

## Emerging Therapies for IBD

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Good morning, everyone. My name is Bruce Sands. I'm a gastroenterologist at Massachusetts General Hospital. Over the years, I've been involved in a fair number of clinical trials in IBD including new therapies, compound biologics and even devices. This session is about emerging therapies for IBD.

I am going to address two abstracts at the same time. This first abstract is Hommes, et al., and the second by D'Haens from Leuven, Belgium.

***Abstract 223575: "The ideal management of Crohn's disease: Top down versus step up strategies. A randomized controlled trial"***

This is a very interesting study. The 12-month results were recorded as a late breaking abstract last year and this is an update and an extension of this information. The hypothesis here is that steroids do not prevent complications in Crohn's disease because they don't effect mucosal healing. We know this from another study in which they used a high dose inductive regimen with prednisolone (1 mg/kg). When you do that for a number of weeks, you can get a clinical remission in roughly 90% of patients, but at the end of it all, only about one third of those patients actually had mucosal healing. The hypothesis here is that if you can achieve mucosal healing, you might affect improvement in the long-term natural history of the disease. Furthermore, they were interested in examining whether the usual step-up therapy, where we start with fairly innocuous medications like antibiotics, ASA compounds, and corticosteroids, if those don't work then immune modulators – azathioprine, methotrexate and finally the heavy guns as we perceive them now, anti-TNF antibodies, would get the patient well. What they're interested in is borrowing a page from the rheumatologists who, for a number of years now, have looked at patients who were newly diagnosed and aggressively treated either using methotrexate or a combination of methotrexate and infliximab. And what they've shown in rheumatology is that you can affect erosion scoring, actual destruction of the joints and a powerful surrogate marker for long-term disability. We don't have a ready equivalent of this surrogate in inflammatory bowel disease. The best we probably have is mucosal healing.

They studied 133 patients at quite a number of centers distributed through Belgium and The Netherlands. These patients were assigned to either receive step-up therapy, which consisted of an initial course of corticosteroids by mouth, and then taper. If they flared, they would get a second course of corticosteroids. If they flared again on taper, they would get an immunomodulator – 6-MP, azathioprine, methotrexate – and if that didn't work, ultimately infliximab. The other group was given a series of three infusions of 5 mg/kg infliximab at weeks 0, 2, and 6 and were simultaneously started on 6-MP or azathioprine. If they flared at any point down the road, they could get a second episodic therapy of infliximab. If that didn't work, they would get corticosteroids. In the overall study, the primary end point was intended to be remission, (CDAI less than 150, no glucocorticosteroids, and no need for resection). The six-month data shows that with top down, 60% received benefits from treatment compared with 41% of patients with step up. That is a statistically significant difference. At month 12, the statistical significance disappeared, where top down had 61% in remission with no steroids, no resection and only 50% for step up. This is not statistically significant. However, at the end of 12 months, 17% of the step-up patients were actually still on glucocorticosteroids with a median dose of 23 mg whereas none of the top down patients were on steroids. It's interesting that when you protocolize the step up therapy, there were 65% of the patients by month 12 who were on immunomodulators, a relatively high number of patients on immunomodulators. You would think that maybe this is a wash at the end of it all.

***Abstract 218359: “A combined regimen of infliximab and azathioprine induces better endoscopic healing than classic step-up therapy in newly diagnosed Crohn's disease”***

The authors present the results of endoscopic healing at two years for the 44 patients who made it out that far. They did baseline colonoscopy at enrollment and they did a second one at year two. They graded each of the five major segments – the ileum and four colonic segments – at 0 for no ulcer, 1 for aphthoid ulcers, 2 for large ulcers, and 3 for ulcerated stenosis. The primary analysis here was no ulcers at month 24. They found with the top down group, complete ulcer disappearance was seen at year two in 71% of patients. Remember, all they had to have in the beginning was induction therapy and then maintenance 6-MP. Now, quite a few got additional doses of infliximab over time, but still it is relatively little exposure to infliximab. By comparison in the step up group, only 30% of patients had complete ulcer disappearance. That is a highly statistically significant result. If you look at the secondary end point of this abstract, there was ulcer reduction in 88% of the top down compared to 47% in the step up. Again, highly statistically significant.

If you believe this story that the presence of mucosal healing is associated with downstream fewer surgeries, fewer hospitalizations, all of which has been shown in ACCENT I and ACCENT II studies with infliximab, then you might assume and take the leap and say that the long-term outcomes may be favorable in these patients, but that has yet to be seen. This study is ongoing.

***Abstract 222089: “Continuation of immunomodulators is not required to maintain adequate infliximab efficacy in patients with Crohn's disease but may improve pharmacokinetics”***

This abstract is by Van Assche, et al., from Belgium. We believe that in patients who are on an anti-TNF biologic (particularly infliximab which is 25% chimeric and immunogenic) that we need to use combination therapy with immunomodulators in order to prevent loss of response because of antibody formation against the drug. These authors pose the question, “Is it possible to use immunomodulators in the induction phase or the first six months and then withdraw them?” If you do that, do you see any impact on the efficacy or the pharmacokinetics of the drug? They took 80 patients, and randomized them to continue or interrupt their immunomodulators (azathioprine or methotrexate)  $\geq$  six months on this combination after starting infliximab (5 mg/kg IV). All patients were in clinical remission at baseline.

They measured infliximab (you can call it trough) serum levels at week 8 right before the next infusion. Infliximab levels were slightly lower in the discontinuation group. The continuation group had a slight rise in their infliximab levels at week 24 and again at week 48. The trend is more important than the absolute levels. In the discontinued immunomodulator group, they saw a slight decrease in infliximab serum levels (-0.647 mg/ml) that was statistically different from the group that continued on immunomodulators. At week 48, they had a decrease (-0.57) from baseline that was no longer statistically significant, perhaps because of drop out patients. It's not entirely clear. Relatively speaking, there was not much change in the dose interval between the immunomodulator continuing group and the discontinuing group. The median time to failure was 17 weeks in the continued group versus 8 weeks in the discontinued group. There were so few patients who actually failed that this was not statistically significant. The number of patients who had complete response was not different between the two groups. Now importantly, there is no description of improved safety. This is really one of the main reasons why you would think about discontinuing immunomodulators.

They suggest that ultimately monotherapy with biologics may be possible. Maybe you need up front induction of tolerance to the biologic, so that you can then have scheduled maintenance doses. Why are we doing combination therapy? Is it really just for prevention of antibodies to biologics or are we getting extra, added benefit from immunomodulators? It's probably a little bit of both.

***Abstract 217026: “Certolizumab pegol administered subcutaneously is effective and well tolerated in patients with active Crohn’s disease: Results from a 26-week, placebo-controlled phase III study (PRECiSE1)”***

This is by Sandborn, et al. Certolizumab pegol is formerly known as CDP870. It is a biologic anti-TNF antibody. It is actually a humanized Fab fragment that has been pegylated. It doesn't have the F<sub>C</sub> portion at all, has a fairly long half-life, and therefore can be given subcutaneously. This was a large, randomized, controlled, phase III trial, one of the pivotal trials for this agent. There were 659 patients with active Crohn's disease with a CDAI in the range of 220-450, what we would call mild to moderate range. They were randomized into two parallel arms. Patients were either randomized to placebo injections or certolizumab pegol at a flat dose of 400 mg subcutaneously at weeks 0, 2, and 4 and then every 4 weeks followed out to week 24. Patients were also prospectively stratified as having a CRP less than 10 or greater than or equal to 10. This was based on a phase II study published by Schreiber showing that there was a higher placebo response rate in patients who had low CRP and that this was disruptive to their evaluation of the endpoint. To hedge their bets in this study, the patients were stratified in this way. Also, stratification occurred by immune modulation use or corticosteroid use. There were actually co-primary endpoints. The percentages of patients with clinical response was depicted by the drop in the CDAI, about 100 or more at week 6, and at weeks 6 and 26 in patients with CRP  $\geq$  10. This is really a very rigorous endpoint. The primary population for analysis was the high CRP population, although they were permitted to look at the entire population. The secondary endpoints here were a more traditional response, CDAI decrease by 70 or more. This was a post-hoc analysis to allow comparison to other agents in the field. Both primary endpoints demonstrated superiority of certolizumab over placebo. If you look at week 6 and 26 you see the placebo response rate drop to 12.3% and certolizumab pegol goes up to 21.5 so you had to be responding to both time points. You see statistical and probably clinical significance overall in the intention-to-treat population. Therefore, it seems that the drug works in the high CRP and in the low CRP patients. You can read through all the various endpoints and results but clearly, this drug works.

***Abstract 216217: “Concomitant immunosuppressive and adalimumab therapy in patients with Crohn’s disease: 1-year results of the CLASSIC II study”***

This talks about adalimumab. Adalimumab a fully human anti-TNF antibody approved for rheumatoid and psoriatic arthritis. CLASSIC II was the follow-up study to CLASSIC I which was a parallel arm, dose-ranging study in which patients were randomized to a series of induction doses of adalimumab followed by one additional dose and then at week 4, were randomized to various arms. It's a complex study to describe but essentially patients who were in remission at week 4 in CLASSIC I were randomized to either a regimen of every other week adalimumab (40 mg) or to weekly adalimumab subcutaneous or to placebo and followed out for one year. The main thrust of this abstract is to determine the difference in remission and response rate in patients who are on immunomodulators plus adalimumab as opposed to those who are not. If you look at the results, adalimumab consistently improved CDAI, with or without immunomodulators. This raises the question of whether you actually are going to want to use an immunomodulator to prevent antibody formation against this drug or not. One strategy would be to do it, one strategy would be to avoid the immunomodulator and, therefore, perhaps save on the side effect profile of the immunomodulator, perhaps in combination with a biologic. These are small numbers in each randomized arm.

These two drugs – adalimumab and certolizumab pegol are almost certainly going to make it onto the market in another year. The field gets very crowded. Exactly how practitioners are going to choose which of these agents to use is open for debate.

The dosing regimens are different for these agents in part because they have different pharmacokinetics. Certolizumab pegol is pegylated. It has a longer half-life than an antibody. The adalimumab has a shorter half-life so it needs to be given weekly or every other week and it is given subcutaneously. Infliximab, the way it has been studied, has been given intravenously. That isn't to say that it couldn't have been given subcutaneously, it's just never been studied in this way. The other difference is that we are talking about flat doses with the subcutaneous agents as opposed to weight-based doses with infliximab. They do have different pharmacokinetics with regard to binding to TNF as well, and therefore you hope that in drug development these issues are sorted out so that the appropriate regimen is hit upon. That is always subject for further study in phase IV, how to vary the dose and regimens. Just as we have learned that not every patient on infliximab goes every eight weeks, sometimes they need a higher dose; sometimes they need a shorter interval. I'm sure we will learn the same sort of things with these agents.

