



Ockham Technical Synopsis is a recurring series prepared for internal staff and consultants of Ockham Development Group Inc. (Ockham). Highlighting current and emerging issues and challenges in clinical research, these publications are intended to disseminate intelligence captured during the execution of key clinical trials and are therefore updated on a continuous basis.

IRRITABLE BOWEL SYNDROME (IBS)

OVERVIEW AND EPIDEMIOLOGY

Irritable Bowel Syndrome is a very common gastrointestinal (GI) disorder. Its cardinal symptom is crampy abdominal pain, which typically occurs in the left lower quadrant and is relieved by a bowel movement. Associated symptoms include an alternation in bowel movements, bloating, and mucus in the stools.

One in five Americans has IBS, making it one of the most common disorders diagnosed by doctors. It occurs roughly twice as often in women as in men, and it usually begins around age 20. However, about half the population with symptoms of IBS never see a physician for their symptoms.

Of interest, the bowel pattern in patients with IBS may be quite variable. It is commonly stated that about a third of patients have a "diarrhea-predominant" pattern, a third "constipation-predominant", and a third alternate between the two. However, a very recent community-based survey¹ reports that over 60% of those with IBS have an alternating pattern while about 16% are constipation-predominant and 23% are diarrhea-predominant.

IBS causes a great deal of discomfort and distress. It is associated with substantial time lost from work and may be a major source of interference in both relationships and in everyday functioning. However, IBS does not in general become more serious over time and does not shorten life or lead to other GI disorders. Of interest, symptoms may wax and wane over time. Although it is not thought that "stress" causes IBS, it is clear that stressful events can exacerbate symptoms in many patients.

Current therapy of IBS is unsatisfactory for the vast majority of patients. Many patients feel that to some extent they can control their symptoms with such non-medical approaches as diet, stress management, biofeedback, hypnosis, and various "herbal" therapies. Although many drugs have been employed for the treatment for IBS, the vast majority have not been

¹ Hung in APS, Chang L, Locke GR, et al. *Aliment Pharmacol Ther* 2005; 21:1365-1375.

shown to be active in randomized controlled trials.² Even with drugs where randomized clinical trials (RCT) provide some evidence of efficacy, the effect size is quite modest and side-effects, sometimes serious, are not uncommon. Despite available treatment regimens, IBS remains a disabling condition for many patients.³

TREATMENT

Treatment for patients with IBS is provided in order to reduce symptoms associated with the disorder. Target symptoms include abdominal discomfort, bloating, and altered bowel habits. It is the position of the American College of Gastroenterology Functional Gastrointestinal Disorders Task Force (ACG Task Force)⁴ that treatment of altered bowel habits in the absence of treatment for other IBS symptoms (such as abdominal discomfort) constitutes less than optimal treatment of the patient with IBS. Regulatory agencies have echoed the Rome II recommendations for randomized trials in IBS by favoring a global patient rating of efficacy as the primary endpoint. [Note: *Rome III: The Functional Gastrointestinal Disorders* – scheduled for release in late Summer 2006⁵ – will be available to companies seeking to develop therapeutic agents for IBS.]

Currently, several different classes of medications are in use for the treatment of IBS. Most have not been shown to be efficacious in properly designed randomized controlled trials. These include antispasmodic agents (e.g., hyoscyamine, dicyclomine), bulking agents (e.g., bran, fiber, calcium polycarbophil, psyllium, etc.), antidiarrheal agents (e.g., Loperamide), and antidepressants (including tricyclics). Other drugs used to provide medical therapy for IBS include the 5HT₄ agonist tegaserod, and the 5HT₃ receptor antagonist alosetron.

In addition, behavioral therapy may be used in treating some cases of IBS. However, population-based studies indicate that only a minority (on the order of 18%) of IBS patients also suffer from psychological disorders.

While the number of well-designed, randomized clinical trials using behavioral therapy for IBS is small, most studies appear to demonstrate that individual IBS symptoms do improve with behavioral therapy, and that this improvement is usually correlated with an improvement in symptoms of depression and anxiety (if present), as well.²

² Klein KB. Controlled treatment trials in the irritable bowel syndrome: a critique. *Gastroenterology*. 1988; 95:232-241.

