of Pain Medicine approximately 100 million people were suffering from OIC in 2013 in the US and consumes close to 80% of the global supply of opioids.

Severe chronic constipation is a major side effect of consumption of opioid and because sufferers are resistant to traditional laxatives, novel targeted therapies are prescribed. Research conducted by Transparency Market Research estimates that the global market for opioid induced constipation treatment is expected to reach US\$4.8 billion by 2023, from \$731.2 million in 2016 (CAGR of 31.2% from 2015 to 2023). By the end of 2023, North America alone is expected to generate US\$4.05 billion of the global revenue from opioid induced constipation treatments.<sup>8</sup>

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## IBS WITH CONSTIPATION

Common triggers for irritable bowel syndrome include food, hormones, stress, and other illness such as gastroenteritis and over growth of intestinal bacteria. Long term management is required for IBS as it is a chronic condition. IBS mostly occurs in people below the age of 45 and is twice more prevalent in women compared to men. In the US there is approximately an 11% prevalence rate of irritable bowel syndrome. IBS can be classified into 3 types based on predominant symptoms – IBS-D where diarrhea is the predominant symptom, IBS-C where constipation is the predominant symptom, and IBS-M with mixed symptoms. Around 35% IBS patients are likely to be affected with constipation.

Treatment is mainly focused on relieving the symptoms of IBS so that patients can live a normal life. Mild irritable bowel syndrome can be managed by changes in lifestyle and diet, whereas moderate to severe IBS requires medication. First line treatment for all types of IBS include dietary modification, exercise, counselling, and avoiding the triggers. If these treatment options do not help,

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<sup>7</sup> De Giorgio et al. (2015) BMC Gastroenterology 15:130

<sup>8</sup> Opioid Induced Constipation Treatment Market: (Mu-opioid Receptor Antagonist, Chloride Channel Activator, and Others; Solid, Semi-solid, and Liquid): Global Industry Analysis, Size, Share, Growth, Trends, and Forecast 2015 - 2023)

in IBS-C laxatives and fiber supplements are used. However, overall relief provided by these treatments are not satisfactory and usually lead to adverse effects.

#### 4.1.4 TREATMENT

The market for constipation therapeutics is divided into 3 main segments: non-pharmacological consumer health market products, OTC laxatives and prescription pharmaceuticals. Specific drugs are also indicated for opioid induced constipation.

#### NON-PHARMACOLOGICAL TREATMENTS

Non-pharmacological treatment (which consists of diet and lifestyle modifications) and management of medication-induced causes, are considered first steps in the effective management of constipation, including in the older population. Modifications such as increasing intake of fluids and fibres are recommended prior to initiating other forms of therapy, such as laxatives.

Ingestion of natural fibre sources from fruits, vegetables, and cereals, is nutritionally superior to purified fibre supplements. However, as advising patients to eat more fruits and vegetables is frequently unsuccessful, patients may prefer a soluble fibre supplement, such as wheat, psyllium (both naturally occurring), methylcellulose (semi-synthetic), or calcium polycarbophil (synthetic). These agents can also be regarded as bulking forming laxatives by increasing stool bulk by holding liquid in the gut.

Faecal flora changes markedly with age but it is not known whether this is a cause or the effect of constipation. Probiotics, such as bioyoghurts and dietary supplements are a common treatment because of their lack of side effects and absence of inference with medication.

#### LAXATIVE AND PHARMACOLOGICAL TREATMENTS

According to BCC Research it is estimated that more than \$800 million is spent on over-the-counter laxatives in the United States every year<sup>5</sup>. However, only a minority of total patients (approximately 25%) use medical treatments.

In the older population, the use of laxatives must be individualized with special attention paid to cardiac and renal co-morbid conditions, drug interactions, and side effects. Laxative compounds commonly used to treat chronic constipation include:

Type	Laxative agent	Agents contraindicated, or used with caution in elderly <sup>9</sup>
<b>Bulk-forming laxatives</b>	Natural fibres (e.g. psyllium/ispaghula husk)	Avoid in patients with cognitive impairment, fluid restrictions, dysphagia and those who

<sup>9</sup> Kosar L, Schuster B. RxFiles drug comparison charts. 10th ed. Saskatoon, SK: RxFiles; 2014. Constipation and laxatives

Type	Laxative agent	Agents contraindicated, or used with caution in elderly <sup>9</sup>
	Semi-synthetic fibres (e.g. methylcellulose) Synthetic fibres (e.g. Polycarbophil)	are bedridden
<b>Osmotic laxatives</b>	Magnesium hydroxide, magnesium citrate, magnesium sulfate, sodium phosphate. Polyethylene glycols with or without electrolytes (e.g. Macrogol, Miralax)	Avoid in individuals with cardiac or renal dysfunction, dehydration or serious electrolyte dysfunction
<b>Osmotic: Disaccharides and alditols</b>	Lactulose (Constulose), sorbitol.	
<b>Emollients laxatives</b>	Paraffin oil, docusate sodium (Colace)	Docusate: lack of evidence for prevention and treatment of constipation (ie, no harm, but ineffective)  Oral mineral oil should be avoided for older adults owing to concerns about aspiration
<b>Stimulant laxatives</b>	diphenylmethane derivatives (bisacodyl, sodium picosulfate) Anthraquinones (senna, aloe, cascara)	Sodium picosulfate used with caution

Targeted drug treatment options for laxative-resistant, chronic constipation<sup>10</sup>:

Drug	Mechanism of action	Effect	Marketing approval
<b>Lubiprostone, Mallinckrodt (Amitiza)</b>	Type 2 chloride channel activator	Chloride secretion with distension of intestinal walls and activation of peristalsis and acceleration of intestinal transit.	Approved for chronic idiopathic constipation; constipation caused by irritable bowel syndrome (IBS-C) in women; and opioid-induced constipation in patients with chronic, non-cancer pain.
<b>Linacotide, Ironwood Pharma (Linzess, Constella)</b>	Guanylate cyclase C receptor peptide agonist	Increase of secretion of chloride, bicarbonate and water into intestinal lumen.	Approved for chronic idiopathic constipation and constipation caused by irritable bowel syndrome (IBS-C). In development for opioid induced constipation
<b>Plecanatide,</b>	Guanylate cyclase C	Activation of peristalsis	Approved in the US for chronic

<sup>10</sup> Will be a mix of BCC and Global Data...

Drug	Mechanism of action	Effect	Marketing approval
<b>Synergy Pharma (Trulance)</b>	receptor agonist	and acceleration of intestinal transit.	of idiopathic constipation in adults
<b>Prucalopride, J&amp;J (Resolor)</b>	5-HT4 serotonin receptor agonist	Excitatory activity of neurons of the myenteric plexus, stimulates intestinal motility.	EU approved for chronic constipation; not yet approved in US
<b>Cisapride (Alzide)</b>	5-HT4 serotonin receptor agonist		Approved in India only
<b>Tegaserod, Novartis (Xavena, Zelmac)</b>	5-HT4 serotonin receptor agonist		Approved in South Africa and South Korea only; withdrawn from the US market
<b>Elobixibat, AZ (Goofice)</b>	Enantiomer of 1,5-benzothiazepine.	Bond and inhibits the ileal bile acid transporter.	Approved in Japan only

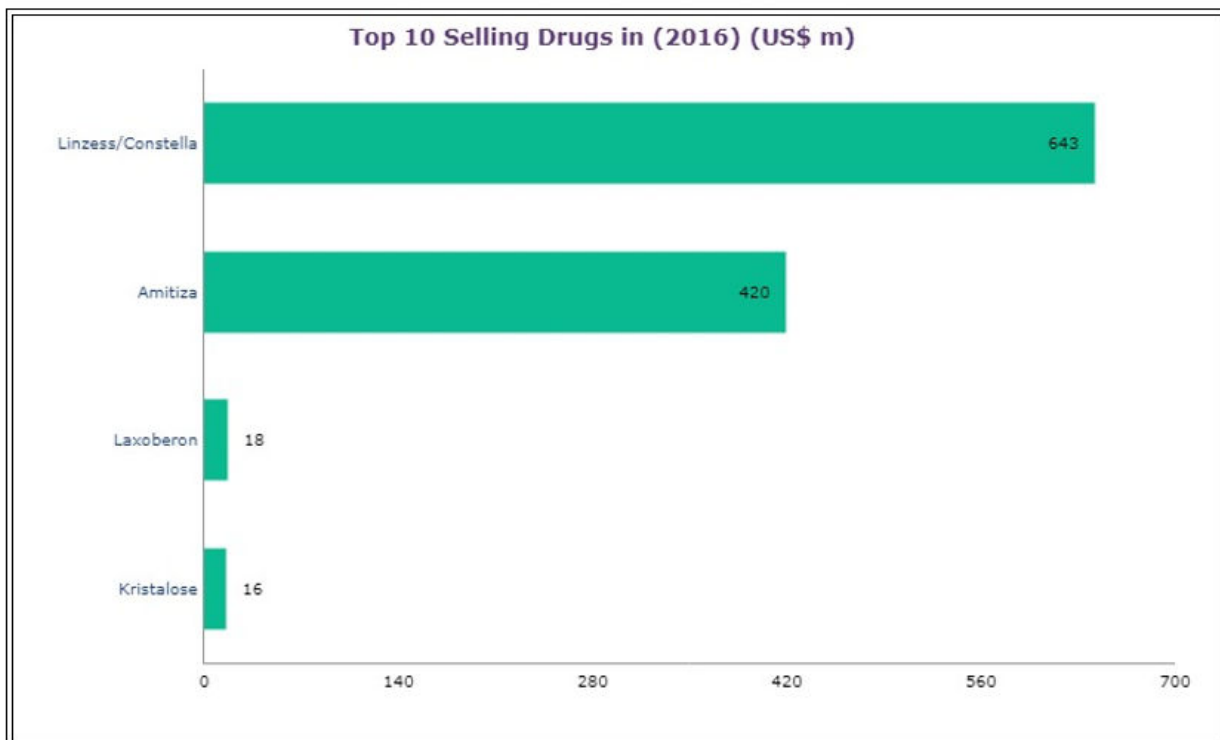
Laxatives most commonly used in clinical practice in the US include milk of magnesia, lactulose, senna compounds, bisacodyl and polyethylene glycol (PEG) preparations<sup>11</sup>. There is limited evidence to guide the order in which the agents should be used in older adults, but often a bulk-forming agent would be initiated first (except in those who are bedridden, are cognitively impaired, or have other contraindications). For patients with a contraindication or lack of response to a bulking agent, an osmotic agent, such as PEG 3350 or lactulose, is indicated<sup>12</sup>.

In the UK NICE has published a clinical knowledge summary on chronic constipation in adults as a practical resource for primary care professionals (it is not formal NICE guidance), which also advises drug treatment with laxatives if the individual has ongoing symptoms despite having made changes to their diet and lifestyle, and investigating the role of any drugs that may be contributing to or causing constipation. Bulk-forming laxatives are usually suggested initially, and if symptoms remain, a switch to an osmotic laxative, such as a macrogol is recommended, followed by lactulose if macrogol is ineffective or not tolerated. Drug treatment with prucalopride or lubiprostone may then be recommended if at least two laxatives from different classes have been tried at the highest tolerated recommended doses for at least 6 months.

Of the prescription drugs, Linaclotide led sales in 2016, ending Amitiza's dominance of the market, which achieved sales of \$420million in 2016. The laxatives, sodium picosulfate and lactulose, achieved third and fourth place respectively.

<sup>11</sup> Rao SS. Constipation: Evaluation and treatment of colonic and anorectal motility disorders. Gastroenterol Clin North Am. 2007

<sup>12</sup> Schuster B et al, (2015) Constipation in older adults. Can Fam Physician. 61(2)



Sales of linaclotide are on track to exceed \$1 billion in the US alone by 2020. In 2021, linaclotide is expected to achieve blockbuster sales of \$1.2 billion in the U.S., France, Germany, Italy, Spain, the U.K. and Japan.

**TREATMENT FOR OPIOID INDUCED CONSTIPATION**

A new class of drugs acting peripherally as mu-opioid receptor antagonists (PAMORAs) are approved to provide relief from constipation associated with chronic opioid use. They selectively displace opioids from mu-opioid receptors outside the CNS, decreasing the constipating effects of opioids:

Drug name (Brand name)	Company	Marketing approval
<b>Methylnaltrexone (Relistor)</b>	Valeant Pharma International Inc	<p>opioid-induced constipation in patients with advanced illness receiving palliative care when response to laxatives has not been sufficient.</p> <p>opioid-induced constipation in patients with chronic noncancer pain who are treated with opioids.</p> <p>It is available as an injectable solution for subcutaneous use.</p>
<b>Naloxegol (Movantik)</b>	AstraZeneca	opioid-induced constipation in adults with chronic noncancer pain
<b>Naldemedine (Symproic)</b>	Shionogi	opioid-induced constipation in adults with

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Drug name (Brand name)	Company	Marketing approval
		noncancer pain.

#### 4.1.5 MARKET DRIVERS

An increasing geriatric population and changing dietary habits in developed as well as developing markets is expected to increase the incidences of functional/idiopathic constipation.

Although the prescription laxative market has historically been relatively flat, an increase in opioids consumption for relieving chronic pain is another factor driving the growth of the global constipation treatment market.

The global constipation treatment market is hindered by the continuous reliance of a majority on over-the-counter (OTC) drugs, as well as on generic laxatives.