***Abstract 218825: "Natalizumab induces sustained response and remission in patients with active Crohn's disease: Results from the ENCORE trial"***

This is from Targan, et al. ENCORE, stands for Efficacy of Natalizumab in Crohn's Disease Response and Remission. This is a phase III randomized, double-blinded placebo controlled trial. You could look at this as a make-up trial because previously ENACT I, which was intended to be a pivotal trial for this agent, missed its primary endpoint at week 10 with a p-value of .051. ENACT 2 published in the *New England Journal of Medicine* clearly showed that Natalizumab has maintenance benefit. This study was conducted to establish that Natalizumab truly has an inductive effect. They took 509 patients with mild to moderately active Crohn's disease (CDAI range 220-450) and a C-reactive protein greater than the upper limit of normal. They did this because in their post hoc analyses of ENACT 1 they could clearly show that the placebo response rate was higher in the low CRP patients. Actually this was a "dose effect". That is, the higher the CRP the lower the placebo response rate, although the drug effect didn't change by very much. The patients in this study were randomized 1:1 to either natalizumab 300 mg or placebo as an infusion monthly. They got it at weeks 0, 4, and 8 and safety was followed to week 12. The primary endpoint was clinical response, a decrease in the CDAI by 70 or more by week 8, and sustained to week 12. That's a relatively stringent end point. You actually do not hurt yourself by setting more stringent endpoints, because the effect seems to be that it minimizes the placebo response rate and thereby enhances your study result. The secondary endpoint was remission, standard criteria of CDAI less than 150 by

week 8 and sustained through week 12. The results clearly show that there is an inductive effect. The response to natalizumab in weeks 8 and 12 combined was 48%, placebo 32%; highly statistically significant. If you look at remission rates for the same time points, natalizumab hit 26%, placebo, 16% so there is a treatment effect here of 10%. Again, statistically significant at  $p=0.02$ . The adverse events in the short-term study were similar between the groups. My commentary on this is that this was clearly much needed information to permit this drug to seek approval in Crohn's disease. As most of you in the room probably know, the future of this drug is a little bit uncertain at the moment because of the advent of progressive multifocal leukoencephalopathy (PML) in three patients (including one Crohn's patient) out of approximately 3,000 patients treated with the drug. Remember, this drug was released as a treatment for multiple sclerosis in the U.S. market and pulled off the market three months later when these PML cases were discovered. The interesting thing here is that PML is known to be a consequence of JC virus infection in the brain. One of the potential reservoirs for JC virus turns out to be the colon. In fact, a well-regarded investigator, Rick Boland, believes that this is a major reservoir and also that JC virus may be involved in the pathogenesis of colon cancer, although we don't completely understand why this agent may lead to PML in some patients. The hypothesis would be that you are releasing the JC virus from this reservoir and that you are removing the inhibition preventing the same virus from being patrolled when it gets to the central nervous system compartment and therefore allowing it to get a foot hold in the brain and cause this life-threatening, actually usually fatal infection.

Now a companion to this is abstract 225804 in the additional reading section of your packet. This is by Sandborn and Targan reporting on the safety evaluation of more than 3,500 patients in the clinical trials done for Crohn's, MS, and rheumatoid arthritis with natalizumab. Really, the take home message here is that there were no other cases other than the three that were described. There were four cases reported in the post-marketing surveillance. These did not pan out to be true cases of PML so the number of .1% really sticks. The other point raised by this abstract is there was no clear way to do serum screening or surveillance for JC virus that they could discern in this large safety evaluation.

You could look at this as just another opportunistic infection which we have seen with other biologics. However, I think emotionally people feel differently when it's something in the brain which we don't understand very well. It seems scarier. I will point out, though, that physicians seem to be more concerned about this than the patients. We did a study where we queried some patients who were completely naïve to natalizumab, some patients who had been in natalizumab trials for Crohn's disease, and another cohort who were derived from internet respondents. We looked at how much risk they were willing to assume over 10 years – risk of PML, lymphoma, or serious life threatening infection. It's surprising how high the rates the patients are willing to accept in order to go from severe active disease to remission. Patients are willing to accept as much as a 7% mortality spread over a period of 10 years, which is a shockingly high number and reproduced in all three of the cohorts. So, I think the point is that while we may feel very conservative about it, patients often feel very differently about it when they are faced with the disease. It is quite interesting and something that we have to address in the future. How do we deal with these risks, how do we explain them to patients, and how do we help the patients work through whether they want to assume these risks or not?

**Abstract 221903: “A phase I study: Visilizumab therapy in Crohn's disease patients refractory to infliximab treatment”**

This was a small, open label study of visilizumab which is a humanized anti-CD3 antibody that has previously been reported in ulcerative colitis studies. Again, those were all open label, not blinded studies, but have shown a fairly remarkable result in steroid refractory ulcerative colitis. Doses of 5 to 15 mcg/kg IV were given as a daily bolus for two days in a row. Here we have an open label study of 10 mcg/kg again given IV at day 0 and day 1 intravenously. These were pretty sick patients. They had to

have had a CDAI greater than 250 and all had a CRP that was above normal. They all had to have endoscopic evidence of active disease. They were not permitted to have fistulas. The primary analysis here was a CDAI drop of 100 or more at day 59. They had 18 patients studied; eight have been followed out to day 59 at the time the abstract appeared. These were quite sick patients. The median CDAI was 386 with a range of 308 to as high as 516. The median CRP (30.5) was much higher than just above normal. Three of the patients were considered to be steroid refractory and five were steroid dependent. The steroid median dose was 20 mg per day. All the patients have previously been treated with infliximab. Two of them had been primary non-responders who had been treated and had never seen a response to the infliximab. One had severe infusion reactions; five had secondary loss of response to infliximab. Six out of eight of these patients had a clinical response (drop of 100 in the CDAI at day 59). The median CDAI at day 59 was down to 218 from 386.5. Three out of eight of these patients had a remission, (CDAI less than 150 at any point during the study). As far as safety, they saw some episodes of mild to moderate cytokine release syndrome. Half of the patients had a transient elevation in liver function tests but these tended to normalize.

This drug has a novel mechanism of action. It's an anti-CD3 antibody. Think of this as a humanized OKT3. Because it's a different mechanism, it could work in patients who are refractory to drugs that have other mechanisms such as anti-TNF antibodies. That seems to be the case at least for the two primary non-responders to infliximab in this study. The real question here is how would we use this drug? Part of what it does is lysis of lymphocytes. You see the CD4 counts drop; you see the CD8 counts drop. You do see Epstein-Barr virus titers rise particularly in patients who have some baseline titer. The question is, "If you are giving this drug episodically, how many times can you give it?" What is the strategy in which you would put it into place and who is the appropriate patient for this?

I would just say it's always nice to have something else in your bag of tricks and this could be something very different.

***Abstract 220450: "Combined data from two pivotal, randomized, placebo-controlled, phase III studies show that SPD476, a novel mesalamine formulation given once or twice daily, is effective for the induction of remission of mild-to-moderate ulcerative colitis"***

We could stop right there. They put everything right into the title. This is a report combining two pivotal trials; phase III studies designated 301 and 302 of this interesting new formulation of mesalamine. This formulation has a polymer film that delays release until the tablet actually gets to the ileum and then embedded within this is what's called MMX or Multi Matrix System™ which as I understand it, is a sort of melting wax matrix that also has drug granules in it that allows good dispersion of the drug and probably adherence to the mucosa. The idea is that this would be a way of getting very concentrated tablets and getting the drug to the mucosa in the large bowel and also to reduce the number of tablets that a patient would have to take to get a response and remission. These were all patients who had mild to moderate UC. There were a total of 170 patients or so in each of three arms. In one arm, patients were given 2.4 grams per day. These are 1.2 gram tablets so they were either taking two tablets once a day or one tablet twice a day. The 4.8 gram arm in both studies was four tablets taken once a day. Placebo was combined from both groups. The primary endpoint was an ulcerative colitis disease activity index of less than or equal to 1, rectal bleeding and stool scored 0, and more than 1 point reduction in the sigmoidoscopy score at week 8, so a fairly stringent endpoint for remission. In the combined analysis at week 8, the placebo remission rate was 17.5%. The 2.4 gram per day remission rate was 37.2% which was statistically significant and the 4.8 gram per day was 35.1% again, statistically significant over placebo. Clearly, numerically, the 2.4 grams per day and the 4.8 grams per day looked exactly the same, which suggests that they are really at the shoulder of the dose response curve when you've gotten to 2.4 grams of mesalamine delivered through this mechanism. Ten patients reported 13 serious adverse events;

seven in placebo, four in the 2.4 gram, and two in the 4.8 gram. This included two cases of pancreatitis which is well known to occur in patients getting mesalamine, although rarely. The following abstracts in the additional reading section of your packet (221121, 221351 and 221420) add some more information to the abstract I just described. Abstract 221121 by Sandborn et al., looks at whether 5-ASA naïve or discontinued patients or people who were already on less than or equal to 2 grams per day of oral mesalamine did better when they switched to 4.8 grams. It appeared that there was a slight incremental benefit to doing that, just as has been seen with the 800 mg preparation of Asacol in the ASCENDT I and II studies. Abstract 221351 by Lichtenstein is another analysis looking at whether mildly ill patients did as well as moderately ill patients. They did about the same. Then the abstract 221420 by Kamm, et al., looked at whether the drug works better in left-sided versus extensive disease. Again, they look about the same. My commentary on the set of abstracts is that this is one small step for mankind. This is an old drug delivered in a new way. Clearly, what it may do is improve adherence particularly for long-term maintenance treatment and perhaps in the induction phase of a flare. It's an incremental improvement but at least from the patient's perspective and in terms of adherence, it may be a real significant improvement.

The question is whether or not we will switch our patients to this if they are already on a mesalamine preparation that's presumably working for them, or will it mainly be new prescriptions? I don't know. We will see.

***Abstract 221700: "Optimization of 6-thioguanine production by allopurinol in inflammatory bowel disease patients not responding to azathioprine/6-mercaptopurine leads to improved disease activity, reduced corticosteroid requirements and normalization of liver enzymes"***

This is by Miles Sparrow of the Chicago group working with Brigham and Women's Hospital in Boston. The background here is that overall 40% of patients don't respond to 6-MP, or azathioprine and some proportion of these patients have high activity of thiopurine methyltransferase. As you know, azathioprine is non-enzymatically converted into 6-MP. There are a number of important enzymes. Thiopurine methyltransferase (TPMT) is the one that shunts 6-MP to 6-MMP. It also has other shunting effects all of which lead away from what we believe is the major active component or metabolite, which is 6-thioguanine, although this is not the only active metabolite. Levels of 6-thioguanine appear at the end and correlate with response in a number of studies and in a recent meta-analysis. Patients who are heterozygous for TPMT genotype and have, therefore, intermediate activity achieve very high levels of 6-TGN and are also more likely to respond to the drug and are more likely to have leukopenia, whereas patients who have very high levels of activity, they may have normal genotype, but for whatever reason they have high activity, will preferentially shunt more of the drug into 6 methylmercaptopurine, which has been associated with liver function abnormalities. Very little of the drug will get to this metabolite and therefore the likelihood of that response is low. I'll point out one other enzyme, xanthine oxidase (XO) which is in the pathway converting 6-MP to 6-thiouric acid. Allopurinol is a potent inhibitor of xanthine oxidase. One of the contraindications to 6-MP or Azathioprine in the package insert, is concomitant treatment with allopurinol because it is very likely that you are going to see leukopenia in those patients. I'm not sure how these investigators got this idea, but essentially what they are doing is reducing the dose of azathioprine or 6-MP by at least 50% and then adding allopurinol to the regimen. They are showing that when you do this many of these patients will respond. Their liver function abnormalities will improve. They will also have a marked decrease in 6-MMP and a marked increase in 6-TGN. So, unless allopurinol is working somewhere else - perhaps on TPMT itself - it's hard to understand how blocking this would improve this differential distribution of the metabolites. There is a companion abstract, number 226492 in the additional reading section, which is a much smaller experience. They had eight patients and measured TPMT in these patients before and after allopurinol. The bottom line is there is really no change in the TPMT activity. Clearly, what allopurinol is doing here has nothing to do with TPMT, but it is not clear how blocking XO actually improves distribution. There are things about this

pathway that we just do not understand. I wouldn't recommend that any of you do this at home. It can be risky even if you are reducing the dose in half. Many of these patients will have a drop in their white count and some patients will still have profound leukopenia so you really could put a patient in danger. I don't recommend this although it is quite interesting.

***Abstract 224346: "The treatment with an oral spherical adsorptive carbon (AST-120) improves anal fistula, PDAI and CDAI scores – A randomized double-blind placebo-controlled trial"***

This is exactly what it says. We know next to nothing about what this oral spherical adsorptive carbon is. We don't know what the dose is that they used of this agent. We don't know why they even thought to use this in fistulizing Crohn's disease, but they did the study. They essentially took patients with fistula and randomized them to drug or placebo for eight weeks. This was said to be a multicenter trial done in Japan. They did fistula counts using the Present criteria for fistula closure, meaning a response is 50% or more of the draining fistulas are closed at the four and eight week endpoints. Remission was closure of all of the fistulas at weeks 4 and 8. They also did the CDAI, although they don't actually report on the values. They also did a perianal disease activity index and they don't report on the values of that. What they do say is that the fistula response rate in the treated group response was 37% compared to 10% with placebo and this was statistically significant. Remission was 29.6% compared to 6.7% placebo, again very statistically significant. I'm not even sure how to comment on this abstract except that we don't understand anything about why this should work. I am eager to hear the presentation and find out more about what they were thinking and what they were doing with it. We will have to see what the presentation shows and wait to see validation in another study before we all start giving spherical carbon particles.