³ National Digestive Diseases Information Clearinghouse (NIDDC)

⁴ www.acg.gi.org/patients/ibsrelief/pdf/gs20037147p.pdf

⁵ <http://www.romecriteria.org/>

According to the ACG Task Force, IBS is a disorder in which biochemical or structural markers are absent; as such, IBS is diagnosed based on various symptom-based criteria, including the Manning Criteria and Rome Criteria. Currently, the Rome II Criteria are the most widely used research criteria and are expected to be the admission criteria to RCTs by regulatory agencies. According to these diagnostic criteria, IBS is marked by "abdominal pain or discomfort associated with disorders of defecation." Experts associated with the ACG Task Force are not in favor of using IBS subtype designations (i.e., "diarrhea-predominant" or "constipation-predominant"), but rather prefer the use of symptom-based descriptions to guide management of the disorder and its treatment (e.g., "IBS with diarrhea" or "IBS with constipation").

NEW DRUGS IN DEVELOPMENT

Drugs currently in development for IBS include renzapride (Alizyme Therapeutics, Ltd.), cilansetron (Solvay Pharmaceuticals), asimadoline (Merck & Co.), and talnetant (GlaxoSmithKline).

According to its corporate Web site⁶, Alizyme is developing renzapride for the treatment of IBS and has successfully completed a 510-patient Phase IIb clinical trial in constipation-predominant IBS (c-IBS) patients, as well as a separate 160-patient Phase IIb clinical trial in mixed-symptom IBS (m-IBS) patients. In addition, a 48-patient pharmacokinetic/ pharmacodynamic (PK/PD) study was completed at the Mayo Clinic in c-IBS patients.

Renzapride has both 5-HT₄ agonist and a 5-HT₃-antagonist activity. These receptors influence intestinal motility and sensitivity. The dual mechanism of action of renzapride gives it a distinctive pharmacology and distinguishes it from its potential competitors. The company hopes to have the drug on the market by 2007. It should be noted that other drugs in this class (e.g., cisapride) have failed to show efficacy in the treatment of IBS.

Cilansetron [KC 9946] is a serotonin-3 receptor (5-HT₃) antagonist under development by Solvay Pharmaceuticals for the treatment of IBS with diarrhea predominance (IBS-D) in both men and women. In April 2004, Solvay submitted a New Drug Application (NDA) for cilansetron in the U.K. (for the European Union) for the treatment of IBS-D in both men and women. Solvay submitted the NDA for cilansetron in the U.S. in June 2004 and included an extensive Appropriate Use Plan as part of its submission. The NDA submission was based on efficacy and safety studies in around 4,000 patients worldwide with IBS-D.

⁶ www.alizyme.co.uk

The FDA accepted for filing and granted priority review status for this NDA application in September 2004. According to Solvay's first-half 2004 results, cilansetron is due to begin Phase II clinical trials in Japan for the treatment of IBS-D.⁷

In April 2005, Solvay received a 'not-approvable' action letter from the U.S. Food and Drug Administration (FDA) on its NDA for cilansetron for the treatment of IBS-D in both men and women. The letter requested additional clinical trials, and Solvay is currently examining its options and will discuss future steps with the FDA.

While very little information is currently available on asimadoline (Merck & Co.), GlaxoSmithKline is known to have several compounds in development for IBS, including 876008, a corticotrophin-releasing factor (CRF1) antagonist (Phase I), Entereg, a peripheral mu-opioid antagonist (Phase I), and talnetant, an NK3 antagonist (Phase II).⁸

ISSUES IN IBS DRUG DEVELOPMENT

Despite recent drug approvals in the U.S., IBS remains a poorly understood syndrome that is typically treated with sub-optimal results. Expert clinicians generally agree that the syndromic nature of the disorder makes it one with a truly heterogeneous pathophysiology.

The complexity caused by lack of a clear central model of pathogenesis is compounded by the absence of an accepted animal model for IBS. As such, assessing potential compounds as treatments for IBS and designing rational clinical trials to test these treatments have historically posed serious methodologic challenges for biotechnology and pharmaceutical companies working in this indication.