## 4.2 THE MARKET FOR TREATING CONSTIPATION IN ANIMALS

Chronic constipation is a highly debilitating condition that not only affects humans but also a number of animal species. Companion animals and horses are known to suffer from the condition and within species, prevalence is higher in certain breeds. The causes depend on the species and any underlying conditions that may be known to contribute to constipation:

Species	Causes
<b>Dogs</b>  <b>prevalence of constipation is higher in:</b> <b>English Bulldogs</b> <b>Boston Terriers</b> <b>German Shepherds</b>	Old age and immobility Dehydration Obesity Systemic diseases e.g. neuromuscular disease, diabetic gastroparesis, neoplastic GI obstruction, anal sac inflammation Long term opioid use (e.g. tramadol) Chemotherapeutics (e.g. vincristine) Obstruction due to foreign object ingestion
<b>Cats</b>  <b>Breeds/groups most affected include:</b> <b>Siamese</b> <b>Domestic Shorthair</b> <b>Manx</b> <b>Middle-aged and male cats</b>	Old age and immobility Dehydration Obesity Systemic diseases e.g. diabetes, bladder infection, anal sac infection, colitis or IBS Pain from trauma to the low back Hairball impaction Idiopathic
<b>Horses</b>	Dehydration

	<p>Impaction colics due to faecal material, parasites or sand</p> <p>Nutrition, e.g. impaction from poor food quality, inability to access free forage</p> <p>Stress</p> <p>Severe hind limb pain/injury</p> <p>Long term use of anticholinergic medications e.g. atropine</p>
<b>Rabbits</b>	<p>Digestive system resembles horses. Causes include:</p> <p>Dehydration</p> <p>Obesity</p> <p>Inactivity</p> <p>Spinal trauma</p> <p>Nutrition, e.g. low fibre diet, diet high in carbohydrates (i.e. fruit), diet high in protein (i.e. nuts)</p> <p>Hairballs</p>
<b>Rodents</b> <b>(Guinea pigs and chinchillas)</b>	<p>Old age</p> <p>Dehydration</p> <p>Obesity</p> <p>Lack of exercise</p> <p>Spinal pain</p> <p>Dental disease</p> <p>Nutrition, e.g. low fibre diet, diet high in carbohydrates (i.e. fruit), diet high in protein (i.e. nuts)</p>

Signs of constipation in pets and horses are summarized as:

1. Increased straining
2. Failure to defecate
3. Faecal matter, if passed, is reduced in quantity and is usually dry and hard
4. Presence of blood in stool
5. Faeces that are particularly foul smelling
6. May continuously get in and out of litter box without passing fecal material
7. Circling or pacing the stall with intermittent straining
8. Decreased activity and lethargy likely due to pain
9. Painful and/or bloated abdomen
10. Decreased interest in food
11. Irritability

As for humans, some drugs (eg, opioids, diuretics, antihistamines, anticholinergic agents, sucralfate, aluminum hydroxide, potassium bromide, and calcium channel-blocking agents) promote constipation via differing mechanisms.<sup>13</sup>

Diagnosis requires collecting data to understand the history of how long the condition has been going on for, and discussing changes in the animal's diet or daily toilet habits, performing physical examinations (abdominal and oral). Blood tests are routinely undertaken to rule in/out any other disease processes that may be contributing to the constipation.

#### 4.2.1 MARKET SIZE

According to an industry trade group, the global market for animal medicines is about one-fortieth of that spent on human medicines<sup>14</sup>.

We were not able to find any information on the prevalence of constipation in companion animals and horses. However, according to the American Pet Products Association, results from their 2017 survey indicated 60% of households in the US own dogs (totaling 89.7million dogs), with 47% and 3% owning cats (94.2 million) and horse (7.6 million) respectively. Dog owners estimated they spent \$257 in routine vet visits compared with \$182 for cat owners, but these figures are likely to be lower than the real figure as they are based on recollection of spending only.

#### 4.2.2 TREATMENT

As for humans, most treatments are focused on non-pharmacological approaches in the first instance, such as giving fluids for dehydration, increasing the amount of fiber in the animal's diet and decreasing the amount of carbohydrates, or where there is foreign body obstruction, the surgical removal of the obstruction.

Medication options available depend upon the species of animal and the exact type of gastric distress experienced. Pain control is usually considered as a treatment option in addition:

Type	Agent	Species specific information
<b>Laxatives</b>	Paraffin oil	Risk of lung aspiration – best administered by vet
	Lactulose	Use with caution in diabetic animals. Not recommended for rabbits and rodents due to severe diarrhoea as a side effect
<b>Macrolide antibiotic</b>	Erythromycin	Must not be given orally to rabbits,

<sup>13</sup> <https://www.msdsvetmanual.com/digestive-system/diseases-of-the-stomach-and-intestines-in-small-animals/constipation-and-obstipation-in-small-animals>

<sup>14</sup> <https://www.thebalance.com/of-the-largest-animal-pharmas-2663221>

Type	Agent	Species specific information
	Azithromycin	guinea pigs or other rodents
<b>H2 blockers</b>	Ranitidine (Zantac), Nizaditine	
<b>5-HT4 receptor antagonist</b> <b>serotonin agonist/5-HT3 receptor antagonist</b>	Cisapride (Propulsid)	Used successfully in cats with IBS
<b>5-HT4 receptor agonist</b>	Prucalopride (Resolor)	
<b>Dopamine antagonist</b>	Metoclopramide (Reglan) Domperidone	Use limited due to CNS side effects Domperidone does not cross the blood brain barrier
<b>Cholinergic agonist</b>	Bethanechol	Not recommended for use in rabbits or rodents
<b>Acetylcholinesterase inhibitor</b>	Neostigmine	Not recommended for use in rabbits or rodents
<b>Type 2 chloride channel activator</b>	Lubiprostone (Amitiza)	Pilot study in guinea pigs showed effectiveness in reversing opioid induced constipation. No studies conducted in cats, dogs or horses
<b>Guanylate cyclase C receptor agonist</b>	Linaclotide (Linzess)	
<b>Toxins</b>	Botulinum	?

Continued or long-term use of laxatives is generally discouraged unless absolutely necessary. There is generally a lack of available products to treat chronic constipation and off-label use for drugs approved for humans are an option for vets, although compounding will be required to generate treatments at the correct dosage and formulation for the animal<sup>15</sup>. Chronic constipation that is unresponsive to medical management (e.g. some cats with megacolon) may be treated by surgical therapy (subtotal or total colectomy) which has associated risks and significant cost implications.<sup>16</sup>

<sup>15</sup> PetTalk (2012), volume 15(4): Constipation The Moving Truth about a Tough Topic in Pets!

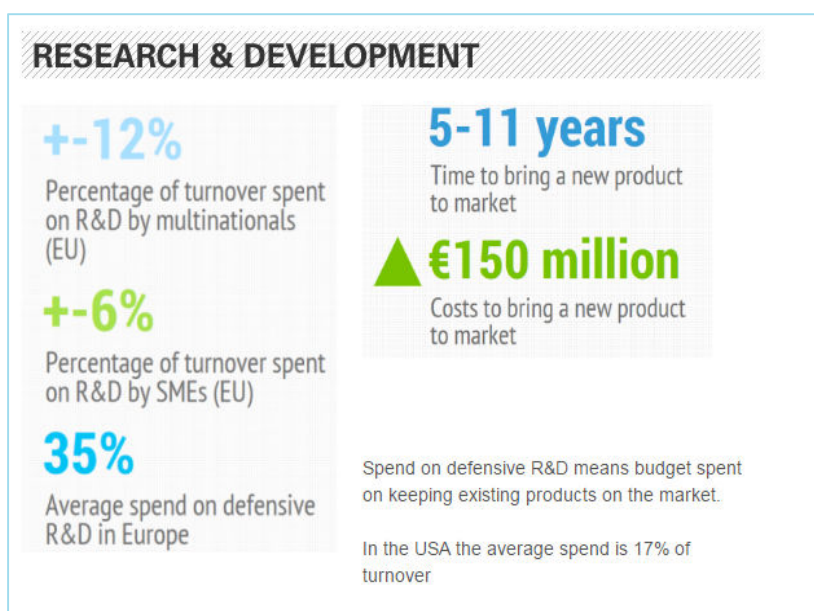
<sup>16</sup> <https://www.msddvetmanual.com/digestive-system/diseases-of-the-stomach-and-intestines-in-small-animals/constipation-and-obstipation-in-small-animals>

### 4.2.3 MARKET DRIVERS

As discussed above, the rise in pet ownership is driving a rise in the companion animal pharmaceutical product market, with total U.S. pet industry expenditures projected by the American Pet Products Association to rise by almost \$3 billion to just over \$69 billion in 2017. Today, 60 percent of the revenue of U.S. animal health companies comes from companion animal products, and 40 percent comes from livestock products. In the rest of the world, these proportions are reversed.

Pet owners are willing to spend more on their pets and are seeking products that will let their pets live longer, healthier lives. This market opportunity is driving new business models and is leading to the establishment of new companies focused on pet products.

The development of a new animal drug can take up to 10 years and cost up to \$100 million prior to approval by the FDA. In Europe, the costs are estimated at €150 million



## 4.3 LEADING COMMERCIAL PLAYERS

### 4.3.1 HUMAN HEALTH

Leading companies in the constipation treatment market (based on sales<sup>17</sup>) include:

Company	Marketed	Pre-	Phase III	Phase II	Preclinical	Discovery

<sup>17</sup> Source: Global Data, data extracted 13 April 2018. Ordered highest-lowest annual revenue

Company						
			Registration			
Sanofi	3					
Abbott	2					
Teva	3					
Takeda Pharmaceutical Co Ltd	2	1*	1*			
Allergan Plc	1					1
Reckitt Benckiser Group Plc	1					
Astellas Pharma Inc	1*	1*			1	
Shire Pharmaceuticals	1*	1*				
Eisai	2					
Perrigo Company Plc	3					
Chugai Pharmaceutical Co Ltd (Subsidiary of Roche)	1					
Sun Pharmaceutical Industries Ltd	2					
Sumitomo Dainippon Pharma Co				1		
Mallinckrodt	1*	1*	1*			
Aspen Pharmacare	3					
Ironwood Pharmaceuticals Inc			1*		2*	
EA Pharma Co Ltd	1	1	1			

Key:

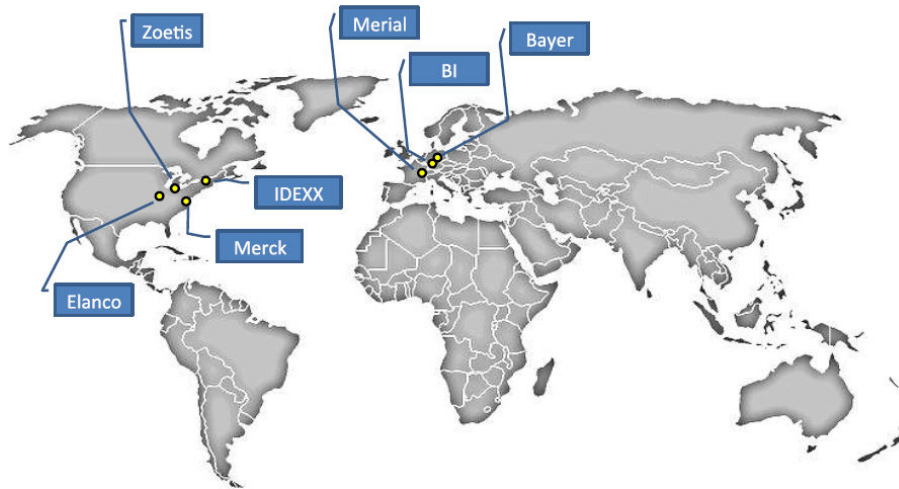
\* same product

	Laxatives or non-proprietary agents
	Small molecule
	Biologic

Brief details of some of the key companies which are actively researching into constipation treatments identified by the secondary market research or the patent landscaping are given in Appendix 1.

### 4.3.2 ANIMAL HEALTH

In the animal health industry, there are a very small number of Tier 1 players, and some smaller Tier 2 companies which are often more regionally based. We were not able to identify which of these companies leads the market in treatments for companion animal constipation.



Tier 1 animal health companies (NB Boehringer-Ingelheim has now merged with Merial)



Tier 2 animal health companies

## 4.4 COMPETITIVE APPROACHES

### 4.4.1 COMPETITORS

Most healthcare organizations still consider standard laxatives as the first line of treatment for constipation as they are cheap and widely available. For example, a study comparing the costs of laxatives in Canada in 2014 revealed Lactulose cost CA\$13/mo, while PEG 3350 CA\$24/mo. In

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contrast the prescription only medicines Lubiprostone, Linaclotide and Prucalopride cost from \$80/mo to \$240/mo<sup>18,19</sup>.

#### 4.4.2 PIPELINE

A search was conducted on Global Data<sup>20</sup> for therapeutics in active development for constipation (functional constipation; chronic idiopathic constipation; IBS-C). A number of drugs previously discussed in earlier sections either expanding their therapeutic indication or geographical marketing approval have been omitted for the sake of conciseness. Drugs acting on 5-HT<sub>4</sub>R predominate the pipeline of activity:

Drug Name	Company Name	Indication	MOA	Development Stage	Drug Geography
AJG-555	EA Pharma Co Ltd	Constipation	laxative	Pre-Registration	Japan
BLI-400	Braintree Laboratories Inc	Constipation	laxative	Phase III	Global
BLI-801	Braintree Laboratories Inc	Constipation	laxative	Phase III	Global
SK-1202	Sanwa Kagaku Kenkyusho Co Ltd	Constipation	undisclosed	Phase III	Japan
tenapanor	Ardelyx Inc	Constipation; Irritable Bowel Syndrome	NHE3 inhibitor	Phase III	United States
DSP-6952	Sumitomo Dainippon Pharma Co Ltd	Constipation; Irritable Bowel Syndrome	serotonin-4 receptor partial agonist	Phase II	Japan
ENT-01	Enterin Inc	Constipation	alpha synuclein	Phase II	United States
lovastatin MR	Synthetic Biologics Inc	Constipation; Irritable Bowel Syndrome	gut microbes (methanogens)	Phase II	United States
naronapride	Renexion LLC	Constipation; Functional (Non Ulcer) Dyspepsia; Reflux Esophagitis (Gastroesophageal Reflux Disease)	5HT <sub>4</sub> agonist	Phase II	Global
NGM-282	NGM Biopharma Inc	Constipation; Non-Alcoholic Steatohepatitis (NASH)	FGFR4 and FGFR1 agonist	Phase II	Global

<sup>18</sup> Kosar L, Schuster B. RxFiles drug comparison charts. 10th ed. Saskatoon, SK: RxFiles; 2014. Constipation and laxatives.