***Abstract 213827: "Atorvastatin decreases Seo index in patients with short duration of disease in ulcerative colitis: A randomized placebo-controlled clinical trial"***

The background here is that it is well understood that statins have anti-inflammatory effects in general. In fact, there are animal models of colitis where statins have shown a reduction in inflammation. There is a case series showing some improvement in colitis. Peter Higgins at the University of Michigan undertook this study in a controlled way. He took 36 patients with mild to moderate ulcerative colitis who are on stable medications and randomized them 1:1 to atorvastatin or placebo. The primary analysis here was the change in the Seo index controlling for baseline Seo index. Dr. Higgins has had biostatistical training as well as being a gastroenterologist, so he is very sophisticated in his analysis for this really small number of patients. A decrease in the Seo index of 30 or more was thought to be a clinically significant improvement. Seo index less than 120 was remission. He looked at six pre-specified covariates to put into a multivariate model to identify subsets who would have improvement or response with this treatment. He also looked at the inflammatory bowel disease questionnaire (IBDQ). The long and short of it is when they looked at the final Seo index controlled for the baseline Seo index, the atorvastatin group had achieved 132.1 (lower is better with this index) and the placebo group 157.6. This was close to statistical significance ( $p=0.06$ ) but when they controlled for an interaction with duration of the disease, the final Seo index was 46 points lower in the atorvastatin group than in the placebo group and this was statically significant. So, I think we can leave it at that. They didn't see any really important adverse events. There were no liver function abnormalities, no creatine kinase abnormalities, and we conclude that this was modestly beneficial. Certainly, you would say that this is interesting. It is very preliminary. It certainly deserves further study as a class of agents in general. Perhaps every person in the world should be on an aspirin, a beta-blocker, an ACE inhibitor, and a statin and we will all live to 110 years of age!

***Abstract 214088: “A safety and efficacy study of a novel formulation of prednisolone metasulfobenzoate (PREDOCOL) in the induction of remission and maintenance in ulcerative colitis”***

This is a safety and efficacy study of a novel formulation of prednisolone metasulfobenzoate (PREDOCOL) in the induction of remission and maintenance in ulcerative colitis. The background here is that there is an almost 20-year-old study showing that prednisolone metasulfobenzoate is topically effective and really very poorly absorbed from the colon. The idea here was to take this poorly absorbed agent, encapsulate it in an Eudragit L capsule which releases the drug in the ileum or thereabout, put about 200 controlled release drug pellets into this capsule and see if this would be beneficial. The idea of treating with steroids is we give it as a taper. We treat, we taper down, and the idea is to get the patient off of the agent. Here the notion is longer term treatment with a poorly absorbed steroid, essentially. In this study, 59 patients got PREDOCOL 40 mg per day for six months, another 61 patients were assigned to PREDOCOL (60 mg a day) for six months, and then the third arm was actually an active arm, 61 patients assigned to prednisolone (40 mg a day) with a tapering regimen over eight weeks. All this was given as a BID divided dose. They looked at steroid side effects by visual analog scale. They also measured the Powell-Tuck score, which was one of the ulcerative colitis indices, physician global assessment, and sigmoidoscopy by Baron score. The design was intended to be non-inferiority in terms of efficacy to prednisolone taper. The long and short of it is that at least for the 40 mg group, it appeared that there was a remission benefit over the six months of treatment. I found this to be really intriguing, similar to what has recently been done with asthma; give longer term steroids to suppress the disease. We don't do that in inflammatory bowel disease because of the long-term side effects. If we could give steroids continuously and in a safe fashion, would we want to do that? Would that actually make patients feel well? Would it heal the mucosa and keep it healed? I don't know but this sort of opens that question because it looks like this might be relatively safe. There is certainly a lot more that we have to learn about this. We need to learn about suppression of the hypothalamic pituitary adrenal axis and lots of other things. But, as a proof of principle, it is somewhat intriguing.

Thank you for your participation and your listening this morning.

**Abstracts Discussed**

**223575: The Ideal Management of Crohn's Disease: Top Down Versus Step Up Strategies, A Randomized Controlled Trial.** Daniel Hommes, Filip Baert, Gert van Assche, Filip Caenepeel, Philippe Vergauwe, Hans Tuynman, Martine De Vos, Sander van Deventer, Larry Stitt, Paul Rutgeerts, Brian Feagan, Geert D'Haens

Current management of moderate-severe Crohn's disease (CD) consists of glucocorticosteroids (GCS), leading to a 26% 1-year remission rate, steroid dependency and significant toxicity. This study examined if more aggressive induction therapy with infliximab (IFX) and azathioprine (AZA) would lead to higher remission rates, lower toxicity and fewer complications. Methods. 133 CD pts with CDAI > 220, diagnosed < 4 years ago and never treated with GCS/immunomodulators/IFX were randomized to (1) top-down (TD) treatment with 3 infusions of IFX (w 0, 2 and 6) and AZA 2-2.5 mg/kg/day or (2) step-up (SU) therapy with topical (budesonide 9mg/day) or systemic (prednisone 40 mg/day) GCS. In the TD group, relapse was treated with repeat IFX infusions and GCS when they failed to respond to IFX. In the SU group, AZA was added in case of repeated need for GCS or dependency and IFX was only given after failure of immunosuppression. Patients were examined at week 0, 2, 6, 10 and 14 and every 3 months thereafter until month 24. The primary endpoint was remission (CDAI <150 without GCS and no resection) at month 6 and 12; secondary endpoints included overall treatment success (remission at week 14 and beyond, no resection, no GCS or IFX after week 14), mean CDAI scores, toxicity and prolonged remission up to month 24. Results. Baseline characteristics were similar in both groups (mean CDAI at inclusion 331 TD vs. 306 SU), 19 pts dropped out before month 12. Induction therapy was successful in 81% and 73% of TD and in 60% and 67% of SU pts at week 10 and 14. Remission without GCS and without resection was attained in 60 % (TD) vs. 41 % (SU) (p=0.03) at 6 months and in 61 % (TD) vs. 50 % (SU) at 12 months (p= 0.19). At 6 months, 31 % of patients in the SU group were still receiving GCS (median dose 26 mg/day) compared with 0 % for TD; at 12 months, 17 % of pts in SU were remained on GCS (median dose 23 mg) compared with 0% for TD (p< 0.001). At 6 and 12 months 84% and 93 % of pts were using immunomodulators in the TD group, versus 41% and 65 % in the SU group (both p< 0.001). Overall treatment success was seen in 29% TD and 5% SU pts (p<0.001). During the first 12 months, 13% of patients in the SU group needed IFX infusions to induce remission and 41% of patients in the TD group required at least one further IFX infusion. Serious adverse events were observed in 49% of TD and 41% of SU pts (NS). Conclusion. Aggressive induction with IFX + AZA is superior to sequential SU therapy for reducing exposure to GCS and attaining overall treatment success. 41% of TD patients needed further IFX infusions after induction. Complete results until month 24 will be available at DDW.

**218359: A Combined Regimen of Infliximab and Azathioprine Induces Better Endoscopic Healing Than Classic Step-Up Therapy in Newly Diagnosed Crohn's Disease.** Geert R D'Haens, Daan Hommes, Filip Baert, Martine De Vos, Filip Caenepeel, Gert Van Assche, Guy Lambrecht, Jean Claude Coche, Severine Vermeire, Marijke Van Camp

Current guidelines for treatment of moderate-severe Crohn's disease (CD) recommend corticosteroids and at a later stage immunosuppressives (IS) such as azathioprine. Often, CD complications develop during the period prior to the initiation of IS, probably because of insufficient mucosal healing with steroid regimens. We examined if a strong induction regimen with anti-TNF therapy in combination with IS given in an early phase of the disease induced better mucosal healing than 'classic' step-up treatment with corticosteroids. Methods: 133 patients with recently diagnosed CD were enrolled in a prospective trial and randomised to receive treatment with 3 infusions of 5 mg/kg infliximab (IFX) + azathioprine 2-2.5 mg/kg/day (TD or 'top-down' treatment) or corticosteroids at standard dosage (SU or 'step-up' treatment). In the latter group, IS was added in case of relapse and need for further steroids; IFX was given if IS failed. Patients enrolled at 8 centers participated in this substudy and had ileocolonoscopy 2 years after enrollment. Results were compared by a blinded investigator with the endoscopy reports at diagnosis. In 5 ileal and colonic segments lesions were scored as follows: 0=no ulcers, 1= aphthoid ulcers, 2=larger ulcers, 3= ulcerated stenosis. The primary endpoint was disappearance of all ulcers; the secondary endpoint was percentage of reduction of all CD lesions. Results: 44 pts have reached year 2 and underwent repeat endoscopy. 24 pts received TD therapy and 20 classic SU therapy. The characteristics of the pts and the baseline endoscopies in both groups were comparable. At year 2, all pts in the TD group received IFX and IS vs 45% IFX and 60 % IS in the SU group. The interval between the last IFX infusion and the second endoscopy was 15.8±8.7 months in TD vs 7.44±4.4 months in SU (p=0.001) and the mean duration of IS was 24 months in TD vs 19 months in the SU group. Complete ulcer disappearance was seen in 17/24 TD pts (71%) vs in 6/20 SU pts (30%)(p<0.001). Mucosal healing was significantly more pronounced in TD patients (ulcer reduction 88 % versus 47 %, p<0.001; in TD the score went from 5.75 ± 2.47 to 0.75 ± 1.60, in SU from 5.40 ± 2.41 to 3.25 ± 2.97, p<0.001). Conclusion: the 'top-down' strategy with IFX+IS is superior to induce mucosal healing two years after the start of therapy. This superiority vs classic 'step-up'-therapy is maintained even in patients who receive IFX and IS later on. Since persisting lesions lead to development of complications and healing is associated with a reduction in surgery and hospitalisations, this strategy should be considered in all patients with severe newly diagnosed Crohn's disease.

**222089: Continuation of Immunomodulators Is Not Required To Maintain Adequate Infliximab Efficacy In Patients With Crohn's Disease But May Improve Pharmacokinetics.** *Gert A Van Assche, Gilles Paintaud, Geert D'haens, Filip Baert, Severine Vermeire, Maja Noman, Herve Watier, Charlotte Magdelaine, Paul Rutgeerts*

**Background.** Concomitant immunomodulators at the start of infliximab treatment improve long-term duration of response in parallel with sustained infliximab serum levels. **Aims:** to investigate the role of immunomodulators in maintaining adequate infliximab trough levels and long-term efficacy in patients beyond 6 months of combined therapy. **Methods.** 80 patients were randomized to continue (CON, n=40) or to interrupt (DIS, n=40) immunomodulators (azathioprine or methotrexate) ≥6 months after the start of infliximab (5 mg/kg IV) in combination therapy. All patients were in clinical remission at baseline. Infliximab serum levels were determined q8 wks. (before every infusion) and efficacy and adverse events were assessed at the same time-points. Patients requiring a change in IFX dosing strategy due to a disease flare (increase in CDAI ≥ 70) or to a de novo fistula, were considered failures but were followed for efficacy and safety. **Results.** Patients in the 2 treatment groups had comparable overall IFX trough levels (median CON: 3.2 (percentile 25-75: 1.4-5.4), DIS 2.4 (0.9-5.3) µg/mL (CON) (median follow up: 83 wks.), but high inter-individual variations were observed. For the change of IFX levels over time we observed a trend towards decrease in the discontinuation group (median change baseline to Wk 24: +0.32 (0.005-1.8) (CON), -0.647 µg/mL (-2.0-1.28) (DIS, p=0.05), baseline to Wk48: +1.29 (0.9-3.0) (CON), -0.57 (-2.2-3.1) µg/mL (DIS, p=0.18). Fourteen/40 (35%) (CON) and 13/40 (32%, p=0.81) (DIS) patients required a change in dosing interval. Two more patients in each group failed because of tolerability or lack of compliance. The median time to failure was: CON 17 wks. (25-75 perc.:8-25) , and DIS 8 wks. (6.5-25.5) (CON) respectively (p=0.82). A ≥50% decrease in infliximab trough levels preceded clinical relapse in only 1/13 (CON) and 4/13 (DIS, p=0.18) patients respectively. IFX was interrupted due to complete loss of response or tolerability in 2/40 (CON) and 4/40 (DIS, p=0.40) patients respectively. All others regained clinical response with changes in IFX treatment schedule. **Conclusion.** Discontinuation of immunomodulators after at least 6 months of combined treatment with systematic IFX maintenance does not affect long term efficacy but may lead to lower trough levels.

