

Key Events

Gastrointestinal

Last Updated: 4th June 2007

Date	Event	Status
19–24 th May 2007	Report from Digestive Disease Week	Reported
10 th April 2007	Withdrawal of Novartis' Zelnorm from US market	Reported

Report from Digestive Disease Week 2007

Wood Mackenzie View

The gastrointestinal sector in recent times has become somewhat of a medical dichotomy. It includes conditions that are highly satisfied, such as GERD and peptic ulcer disease, as well as others where the basic underlying causes for the disease are still under investigation (e.g. IBD and IBS). This year's DDW focused primarily on the various methods for treating high-risk IBD patients (specifically Crohn's disease) and the merits of early use of immunosuppressants and novel biologics. Many physicians also discussed adding natalizumab to their medical armamentarium should it gain approval for the treatment of Crohn's disease later this year. Yet despite the potential efficacy these biologic treatments offer, long term safety was cited as a key concern among many physicians.

The recent suspension of Novartis' tegaserod (branded Zelnorm/Zelnorm) in several countries, including the US, has created a significant treatment gap for irritable bowel syndrome (IBS). This gap left many companies eager to capture the attention of the 18,000+ attendees, many of which are now in need of a treatment for this highly prevalent condition. Several companies presented positive data demonstrating limited efficacy, yet the need for a safe and effective treatment remains obvious.

With many large pharmaceutical companies having already announced their plans to de-emphasise their research in the gastrointestinal sector, the likely source of the next breakthrough in this sector is expected to be from smaller specialty pharmaceutical companies (e.g. Salix and to a lesser extent, Shire) that are able to finally isolate the causes for these conditions and develop products that effectively target these mechanisms of treatment. Additionally, many physicians continue to treat these GI diseases on a case by case basis, further emphasizing the need to find a consistent treatment paradigm that works effectively for all patients. Therefore, it appears that while new medicines and technology continue to improve both the diagnosis and treatment of GI-related conditions, curative therapies are not likely to emerge within the next 4-5 years, with most treatment focusing on achieving and maintaining remission and/or symptom free patients.

Key Developments for Irritable Bowel Syndrome (IBS)

As expected, the recent suspension of tegaserod has left many gastroenterologists without an approved treatment for patients with constipation predominant irritable bowel syndrome (IBS-c). Given the current therapeutic void for IBS, many companies took the opportunity to present the most recent clinical data for relevant programmes which target this highly prevalent condition. The following products/programmes reported new clinical data during the conference

- lubiprostone (Takeda/Sucampo) – Branded Amitiza, this chloride channel agonist was approved for chronic idiopathic constipation in early 2006, and is in Phase III development for IBS-c. The companies presented new data from its two Phase III studies which demonstrated that lubiprostone was associated with an improved overall response compared to patients receiving placebo. The trials, which enrolled 1,171 patients with IBS-c and measured progress using an overall patient-focused symptom scale over a 12 week trial period. While this data will certainly support its sNDA submission for IBS-C later this year, it is likely to drive some off-label use of the product prior to its approval.
- linaclotide (Microbia) – A guanylate cyclase-C (GC-C) activator was previously referred to as MD-1100. At DDW, positive results were presented for its Phase II trials which demonstrated the compound had a dose-dependent effect accelerating the emptying of the ascending colon in the 24 patients receiving the compound (n=36) during a 5-day treatment period. The compound was also associated with improved stool consistency, frequency, and ease of pain management. In addition to its potential efficacy, the compound was safe and well tolerated (with zero serious safety issues reported) and did not appear to affect gastric emptying or small bowel transit. As Microbia plans to advance this programme into phase III development (a timetable has yet to be announced), we intend to monitor its progress with great interest.

- alosetron (GlaxoSmithKline) – Branded Lotronex, the product was approved in February 2000 for women with diarrhoea-predominant IBS (IBS-d) and later withdrawn due to an increased risk of ischaemic colitis, serious constipation, and hospitalisation (including 2 fatalities). Following the company's appeal, the product was re-introduced under a safety monitoring programme and with a very restrictive label (women with severe IBS-d only). The data presented showed a stable adverse event profile, with associated rates of ischaemic colitis, serious constipation, and complications that were considerably lower within the more restricted patient cohort. Unfortunately, we do not believe the stabilisation of adverse events will lead to increased interest from gastroenterologists, which must apply to GSK under the current safety programme. Therefore, we do not believe sales will improve anytime soon.