<sup>19</sup> Clin Interv Aging. 2010; 5: 163–171

<sup>20</sup> Data extracted 13 April 2018



Drug Name	Company Name	Indication	MOA	Development Stage	Drug Geography
relenopride hydrochloride	SK Biopharma Co Ltd	Constipation; Irritable Bowel Syndrome	5-HT4 receptor partial agonist	Phase II	South Korea; United States
YH-12852	Yuhan Corp	Constipation; Postoperative Ileus	5-HT4 receptor agonist	Phase II	Global
DA-6886	Dong-A ST Co Ltd	Constipation; Irritable Bowel Syndrome	5-HT4 agonist	Phase I	South Korea
RQ-00000010	RaQualia Pharma Inc	Constipation; Functional (Non Ulcer) Dyspepsia; Gastroparesis	5-HT4 receptor partial agonist	Phase I	United Kingdom
ASP-7663	Astellas Pharma Inc	Constipation (drug induced)	TRPA1 agonist	Preclinical	Global
J-027	Vanda Pharmaceuticals Inc	Constipation	cystic fibrosis transmembrane conductance regulator (CFTR)	Preclinical	Global
ZS-06	Zensun (Shanghai) Sci & Tech Co Ltd	Constipation	laxative	Preclinical	Global
Biologic for Irritable Bowel Syndrome with Constipation	Allergan Plc	Constipation; Irritable Bowel Syndrome	Undisclosed (microbiome?)	Discovery	Global
5-BIOP	Technical University of Munich	Constipation; Functional (Non Ulcer) Dyspepsia	putative 5-HT (1P) receptor agonist	Discovery	Global

#### 4.4.3 COMPETITIVE POSITION

##### TNF-ALPHA ANTAGONISTS FOR THE TREATMENT OF CONSTIPATION

TNF-alpha inhibitors are a class of biological medicines authorised for the treatment of inflammatory and autoimmune conditions, such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, and psoriatic arthritis. The TNF-alpha inhibitors authorised in the UK are adalimumab, certolizumab, etanercept, golimumab, and infliximab. TNF-alpha inhibition increases susceptibility to infectious diseases, including tuberculosis) and increases the risk of reactivation of latent tuberculosis). All approved antagonists interact with a variety of vaccines that increase the risk of generalised infection that could possibly be life-threatening, including the influenza vaccine. With the exception of Etanercept, all drugs are contraindicated in individuals with moderate or severe heart failure, and all drugs are contraindicated in individuals with either active or severe infections<sup>21</sup>.

<sup>21</sup> MHRA Drug Safety Update: TNF-alpha inhibitors

Biologic pharmaceuticals are generally known to be more expensive than chemically synthesized agents. In the UK, Etanercept costs the NHS anywhere between £328 - £715 per month, depending on the distributor and the type of injection delivery system<sup>22</sup>.

A search conducted on Global Data<sup>23</sup> returned zero results for drugs targeting TNF-alpha for the treatment of constipation.

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#### 4.4.4 REGULATORY ISSUES

We have not looked in detail at the regulatory route for a novel TNF-alpha antagonist for an indication of constipation. However, key issues in allowing uptake of such a drug will surround reimbursement status and an assessment of cost-benefit. Any new drug for the treatment of constipation will need to differentiate itself from its competitors, which include very low cost laxatives as well as prescription medicines.

Safety is also an important issue when it comes to treatment of the elderly population, who will often have other co-morbidities. The potential side-effects from TNF-alpha antagonists may be acceptable in a serious chronic disease such as rheumatoid arthritis, but the regulatory barriers would be higher for a condition such as constipation. If there is a market for the healthy elderly, it would be important to show that any new drug with this mode of action does not have unwanted effect on the heart or the kidney. Similarly, the route of administration via needle infusion may be acceptable for severely affected patients, but is unlikely to be preferred until other less invasive options have been exhausted. It would certainly not be possible to position this type of drug as an over the counter or home administration product without reformulation.

Given the availability of low-cost, very safe, and relatively efficacious OTC alternatives, a high-cost, injectable medicine with the potential for severe side effects and which causes a reduction in immune competence would rank very low down the list of treatment options for what is a distressing, but not life-threatening condition. We would therefore expect the market share for a treatment of this nature to be a very small segment of the overall market.

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<sup>22</sup> For 4 x 50mg per 1ml

<sup>23</sup> Search conducted 12 April 2018

## 5 INTELLECTUAL PROPERTY LANDSCAPE AND OPPORTUNITIES

The initial research establishing the potential link between anti-TNF- $\alpha$  drugs and relief of constipation has been published by the team, but no IP protection has yet been put in place. However, the opportunity for IP protection for this work may arise from further translational research to identify and develop treatments which combine TNF- $\alpha$  antagonism with targeted delivery mechanisms, allowing them to act directly on the colon. This may be through re-formulation of existing biologics, or the identification of novel compounds.

### 5.1 BROAD PATENT SEARCH

In order to understand the scope of third party patents relating to anti-TNF drugs in constipation, IP Pragmatics used their subscription patent landscape tool, Derwent Innovation. This is a comprehensive patent database and patent landscaping tool that can quickly identify competing or synergistic patents and their assignees as part of an overall IP analysis. This tool can also help identify potential licensees and co-development partners. The initial search was focused on identifying the general trends regarding patents surrounding treatment of chronic constipation in the elderly.

The following document collections were searched:

*Full Text:* US Granted; US Applications; European Granted; European Applications; WIPO Applications; Australian Innovation; Australian Granted; Australian Applications; British Granted; British Applications; French Applications; French Granted; German Granted; German Utility Models; German Applications; Canadian Granted; Canadian Applications; Russian Utility Models; Russian Applications

*Bibliographic:* Japanese Applications; Korean Granted/Examined; Korean Applications; Other Authorities (covered by INPADOC); plus enhanced Derwent World Patent Index (DWPI) data fields

A broad general search was used to illustrate the level of activity in the field. In order to restrict the search set to patents which may still be in force, the search was limited to the last 20 years:

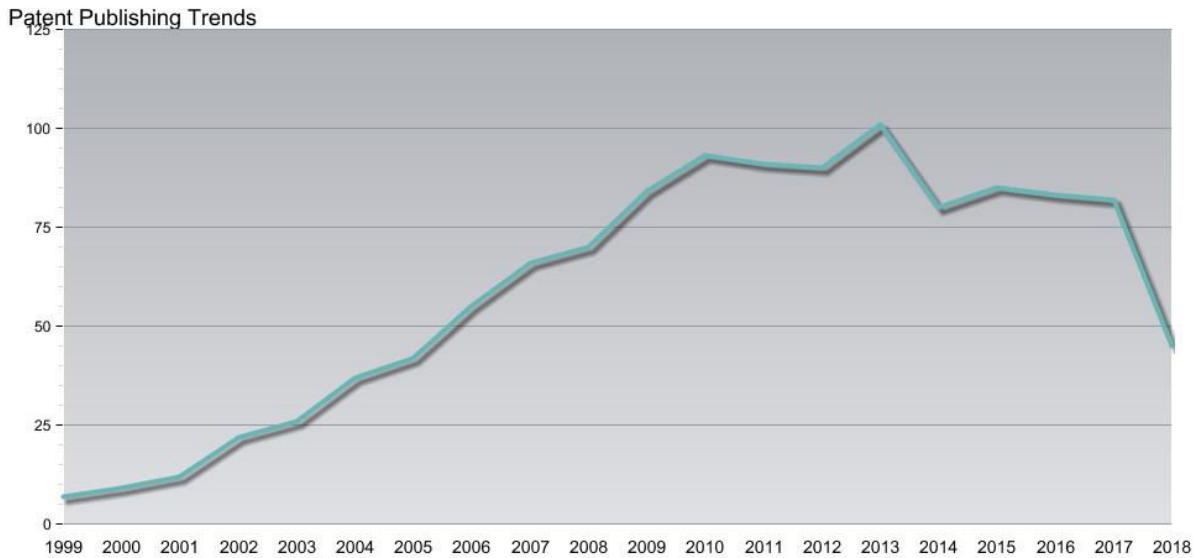
(CTB=(constipat\*) OR IC=(A61P000110)) AND CTB=(elderly or old or older or age or ageing or aging) AND CTB=(chronic) AND DP>=(19980101);

- This searched the claims, title and abstracts of patents published from 1998 and identified 5,010 individual patent cases in 464 INPADOC patent families.

The IC term used in the search is for the International Patent Classification (IPC) code. The IPC codes provide a hierarchical system of language independent symbols for the classification of patents and utility models according to the different areas of technology to which they pertain. The IPC divides technology into eight sections with approximately 70,000 subdivisions. The appropriate IPC symbols are indicated on each patent document, of which more than 1,000,000 were issued each year in the last 10 years. The IPC code in this search relates to drugs for gastro-intestinal disorders, specifically laxatives.

### 5.1.1 GENERAL TRENDS

The patents identified in this broad search were analysed to identify some overall trends and features of this patent space. The following graph shows the new patent family publishing trends in this field by year:

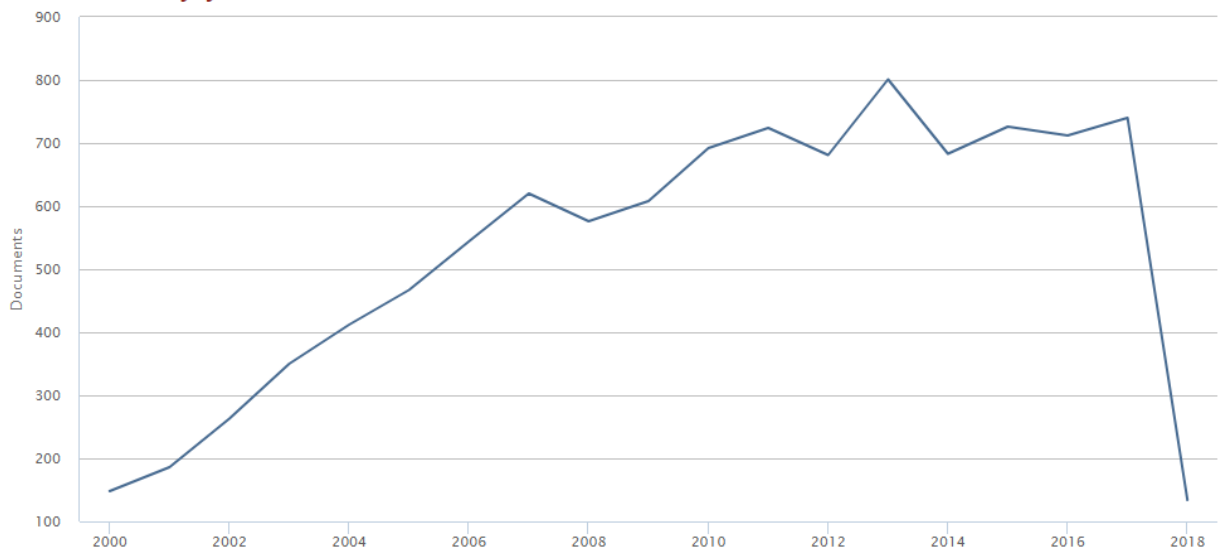


Source: Derwent Innovation®, [www.derwentinnovation.com](http://www.derwentinnovation.com)

It can be seen that there was a steady rise in activity during the 2000s, but since then there has been a slight decline in new patenting activity. The data for 2018 are not yet complete, hence the sharp drop in activity at the end of the chart. There are approximately 80 new patent families published each year for this topic, which is a fairly low number compared with many other therapeutic indications.