**217026: Certolizumab Pegol Administered Subcutaneously Is Effective And Well Tolerated In Patients With Active Crohn's Disease: Results From A 26-Week, Placebo-Controlled Phase III Study (PRECiSE 1).** *William J Sandborn, Brian G Feagan Simeon Stoinov, Pieter J Honiball, Paul Rutgeerts, Juliet A McColm, Alison Innes, Stefan Schreiber*

**Background:** Certolizumab pegol (CDP870) is a PEGylated Fab' fragment of a humanized monoclonal antibody that neutralizes tumor necrosis factor-α. A Phase III, randomized, double-blind, multicenter study assessed efficacy and tolerability of certolizumab pegol in active Crohn's disease (CD). This is the largest long-term induction study of a biologic agent performed to date in CD. **Methods:** Adult patients (pts) with moderate-severe CD (CD Activity Index [CDAI] 220-450 points) were randomized to receive subcutaneous (sc) certolizumab pegol 400mg or placebo (PBO) at Weeks (Wks) 0, 2, 4, then 4-weekly up to Wk 24. Pts were stratified at baseline according to C-reactive protein (CRP) level (<10mg/L or ≥10mg/L) and immunosuppressant/corticosteroid use. Safety and efficacy were determined at Wks 0, 2, 4, 6, 8, 12, 16, 20, 24 and 26/withdrawal. The co-primary endpoints were the percentages of pts with a clinical response (decrease in CDAI ≥100) at Wk 6, and at Wks 6 & 26, in pts with baseline CRP ≥10mg/L. Secondary endpoints included 70-point response (decrease in CDAI ≥70, post-hoc analysis), and remission (CDAI ≤150) in the CRP ≥10mg/L stratum, response and remission in the overall intention-to-treat (ITT) population, and CRP levels (last observation carried forward; LOCF, post-hoc analysis) in both populations. **Results:** Both primary endpoints showed a significant advantage for certolizumab pegol over PBO. Responses (70- and 100-point) at Wks 4, 6 and Wks 6 & 26 were significantly higher (p<0.05) for certolizumab pegol vs PBO in the CRP ≥10mg/L stratum and the overall ITT population (n=659) (Table). Remission at Wk 4 was significantly higher for certolizumab pegol vs PBO; there were positive trends at Wk 6 and Wks 6 & 26. Median CRP levels were significantly lower for certolizumab pegol vs PBO at Wks 6 and 26 (p≤0.01, changes from baseline) (Table). Overall, no safety signals of concern were observed. **Conclusions:** Monthly certolizumab pegol 400mg sc demonstrated significant efficacy and was well tolerated compared with PBO in pts with active CD.

	Baseline CRP ≥10mg/L		Overall ITT population	
	PBO n=156	Certolizumab pegol 400mg n=146	PBO n=328	Certolizumab pegol 400mg n=331
70-point response (% pts) <sup>a</sup>				
Wk 4 Wk 6 Wks 6 & 26	30.3 33.1 14.9	50.3** 46.9* 29.2**	33.7 37.8 22.5	44.0** 46.2* 32.0**
100-point response (% pts) <sup>a</sup>				
Wk 4 Wk 6 Wks 6 & 26	20.6 26.0 12.3	32.9* 37.2* 21.5*	21.8 26.8 16.0	28.7* 35.2* 23.1*
Remission (% pts) <sup>a</sup>				
Wk 4 Wk 6 Wks 6 & 26	9.7 16.9 8.4	20.1* 21.9 13.1	11.3 17.2 9.8	19.5** 21.6 14.4
Median CRP LOCF (mg/L)				
Wk 0 Wk 6 Wk 26	25.5 23.0 27.0	28.0 13.5 15.0	8.5 9.0 9.0	7.0 4.0 4.0

\*p≤0.05, \*\*p≤0.01 vs PBO <sup>a</sup>n is decreasing over time

**216217: Concomitant Immunosuppressive and Adalimumab Therapy in Patients With Crohn’s Disease: 1-Year Results of the CLASSIC II Study.** *R Panaccione, Stephen B Hanauer, Richard Fedorak, Paul Rutgeerts, William J Sandborn, Paul Pollack*

**BACKGROUND** Adalimumab, a fully human anti-TNF monoclonal antibody, is approved for the treatment of rheumatoid arthritis and psoriatic arthritis. In CLASSIC I, a 4-week randomized controlled study of adalimumab in the induction of remission in patients with active Crohn's disease (CD), immunosuppressant (IMM)—azathioprine, 6-MP, or methotrexate—use was permitted if patients entered the study on a stable IMM dose for 12 weeks prior to screening. IMM use did not influence the response to adalimumab in CLASSIC I. **PURPOSE** To assess the effect of concomitant IMM on the efficacy of adalimumab over 1 year in CLASSIC II. **METHODS** All patients in CLASSIC II completed CLASSIC I and received adalimumab 40 mg sc at Weeks 0 (Week 4 of CLASSIC I) and 2. Patients with CDAI≥150 at Weeks 0 and/or 4 received open-label (OL) adalimumab 40 mg sc every other week (eow), weekly dosing was permitted for flare or persistent non-response. Patients with CDAI<150 at both Weeks 0 and 4 were randomized to receive adalimumab, 40 mg sc eow or weekly, or placebo for up to 1 year. CDAI was assessed at each study visit. Information on concomitant IMM use was collected at the start of the study through 56 weeks of treatment. The relationship of IMM and adalimumab on remission (CDAI<150) and Δ100 CDAI response (decrease in CDAI score ≥100 points) and their potential interaction was assessed. **RESULTS** Of 276 patients enrolled in CLASSIC II, 30% received concomitant IMM (IMM+). In the OL cohort (N=221), 46% of IMM+ patients achieved CDAI<150 and 64% achieved Δ100 CDAI, versus 40% and 60% of those not receiving IMM (IMM-), respectively. Results in the randomized cohort (N=55) are summarized in the table. IMM status did not notably influence the efficacy of adalimumab. **CONCLUSION** Adalimumab consistently improved CDAI outcomes with or without IMM use. Concomitant adalimumab and IMM will be evaluated in larger, long-term CD studies.

**Week 56 Remission and Response: CLASSIC II Randomized Cohort**

Therapy		CDAI<150			Δ100 CDAI		
		Total	IMM+	IMM-	Total	IMM+	IMM-
Placebo	N	8/18	1/3	7/15	10/18	1/3	9/15
	%	44	33	47	56	33	60
40 mg eow	N	14/19	4/4	10/15	14/19	4/4	10/15
	%	74	100	67	74	100	67
40 mg weekly	N	15/18	4/5	11/13	16/18	5/5	11/13
	%	83	80	85	89	100	85

LOCF

**218825: Natalizumab Induces Sustained Response and Remission in Patients with Active Crohn's Disease: Results from the ENCORE Trial.** *Stephan R Targan, Brian Feagan, Richard Fedorak, Bret Lashner, Remo Panacionne, Daniel Present, Andreas Raedler, Paul Rutgeerts, Zsolt Tulassay, Miroslava Volfova, Douglas C Wolf, William Sandborn*

**Purpose:** ENCORE (Efficacy of Natalizumab in Crohn's Disease Response and Remission) was a phase 3, international, randomized, double-blind, placebo (pbo)-controlled trial that evaluated the efficacy and safety of natalizumab induction therapy in Crohn's patients with moderately to severely active disease and objective evidence of active inflammation (elevated C-reactive protein [CRP] levels). **Methods:** Patients (N=509) with Crohn's Disease Activity Index (CDAI) scores between 220 and 450 (inclusive) and CRP levels greater than the upper limit of normal (2.87 mg/L) were randomized 1:1 and received natalizumab (300 mg; n=259) or pbo (n=250) infusions at weeks 0, 4, and 8. Efficacy and safety were assessed at weeks 4, 8 and 12. The primary endpoint examined the ability of natalizumab to induce a clinical response (≥ 70 point decrease in baseline CDAI score) by week 8 that was sustained through week 12. Additional efficacy endpoints included the proportion of patients achieving a clinical remission (CDAI < 150) by week 8 and through week 12, and the proportion of patients in response or remission at any assessment. **Results:** A significantly higher proportion of patients in the natalizumab group were in response at both weeks 8 and 12 compared to patients in the pbo group (48% [124/259] vs. 32% [81/250], p < 0.001). Response at week 4 (following the first infusion) was 51% [133/259] for natalizumab vs. 37% [92/250] for placebo, p = 0.001, and remained significantly higher in the natalizumab group at all subsequent assessments (p < 0.001 for all comparisons with pbo). Remission at both weeks 8 and 12 was also achieved by a higher proportion of patients in the natalizumab group compared with pbo (26% [68/259] vs. 16% [40/250], p=0.002). Patients receiving natalizumab also had superior remission rates at all assessments (p ≤ 0.009 for all comparisons with pbo). The incidence and types of adverse events were similar between groups. **Conclusions:** Natalizumab induced response and remission by week 8 that was sustained through week 12. The response and remission rates

for natalizumab were superior to placebo at all timepoints beginning at week 4, thus confirming the efficacy of natalizumab as induction therapy. Natalizumab was well tolerated, with adverse events not significantly different than pbo.

**221903: A Phase I Study: Visilizumab Therapy in Crohn's Disease (CD) Patients Refractory to Infliximab Treatment:**  
*Daan Hommes, Stephen Targan, Daniel C Baumgart, Axel U Dignass, Lloyd Mayer, James N Lowder*

**Purpose:** Studies of visilizumab, a humanized anti-CD3 antibody, in ulcerative colitis (UC) patients, show its tolerability and clinical activity at doses ranging from 5 to 15mg/kg administered on 2 consecutive days. The current open-label study was designed to evaluate the safety and clinical activity of 10 µg/kg visilizumab doses in patients with moderate-to-severe inflammatory non-penetrating Crohn's disease. **Methods:** Subjects with a diagnosis of CD, a Crohn's Disease Activity Index (CDAI) > 250, a C-Reactive Protein (CRP) > 4 mg/L (above normal), and endoscopic evidence of active inflammatory disease were treated with bolus intravenous visilizumab on days (D) 0 and 1. A clinical response was defined as a decrease of CDAI at D59 of more than 100 points below the baseline value. **Results:** The protocol will enroll a total of 18 subjects. To date, a total of 12 subjects have enrolled, 8 of them have been followed for at least 59 days and are discussed below. The median baseline CDAI was 386.5 (308-516). The median baseline CRP was 30.5 mg/L (2.0-69). All subjects were steroid refractory (n=3) or dependent (n=5) with a median dose of 20 mg/D prednisone. All subjects had received infliximab; 2 were primary non-responders, 1 had an intolerable infusion reaction and 5 had lost activity after an initial response. Six of the 8 subjects had a day 59 clinical response. The median D59 CDAI was 218 (150-366). Three complete remissions (CDAI<150) at any time and 1 at D59 were observed. Both primary infliximab failures responded to visilizumab. In visilizumab responders, the CRP decreased quickly after drug administration and it remained low in 2 subjects who achieved clinical remission. Mild to moderate cytokine release syndrome occurred in the majority of subjects. The adverse event (AE) profile of severity, incidence and drug relatedness was similar to that seen in those UC subjects who received 10 µg/kg visilizumab. No lymphoproliferative, malignant or life-threatening AEs were reported. Transient elevations of transaminases were observed in 4 of 8 subjects. **Conclusion:** Two 10 µg/kg visilizumab doses administered as an IV bolus on consecutive days were tolerated and produced a rapid and sustained improvement in 6/8 steroid and infliximab resistant CD subjects.