Discussion of “top down” approaches for the treatment of IBD

In addition to IBS, much attention was paid to the varying methods for the treatment of inflammatory bowel disease (IBD), consisting of both ulcerative colitis (UC) and Crohn's disease (CD). However, instead of focusing on emerging therapies which remain in development, most of the effort was spent on methods for identifying patients of significant risk and the best way to treat these patients. The key patient group are those with disabling Crohn's disease meeting the following criteria

- Patient age < 40 at the time of diagnosis
- Perianal disease (affecting the anus and/or surrounding tissues) at diagnosis
- Corticosteroid treatment given as part of initial therapy

Patients that meet at least 2 of the above criteria are expected to have a significantly high risk for developing a severe disease phenotype surgery and to require multiple surgical interventions to alleviate the associated symptoms. For these and other patients with aggressive IBD, the feeling of many presenters was to advocate an aggressive approach to treatment. Instead of starting these patients on corticosteroids or mesalamine therapies and gradually stepping up to stronger therapies as the disease progressed, these patients should be given higher doses of immunosuppressants and/or biologics as first line therapy to first induce remission and then subsequently taper down to lower doses and even corticosteroids for maintenance therapy. This type of treatment approach is often referred to as “top down” therapy, as opposed to the more common “step up” therapy. While most gastroenterologists resist the adoption of any broad treatment approaches, the “top-down” approach appears to be gaining momentum (especially given its success for the treatment of rheumatoid arthritis) and could lead to increased use of azathioprine/6-MP, methotrexate, and novel biologics.

Clinical updates for IBD programmes/products:

During Digestive Disease Week 2007, several companies presented new and/or updated clinical data for their products and programmes which target inflammatory bowel disease (IBD) including:

- Lialda (mesalamine – launched) – Shire presented post-hoc analyses, including secondary endpoint results, from its long-term phase III 303 extension study for Lialda, its recently approved once-daily oral treatment for ulcerative colitis. The results showed that Lialda effectively maintained remission in 68% of the 171 patients receiving the drug once-daily (2.4g/day) and over 89% not requiring a change in treatment due to relapse. Furthermore, higher doses of Lialda (4.8g/day) were found to induce remission in 64% of patients who were initially refractory to this initial dose of Lialda or Asacol (from parent studies 301 and 302), with 57% maintaining remission for at least one year.
- Remicade (infliximab - launched) – Centocor (J&J) presented long-term data from its ACT trial extensions demonstrating Remicade's efficacy for maintaining remission in patients with moderately to severely active ulcerative colitis which had previously responded to Remicade. While patients who did not initially respond to Remicade were excluded from this extension study, those that did respond maintained a very high response rate, with 97% or responders reporting little or no disease activity after 2 years.
- Cimzia (certolizumab – filed) – UCB presented long-term data from its PRECiSE 3 study which demonstrated that a majority of Crohn's disease patients (all previously enrolled in PRECiSE 1 or 2 trials) receiving once-monthly Cimzia treatment maintained significantly high rates of response (85%) and remission (74%) from weeks 52-80 using the Harvey-Bradshaw Index. The study also met its primary endpoint upon demonstrating a positive safety profile with rare and mild side effects. While these results are indeed promising, they are not significantly better than either Humira or Remicade. Thus, we believe the FDA's request for more efficacy data could actually benefit UCB should this additional data improve upon its already appealing cost-profile and proposed less-frequent dosing schedule.
- sargramostim (GM-CSF – Phase III) - Data presented for sargramostim for the treatment of moderate to severe Crohn's disease showed the product failed to meet either of the two primary endpoints of achieving a clinical response (reducing CDAI score by 100 points or greater) or achieving remission (CDAI≤150) after 8 weeks of treatment. The failure to meet these endpoints, which had been set by and met during the previous NOVEL 4 Phase II trial, was believed to have been partially caused by regional variations in the data set which prevented any chance of rendering statistically significant result. Unfortunately, we believe that this data could ultimately lead to the termination of this programme, which has yet to demonstrate the efficacy of currently available CD therapies.

- Nuvion (visilizumab - Phase II) – Investigators from the Mayo Clinic presented long-term Phase II data for PDL's Nuvion, an antibody in development for IV steroid-refractory ulcerative colitis, in which 89 of 138 patients receiving Nuvion achieved a clinical response within 30 days. Of these responders, only 35% ended up requiring rescue therapy during follow-up observation. Further follow-up, however, showed that rescue therapy (both medical and surgical) was needed in over half (53%) of the patients involved and a third (33%) had undergone a colectomy. While not overwhelming, these results certainly justify PDL's decision to advance Nuvion into Phase III development for what appears to be a potential niche indication which is currently underserved by broad-spectrum antibiotics such as vancomycin and metronidazole.

Zelnorm withdrawn, what's next?