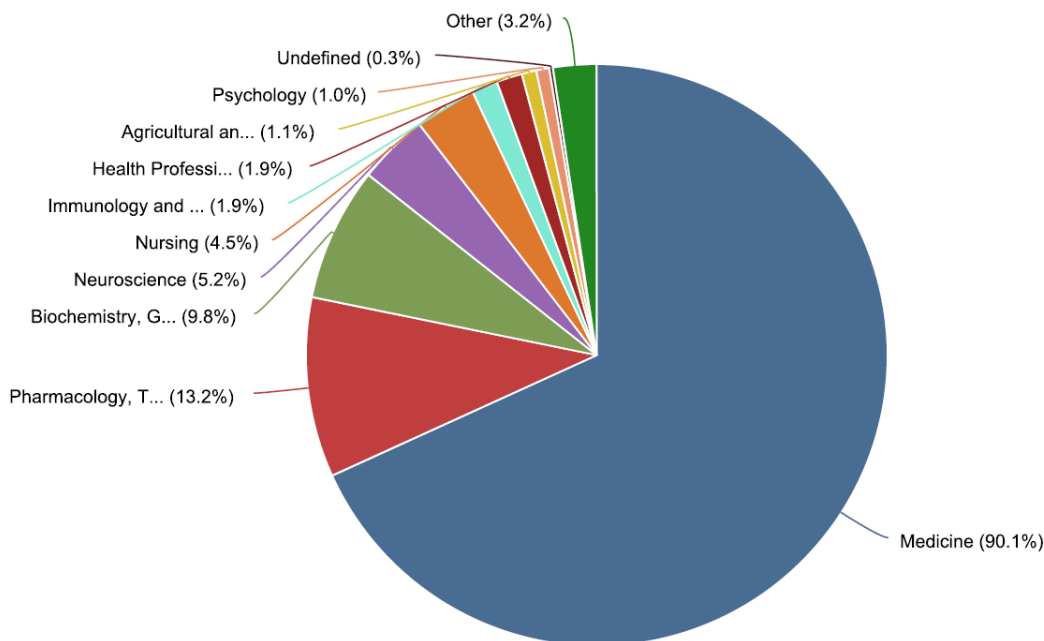
A similar trend can be seen from a search of the academic literature, carried out in Scopus. After 1999, the number of publications relating to chronic constipation has increased steadily year on year. In most recent years, approximately 700 articles or reviews are published each year:

### Documents by year



Source: Scopus

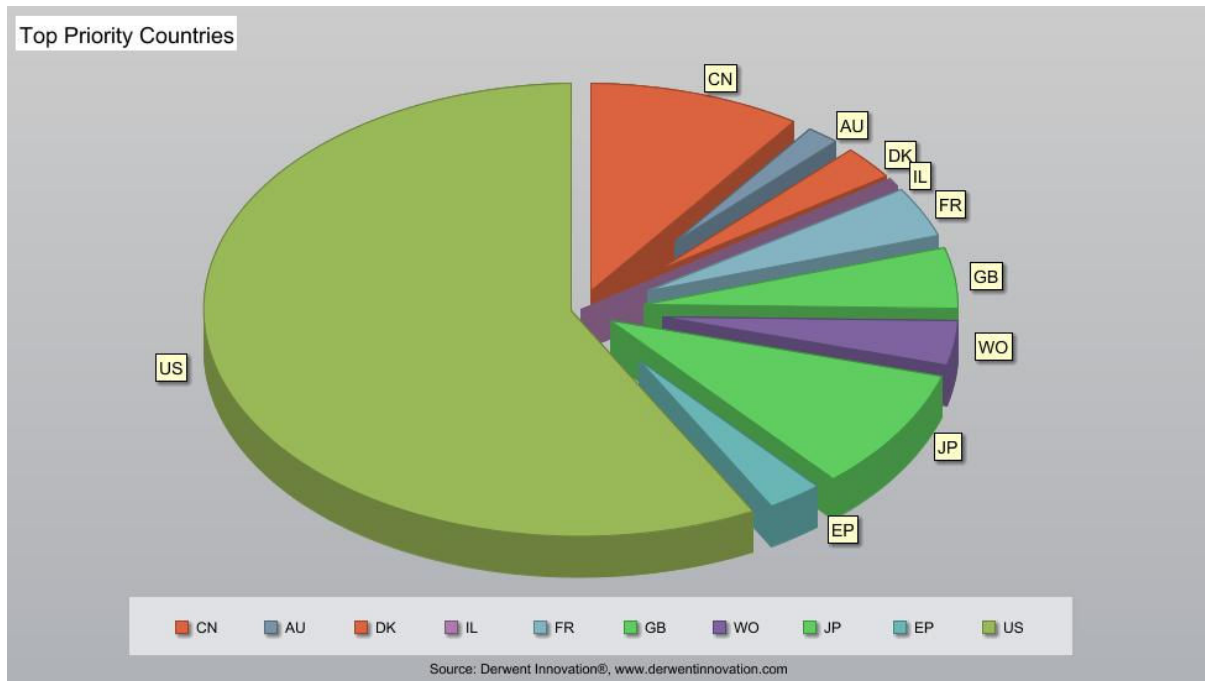
Of the 10,067 publications over this period, the majority fall within the category of medicine. Veterinary publications make up only 46 documents (0.5%):



Source: Scopus

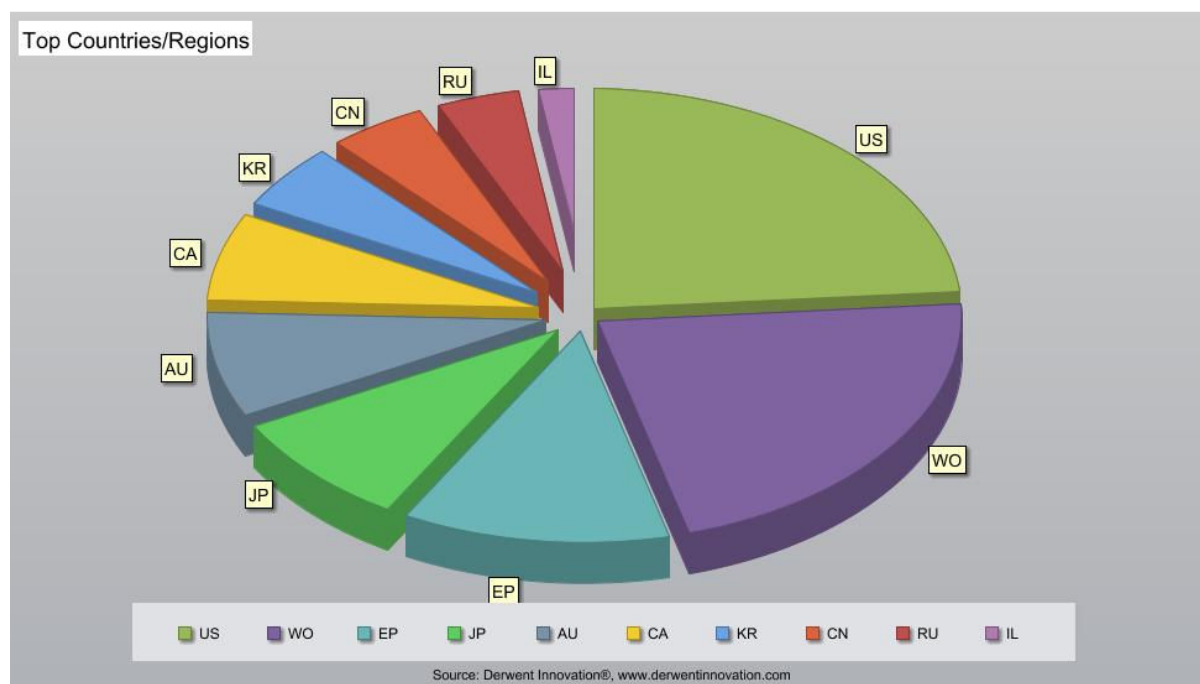
The broad patent search was then analysed by top priority countries, to see where the patent applications are initially being filed. This can be a good indication of the countries where the majority of the research and innovation in a particular technology field is taking place since

organisations generally file patent applications first in the local territory where their research bases are located.



In this case, the majority of patenting activity comes from the US, with more than half of the overall patenting activity. This reflects the US being the home to several of the major pharmaceutical companies. From the remaining territories, Asia is also strong through Japan and China, as well as Europe (including France, Denmark, GB, Denmark, Austria and Israel).

The countries in which assignees have chosen to protect inventions in a particular sector can be used as an indication of the territories these organisations consider are commercially important to protect for their products. This is shown in the chart below:



This analysis identifies the major markets for sale and/or manufacture of these products, which can be seen to be worldwide. The top 5 markets include the U.S., Europe, Japan and Australia, while direct PCT filing is also important. Other strong territories are Canada, South Korea, China, Russia, and Israel.

### 5.1.2 TOP ASSIGNEES

The top assignees in this search are shown in the table below. Individual inventors and unspecified assignees have been removed from this list for clarity. Document count refers to the number of patent families (rather than individual patents). The table includes some of the major pharmaceutical companies:

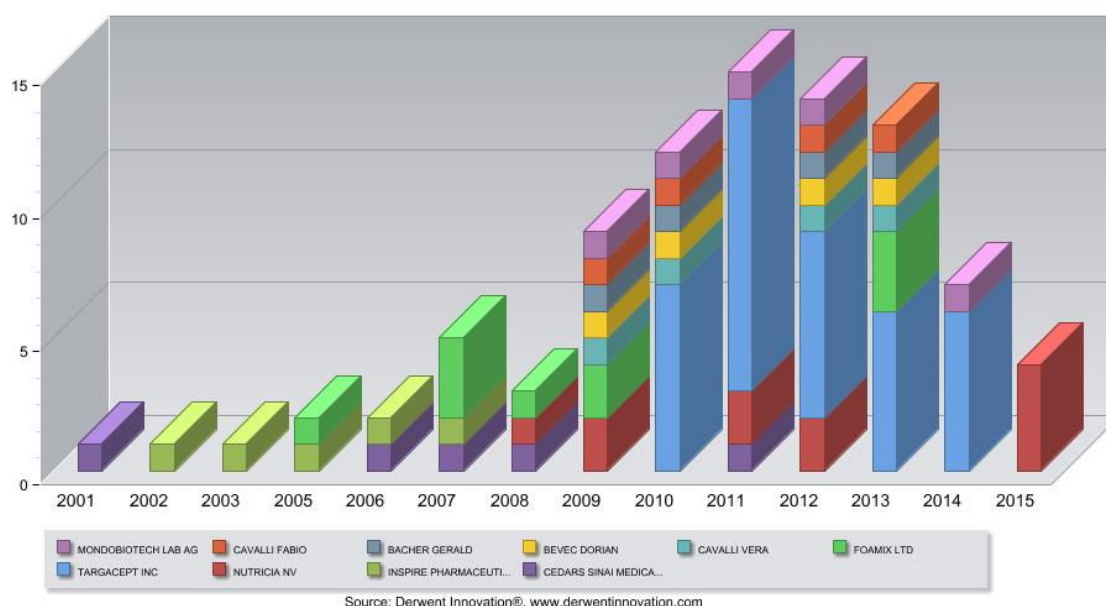
DWPI Assignee/Applicant	Document Count	Percentage
TARGACEPT INC/TRGA	45	6.09%
CATALYST BIOSCIENCES INC/CATA-N	17	2.30%
BRISTOL-MYERS SQUIBB CO/BRIM	16	2.17%
FOAMIX LTD/FOAM-N	14	1.89%
FOAMIX PHARM LTD/FOAM-N	14	1.89%
GLAXO GROUP LTD/GLAX	14	1.89%
AVENTIS PHARM AS/AVET	14	1.89%
AVENTIS PHARMA SA/AVET	14	1.89%
NEUROSEARCH AS/NURO	13	1.76%
SALIX PHARM INC/SALI-N	11	1.49%
TRANZYME PHARMA INC/TRAN-N	10	1.35%
TAKEDA PHARM CO LTD/TAKE	10	1.35%
HELSINN HEALTHCARE SA/HELS-N	9	1.22%
TAKEDA CHEM IND LTD/TAKE	9	1.22%
TAKEDA PHARM IND CO LTD/TAKE	9	1.22%
TAKEDA PHARM/TAKE	9	1.22%
ICAGEN INC/ICAG	9	1.22%
VERTEX PHARM INC/VERT	8	1.08%
NUTRICIA NV/DNON	7	0.95%
SOC CONSEILS RECH & APPL SCI/SCRC	7	0.95%
SALIX PHARM LTD/SALI-N	7	0.95%

DWPI Assignee/Applicant	Document Count	Percentage
OCERA THERAPEUTICS INC/OCER-N	6	0.81%
CHIASMA/CHIA-N	6	0.81%
CHIASMA INC/CHIA-N	6	0.81%
CHIASMA LTD/CHIA-N	6	0.81%

The most prolific company, Targacept was taken over by the second, Catalyst Biosciences in 2015. Targacept had a drug development program in constipation-predominant IBS, but this is no longer a focus for Catalyst Biosciences.

By plotting the top assignees against patent publication year, the most prolific organisations patenting in this field in recent years can be identified, as illustrated in the figure below.

Top Assignees by Year



## 5.2 PATENT LANDSCAPING

Derwent Innovation can be used to generate sophisticated patent landscapes to visualise the relationship between patents in a common field based on key words within the claims and/or abstracts/text of individual patents within the searched field. This can be used to locate competing or similar patents to the patents of interest. As with a geographic landscape the contour lines and intensity of peaks on the patent landscape represent areas of high patent activity with closely related concepts.