**220450: Combined Data from Two Pivotal, Randomized, Placebo-Controlled, Phase III Studies Show that SPD476, A Novel Mesalamine Formulation given Once or Twice-Daily, is effective for the Induction of Remission of Mild-to-Moderate Ulcerative Colitis.** *William J Sandborn, Michael A Kamm, Gary R Lichtenstein, Miguel Gassull, Stefan Schreiber, Lechoslaw Jackowski, Prabhakar Boddu, Natalya Gubergrits*

**Background:** Mesalamine (5-ASA) is a first-line treatment for mild-to-moderate ulcerative colitis (UC). Presently available formulations are associated with inconvenient multiple-daily dosing, which can lead to patient non-compliance, thus reducing drug effectiveness and overall treatment success. Here we report an analysis of combined efficacy and safety data from two, prospective, randomized, multicenter, double-blind, placebo-controlled, phase III studies (SPD476-301 [Study 301] and SPD476-302 [Study 302]) investigating SPD476, a novel, high-strength (1.2g/tablet), once-daily formulation of mesalamine. SPD476 uniquely combines a gastro-resistant polymer film, delaying release of the active drug until the terminal ileum, and MMX Multi Matrix System™ (MMX) technology, extending consistent delivery of 5-ASA throughout the entire colon. **Methods:** Eligible subjects had mild-to-moderate UC. Data were combined for subjects receiving SPD476 2.4g/day (given once daily [QD; Study 302] or twice daily [BID; Study 301] combined n=172), SPD476 4.8g/day (given QD [Studies 301 and 302] combined n=174) or placebo (combined n=171). The proportion of subjects in remission (primary endpoint: UC disease activity index of ≤1, with a rectal bleeding and stool frequency score of 0 and ≥1 point reduction in sigmoidoscopy score from baseline) at week 8, was compared for the SPD476 groups vs the placebo group. **Results:** A statistically significantly greater percentage of subjects achieved remission in the SPD476 2.4g/day group compared with the placebo group (37.2 vs 17.5% [p<0.001]). Similarly, a statistically significantly greater percentage of subjects in the SPD476 4.8g/day QD group achieved remission compared with the placebo group (35.1 vs 17.5% [p<0.001]). A total of 10 subjects reported 13 serious adverse events (7 with placebo, 4 with SPD476 2.4g/day BID [aggravated UC=1; pancreatitis=1; perianal abscess=1; urinary retention=1] and 2 with SPD476 4.8g/day QD [viral gastroenteritis=1; pancreatitis=1]). Only pancreatitis was considered to be possibly and probably related to study medication. Both cases were resolved following discontinuation of the study drug. **Conclusions:** These data show that this unique formulation of SPD476, combining a high dose of 5-ASA per tablet and MMX technology, was well tolerated and effective for the induction of remission of mild-to-moderate UC at doses of 2.4g/day and 4.8g/day given once or twice daily. The efficacy and convenience of SPD476 is anticipated to improve patient compliance and enhance overall treatment success.

**221700: Optimization of 6-Thioguanine Production by Allopurinol in Inflammatory Bowel Disease Patients Not Responding to Azathioprine/ 6-Mercaptopurine Leads to Improved Disease Activity, Reduced Corticosteroid Requirements and Normalization of Liver Enzymes.** *Miles Sparrow, Scott A Hande, Sonia Friedman, Dingcai Cao, Stephen B Hanauer*

Background: At least 40% of IBD patients do not respond to the immunomodulators azathioprine(AZA) or 6-mercaptopurine(6-MP). Many non-responders have high/normal thiopurine methyltransferase (TPMT) activity and preferentially metabolize 6-MP to 6-methylmercaptopurine(6-MMP). Aim: We describe the clinical response to adjunctive allopurinol, used to shunt 6-MP metabolism towards the active metabolites 6-thioguanine nucleotides (6-TGN), in 6-MP/AZA non-responders. Methods: 21 outpatients (13 CD, 6 UC, 2 IC) from 2 IBD clinics who were clinical non-responders to AZA/6-MP and whose metabolite profiles demonstrated preferential metabolism towards 6-MMP>6-TGN were included. Subjects were commenced on allopurinol 100 mg daily and the current dose of 6-MP/AZA was reduced by 50-75%. Patients were followed clinically with weekly CBCs and serial 6-TGN and 6-MMP levels. Partial Harvey Bradshaw Index scores (pHBI-Number of bowel movements, pain, well being)) were used to assess response in CD patients, Mayo Scores (without endoscopy) were used to assess patients with UC & IC. Results: Median doses of AZA(6 patients) pre- and post allopurinol were 200 mg(50-250) and 92 mg(50-100) respectively; and median doses of 6-MP(15 patients) pre-and post allopurinol were 87 mg(0-125) and 51 mg(25-100) respectively. After initiating allopurinol, 6-TGN levels increased from a mean of 187.2 ( $\pm$  SEM)  $\pm$ 16.7 to 387.3 $\pm$ 37.4 pmol/ 8 x 10<sup>8</sup> RBCs(p < 0.001) while 6-MMP levels decreased from a mean of 10517.1 $\pm$ 1212.3 to 1919.3 $\pm$ 423.6 pmol/ 8 x 10<sup>8</sup> RBCs(p < 0.001). The addition of allopurinol led to a decrease in WBC from a mean of 8.6 $\pm$ 1.0 to 6.1 $\pm$ 0.6 x 10<sup>8</sup>/L(p = 0.003). Analysis of disease activity indices showed that the addition of allopurinol led to a reduction in the pHBI in CD patients from a mean of 4.9 $\pm$ 1.0 to 1.5 $\pm$ 0.3 points(p=0.001) and in UC patients the Mayo Score decreased from a mean of 4.1 $\pm$ 0.7 to 2.9 $\pm$ 0.7 points(p=0.13). The addition of allopurinol enabled a reduction in prednisone dosage from a mean daily dose of 17.6 $\pm$ 3.9 to 1.8 $\pm$ 0.7 mg (p<0.001) and led to normalization of transaminases with mean ALT levels reducing from 101.6 $\pm$ 26.9 to 33.9 $\pm$ 5.2 IU(p=0.01), and mean AST levels reducing from 42.5 $\pm$ 8.1 to 23.5 $\pm$ 1.6 IU(p=0.12). Conclusions: The addition of allopurinol to thiopurine non-responders with high/normal TPMT activity and preferential shunting to 6-MMP appears to be an effective and safe means of optimizing 6-TGN production, leading to improved disease activity scores, reduced corticosteroid requirements and normalization of hepatic transaminases. Long-term efficacy and safety related to potential nodular regenerative hepatic changes will be monitored.

**224346: The Treatment with an Oral Spherical Adsorptive Carbon (AST-120) Improves Anal Fistula, PDAI and CDAI Scores -A Randomized Double-Blind Placebo-Controlled Trial.** Yoshihiro Fukuda, Masakazu Takazoe, Akira Sugita, Tadashi Kosaka, Toshihiko Tomita, Kazutoshi Hori, Ken Fukunaga, Hiroto Miwa, Takayuki Matsumoto, Hiromasa Koizuka, Takashi Sakagami, Takashi Shimoyama

BACKGROUND Crohn's disease (CD) patients are often suffering from anal fistulas, leading difficult lives. The current therapies with various drugs including anti-TNF- $\alpha$  antibodies are effective in most of fistulizing CD, but anal fistulas are still remaining unhealed in some patients. Surgical treatment including fecal diversion and stoma is indicated, however, not all of patients can accept it. We conducted a randomized, double-blind, placebo-controlled multi-center clinical trial of an oral spherical adsorptive carbon (AST-120). METHODS CD patients with active fistula under medical treatments were randomly assigned to receive either AST-120 or placebo for 8 weeks. The number and status of draining fistulas were evaluated by the investigators at 0, 4 and 8 weeks. The improvement was a reduction of 50% or more from base line in the number of draining fistulas observed both at 4 and at 8 weeks. The fistula remission was defined by closure of all draining anal fistulas both at 4 and 8 weeks. Severities of symptoms related to CD were graded referring to a patient diary. Also, Crohn's Disease Activity Index (CDAI) and Perianal Disease Activity Index (PDAI) were evaluated. RESULTS Sixty-two patients were evenly assigned to both group and were given AST-120(n=27) or placebo(n=30). The fistula improvement rate in the AST-120 group (37.0 % ) was significantly greater than that in the placebo group (10.0 % ) (p=0.025). The fistula remission rate in the AST-120 group (29.6 % ) was significantly greater than that in the placebo group (6.7 % ) (p=0.035). Symptomatic scores such as drainage amount, perianal pain and fecal consistency were significantly improved in the AST-120 group but not in the placebo group. PDAI scores significantly improved both at 4 weeks and at 8 weeks in the AST-120 group compared with those in the placebo group (p=0.004 and p=0.005, respectively). Also CDAI scores significantly improved both at 4 weeks and at 8 weeks in the AST-120 group compared with those in the placebo group (p=0.007 and p=0.001, respectively). The AST-120 treatment was generally well tolerated and was observed no life threatening adverse events. CONCLUSIONS The AST-120 treatment is safe and effective for the control of intractable anal fistulizing CD.

**213827: Atorvastatin Decreases Seo Index in Patients with Short Duration of Disease in Ulcerative Colitis: A Randomized Placebo-Controlled Clinical Trial.** Peter D Higgins, Tahira Khan, John Mapili, Ellen M Zimmermann

Background: Statin medications have systemic anti-inflammatory effects. Studies in animal models and a case series in humans have shown improvement in colitis with statins. Aims: 1) To determine whether the Seo Index is improved in a randomized controlled 24-week pilot study of daily oral atorvastatin 40 mg in patients with mild to moderate ulcerative colitis; 2) To identify any subgroups of patients most likely to respond to atorvastatin. Methods: Thirty-six patients 18 to 70 years of age with mild to moderately active ulcerative colitis despite a variety of stable medications were randomized to placebo or 40 mg daily oral atorvastatin for 24 weeks. Subjects were allowed to leave the study after a final evaluation if a symptomatic flare occurred. In an intention-to-treat analysis, the final Seo Index when controlled for baseline Seo Index was the primary outcome. A decrease in the Seo Index of >30 points was considered clinically significant improvement, and a Seo score of less than 120

points was considered remission. Six pre-specified covariates of disease duration, disease extent, baseline CRP, thiopurine use, steroid use, and pANCA titer were evaluated in a multivariate model to identify subsets of subjects with improved responses. Similar assessments with the IBDQ (>205 for remission, >20 change for improvement) were performed to evaluate effects on quality of life. Results: The final Seo Index was 132.1 points in patients randomized to atorvastatin, and 157.6 points in patients on placebo (p=0.06). The disease duration covariate had a significant interaction with therapy, with longer duration of disease leading to less response. After controlling for this interaction, the final Seo Index was 46 points lower in patients randomized to atorvastatin vs. placebo (p=0.02). Clinically significant improvement was seen in 40% of patients on atorvastatin, compared to 25% with placebo. Clinical remission was achieved in 45% of patients on atorvastatin, compared to 25% with placebo. With the IBDQ endpoints, 50% of patients had clinically significant improvement on atorvastatin vs. 19% on placebo, and 35% of patients achieved remission on atorvastatin vs. 31% on placebo. The atorvastatin group had one significant adverse event: a fall with head injury probably unrelated to drug. No significant elevations in liver tests or creatine kinase occurred. Conclusions: Daily oral atorvastatin 40 mg appears to be moderately beneficial in a subset of patients with shorter duration of disease in this pilot study of atorvastatin for ulcerative colitis. The anti-inflammatory effects of atorvastatin in ulcerative colitis warrant further study.