Recap of events

On March 30th, Novartis announced that it had suspended sales of Zelnorm (tegaserod), a treatment for irritable bowel syndrome (IBS), due to evidence of increased incidence of serious ischemic events (e.g. heart attack, stroke). The withdrawal complied with a request issued by the FDA, which had identified 13 ischemic events (including one fatality) within a combined analysis of 29 placebo-controlled trials where a total of 11,614 patients who had received tegaserod. While Novartis has complied with the FDA's request, it has also stated that it is not convinced for the causal link between tegaserod and the events. Both the FDA and Novartis have noted that all affected patients had pre-existing cardiovascular conditions.

Current Situation

IBS remains one of the most prevalent conditions, accounting for 12% of visits to primary care physicians and 28% of referrals to gastroenterologists. IBS remains the most prevalent digestive disorder and the costs for treating the condition are significant, especially when considering that IBS is the second leading cause of work-place absenteeism (behind the common cold). Furthermore, a study of IBS patients found that persons affected with severe IBS symptoms had significantly lower quality of life measurements when compared to other common diseases. We suspect that Zelnorm's rapid initial uptake was a result of these factors as well as a lack of currently available efficacious treatments.

Development for IBS has been anything but simple for most companies. Zelnorm itself has been rejected twice by the EU's CHMP and Solvay's Calmactin (cilansetron) was rejected by the FDA in 2005. Like Zelnorm (a 5-HT₄ agonist), Calmactin (5-HT₃ antagonist) targets the neurotransmitter serotonin (5-HT types 3 and 4) receptor pathway, albeit in a slightly different manner. In addition, two previously approved IBS treatments have been withdrawn including J&J's Prepulsid (5-HT₄ agonist) and GSK's Lotronex (5-HT₃ antagonist), which were pulled from the market in 2000 due to increased risk of severe gastric ischaemia. Since the source of its ischemia was GI focused (and not cardiovascular), Lotronex was later reintroduced in November 2002 with a very restricted indication base and close patient monitoring.

The removal of Zelnorm from the US has left approximately 12 million IBS patients (approximately 70% are women) without an approved treatment option, making an already large area of unmet medical need even greater. While the concern over ischemic events is not to be taken lightly, the withdrawal of Zelnorm has created a clear treatment gap for IBS, especially IBS-c (IBS with predominant constipation). This observation is further supported by the FDA's acknowledgement that Zelnorm's withdrawal poses a significant clinical management problem for patients currently using the drug. To help patients with severe IBS, Novartis is discussing with the FDA a way to make Zelnorm available. One of the methods of access being discussed is through a Treatment IND, a special investigational protocol where desperately ill patients are able to obtain medication early in the development process. However, we believe this is unlikely as the adverse events associated with Zelnorm use (e.g. stroke, heart attack, etc) are life-threatening, unlike a vast majority of IBS cases.

Future Outlook

Wood Mackenzie believes that while many leading pharmaceutical companies (e.g. Pfizer and AstraZeneca) have announced that they are no longer focused on developing treatments for gastrointestinal indications, the IBS market has re-emerged as an area of significant interest. That said, we anticipate that programmes which target the serotonin (5-HT) receptor pathway will face additional regulatory scrutiny.

Unfortunately, the majority of advanced programmes for IBS indeed serotonin receptors including Solvay's Calmactin (5-HT₃ antagonist - filed), Alizyme's renzapride (dual 5-HT₃ antagonist / 5-HT₄ agonist - Phase III), and Dynogen's DDP733 (partial 5-HT₃ antagonist - Phase II). Therefore, we expect these products to face further regulatory delays should the companies continue to pursue this IBS indication, based on the expected need for additional cardiovascular safety trials. Conversely, we expect other products and programmes with different mechanisms of action to benefit greatly from Zelnorm's withdrawal. The first, Takeda's chronic constipation treatment Amitiza (lubiprostone), is a CIC-2 chloride channel activator in Phase III for IBS and is expected to gain approval in 2008. The second, Salix's Xifaxan (rifaximin), is a gastrointestinal specific antibiotic approved for diarrhoea and in Phase II for IBS. With the current gap in IBS treatment, we believe that Amitiza will experience a small increase in off-label use for IBS, followed by a much larger increase should the product gain FDA approval.

For Zelnorm, Wood Mackenzie believes that the nature of the cardiovascular risks associated with Zelnorm will ultimately prohibit Novartis from successfully reintroducing the product in the US within our forecast period (through 2013). However, should Novartis convince the FDA that the cardiovascular side-effects can be managed and successfully reintroduces Zelnorm in the US, we predict its label to be highly restrictive and its target population to be significantly reduced.

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