The patent set was mapped using Derwent Innovation’s proprietary ThemeScope™ mapping tool. ThemeScope uses term frequency and other algorithms to cluster documents based on shared language – in this case the English Title, Abstracts and Claims from the patents together with the DWPI-enhanced Titles and Abstracts were mapped. It uses several algorithms to perform terminology-based clustering. The text from one record is compared with the text from all other patent records within the search collection. The map uses vectors to give each patent record a

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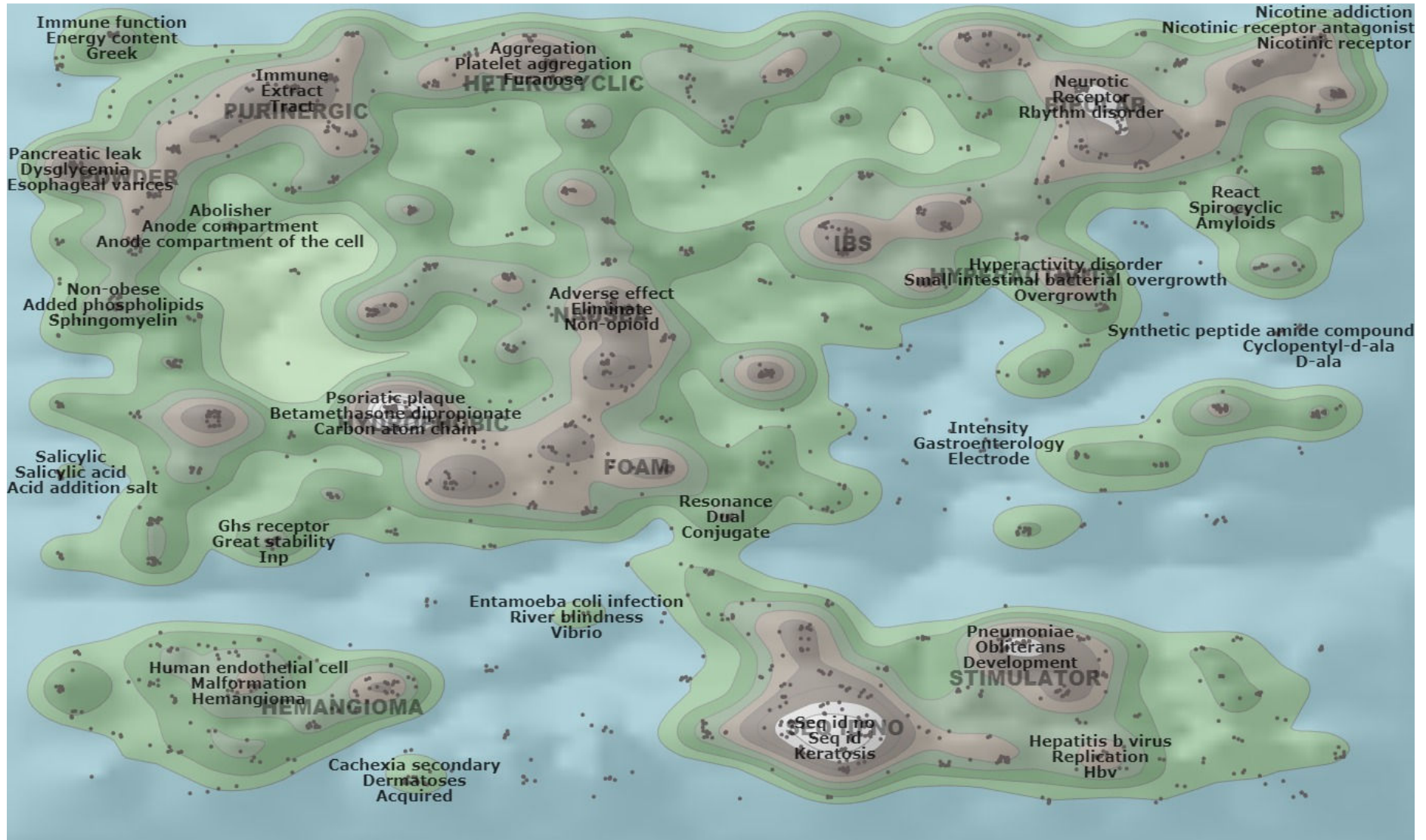
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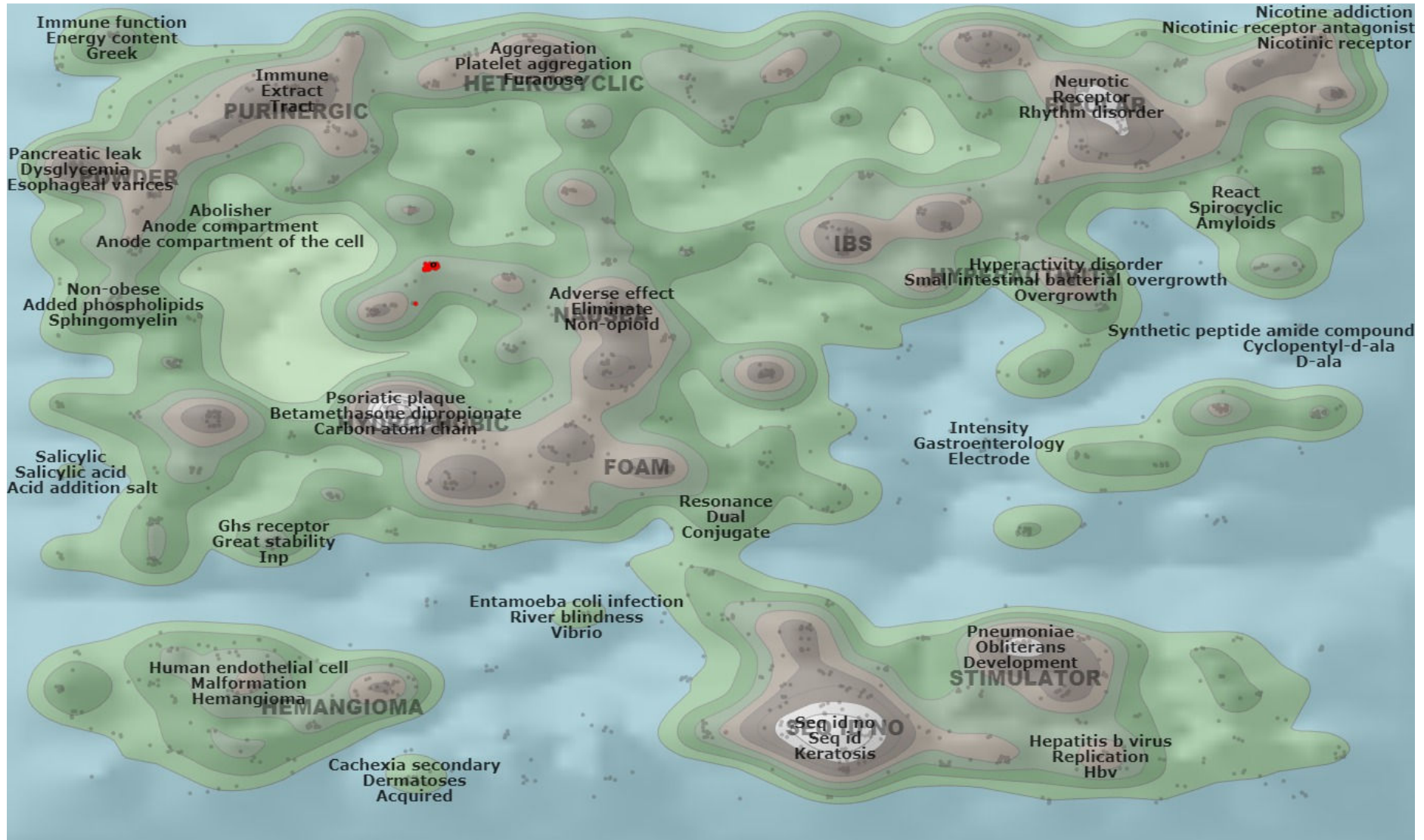
a: 47 Mount Pleasant, London, WC1X 0AE, UK | Forth House, 28 Rutland Square, Edinburgh, EH1 2BW, UK



proximity score to all of its peers. The outcome of this analysis is a visualisation of the patent space with each patent (dot) represented once in the map, with patents in close proximity sharing more phraseology than those located apart. Each peak is labelled with the key terminology concepts contained in the patents within the cluster.

The resulting maps are shown below. The first chart shows the overall landscape. The second chart shows the patents within this landscape which refer to etanercept within their title, abstract or claims. This highlights a small group of related patent families, but on further inspection these do not relate to the use of etanercept for constipation. The third chart shows more generally which patents are concerned with TNF or anti-inflammatories. These can be seen to be spread across the whole landscape, and not concentrated into any particular region.



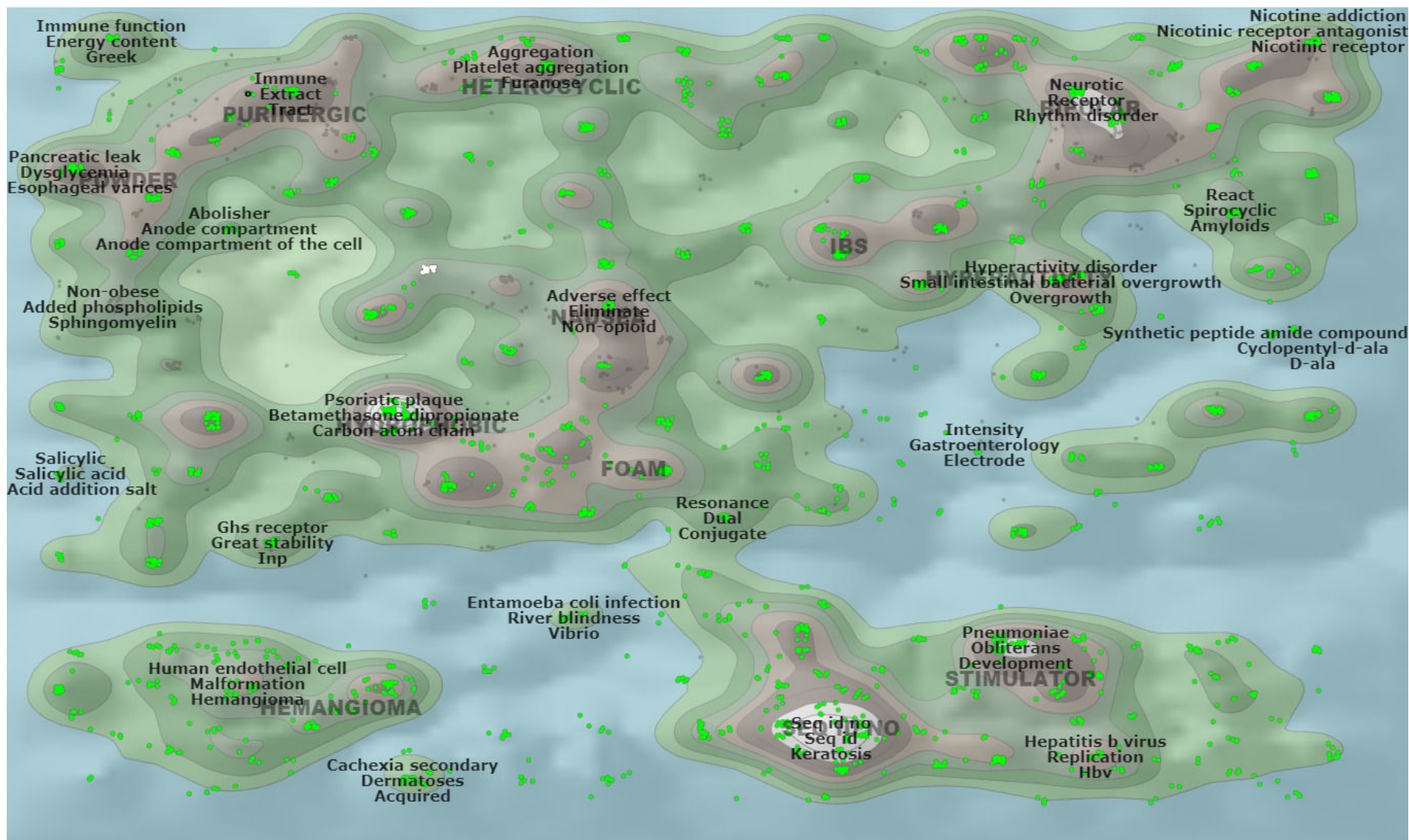


Red dots show patents relating to etanercept

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Green dots show patents relating to anti-inflammatories

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### 5.3 FOCUSED SEARCH FOR ANTI-TNF DRUGS IN CONSTIPATION

A more focused search was carried out to identify if any patents concern the link identified by the team of anti-TNF drugs, specifically etanercept, in the treatment of constipation. The search was complicated by the fact that anti-TNF drugs are commonly prescribed for ulcerative colitis, which has constipation as one of its symptoms.

(CTB=((tnf or tnfalpha or tnfa or antitnf or (tumour adj necrosis) or (tumor adj necrosis) or enbrel or etanercept or etacept or benepali or erelzi)) OR IC=((C07K0014525))) AND CTB=(constipat\*) AND DP>=(19980101);

The IPC code used in this search is for tumour necrosis factor (TNF).

- This searched the claims, title and abstracts of patents published from 1998 and identified 2,668 individual patent cases in 193 INPADOC patent families.

The top assignees in this search are shown in the table below. Individual inventors and unspecified assignees have been removed from this list for clarity. Document count refers to the number of patent families (rather than individual patents).

DWPI Assignee/Applicant	Document Count	Percentage
NESTEC SA/NEST	18	3.90%
PROMETHEUS LAB INC/PROM-N	17	3.68%
PROGENICS PHARM INC/PRGN	15	3.25%
BIOSUCCESS BIOTECH CO LTD/BIOS-N	10	2.16%
MAPIKS EHS EHJ AR EHL/MAPI-N	10	2.16%
GLENMARK PHARM INC U/GLMK	9	1.95%
GLENMARK PHARM SA/GLMK	9	1.95%
STEALTH BIOTHERAPEUTICS CORP/STEA-N	9	1.95%
UNIV SOUTHERN CALIFORNIA/USCA	6	1.30%
EPEIUS BIOTECHNOLOGIES CORP/EPEI-N	6	1.30%
STEALTH PEPTIDES INT INC/STEA-N	6	1.30%
CELGENE CORP/CGEN	5	1.08%
GLAXOSMITHKLINE/GLAX	5	1.08%
BIOSEARCH SA/BIOS-N	5	1.08%
PULEVA BIOTECH SA/PULE-N	5	1.08%
DAVIDSON LOPEZ LLC/DAVI-N	5	1.08%
LOPEZ LLC DAVIDSON/LOPE-N	5	1.08%
ADVINUS THERAPEUTICS LTD/ADVI-N	4	0.87%
SYNERGY PHARM INC/SYNE-N	4	0.87%
GLAXOSMITHKLINE ISTRAZIVACKI CENTAR ZAGR/GLAX	4	0.87%
GLAXOSMITHKLINE ISTRAZIVACKI CENT ZAGREB/GLAX	4	0.87%
PLIVA ISTRAZIVACKI INST DOO/PLIV	4	0.87%
DA VOLTERRA/VOLT-N	4	0.87%

The patent families identified by this search were scanned manually for relevance. No patents which disclose the use of anti-TNF drugs specifically for constipation were identified, but as mentioned above, constipation is one of the symptoms which may be indicative of a therapeutic indication for this class of drug. The most relevant patents from this search are shown in the table below:

**Note:** To access the full text of these patents, please click on the hyperlinked publication number to retrieve a summary of the patent. A pdf of the original file can then be downloaded by clicking the pdf logo located just to the left of the words “Full View” at the top left of the screen.