**214088: A Safety And Efficacy Study Of A Novel Formulation Of Prednisolone Metasulfobenzoate (PREDOCOL) In The Induction Of Remission And Maintenance In Ulcerative Colitis.** Jonathan M Rhodes, Richard Robinson, Ian Beales, Stirling Pugh, Richard Dickinson, Michael Dronfield, Steven Wilkinson

Background/Aims Prednisolone metasulfobenzoate is effective topically in ulcerative colitis but is sparingly absorbed from the colon (McIntyre et al, Gut 1985). A modified-release oral formulation has been developed (Predocol) comprising a Eudragit L-coated capsule containing 200 controlled-release drug pellets. A pilot study showed very low systemic absorption. This study compares the safety and efficacy of Predocol with prednisolone in ulcerative colitis. Methods Patients were randomised to one of three treatment groups in a double-blinded study. Group A (n=59) received Predocol 40 mgs /day for 6 months plus placebo, Group B (n=61) received Predocol 60 mgs/day for 6 months plus placebo, and group C (n=61) received Prednisolone 40 mg/day for 2 weeks which was then tapered to 30mg/day weeks 3 and 4, 20mg/day weeks 5 and 6, 10mg/day week 7, 5mg/day week 8 then placebo only until 6 months. All drugs were given in twice daily divided doses. Steroid-related side effects and efficacy were assessed by patients using a visual analogue scale (VAS) where 10cm = symptom-free and 0=worst possible. Efficacy was also assessed by Powell-Tuck score, Physician global score and Baron endoscopic grading. The trial was designed to assess non-inferiority. Results Predocol at 40mgs per day but not at 60mgs/day showed non-inferiority compared to prednisolone at 2 months and 6 months (Table). Physician’s global assessment confirmed non-inferiority for Predocol 40mg vs prednisolone at month 2 (remission 36% and 43% respectively) and month 6 (remission 65% and 43% respectively). Similar efficacy was observed using Powell-Tuck and Baron grades. Patient’s global assessment of steroid-related side-effects at 2 months was better for Predocol 40 mgs or 60 mgs (p=0.001 and 0.002 respectively) compared with prednisolone. Predocol was also significantly better than prednisolone on patient’s scoring for moon face, hirsutes, flushing, mood changes and insomnia. Conclusion Predocol 40 mgs per day is non-inferior in efficacy compared with a conventional tapering prednisolone regimen and is associated with fewer steroid-related side effects.

Patient's Global Symptom VAS [cm, mean(sd)] (0=worst possible, 10=symptom-free)					
	Entry	2 weeks	4 weeks	2 months	6 months
Predocol 40mg	3.99 (2.06)	6.26 (2.36)	7.09 (2.68)	8.20 (1.78)	8.20 (2.80)
Predocol 60mg	2.97 (1.76)	5.38 (2.46)	6.82 (2.01)	7.47 (2.28)	6.84 (2.84)
Prednisolone	3.95 (2.12)	7.61 (2.11)	7.98 (2.39)	8.03 (2.16)	7.94 (2.40)
Patient's Global Steroid Side-Effect VAS [cm, mean (sd)] (0=worst possible, 10=symptom-free)					
	Entry	2 weeks	4 weeks	2 months	6 months
Predocol 40mg	-	8.38 (2.20)	8.29 (9.50)	8.14 (2.59)	9.04 (2.12)
Predocol 60mg	-	8.18 (2.61)	8.39 (2.14)	8.07 (2.59)	7.48 (2.73)
Prednisolone	-	6.55 (2.45)	6.44 (2.65)	6.74 (2.77)	9.16 (1.58)

**Additional Reading: Emerging Therapies for IBD**

**217062: Safety and Tolerability of Subcutaneous (sc) Certolizumab Pegol in Active Crohn’s Disease (CD): Results from Two Phase III Studies (PRECiSE program).** Stefan Schreiber, Brian Feagan, Stephen B Hanauer, Paul Rutgeerts, Juliet A McColm, William J Sandborn

**Background:** Tolerability and safety of certolizumab pegol were examined in 2 parallel Phase III trials (PRECiSE program) in active CD (CD Activity Index [CDAI] score 220-450) involving more than 1300 patients (pts). **Methods:** In PRECiSE 1, pts

received sc certolizumab pegol 400mg (n=331) or placebo (PBO; n=329) at Weeks (Wks) 0, 2, 4, then 4-weekly up to Wk 24. In PRECiSE 2, 668 pts received open-label sc certolizumab pegol 400mg at Wks 0, 2, 4. Pts who responded at Wk 6 received double-blind certolizumab pegol 400mg (n=216) or PBO (n=212) 4-weekly from Wks 8-24. Adverse events (AEs) were monitored (n=1328). **Results:** Most AEs in both trials were mild or moderate. In the double-blind phases, the overall incidence of AEs was comparable for certolizumab pegol and PBO. For certolizumab pegol, the most common AEs included headache and nasopharyngitis (both studies), abdominal pain (PRECiSE 1), and cough (PRECiSE 2); the most frequently occurring infections included nasopharyngitis, urinary tract (UTI) and upper respiratory tract infections. In PRECiSE 1, 10.3% of certolizumab pegol and 7.0% of PBO pts had serious AEs (SAEs). Corresponding data for the double-blind phase of PRECiSE 2 were 5.6% and 6.6%, respectively. Non-CD-related infection SAEs were infrequent in the PRECiSE 2 double-blind phase (certolizumab pegol: 1 pulmonary tuberculosis [TB; responded well to anti-TB therapy], 1 pyelonephritis, 1 pneumonia; PBO: 1 bacteremia 6 days after the 1st PBO dose, 1 otitis media) and in PRECiSE 1 (certolizumab pegol: 3 abscesses, 1 UTI; PBO: 1 abscess). Incidence of reported malignancies in PRECiSE 1 was similar between certolizumab pegol (1 lung [10 months after withdrawal] and 1 rectal carcinoma) and PBO (1 non-Hodgkin's lymphoma and 1 cervical carcinoma [linked with human papillomavirus]); none was reported in PRECiSE 2. Injection reactions were less frequent for certolizumab pegol than PBO pts (PRECiSE 1 and 2: 11.8% vs 25.5% and 6.5% vs 19.8%, respectively). One certolizumab pegol-treated pt in each study died (acute myocardial infarction/metastatic lung cancer (as noted above) and Fentanyl overdose); neither death was considered related to study drug. Proportions of pts negative for auto-antibodies at baseline, becoming positive at Wk 26/withdrawal were low (anti-nuclear: ≤8.3%, and anti-double-stranded DNA: ≤1.4%). No cases of lupus were reported. **Conclusions:** Experience in over 1300 pts with CD suggests that treatment with sc certolizumab pegol 400mg is safe and well tolerated. The low incidence of auto-antibodies observed following treatment with certolizumab pegol is strikingly different from that reported for other anti-tumor necrosis factor- $\alpha$  agents.

**217120: How Effective is Anti-TNF- $\alpha$  Therapy? A Re-analysis of the PRECiSE 2 Maintenance Trial of Monthly Subcutaneous Certolizumab Pegol In Active Crohn's Disease Using Remission To Redefine All Efficacy Measures.** Stefan Schreiber, Ian C Lawrance, Juliet A McColm, Ralph Bloomfield, William J Sandborn

**Background:** In most clinical studies of biologics in Crohn's disease (CD), response — defined as a drop of  $\geq 70$  or  $\geq 100$  points on the CD Activity Index (CDAI) — is used as an endpoint. Maintenance trials (eg ACCENT I, PRECiSE 2), where patients (pts) responding to open-label therapy are randomized to receive active agent or placebo (PBO) over 6–12 months, have evolved as a design which separates active treatment from PBO. However, 'remission' (CDAI  $\leq 150$ ) used as an efficacy measure throughout this clinical trial design may better reflect clinical need. Certolizumab pegol is a PEGylated Fab' fragment of a humanized monoclonal antibody that neutralizes tumor necrosis factor  $\alpha$ . In the PRECiSE 2 Phase III trial, 668 pts with active CD (CDAI 220–450) received open-label subcutaneous (sc) certolizumab pegol 400 mg at Weeks (Wks) 0, 2, 4, followed by randomization of Wk 6 responding pts ( $\geq 100$ -point decrease from baseline in CDAI) to every 4 Wk certolizumab pegol 400 mg (n=216) or PBO (n=212) up to Wk 26. Remission (CDAI  $\leq 150$ ) rates at Wk 26 were 47.9% for certolizumab pegol vs 28.6% for PBO (p<0.001) in the overall ITT population (n=425). **Methods:** In a post-hoc analysis, remission after open-label induction at Wk 6 was used to select randomized pts for analysis. Remission rates at Wks 8, 12, 16, 20, 24, and 26 were assessed in this population. In addition, absolute CDAI scores (last observation carried forward) for the overall PRECiSE 2 ITT population were analyzed. **Results:** At Wk 6, 278 pts (42%) were in remission following induction; 132 pts were randomized to certolizumab pegol and 146 to PBO. At Wk 26, 80 pts (60.6%) in the certolizumab pegol arm vs 50 PBO pts (34.2%) were in remission (p<0.001; Table). Median CDAI scores in the overall ITT population remained close to remission levels with certolizumab pegol (Wk 8: 142.0; Wk 26: 148.0), in contrast to PBO (Wk 8: 140.5; Wk 26: 195.4); p<0.001 at Wk 26. **Conclusions:** Using maintenance of remission as an efficacy parameter demonstrates an efficacy signal for certolizumab pegol over PBO in a post-hoc analysis that may better reflect clinical need. Almost two-thirds of pts receiving monthly certolizumab pegol were in remission at Wk 26. Future induction/maintenance trials of biologics using the ACCENT I/PRECiSE 2 trial design could use remission instead of response as a clinically relevant endpoint.

	Overall ITT population % (No. of pts)	
Remission in pts who were in remission at Wk 6	PBO n=146	Certolizumab pegol 400 mg n=132
Wk 6 Wk 8 Wk 12 Wk 16 Wk 20 Wk 24 Wk 26	100 (146) 71.2 (104) 56.2 (82) 44.5 (65) 41.1 (60) 35.6 (52) 34.2 (50)	100 (132) 76.5 (101) 72.7 (96)** 58.3 (77)* 59.1 (78)** 56.8 (75)*** 60.6 (80)***

\*p $\leq$ 0.05, \*\*p $\leq$ 0.01, \*\*\*p $\leq$ 0.001 vs PBO

**219307: Four-Week Results of Adalimumab Treatment in Subjects With Fistulizing Crohn's Disease Who Have Failed Response or Showed Intolerance to Infliximab.** J Hinojosa, F Gomollon, P Nos, M Penate, D Ceballos, MA Gassull

**PURPOSE** To assess the efficacy and safety of adalimumab, a fully human monoclonal antibody targeting TNF- $\alpha$ , for inducing fistula closure in subjects with fistulizing Crohn's disease (CD). **METHODS** In this open-label multi-center study for the

induction of clinical remission and perianal fistula closure, subjects with failed response or intolerance to infliximab and a diagnosis of fistulizing CD (CDAI<220) or both luminal (mucosal) and fistulizing CD (CDAI>220) were treated with subcutaneous adalimumab: 160 mg at Week 0, 80 mg at Week 2, then 40 mg every other week (eow) for 52 weeks. Subjects were routinely assessed for complete or partial ( $\geq 50\%$  decrease in number of draining fistula compared to baseline) fistulae closure, PDAI score, and adverse events (AE). **RESULTS** Of 22 subjects treated with adalimumab, all had been treated previously with infliximab: 5 (23%) had failed response to infliximab, 17 (77%) were infliximab-intolerant. Subjects had luminal and fistulizing CD (45%) or fistulizing CD only (55%). At baseline, the mean PDAI score overall (n=22) was 10.5  $\pm$  2.8; the mean number of fistulae was 2.5 $\pm$ 1.2 in subjects with fistulizing CD only and 3.8 $\pm$ 5.5 in subjects with both luminal and fistulizing CD. Week 4 results are shown in the table. Treatment-related AE were mild to moderate in severity and similar to those observed in studies of ADA in subjects with rheumatoid arthritis. The most common AE were erythema, nausea/dizziness, weakness, and myalgia. One patient dropped out due to non-pruritic erythema. No serious AE's were reported. **CONCLUSIONS** Adalimumab induced complete or partial fistula closure in these subjects and was well-tolerated. No new safety concerns were found in subjects with fistulizing CD compared to other adalimumab-treated populations.