Compounds being evaluated as potential treatments for IBS should be subjected to unusually rigorous scrutiny by multiple experts, including clinicians and basic scientists intimately familiar with the disorder and the particular compound or class of compounds under consideration. In addition, as many of the drugs currently approved for IBS therapy are limited in their effectiveness as adjudicated by expert consensus opinion² – i.e., females only, IBS with constipation only, or abdominal pain only – and as the rate of placebo response can be unusually high in IBS clinical trials, it may not be sufficient to simply follow the development pathway taken by companies obtaining recent FDA approval for treatment of IBS.

⁷ Drugs R D. 2005;6(3):169-173

⁸ science.gsk.com/pipeline/index.htm

Finally, as alluded to above, until the Rome III diagnostic criteria for The Functional Gastrointestinal Disorders are published in 2006, companies looking to develop therapeutic agents for IBS should follow the recommendations of Rome II, as published in the September 1999 issue of *GUT*⁹ – an international journal of gastroenterology and hepatology (Vol. 45, Supplement No II) – and titled *Rome II: A Multinational Consensus Document on Functional Gastrointestinal Disorders*.

IBS DEVELOPMENT SUMMARY

See pages following.

⁹ <http://gut.bmjournals.com/>

IBS DEVELOPMENT SUMMARY

Product Designation	Company	Phase	Brief Drug Description
Trimebutine	AXCAN PHARMA	I	Irritable bowel syndrome is a functional bowel disorder which primarily affects gastrointestinal motility and sensitivity. This chronic, fluctuating disorder can have a significant impact on daily functioning as well as the quality of life. It affects up ...
CH-1504 (MobileTrex)	CHELSEA THERAPEUTICS, INC.	I	In March 2004, Chelsea acquired the exclusive rights to a number of antifolate compounds, including CH-1504, its lead product candidate. These compounds lack the specific metabolism associated with side effects known to occur with marketed antifolates ...
Milnacipran	CYPRESS BIOSCIENCE, INC.	I	Milnacipran is a novel compound which exerts its effect by inhibiting the reuptake of both norepinephrine and serotonin, two neurotransmitters known to play an essential role in regulating pain and mood. It has been approved for the treatment of non-pain ...
DDP-225	DYNOGEN PHARMACEUTICALS, INC.	I	DDP225 is both a noradrenaline reuptake inhibitor and a serotonin type 3 receptor (5-HT ₃) antagonist. Noradrenaline and serotonin are neurotransmitters that are known to be involved in the control of the gastrointestinal system. The unique combination of ...
SB683698 (TR 14035)	GLAXOSMITHKLINE (GSK)	I	Dual alpha4 integrin antagonist (VLA4) ...
SB723620	GLAXOSMITHKLINE (GSK)	I	Corticotropin releasing factor (CRF-R1) antagonist ...
MD-1100	MICROBIA, INC.	I	MD-100 is a novel-mechanism therapeutic candidate to treat irritable bowel syndrome (IBS) effectively relieves gastrointestinal pain and promotes gastrointestinal transit, the key defining attributes of IBS. The orally delivered compound, MD-1100, is a ...
DDP-225	MITSUBISHI PHARMA CORPORATION	I	Dynogen's DDP-200 program addresses the symptoms of OAB, consisting of frequency, urgency, nocturia and urge incontinence. With over 32 million people affected by the disorder and limited treatment options available, the market potential for a novel therapeutic ...
IBS Program	PAIN THERAPEUTICS, INC.	I	This trial uses a proprietary drug to test the idea that IBS patients may be suffering from intestinal neuronal dysfunction," said Remi Barbier, Pain Therapeutics' president and chief executive officer. "The clinical results of this trial may confirm whether ...
SLV317	SOLVAY PHARMACEUTICALS	I	...
SLV317	SOLVAY PHARMACEUTICALS	I	...
R-tofisopam	VELA PHARMACEUTICALS	I	...
AGI-003	AGI THERAPEUTICS, INC.	II	IBS comprises a group of functional bowel disorders in which abdominal discomfort or pain is associated with changes in bowel habit and with features of disordered defecation. Altered intestinal motility is a major component of IBS. IBS is the most common ...
PROBACTRIX	BIOBALANCE CORPORATION (NEW YORK HEALTHCARE, INC.)	II	Earlier PROBACTRIX studies support the continued development of this potentially breakthrough agent, and it is believed this trial will confirm the importance of restoring the intestinal microbial balance in relieving the symptoms of IBS in both men and women ...