Publication Number	Title (English)	Assignee/Applicant	Priority Date	Publication Date
<a href="#">WO2015051337A2</a>	METHODS OF TREATING GASTROINTESTINAL DISORDERS	EMORY UNIVERSITY,US	2013-10-04	2015-04-09
	Method (M1) of improving enteric nerve cell survival in patient in need exhibiting symptoms of colitis, involves administering TNF- $\alpha$ inhibitor to the patient, that reduces neuropeptide-Y (NPY). The method (M1) is useful for improving enteric nerve cell survival in patient in need exhibiting symptoms of colitis. The method (M2) is useful for decreasing tight junction permeability. The method (M3) is useful for diagnosing disorder associated with gastrointestinal motility. The TNF- $\alpha$ inhibitor is useful for improving colonic cell motility, and improving symptoms associated with irritable bowel syndrome, chosen from dyspepsia, bloating, abdominal pain, diarrhea and constipation (all claimed).			
<a href="#">AU2014235209A1</a>	Guanylate cyclase receptor agonists combined with other drugs	Synergy Pharmaceuticals Inc.	2013-03-15   2013-05-23   2014-03-13	2015-10-01
	Composition comprises a guanylate cyclase receptor agonist (GCRA) peptide consisting essentially of sequence as given in the tables 1-8 of the specification and a compound including 5-aminosalicylic acid or its derivative or salt, mercaptopurine, an anti-TNF therapy or an antibiotic. The composition is useful for: preventing or treating a condition including ulcerative colitis, Crohn's disease, irritable bowel syndrome, non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, constipation, constipation associated with use of opiate pain killers, post-surgical constipation, constipation associated with neuropathic disorders, gastroesophageal reflux disease, Celiac disease, gastroparesis, heartburn, poor gastrointestinal motility, congestive heart failure, hypertension, benign prostatic hyperplasia, colon cancer, lung cancer, bladder cancer, liver cancer, salivary gland cancer or skin cancer, bronchitis, tissue inflammation, organ inflammation, respiratory inflammation, asthma, chronic obstructive pulmonary disease, lipid metabolism disorders, biliary disorders, cardiovascular disease, obesity and an endocrine disorder in a subject; colonic cleansing in a subject (all claimed); treating gastrointestinal disorders e.g. irritable bowel syndrome, inflammatory bowel disease and excessive acidity, cardiac disorders including eye disorders, oral disorders, blood disorders, liver disorders, skin disorders and prostate disorders, where the lipid metabolism disorders include e.g. dyslipidemia, hyperlipidemia and hypercholesterolemia, and the biliary disorders include gallbladder disorders and lung disorders. No biological data given.			
<a href="#">AU2012211459A1</a>	(R)-N-methylnaltrexone, processes for its synthesis and its pharmaceutical use	Progenics Pharmaceuticals Inc.	2006-05-25	2012-08-30
	A composition comprises (R)-N-methylnaltrexone (R-MNTX). The composition is free of high performance liquid chromatography (HPLC) detectable S-MNTX at a detection limit of 0.02%, and at a quantitation limit of 0.05%. For treating or preventing opioid-induced side effects (e.g. constipation, immune suppression, inhibition of gastrointestinal motility, inhibition of gastric emptying, nausea, emesis, incomplete evacuation, bloating, abdominal distension, increased gastroesophageal reflux, hypotension, bradycardia, gastrointestinal dysfunction, pruritus, dysphoria, and urinary retention); to promote gastrointestinal motility, gastric emptying or relief of constipation where a patient is receiving an opioid for pain resulting from surgery; for treating or preventing endogenous opioid-induced gastrointestinal dysfunction (e.g. inhibition of gastrointestinal motility, constipation and postoperative bowel dysfunction); for preventing or treating idiopathic constipation; for treating irritable bowel syndrome; for inducing laxation; and for preventing or treating post-operative bowel dysfunction (e.g. delayed gastric emptying or inhibition of gastrointestinal motility) (claimed).			
<a href="#">IT1407225B</a>	Composition used for treating	MAPIKS EHS EHJ AR EHL   EHPHTEYN O I   EPSHTEIN O		2014-03-28

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Publication Number	Title (English)	Assignee/Applicant	Priority Date	Publication Date
	disease/condition of functional etiology of gastrointestinal tract comprises activated-potentiated form of antibody to histamine, antibody to tumor necrosis factor-alpha and antibody to brain specific protein	I   EPSHTEIN O L   EPSHTEIN O   EPSTEIN O I   ILIICH E O		
	A combination pharmaceutical composition (C1) comprises a) an activated-potentiated form of an antibody to S-100 protein, b) an activated-potentiated form of an antibody to histamine, and c) an activated-potentiated form of an antibody to tumor necrosis factor-alpha (TNF- $\alpha$ ). For treating disease or condition of functional etiology of the gastrointestinal tract, where the disease or condition is psychosomatic in nature, irritable bowel syndrome, abdominal pain, diarrhea, constipation, or is a distortion in the motor-evacuatory function of the gastrointestinal tract (where the irritable bowel syndrome is predominantly by abdominal pain and flatule, diarrhea, or by constipation) (claimed).			
<a href="#">AU2014331812A1</a>	Agonists of guanylate cyclase useful for downregulation of pro-inflammatory cytokines	Synergy Pharmaceuticals Inc.	2013-10-09   2014-10-09	2016-04-28
	A composition comprises a guanylate cyclase receptor agonist (GCRA) peptide comprising of the sequence of any one of Tables 1-7, given in the specification, and a Nuclear Factor (NF)-kappaB inhibitor, a c-Src tyrosine kinase inhibitor, a 5-aminosalicylic acid (5-ASA) agent, a c-Myc inhibitor, or an I kappaB kinase (Ikk) inhibitor. The composition is used for preventing or treating a condition selected from colitis, ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, constipation, constipation associated with use of opiate pain killers, post-surgical constipation, IBS-associated constipation, constipation associated with neuropathic disorders, gastroesophageal reflux disease (GERD), Celiac disease, gastroparesis, heartburn, poor gastrointestinal motility, congestive heart failure, hypertension, benign prostatic hyperplasia (BPH), gastrointestinal cancer, lung cancer, bladder cancer, liver cancer, salivary gland cancer, skin cancer, bronchitis, tissue inflammation, organ inflammation, respiratory inflammation, asthma, chronic obstructive pulmonary disease (COPD), lipid metabolism disorder, biliary disorder, cardiovascular disease, obesity and an endocrine disorder; treating or alleviating a symptom of a NF-kappaB mediated inflammation; modulating NF-kappaB induction in a cell; and modulating NF-kappaB-dependent target gene expression in a cell (all claimed).			
<a href="#">JP2005200316A</a>	FEED, FEED ADDITIVE AND CHEMICAL FOR ANIMAL COMPRISING PULVERIZED MATERIAL AND/OR EXTRACTED MATERIAL OF LOTUS	TOOYOO GIJUTSU KENKYUSHO KK   NIPPON ALLERGIE OYO KENKYUSHO KK	2004-01-13	2005-07-28
	Feed for animals, containing crushed material and/or extract of a lotus, is new. The feed is useful for treating allergic disease such as pollinosis, bronchial asthma and atopic dermatitis, and constipation in animals such as dog, cat, horse, pig, cow, goat, sheep, etc.			
<a href="#">AU2006211996A1</a>	Colonic delivery of active agents	Centre National de la Recherche Scientifique,FR   Da Volterra,FR	2005-02-09   2006-02-09	2007-08-16
	An oral drug delivery device comprises active agent capable of inactivating antibiotic, and drug delivery device comprising pectin beads, where pectin is crosslinked with calcium ions, and reticulated with polyethyleneimine. For delivering active agents such as aminosalicylate, drugs containing 5-aminosalicylic acid (5-ASA), corticosteroids, immunomodulators, cyclosporine A, TNF $\alpha$ , thiazolidinedione and glitazones for treating Crohn's disease and ulcerative colitis, for delivering active agent selected from anti-proliferative agents, agents			

Publication Number	Title (English)	Assignee/Applicant	Priority Date	Publication Date
	for DNA modification or repair, DNA synthesis inhibitors, DNA/RNA transcription regulators, enzyme activators, enzyme inhibitors, gene regulators, HSP-90 inhibitors, microtubule inhibitors, agents for phototherapy and therapy adjuncts for treating colon cancer, delivering active agent selected from stimulant laxatives, osmotic laxatives, stool softeners, bulking agents and anticholinergic medications for treating irritable bowel syndrome or constipation. Also used as diagnostic agent when encapsulated agent is diagnostic agent selected from radiolabeled compounds, radiopaque compounds and gases, for diagnosing disorder in colon (all claimed).			
<a href="#">HK1228777A0</a>	Composition used for preventing or treating a condition, e.g. ulcerative colitis, heartburn, hypertension, cancer, and obesity, comprises a guanylate cyclase receptor agonist peptide	SYNERGY PHARM INC		2017-11-10
	A composition comprises a guanylate cyclase receptor agonist (GCRA) peptide comprising of the sequence of any one of Tables 1-7, given in the specification, and a Nuclear Factor (NF)-kappaB inhibitor, a c-Src tyrosine kinase inhibitor, a 5-aminosalicylic acid (5-ASA) agent, a c-Myc inhibitor, or an I kappaB kinase (Ikk) inhibitor. The composition is used for preventing or treating a condition selected from colitis, ulcerative colitis, Crohn's disease, irritable bowel syndrome (IBS), non-ulcer dyspepsia, chronic intestinal pseudo-obstruction, functional dyspepsia, colonic pseudo-obstruction, duodenogastric reflux, constipation, constipation associated with use of opiate pain killers, post-surgical constipation, IBS-associated constipation, constipation associated with neuropathic disorders, gastroesophageal reflux disease (GERD), Celiac disease, gastroparesis, heartburn, poor gastrointestinal motility, congestive heart failure, hypertension, benign prostatic hyperplasia (BPH), gastrointestinal cancer, lung cancer, bladder cancer, liver cancer, salivary gland cancer, skin cancer, bronchitis, tissue inflammation, organ inflammation, respiratory inflammation, asthma, chronic obstructive pulmonary disease (COPD), lipid metabolism disorder, biliary disorder, cardiovascular disease, obesity and an endocrine disorder; treating or alleviating a symptom of a NF-kappaB mediated inflammation; modulating NF-kappaB induction in a cell; and modulating NF-kappaB-dependent target gene expression in a cell (all claimed).			
<a href="#">US20160287525A1</a>	COMPOSITIONS FOR COLONIC DELIVERY OF DRUGS	BANNER LIFE SCIENCES LLC   BANNER LIFE SCIENCES LLC,High Point,NC,US	2015-04-06	2016-10-06
	An oral pharmaceutical composition comprises controlled-release matrix encapsulated in soft capsule shell. The controlled-release matrix comprises lipid(s) or lipophilic vehicle(s), hydrophilic polymer(s), hygroscopic polymer(s), nonionic surfactant(s), and active pharmaceutical ingredient(s). The matrix dissolves in the colon. Pharmaceutical composition in the form of soft capsule or enteric soft capsule, used for treating, preventing, ameliorating, retarding progression, delaying onset, or reducing symptoms of bowel disease including inflammatory bowel disease, irritable bowel syndrome, colon cancer, or colorectal cancer (claimed).			
<a href="#">IN200904408P1</a>	Delayed release oral solid dosage form, useful to treat e.g. ulcerative colitis, comprises a core comprising a drug and a diluent; and a delayed release material comprising one or more natural or synthetic gums	PENWEST PHARMACEUTICALS CO.	2003-09-19	2012-04-27
	Delayed release oral solid dosage form (A) comprises a core (I) comprising a drug, which can be absorbed in the colon and a diluent; and a delayed release material (II) compression coated onto the surface of (I), (II) comprising one or more natural or synthetic gums. (A) is useful to treat Crohn's disease and/or ulcerative colitis in humans (claimed). (A) is useful to treat colon cancer.			



An alternative focused search strategy was then used, to focus on the wider topic of chronic constipation and gastro-intestinal diseases in the elderly, combined with anti-TNF drugs:

(CTB=((tnf or tnfalpha or tnfa or antitnf or (tumour adj necrosis) or (tumor adj necrosis) or enbrel or etanercept or etaccept or benepali or erelzi)) OR IC=((C07K0014525))) AND (CTB=(constipat\*) OR IC=(A61P000110)) AND CTB=(elderly or old or older or age or ageing or aging) AND CTB=(chronic) AND DP>=(19980101);

- This searched the claims, title and abstracts of patents published from 1998 and identified 290 individual patent cases in 24 INPADOC patent families.

The top assignees in this search are shown in the table below. Individual inventors and unspecified assignees have been removed from this list for clarity. In this case, the document count refers to the number of individual patents (rather than patent families).