**PDAI Scores and Fistula Closure at Week 4 of Adalimumab Treatment**

	Luminal and Fistulizing (n=10)	Fistulizing (n=12)	All (n=22)
<b>Median PDAI</b>	4.7 $\pm$ 2.2	6.1 $\pm$ 3.6	5.8 $\pm$ 3.1
<b>Complete closure n/N (%)</b>	3/10 (30%)	2/12 (17%)	5/22 (23%)
<b>Partial closure n/N (%)</b>	4/10 (40%)	5/12 (42%)	9/22 (41%)

Intention to treat analysis

**225804: A Safety Evaluation for Progressive Multifocal Leukoencephalopathy (PML) in Greater Than 3,500 Patients with Crohn's Disease (CD), Multiple Sclerosis (MS), and Rheumatoid Arthritis (RA) Previously Treated with Natalizumab in Clinical Trials.** *William Sandborn, Stephan Targan*

**Introduction:** Natalizumab is a humanized IgG<sub>4</sub> monoclonal antibody against  $\alpha 4$  integrins. It was approved by the FDA in November 2004 for the treatment of MS. Phase 3 trials for CD, had completed enrollment, and a Phase 2 trial in RA was ongoing. Clinical trials and marketing were voluntarily suspended in February 2005 based on the reports of 2 patients receiving combination therapy with natalizumab and interferon beta-1a in a MS clinical trial who developed PML. Subsequently, a previously diagnosed malignant astrocytoma in a natalizumab-treated patient with previous exposure to azathioprine was reclassified as PML. Thereafter, a safety evaluation was performed in all patients who had recently been treated with natalizumab in clinical trials to screen for PML. **Methods:** The safety evaluation protocol included informed consent and an urgent additional follow-up visit(s) to include a physical exam, referral to a neurologist, brain MRI, polymerase chain reaction (PCR) analysis of cerebral spinal fluid (CSF) and serum for JC virus. MRI scans of the brain were performed and interpreted at each center. MRI images were also sent to a core laboratory facility for central interpretation by a neuroradiologist with expertise in white matter disease. An independent adjudication committee (IAC) consisting of experts in JC virology, neurological and clinical manifestations of PML, and MRI imaging of neuroinflammation was created to adjudicate all suspected cases of PML and make a final determination of whether the patient had PML. In addition to patients from clinical trials, 4 post-marketing MedWatch reports of suspected PML were also referred to the IAC. **Results:** Enrollment in the safety evaluation included 87% (1,275), 91% (2,248) and 92% (296) of all eligible CD, MS, and RA patients, respectively. Neurological exams and MRIs were completed in >97% of CD, MS, and RA patients. CSF was analyzed for JC virus in 6% of CD, 16% of MS, and 4% of RA patients, and plasma in 88% of CD, 56% of MS, and 95% of RA patients. No additional cases were judged by the IAC to have PML. The 4 post-marketing cases referred to the IAC were also judged not to have PML. **Conclusions:** Results of this analysis suggest that the absolute risk of developing PML during therapy with natalizumab is low (approximately 0.1%). It is not yet clear whether any screening strategy for the early detection of PML will be effective. The potential clinical benefit of natalizumab in selected patients with moderate to severe CD needs to be carefully weighed against the small risk of PML.

**221121: SPD476, A Novel, High-Strength 5-ASA Formulation Induces Remission of Active, Mild-to-Moderate Ulcerative Colitis In Subjects That Are Switched From Low-Dose Oral 5-ASA Therapy or Are 5-ASA Naïve: An Analysis of Pooled Data From Two Phase III studies.** *William J Sandborn, Michael A Kamm, Gary R Lichtenstein, Miguel Gassull, Stefan Schreiber, Lechoslaw Jackowski, Prabhakar Boddu, Natalya Gubergrits*

**Background:** Reasons for patients switching from one therapy to another within a drug class may include improved convenience and/or clinical efficacy. During switching it is essential to maintain or even improve disease control. Here we report an analysis of subjects with ulcerative colitis (UC) who were switched from prior low-dose oral 5-ASA therapy to moderate or high-dose SPD476, a novel, high-strength (1.2g/tablet) oral formulation of 5-ASA that uniquely combines a gastro-resistant film to delay drug release until the terminal ileum, with MMX Multi Matrix System™ technology to extend consistent

release of the active drug throughout the entire colon. **Methods:** Data from two phase III studies (SPD476-301 and SPD476-302) of subjects with active, mild-to-moderate UC who received SPD476 2.4g/day (given once or twice daily), SPD476 4.8g/day (given once daily) or placebo (Pb) were combined and further analyzed for subjects who were switched from prior low-dose oral 5-ASA therapy (discontinued oral 5-ASA therapy [ $\leq 2\text{g/day}$ ]  $\leq 5$  days prior to baseline) and subjects who were 5-ASA naïve (no prior oral 5-ASA or had discontinued oral 5-ASA therapy [ $\leq 2\text{g/day}$ ]  $>5$  days prior to baseline). Remission (UC-disease activity index score of  $\leq 1$  with rectal bleeding and stool frequency scores of 0 and a  $\geq 1$  point reduction in sigmoidoscopy score from baseline) rates at week 8 were analyzed. **Results:** No difference in disease severity between treatment groups at baseline was observed. In the switched group, significantly more subjects receiving SPD476 4.8g/day and numerically more subjects receiving SPD476 2.4g/day achieved remission compared with Pb (Table 1). In the 5-ASA naïve group, significantly more subjects achieved remission following either dose of SPD476 compared with Pb (Table 1). **Conclusions:** SPD476 was effective for the induction of remission of active, mild-to-moderate UC in subjects switched from recent oral 5-ASA therapies and subjects who were 5-ASA naïve. These data show that subjects with active UC, despite prior oral 5-ASA therapy, can achieve remission following therapy with SPD476. The 4.8g dose may give the best result in this setting. Switching to SPD476 may improve patient compliance and treatment success.

**Table 1.** Summary of remission rates

Subjects	Pb			SPD476 2.4g/day			SPD476 4.8g/day		
	n	Remission n (%)	95% CI	n	Remission n (%)	95% CI	n	Remission n (%)	95% CI
Switched	91	19 (20.9)	13.3, 30.0	88	28 (31.8)	23.0, 42.2	80	30 (37.5)*	27.1, 48.1
5-ASA naïve	80	11 (13.8)	7.3, 22.6	84	36 (42.9)***	32.7, 53.7	94	31 (33.0)**	24.6, 43.8

\*p<0.05; \*\*p<0.01; \*\*\*p<0.001 vs Pb; CI = confidence interval

**221351: Once- And Twice-Daily SPD476, A Novel, High-Strength Formulation of 5-ASA, Induces Remission of Both Mild and Moderate Ulcerative Colitis: A Prespecified Analysis of Combined Data From Two Pivotal, Randomized, Placebo-Controlled, Phase III Studies.** Gary R Lichtenstein, Michael A Kamm, William J Sandborn, Miguel Gassull, Stefan Schreiber, Lechoslaw Jackowski, Prabhakar Boddu, Natalya Gubergrits

**Background:** Existing 5-ASA (mesalamine) formulations for the treatment of ulcerative colitis (UC) require multiple-daily dosing, which may lead to patient non-compliance and thus reduced treatment efficacy. SPD476 is a novel, high-strength (1.2g/tablet), once-daily formulation of 5-ASA that uniquely combines a gastro-resistant polymer film, to delay release of the active drug until the terminal ileum, and MMX Multi Matrix System™ (MMX) technology to extend consistent delivery of 5-ASA throughout the entire colon. In two pivotal, randomized, placebo-controlled, phase III studies (SPD476-301 [Study 301] and SPD476-302 [Study 302]), SPD476 was well tolerated and effective for the induction of remission of mild-to-moderate UC (a score of 4-10 on the UC disease activity index [UC-DAI]). To demonstrate the efficacy of SPD476 in subjects that experienced either mild (UC-DAI score 4 to  $<6$ ) or moderate (UC-DAI score 6-10) disease, a prespecified analysis of combined data from these studies was performed. **Methods:** Data from these two phase III studies were analyzed for subjects with mild disease who received SPD476 2.4g/day (given once daily [QD; Study 302] or twice daily [BID; Study 301] combined n=67), SPD476 4.8g/day (given QD [Studies 301 and 302] combined n=70) or placebo (combined n=58). Similarly, data were analyzed for subjects with moderate disease for each treatment regimen (combined n=104, 103 and 112, respectively). The proportion of subjects with either mild or moderate disease achieving remission (primary endpoint: UC-DAI score of  $\leq 1$ , with a rectal bleeding and stool frequency score of 0 and  $\geq 1$  point reduction in sigmoidoscopy score from baseline) after 8 weeks treatment with SPD476 2.4g/day or 4.8g/day were compared with placebo. **Results:** At week 8, a significantly greater percentage of subjects with mild disease receiving SPD476 2.4g/day achieved remission compared with placebo (44.8 vs 20.7%; p=0.004), while a numerically greater proportion of subjects with mild disease receiving SPD476 4.8g/day achieved remission (35.7 vs 20.7%; p=0.061). Similarly, a significantly larger proportion of subjects with moderate disease achieved remission following treatment with SPD476 2.4g/day or 4.8g/day compared with placebo (32.7%; p=0.004 and 35.0%; p=0.001 vs 16.1%, respectively). Disease severity was not a predictor of response to treatment. **Conclusions:** This unique 5-ASA formulation, utilizing MMX technology, was effective for the induction of remission of active, mild and moderate UC at doses of 2.4g/day and 4.8g/day. SPD476, by offering treatment of mild and moderate disease with a simple dosing regimen, may improve overall treatment success.

**221420: SPD476, A Novel Formulation of 5-ASA Given Once or Twice Daily, Is Effective for the Induction of Remission of Left-Sided and Extensive Ulcerative Colitis: An Analysis of Combined Data From Two Pivotal, Randomized, Placebo-Controlled Phase III Studies.** Michael A Kamm, Gary R Lichtenstein, William J Sandborn, Miguel Gassull, Stefan Schreiber, Lechoslaw Jackowski, Prabhakar Boddu, Natalya Gubergrits

**Background:** Nearly 80% of patients diagnosed with ulcerative colitis (UC) have left-sided disease, affecting the colon below the splenic flexure. 5-ASA treatment regimens, the standard of care, often require inconvenient multiple-daily, oral dosing or

enema administration in order to induce remission. Such regimens can lead to patient compliance issues, which may reduce drug efficacy. SPD476 is a novel, high-strength (1.2g/tablet), once-daily (QD) formulation of 5-ASA that uniquely combines a gastro-resistant film, to delay initial drug release until terminal ileum, and MMX Multi Matrix System™ (MMX) technology, designed to extend consistent delivery of the active drug beyond the splenic flexure. Two phase III studies (SPD476-301 and SPD476-302) have shown that SPD476 2.4g/day (administered QD or twice daily [BID]) or 4.8g/day (administered QD) is effective and well tolerated for the induction of remission of mild-to-moderate UC. **Methods:** In this analysis, data from Studies SPD476-301 and SPD476-302 were combined to compare treatment responses for subjects with left-sided disease and subjects with extensive UC (including pancolitis or involvement of the transverse colon). Subjects with left-sided disease received SPD476 2.4g/day (given QD [SPD476-302] or BID [SPD476-301]; n=137), SPD476 4.8g/day (given QD; n=138) or placebo (n=129). Similarly, subjects with extensive disease received the same treatment (n=35, 35 and 42 for each treatment group, respectively). Subjects with proctitis only (inflammation ≤15cm from the anus) were excluded from the original studies. The percentage of subjects with left-sided or extensive disease achieving remission (UC-disease activity index of ≤1, with a rectal bleeding and stool frequency score of 0 and ≥1 point reduction in sigmoidoscopy score from baseline) following 8 weeks treatment with SPD476 2.4g/day or 4.8g/day was compared with placebo. **Results:** At week 8, a statistically significantly greater proportion of subjects with left-sided UC receiving SPD476 2.4g/day or 4.8g/day achieved remission compared with placebo (37.2% [p<0.001] and 33.3% [p=0.006] vs 18.6%). Similarly, statistically significantly more subjects with extensive UC receiving either dose of SPD476 achieved remission by week 8, compared with placebo (37.1% [p=0.034] and 42.9% [p=0.005] vs 14.3%). No correlation between disease location and treatment activity was observed. **Conclusions:** SPD476, a unique, high-strength formulation of 5-ASA utilizing MMX technology, is effective for the induction of remission of left-sided and more extensive UC at doses of 2.4g/day and 4.8g/day. Additional benefit should accrue from high-strength, once-daily dosing.