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orBec	DOR BIOPHARMA, INC.	II	DOR BioPharma's lead product, orBec™, is an oral form of beclomethasone dipropionate (BDP). A highly potent, orally-active corticosteroid, has shown benefit in the management of the following intestinal diseases: intestinal Graft-Versus-Host Disease, in...
DDP733 (Pumosetrag)	DYNOGEN PHARMACEUTICALS, INC.	II	DDP733 is an oral, locally-acting, serotonin type 3 receptor (5-HT ₃) partial agonist. Serotonin is an important neurotransmitter in the gastrointestinal (GI) system. Previous clinical studies of the compound by Mitsubishi Pharma Corporation and Dynogen ...
Asimadoline (EMR 63 320)	EMD PHARMACEUTICALS, INC. (MERCK KGAA)	II	Asimadoline, EMR 63 320, is a peripherally acting kappa agonist in clinical development for functional gastro-intestinal disorders and visceral pain. Asimadoline is being studied in irritable bowel syndrome (IBS). Additional investigational areas include ...
GLP-1 (glucagon- like peptide)	GASTROTECH PHARMA A/S	II	Glucagon-like peptide-1 (GLP-1) is an endogenous peptide with many important physiological actions including stimulation of insulin release from the pancreas. Furthermore, GLP-1 reduces the gastrointestinal motor activity and increases the compliance ...
Talnetant (SB223412)	GLAXOSMITHKLINE (GSK)	II	Tachykinin (NK ₃) antagonist ...
NEPADUTANT	MENARINI GROUP (MENARINI PHARMACEUTICAL GROUP)	II	A glycosylated bicyclic peptide which is a Tachykinin NK ₂ receptor antagonist ...
Asimadoline (EMD 61753)	MERCK KGAA	II	Asimadoline, EMR 63 320, is a peripherally acting kappa agonist in clinical development for functional gastro-intestinal disorders and visceral pain. Asimadoline is being studied in irritable bowel syndrome (IBS). Additional investigational areas include ...
SR 48692	SANOFI-AVENTIS	II	...
SPI-0211	SUCAMPO PHARMACEUTICALS, INC.	II	SPI-0211, is a novel prostaglandin metabolite (Prostone) analogue currently under development for the treatment of constipation by Sucampo Pharmaceuticals, Inc. (SPI). The pharmacodynamic effects of orally administered SPI-0211 are primarily local and ...
Dextofisopam (R- tofisopam)	VELA PHARMACEUTICALS	II	Dextofisopam, a novel agent, is the R-enantiomer of racemic tofisopam, a molecule used safely outside the United States over three decades for multiple indications, including IBS. Before conducting its positive Phase 2 trial, Vela established composition- ...
Tianeptine	VELA PHARMACEUTICALS	II	Tianeptine's mechanism of action appears to be different from that of other marketed antidepressants. In contrast to the selective serotonin reuptake inhibitors (SSRIs), such as Prozac® and Paxil®, tianeptine enhances the reuptake of serotonin. Serotonin ...
Renzapride	ALIZYME THERAPEUTICS LTD.	III	Renzapride has both full 5-HT ₄ receptor agonist and also 5-HT ₃ receptor antagonist activity. These 5-HT receptors influence gastrointestinal motility and sensitivity. The dual activity of renzapride gives it a distinct pharmacological profile compared ...

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<i>Product Designation</i>	<i>Company</i>	<i>Phase</i>	<i>Brief Drug Description</i>
PTI-901	PAIN THERAPEUTICS, INC.	III	PTI-901 (a single, daily, 0.5 mg oral dose of naltrexone HCl) is the first in a new class of drugs designed to restore the balance of opioid activity in the gut. It is believed that an imbalance of opioid activity in the gut contributes to the symptoms ...
Lubiprostone (SPI-0211)	TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.	III	A novel chloride channel activator ...
Cilansetron	SOLVAY PHARMACEUTICALS	NDA / BLA Approvable Letters	For relief of abdominal pain/discomfort and abnormal bowel habits ...
Lubiprostone (SPI-0211)	SUCAMPO PHARMACEUTICALS, INC.	NDA / BLA Filed	A novel chloride channel activator ...