DWPI Assignee/Applicant	Document Count	Percentage
BIOSUCCESS BIOTECH CO LTD/BIOS-N	<u>96</u>	9.45%
CARA THERAPEUTICS INC/CARA-N	<u>74</u>	7.28%
BIOSUCCESS BIOTECH CO/BIOS-N	<u>45</u>	4.43%
BIOSUCCESS BIOTECH LTD/BIOS-N	<u>45</u>	4.43%
ABBOTT GMBH&CO KG/ABBO	<u>25</u>	2.46%
ABBOTT LAB/ABBO	<u>25</u>	2.46%
ABBVIE INC/ABBI	<u>25</u>	2.46%
PHARMACIA CORP/PHAA	<u>23</u>	2.26%
UNIV CALIFORNIA/REGC	<u>4</u>	0.39%
STEALTH BIOTHERAPEUTICS CORP/STEA-N	<u>2</u>	0.20%
STEALTH PEPTIDES INT INC/STEA-N	<u>2</u>	0.20%
CERA THERAPEUTICS INC/CERA-N	<u>2</u>	0.20%
TAIYO KAGAKU KK/TAIC	<u>1</u>	0.10%
CLEVELAND BIOLABS INC/CLEV-N	<u>1</u>	0.10%

The full set of results for this search is provided in the attached file: chronic constipation in elderly and TNF families.xls. These results were scanned manually for relevance, but do not appear to be directly relevant to the Brighton approach.

#### 5.4 THE UNIVERSITY INTELLECTUAL PROPERTY POSITION

**Important Note:** This analysis is not intended as a legal opinion on freedom to operate or patentability. Instead it aims to identify the complexity of the patent landscape from a commercial perspective in order to identify competing approaches and third party patents that need to be considered; and to identify partners with similar IP that may be combined with the organisation's IP.

An examination of the patent landscape suggests that there is a fairly low interest in patents which address the treatment of chronic constipation in the elderly. The searches carried out have not identified any patents which relate to treatment of constipation directly with anti-TNF- $\alpha$  drugs. However, as constipation is a side-effect of conditions such as ulcerative colitis which is treated with anti-TNF- $\alpha$  drugs, this additional use of this class of drugs may have been considered obvious. The

opportunity to patent the link between anti-TNF- $\alpha$  drugs and relief of constipation has anyway now passed as the research has been published by the team.

The patent literature suggests that investigation of treatments which combine TNF- $\alpha$  antagonism with targeted delivery mechanisms, allowing them to act directly on the colon is not an active area of interest, either in the pharmaceutical companies or amongst academics. We did identify some patents relating to re-formulation approaches to allow biologics to reach the colon, although no specific searching was done for this particular aspect. Where novel compounds with anti-TNF- $\alpha$  activity were being developed, this was for other indications.

There may therefore be an opportunity to develop an intellectual property position around novel compounds or novel delivery mechanisms targeting anti-TNF- $\alpha$  drugs for constipation.

## 6 INDUSTRY FEEDBACK

### 6.1 STAKEHOLDER APPROACHES

In order to further substantiate the findings from the secondary market research and identify potential partners, contacts have been made with a range of relevant healthcare professionals and companies with an interest in constipation and/or TNF- $\alpha$  antagonists for both human and animal health. The aim was to obtain feedback regarding the attractiveness of this new approach and to understand where it sits in the overall commercial landscape. Where possible, IP Pragmatics has followed up with the companies in direct meetings over the phone to try to gain additional insights. However in this case, we have only received limited direct feedback, with many of the responses coming via email and declining a conversation.

Suitable targets were selected from a combination of the market research and IPP knowledge of this industry. The companies contacted are shown in the table below. We also contacted a selection of healthcare experts in the human and veterinary field.

Company	Reason for interest	Comments
<b>Janssen Inc</b>	Pharma companies: with TNF $\alpha$ products; Pharma companies: constipation therapy area	
<b>Medimmune</b>	Pharma companies: with TNF $\alpha$ products	Originator of Abbott's Humira
<b>Merck &amp; Co Inc</b>	Pharma companies: with TNF $\alpha$ products	
<b>Pfizer Inc</b>	Pharma companies: with TNF $\alpha$ products	Originator of Etanercept: market interest for sc injection + biological product for constipation?
<b>Sandoz Inc</b>	Pharma companies: with TNF $\alpha$ products	Have a biosimilar for etanercept
<b>Abbott</b>	Pharma companies: constipation therapy area	Sells lactulose (Duphalac)
<b>Eisai</b>	Pharma companies: constipation therapy area	Laxatives
<b>Novartis</b>	Pharma companies: constipation therapy area	Developed Tegaserod (withdrawn from US market)
<b>Sanofi</b>	Pharma companies: constipation therapy area	Sodium picosulfate laxative POM
<b>Takeda</b>	Pharma companies: constipation therapy area	Laxative and targeted therapy (not their own) Also sell Enbrel in Japan
<b>Bristol-Myers Squibb Co</b>	Pharma companies: ulcerative colitis therapy area	
<b>Celgene Corp</b>	Pharma companies: ulcerative colitis therapy area	
<b>Eli Lilly and Co</b>	Pharma companies: ulcerative colitis therapy area	
<b>GlaxoSmithKline Plc</b>	Pharma companies: ulcerative colitis therapy area	
<b>Johnson &amp; Johnson</b>	Pharma companies: ulcerative colitis therapy area	
<b>Johnson &amp; Johnson Inc</b>	Consumer health companies, esp those with gut health products	

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Company	Reason for interest	Comments
<b>Bayer AG</b>	Consumer health companies, esp those with gut health products	
<b>Bayer Healthcare Animal Health</b>	Animal health companies	manufactures antimicrobials, parasiticides, sedatives, pain killers, and nutritional supplements and feed additives for dogs, cats and horses. Products for food animals include anti-infectives, vaccines, parasiticides and sedatives and pain killers
<b>Boehringer Ingelheim (merged with Merial)</b>	Animal health companies	markets biologicals, vaccines, pharmaceuticals and other care products for use in pets and livestock
<b>Elanco (merged with Novartis Animal Health)</b>	Animal health companies	develops and markets products to treat animal health and increase protein production. Products include flea protection for dogs and cats, drugs to combat parasites in poultry, and vaccines and feed additives for livestock and poultry
<b>Merck Animal Health</b>	Animal health companies	manufactures vaccines, anti-infective and anti-parasitic drugs, fertility management drugs and other specialty pharmaceutical products for companion animals and livestock
<b>Virbac</b>	Animal health companies	manufactures antibiotics, vaccines, antiparasitics, dermatological and dental products for the treatment and care of pets and food animals
<b>Zoetis</b>	Animal health companies	develops vaccines, parasiticides, anti-infectives, medicinal feed additives and drugs for pain, sedation and cancers for pets and farm animals.

Notes from the email responses and interviews are summarised below.

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## HUMAN HEALTH

### 6.1.1 CILAG (JOHNSON & JOHNSON)

Ralf Schmidt, Senior Director, Head of Consumer Business Development EMEA at Cilag.

Cilag is the Consumer Health and Over the Counter Medicines group within Johnson & Johnson

- Ralf found the proposed approach surprising, because as highly priced drugs which are delivered by infusion, Enbrel or Remicade are not the type of treatment that springs to mind for a consumer health business.
- The products that they are involved with are almost exclusively self-medications.
- Digestive health products are definitely of interest to the consumer health team. Not just constipation, also diarrhoea and acid reflux. They are interested in new pre- and pro-biotics.
- For this type of product to work for them, they need a clear understanding of the cost proposition, and how it could be delivered from a practical perspective.

- Alternative routes of delivery, eg suppositories, oral delivery with delayed release, transdermal, are all possible within an OTC environment. Transdermal delivery requires small molecule drugs, and would not be effective for Enbrel.
- He is not an expert in this market indication, but his impression is that the existing OTC medications for constipation are effective enough.
- This approach appears to be too sophisticated for this type of condition. Cost is a particular issue. For OTC drugs, there would be insurmountable regulatory hurdles for this type of drug to be approved for self-medication.
- He will discuss with his colleagues in the pharmaceutical division whether there is a sub-set of patients where there is an unmet medical need that might justify use of a high cost product given by infusion.

*Follow up email received after he consulted further with his colleagues:*

We have looked at the concept again with my colleagues, but came to conclude that we really cannot see it within the consumer healthcare area that we're of course focused on from a perspective of developing new treatment/product solutions. In addition to the obvious areas already discussed (administration route, cost, regulatory framework) there may also be important considerations from an ethical perspective given the typical side effect profile of this type of immunologically active substances – so their use for a condition like constipation would have to be carefully evaluated in that context.

I will be passing your request on to a colleague at Janssen, our Pharma group, so that they can also take a look at your proposal / your questions from a prescription pharmaceutical perspective, and then get in touch with you as they see fit.

No response has yet been received from Janssen, but any additional feedback will be passed on.

---

### 6.1.2 AMGEN

Michelle Fortin, Program Lead of Academic Collaborations  
Elizabeth (Ellie) Robertson, Business Development:

Thank you for reaching out to Michelle with the University of Brighton's partnering opportunity. The message was forwarded to me, as I help facilitate the internal evaluation of available partnering opportunities. Unfortunately, treatments for constipation are not within our strategy and focus, but thank you for thinking of Amgen as a potential partner.

---

### 6.1.3 SANOFI

Adam Keeney, Partnering, Immunology, Sanofi-Genzyme:

This indication is out of scope for us, so I'm afraid I wouldn't have much to offer in the discussion as I do not know this particular space well.

---

#### 6.1.4 MERCK & CO (HUMAN HEALTH)

Jose Freire, Immunology and Respiratory S&E Lead, MRL Business Development & Licensing:

We appreciate you considering Merck. Unfortunately this falls outside of our scope of interest.

---

#### 6.1.5 PROFESSOR ROBIN SPILLER, CLINICIAN

Professor Spiller is Professor of Gastroenterology at the Nottingham Digestive Diseases Centre and NIHR Digestive Diseases and Hepatology Biomedical Research Unit:

While the data is interesting the idea of using TNFa antagonists at the cost of £1000 per treatment and significant risk of serious life threatening infection mean that this will never fly

There are a host of new very safe alternative nonsystemic treatments recently developed e.g. linaclotide or in the pipeline including plecanantide and Tenapanor which are likely to be preferred.

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### ANIMAL HEALTH

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#### 6.1.6 MERCK ANIMAL HEALTH

Peter Opdam, Director, Business Development - Europe at Merck Animal Health:

Constipation in elderly animals is not an area of active interest. But we've always been a company that, at least for specialty pharmaceuticals for companion animals, is opportunistic and we let the science drive our interests. So it may be that we've not come across a compelling candidate and, as such, have not tried to assess this potential market.

Below please find a summary of my colleagues' initial thoughts:

- Constipation is multifactorial – it can be due to pain on defecation, a blockage of some sort (including hairballs), lack of water, etc.
- It is much more prevalent (or at least noticed) problem in cats than dogs.
- In cats, megacolon can be an important cause.
- Most importantly it is not an old age problem, but a middle age thing (average around 6 years).
- In cats we also see obstipation (which is constipation but even worse so the feces in the gut is all dried out and they literally cannot defecate).
- The challenge is that constipation is a clinical sign and not a diagnosis so there are potentially different approaches to treatment depending on the underlying cause.
- It would be a niche segment (comparable to anti-emetics?) but could be bigger because cats with megacolon require much more intensive treatment.
- A biological approach would bring with it the advantage of infrequent administration – but on the other hand would not be really indicated if it is a cat with a hairball.

- Interesting as an approach but cost of the drug would be a concern.
- We would need to explore this further e.g. with KOL.

---

#### 6.1.7 ELANCO

Bruce Taillon, Director, External Innovation:

I have reached out to some internal research colleagues for opinions but I am afraid that it will be hard to pin down a market size. GI issues in dogs is very idiopathic and they can range from chronic inflammation to “garbage can gut”.

[If forced to estimate, I might guess at] a market size of \$10m when you divide the number of dogs that might be constipated by the ones that get taken the vet for the condition.

A big consideration will also be whether it flips the condition to loose bowels which is [not] very good for the pet/owner bond.

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#### 6.1.8 BOEHRINGER INGELHEIM / MERIAL

Boehringer Ingelheim’s animal health business merged with Merial in 2017 to create the second largest animal health organisation in the world.

Ursula Fauth, Head of Global Licensing Animal Health:

Thank you very much for bringing this opportunity to my attention. I have forwarded the information to our team of experts who will meet once a month to discuss and assess opportunities such as this. Since the last meeting has been earlier this week, I expect that I can get back to you towards the end of July.

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#### 6.1.9 ZOETIS

Rudiger Raue, Research Alliances EU:

Thanks a lot for your email. I am very happy to talk to you, but please give me a week to liaise with our commercial people to get a better idea about the market size for such an opportunity.

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#### 6.1.10 PHILIPPA YAM, VET

Philippa Yam is a veterinarian with a specialism in small animal gastroenterology.

- Idiopathic chronic constipation – v rare in dogs. Never saw a case. Only related constipation case was a dog that had eaten a lot of driveway gravel through playing catch where it was painful to pass faeces
- Commonly seen in cats
  - Causes can be secondary – e.g. as a result of road traffic accidents
  - Also primary idiopathic – Hirschsprung’s disease – neuronal disorder – also seen in new born children (rare disease)

- Don't know if it's an issue in horses – will try and identify somebody to speak to
- Management:
  - Laxatives are used very commonly – e.g. lactulose – same as for humans most likely
  - Also will look to improve the diet to ensure sufficient quantities of highly digestible fibre included
  - Also medical management using motility modifiers
    - Did use cisapride but it was hard to obtain (Note: This drug appears to have been shelved)
    - Also metachlopramide
- Cats can end up with end stage constipation (obstipation) – option to resect colon – not common
  - Well accepted procedure that is very successful
  - Cat needs to be monitored after surgery to make sure it is faecally continent
  - Not sure how much it costs nowadays (caveat anyway is that there's a huge difference in prices across the country, and whether this is done at private practice vs a vet institution) but will run into the £'000s (operation = subtotal colectomy for megacolon in cats) but most pet owners will be covered by pet insurance.