**226492: Allopurinol Favorably Affects Aza/6MP Metabolism by Lowering 6-MMP Levels in Patients with Hepatotoxicity from Aza/6MP Without Affecting Red Blood Cell Thiopurine Methyltransferase (TPMT) Activity.** *Purvi C Panchal, Charles J Zielman, Cynthia Schuhmacher, John F Valentine*

Background: 6-Mercaptopurine (6MP) and azathioprine (Aza) are metabolized to 6-thioguanine (6TGN), the putative therapeutic metabolite for the treatment of inflammatory bowel disease. However, many patients are unable to tolerate this class of medication secondary to high levels of the hepatotoxic metabolite, 6-methyl-mercaptopurine (6-MMP). 6MP is metabolized to 6MMP by TPMT and the activity of TPMT is genetically determined. We examined the effect of allopurinol on 6MMP levels and TPMT activity in patients who had hepatotoxicity on Aza or 6MP. Methods: 12 patients (9 with Crohn's disease, 3 with ulcerative colitis) who had elevated transaminases and toxic levels of 6-MMP while on 6-MP or AZA were treated with allopurinol 100mg per day and 6-MP (11) or Aza (1) at 25-30% of their hepatotoxic doses. Weekly liver function tests and complete blood counts were monitored for potential side effects such as hepatotoxicity, leukopenia, anemia, or thrombocytopenia. At four weeks from the initiation of allopurinol, 6-TGN and 6-MMP metabolite levels, and TPMT enzyme activity levels were determined (Prometheus Labs). Results: Complete data is available of 8 subjects and one additional pt is missing TPMT data. With concomitant use of allopurinol and a lower dose of 6-MP or Aza, the mean 6-TGN levels changed from 194 to 283 pM/8x10<sup>8</sup> RBCs (p< 0.04). The mean 6-MMP levels decreased from 21,143 to 598 pM/8x10<sup>8</sup> RBCs (P< 0.0002). There was no statistically significant change found in red cell TPMT activity. The mean TPMT activity prior to allopurinol was 30.42 EU and activity while on allopurinol was 32.39 EU (P=0.3). All patients liver profiles remained normal. Conclusions: In patients with demonstrated hepatotoxicity from 6MP or Aza, institution of low dose 6-MP or Aza along with allopurinol 100 mg/d was able to achieve therapeutic levels of the active metabolite, 6-TGN, while significantly decreasing 6-MMP, the hepatotoxic metabolite, to low or undetectable levels. All patients maintained normal liver profiles. These data confirm that IBD patients who have been unable to tolerate 6-MP or AZA secondary to hepatotoxicity, may now be able to resume 6MP or Aza at lower doses with allopurinol and effectively avoid the hepatotoxic side effects. Furthermore, the addition of allopurinol did not affect TPMT enzyme activity suggesting an alternative mechanism for allopurinol that remains to be determined.

**216019: Treatment of Chronic Refractory Pouchitis-A Controlled Study.** *Bo Shen, Feza Remzi, Bret Lashner, Ana Bennett, Aaron Brzezinski, Rocío Lopez, Jean-Paul Achkar, Ioannis Oikonomou, Kerry Sherman, Marlene Bambrick, Victor Fazio*

Management of chronic refractory pouchitis, one of the most common causes of pouch failure, is often challenging. AIM: to assess efficacy and safety of combined ciprofloxacin and tinidazole therapy in patients with chronic refractory pouchitis as compared with mesalamine therapy. METHODS: Two consecutive cohorts of ulcerative colitis patients with chronic refractory pouchitis (disease > 4 wks and failure to respond to ≥ 4 wks of single-antibiotic therapy) seen in the Pouchitis Clinic were assigned to receive a 4-wk course of ciprofloxacin 1gm/d and tinidazole 15mg/kg/d (N = 16) or a 4-wk course of oral (4gm/d), enema (8 gm/d) or suppository (1 gm/d) forms of mesalamines (N = 10). The Pouchitis Disease Activity Index (PDAI, range 0-18) scores, clinical remission (PDAI < 7), clinical response (reduction in PDAI ≥ 3), the Cleveland Global Quality of Life (CGQL, range 0-1), Irritable Bowel Syndrome-Quality of Life (IBS-QOL, range 34-170), and Short-Form Inflammatory Bowel 90

Disease Questionnaires (SF-IBDQ, range 0-70) scores were calculated pre- and post- therapy and compared between the 2 treatment groups. Adverse effects were documented. RESULTS: The demographic and baseline clinical, baseline PDAI and QOL scores were similar between the 2 groups. The 4-wk ciprofloxacin+tinidazole or mesalamine therapy resulted in significant reduction in PDAI scores, and the antibiotic therapy also led to a significant improvement in all QOL scores (Table). Patients in the antibiotic groups had a greater reduction of the PDAI score and a greater improvement in IBS-QOL and IBDQ scores than the mesalamine group (P < 0.03). The clinical remission and response rates were 88% and 88% for the antibiotic group; 50% and 50% for the mesalamine group (P = 0.07). Two patients in the antibiotic group developed adverse effects (peripheral neuropathy and dysgeusia) who were able to complete the trial, compared to none in the mesalamine group had adverse effects (P = 0.51). CONCLUSIONS: A combined ciprofloxacin and tinidazole therapy was generally well tolerated, was effective in treating patients with chronic refractory pouchitis by inducing remission, reducing disease activity scores and improving QOL scores, and appeared to be more efficacious than mesalamine therapy. The results support notion that chronic refractory pouchitis is of infectious etiology.

Factors	Antibiotic Group		Mesalamine Group	
	Statistics	P value	Statistics	P value
Reduced PDAI Score, mean (SD)	-7.0 (4.4)	<0.0001	-2.1 (2.2)	0.016
Improved CGQL Score, median (25th, 75th %)	0.2 (0.1, 0.3)	0.0002	0.1 (-0.1, 0.2)	0.12
Improved IBS-QOL Score, mean (SD)	-28.9 (30.5)	0.002	-4.3 (16.4)	0.43
Improved SF-IBDQ Score, mean (SD)	12.3 (10.3)	0.0003	4.4 (6.6)	0.064

**226976: An Open Label Pilot Trial of Rifaximin in the Treatment of Patients with Refractory Pouchitis.** *Asher Kornbluth, Michele Kissous-Hunt, James George, Peter Legnani*

Introduction: Patients who undergo the ileoanal anastomosis procedure for ulcerative colitis are at risk for the development of idiopathic inflammation of the pouch, termed pouchitis. This complication occurs in at least 50% of patients followed long-term. Although there is limited randomized controlled trial data for the use of the antibiotics metronidazole and ciprofloxacin, they are the mainstay of therapy for patients with pouchitis, with approximately 80-90% success rates. However about 5-10% of patients are either refractory to these medications or require chronic suppressive antibiotic therapy. Rifaximin is a nonabsorbable antibiotic with a broad range of coverage against small bowel intestinal flora. Objective: The aim of this study was to determine the safety and efficacy of rifaximin in the treatment of patients with refractory pouchitis. Methods: 16 patients who were refractory to all therapies including metronidazole, ciprofloxacin, and probiotic therapy with VSL-3, Lactobacillus, or Saccaromyces boullardi were treated with rifaximin; 6 of these patients had also failed treatment with budesonide 9 mg/day prior to rifaximin. Patients were treated with the addition of rifaximin in doses of 600-800 mg daily. The diagnosis of pouchitis was confirmed in all patients prior to starting rifaximin treatment with pouchoscopy, and severity was defined as moderate-severe using the Pouchitis Disease Activity Index. Results: 11 patients were treated with rifaximin 400 mg BID, and 5 patients were treated with 200 TID. 9 of 11 patients (82%) treated with 400 mg BID demonstrated significant clinical improvement and 4 of 5 patients (80%) treated with 200 mg TID demonstrated clinically significant improvement. There were no adverse effects of treatment, and all patients with clinical response improved within 3 weeks. All patients with previously medically refractory pouchitis who responded to rifaximin continued maintenance therapy with a mean dose of 400 mg/day and sustained clinical improvement during a mean follow up of 16 weeks. Conclusions: In this open-label series of 16 patients with medically refractory pouchitis, rifaximin in doses of 600-800 mg/day was effective in 81%, without toxicity, and was effective for maintenance for a mean of 4 months, with ongoing follow-up. Prospective randomized controlled trials are warranted to define the role of rifaximin in the management of patients with pouchitis

**215113: Autologous Hematopoietic Stem Cell Transplantation (HSCT) For Refractory Crohn's Disease (CD), 4 Year Follow Up** *Robert M Craig, Yu Oyama, Larissa Verda, Laisvyde Statkute, Krosnjar Nela, Kathleen Quigley, Richard Burt*

Purpose: HSCT is being studied in an effort to ascertain its value in inducing a clinical remission in severe CD. Methods: Patients with severe CD who have failed standard therapy (5-ASA, antibiotics, corticosteroids, immunosuppression, and infliximab), whose CDAI was > 250, were accessed for therapy. Stem cells were mobilized from the peripheral blood using cyclophosphamide (2.0 g/m<sup>2</sup>) and G-CSF (10 ug/kg/day), enriched ex vivo by CD34+ selection, and reinfused after immune conditioning with cyclophosphamide (200 mg/kg) and anti-thymocyte globulin (90 mg/kg). Clinical variables, small bowel radiography, colonoscopy and T-cell subsets were followed annually following the HSCT. Results: 19 subjects have undergone the therapy successfully. HSCT had no in-patient mortality, and was complicated only by 24-48 hours of culture negative fever. Usually, diarrhea and abdominal pain resolved prior to hospital discharge. Perianal fistulae and perianal disease were slower to resolve, but gradually improved over months to years. Abdominal masses and colonic strictures have resolved. Two patients had progression of their small intestinal strictures following the transplantation and required surgical resection, but their post-operative courses have been uneventful, and they continue to do well off all Crohn's disease medications. Three patients have

had major relapses, 2 at one year and 1 at 2 years, requiring re-institution of immunotherapy. One had a minor relapse at 1 year requiring re-institution of infliximab, promoting remission (which was ineffective pre-transplant). Following HSCT, a robust rise in CD4+CD25+(bright) T-cells was observed. There was a smaller rise in these T-cells in those who eventually relapsed. In most subjects, serum albumins, hemoglobins, weights, sedimentation rates, and CRPs have improved or normalized. The patient with the longest follow up, at 4 1/2 years post HSCT, remains in remission off all CD medication. Conclusion: This preliminary experience in the first 19 patients who have received this unique therapy continues to be encouraging, although 3 have had major recurrences of the disease. Induction of regulatory T-cells may be partially responsible for the salutary effect. A randomized study is in progress.