*Follow up information:*

Ms Yam supplied an old article she published on the topic in cats - the management of the condition has changed much since then.

She also supplied a reference to a study looking at the use of probiotics for constipation, with the comment: "This looks interesting...cheaper than biologicals!"

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#### 6.1.11 PROF BRUCE MCGORUM

Professor in Equine Medicine at The Royal (Dick) School of Veterinary Studies and The Roslin Institute, Edinburgh University:

- Constipation in horses not seen often
- Possible use in post op ileus which is more common problem than constipation?  
(<https://thehorse.com/116386/equine-postoperative-ileus-insights/>)
- Has forwarded to Zofia Lisowski (also Edinburgh University) who works on equine GI motility, in particular the influence of macrophages on GI motility  
(<https://www.ncbi.nlm.nih.gov/pubmed/29281117>)

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#### 6.1.12 PROF ALEX GERMAN

Liverpool Vet School, Liverpool University, with a specialism in GI vet medicine:

As a quick heads up, there would be more potential for cats rather than dogs. Constipation is not that common in dogs and the causes are heterogeneous, with few being age-related. Constipation is much more common in cats than dogs, with many being related to idiopathic megacolon. So, in

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theory, a new therapy here might be interesting. That said, it's not an age-related condition so it's unclear whether targeting TNF would be helpful. The pathogenetic mechanisms are not well established for megacolon in cats - and there has been very little active research on the condition for at least 20 years. However, it's not clearly an age-related change.

So, in answer to the broad question as to whether the treatment would be a goer in the veterinary market, it might be in cats, but that's a bit of a long shot. It would first need more fundamental research into the causes of megaolcolon in cats before animal trials. I'd be very happy to do that if someone would fund me!

*Further response in relation to mode of administration:*

Injections can be used for one-off therapy for patients attending a vet clinic. However, megacolon is a long-term condition and would require home management. With the exception of insulin (diabetic cats) there are no injectable drugs used in a home setting.

So, if the drug had to be given by injection, that would count against it further as a viable therapy.

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### 6.1.13 OAK TREE VET SURGERY, EDINBURGH

Malcolm Leitch, Vet in a private vet practice

- Generally chronic constipation is seen secondary to other disease, e.g. renal disease
- More commonly seen in cats – again usually as a result of another cause
- Constipation can be a problem for older cats – don't know if it would have the desired effect in this population of patients
- Standard care would be to give laxatives: paraffin, lactulose, or a combination of paraffin + lactulose
  - Lactulose is v cheap – dosage for cats ~2-5ml day. Cost for 500ml = £12
- Occasionally use Cisapride, but it is hard to obtain.
  - Cisapride needs to be specially compounded; Pack of 100 (lasts 50 days) would cost £60
- For colectomy, Malcolm reckons it would cost anywhere between £500-1000. Cat would also require support post-op care (e.g. infection control, and likely to continue to be prescribed laxatives once the cat has recovered)
  - Generally would try to keep any cat that has had this procedure hydrated, and prescribed laxatives, to keep things moving, otherwise it may have to endure regular enemas
- Injectable drugs are not a problem for cats – diabetic cats get injections BID. Also treatment for thrombosis is by injection.
  - Monthly injections can be done at the practice, but anything that needs to be given daily would be done by the owners at home generally
  - Oral medications are not easy to give to cats!
- Regarding horses – see constipation in grass sickness but don't know how relevant this treatment would be for them
  - Ileus – common in horses, though won't be a chronic condition
- Ileus also a big problem in rabbits and guinea pigs that are stressed and unwell – can be fatal

- Generally treat with NSAIDS or metachlopramide (motility agent)
- People don't spend as much on rabbits or guinea pigs as they do with cats

## 6.2 KEY USER REQUIREMENTS

The key messages arising from our primary research are:

- For human health, the concept seems to fall between two different types of pharmaceutical intervention. Chronic constipation is generally seen as an indication that is not of interest to the large prescription medicine pharmaceutical companies, which view it as out of scope for them. It is of more interest to their consumer health divisions, but these are focused on over the counter (OTC) remedies, and for these products injectable products with high cost would never be possible either from a market acceptance or a regulatory standpoint.
- We did not manage to obtain very much direct feedback from those involved with patient care. The feedback we did receive, however, was that there were existing treatments available or in the pipeline which are very safe and efficacious. Whilst the mechanistic concept was interesting, the costs and risks infection were considered to rule out use of the existing anti-TNF drugs as a viable option for this patient group.
- There was a more open-minded attitude within animal health, where an injectable product was seen as less of a disadvantage, and there are clear unmet medical needs, particularly amongst cats.
- However, the biggest problems (such as idiopathic megacolon in cats and ileus in horses) do not appear to be clearly linked to age, and so may be acting through a different mechanism from the one investigated by the team in their aged mouse model.
- Cost was consistently raised as an issue in animal health, particularly as the common treatments, such as laxatives, are very cheap and often efficacious.

## 7 CONCLUSIONS & RECOMMENDATIONS

There is a large market for treatments for constipation, which is dominated by cheap over the counter remedies. It is not a well-defined disease entity, but a general collection of symptoms, which makes it more difficult to develop therapeutics which will target all causes of the effects. Many patients self-medicate, and those that do seek medical help are generally treated with lifestyle changes initially, followed by laxatives, before progressing to prescription drugs. Existing drugs are viewed as effective, and the leading prescription therapy, linaclotide, is expected to reach blockbuster status in several territories. The drug used by the team at Brighton to exemplify their approach is a biologic, which is very expensive, must be given by infusion, and has a suppressive effect on the immune system as well as potential side-effect on the heart and kidneys. Use of this particular drug would therefore be likely to be reserved for a very small sub-set of patients for whom all other options have failed.

Our investigations of the patent landscape, coupled with the limited response received from the pharmaceutical companies in our primary research suggest that although the market is large, it is not an area of high current research interest, which supports the feedback from the primary interviews that constipation is not a disorder with high unmet medical need. The responses obtained to date suggest that this is a therapeutic area which is of highest interest to the OTC segment. In order to enter this market, however, the team would need to identify an active ingredient with a long safety record, which is cheap and (probably) which can be given orally. Even if the existing biologic could be re-formulated for oral delivery, the side effects and immune suppressive activity of anti-TNF- $\alpha$  would make it very difficult to achieve regulatory clearance for an OTC medication. An alternative would be to identify other active ingredients with the desired therapeutic, delivery and safety profile. Some of the larger pharmaceutical companies offer research access to their compound libraries, so this could be a potential route to identify alternative drugs with anti-TNF activity. However, as the existing marketed drugs with this activity are all biologics, it is less likely that these libraries will contain useful molecules which could fit the profile needed.

There is no IP protection currently in place surrounding the Brighton approach. This will be a significant drawback to partnering with a pharmaceutical company with the global reach needed to address this market. Patent protection is essential to allow medicines to compete and to justify the significant investment that is needed to identify and develop and new active molecule, and carry out clinical development work. However, there could be opportunities for IP protection from the identification of novel compounds; the patent landscape in the treatment of chronic constipation is not crowded.

The opportunity for animal health seems more promising, but in this area the underlying causes of problematic constipation are varied, and may not be related to ageing. Further fundamental research is therefore likely to be needed to establish if the causal link identified in the mouse model is relevant to these conditions.

A SWOT analysis of the overall opportunity based on the research summarized in this report is given in the table below:

STRENGTHS	WEAKNESSES
<ul style="list-style-type: none"> <li>• Novel approach, that does not appear to be actively researched by others</li> <li>• Potential to be curative, rather than just treat the symptoms</li> <li>• Large market for treatment of constipation</li> </ul>	<ul style="list-style-type: none"> <li>• Existing treatments are generally cheap, safe and efficacious</li> <li>• Exemplar treatment used by the team has drawbacks in terms of cost, route of administration and side effects</li> <li>• Early stage of development, and a new molecule is likely to be needed to enter this market</li> <li>• Regulatory hurdles for an OTC product are high</li> <li>• Little interest identified in pharmaceutical companies for new approaches to constipation</li> </ul>
OPPORTUNITIES	THREATS
<ul style="list-style-type: none"> <li>• Additional data on the effectiveness of etanercept compared with OTC laxatives in the Brighton mouse model could help to demonstrate superior activity for this approach</li> <li>• Identification of small molecule anti-TNF drugs would open up the potential for OTC drugs</li> </ul>	<ul style="list-style-type: none"> <li>• Lack of registered IP protection is likely to significantly impact on the ability to gain traction with pharmaceutical companies</li> </ul>

**APPENDIX 1: SELECTED COMPANY DETAILS****ARDELYX INC.**

34175 Ardenwood Blvd., Ste. 200  
Fremont, CA 94555  
Tel: 510/745-1700  
Website: [www.ardelyx.com](http://www.ardelyx.com)

Ardelyx focuses on non-systemic and reduced risk therapies. Tenapanor is a Phase 3 promising drug being studied for Constipation Predominant Irritable Bowel Syndrome. Results of two Phase 3 trial are expected in 2017.

**ASTELLAS PHARMA INC.**

2-5-1, Nihonbashi-Honcho  
Chuo-Ku 103-8411  
Tokyo, Japan  
Tel: +81-3-3244-3000  
Website: [www.astellas.com](http://www.astellas.com)

Astellas Pharma is headquartered in Tokyo, Japan. Astellas has more than 17,000 employees worldwide. In November 2015, Astellas Pharma and U.S.-based Ironwood Pharmaceuticals released results of a Phase 3 trial of linaclotide conducted in Japan in adults with irritable bowel syndrome with constipation (IBS-C). The double-blind, placebo-controlled trial randomized 500 adults with IBS-C in Japan. Following that, a new drug application (NDA) seeking approval of linaclotide for the treatment of adults with irritable bowel syndrome with constipation (IBS-C) in Japan was filed with the Japanese Ministry of Health, Labor and Welfare, in February 2016.

**ASTRAZENECA**

2 Kingdom St.  
London W2 6BD  
United Kingdom  
Tel: +44(0)20-7604-8000  
Website: [www.astrazeneca.com](http://www.astrazeneca.com)

AstraZeneca is a pharmaceutical and biologics company headquartered in the U.K. The company was established in 1985 as Zeneca Group, then merged with Astra USA and became AstraZeneca in 1999. It offers several therapies in the area of gastrointestinal medicine like omeprazole (Prilosec) supplied as delayed-release capsules administered orally. Elobixibat is a Phase 2 therapy studied for the treatment of constipation, predominantly Irritated Bowel Syndrome (IBS-C).

**SUCAMPO PHARMACEUTICALS INC.**

805 King Farm Blvd., Ste. 550  
Rockville, MD 20850  
Tel: 301/961-3400  
Website: [www.sucampo.com](http://www.sucampo.com)

Sucampo is a biopharmaceutical company working in the area of gastroenterology and focused on areas of unmet and underserved needs. It has discovered and developed an approved pharmaceutical product, Amitiza (Lubiprostone), for treating irritable bowel syndrome with constipation in adults, chronic constipation, chronic idiopathic constipation in adults and opioid-induced constipation. Lubiprostone is being studied for Pediatric Functional Constipation and is in Phase 2 developmental stage.

#### SYNERGY PHARMACEUTICALS INC.

420 Lexington Ave., Ste. 2012  
New York, NY 10170  
Tel: 212/297-0020  
Website: [www.synergypharma.com](http://www.synergypharma.com)

Synergy Pharmaceuticals is engaged in the discovery and development of novel gastrointestinal therapies. Plecanatide is the first uroguanylin analog presently being studied for treating irritable bowel syndrome with constipation (IBS-C). Plecanatide is a PHM046C - Gastrointestinal Therapeutics and Diagnostics: Technologies and Global Markets Copyright © BCC Research, Wellesley MA USA, Website: [www.bccresearch.com](http://www.bccresearch.com) 182 peptide made up of 16 amino acids. It is the first therapy studied to replicate the function of uroguanylin, a naturally occurring human GI peptide. It works in the upper GI tract to stimulate digestive fluid movement and helps in regular bowel function. The company's second uroguanylin analog, Dolcanatide, is being explored for ulcerative colitis.

#### VALEANT PHARMACEUTICALS

2150 St. Elzéar Blvd. West  
Laval, Quebec H7L 4A8  
Canada  
Tel: 800/361-1448  
Website: [www.valeant.com](http://www.valeant.com)

Valeant Pharmaceuticals specializes in dermatology, eye health, gastrointestinal diseases and disorders, neurology and consumer healthcare. Xifaxan was approved by the FDA in 2015 for treatment of irritable bowel diseases with diarrhea. Following the acquisition of Salix Pharmaceuticals in 2015, Valeant entered a new therapeutic area, gastrointestinal disorders. Among Salix's key products are Xifaxan 550 mg (indicated for irritable bowel syndrome with diarrhea and hepatic encephalopathy), Xifaxan 200 mg (traveler's diarrhea), Relistor (opioid-induced constipation) and Uceris and Apriso (ulcerative colitis). Other GI products include Ruconest, Giazio, Moviprep, Osmoprep, Solesta, Fulyzaq, Deflux, Glumetza, Cycloset and Zegerid