Transcript: Promacta ENABLE 1 Panel Discussion
November 7, 2011

JOHN HIGGINS:

Thank you everybody for joining us this evening. I'm John Higgins the CEO of Ligand Pharmaceuticals. I've met most of you. We are delighted to be here today in San Francisco at the liver meeting, joined Dr. Afdhal and Dr. Giannini, two important investigators in the ENABLE 1 and ENABLE 2 trials. This is a very important day for Ligand and for GSK. It's the first time most of the world is seeing the data. Much more data is out for ENABLE 1. But we also were pleased to see that GSK has released their initial preliminary top line data from ENABLE 2.

We have until about 7:00 with our panelists, so without further ado I'd like to introduce the program. Dr. Chris James, an analyst with MLV will be moderating the program. He'll have some introductory remarks and then have some questions and we'd like to make this interactive and really a casual session. Please, if you want more food or drinks help yourself, but this is a very important program for Ligand. We participated with GSK in the discovery effort in the late '90's and really are very pleased with the progress and their success to date. With that I'll turn it over to Chris, thank you.

CHRIS JAMES:

Thanks John. I'll try to be brief with the prepared remarks. Good evening and welcome to the Promacta ENABLE Data Panel hosted by Ligand Pharmaceuticals obviously. My name is Chris James. I'm an analyst at, at MLV; it's a relatively new boutique investment bank. I've been following Ligand actually for a few years now and the Promacta story which is a bit near and dear to my heart. I'll be moderating tonight. I'd like to emphasize that Ligand is one of my top pick stocks. I have a buy rating and it's a buy at $30 price target. And mostly as a result of the phenomenal leadership of John.

As you all know, Promacta is a drug that's extremely good at raising platelets. It was discovered by Ligand and GSK and back in the '90's and today it's commercialized by GSK. Ligand is receiving a significant royalty on sales. It was first approved for idiopathic thrombocytopenia purpura or ITP back in 2009 and it appears to be headed for about a run rate of about one hundred million in annual sales in 2011. GSK has made it very clear from the beginning that there will be multiple patient populations where Promacta could be used to alleviate thrombocytopenia. And today we're here to talk about the data obviously and the ENABLE study, the second indication to seek approval and this is a Hep C related thrombocytopenia

So as you all know, this afternoon we had the late breaking session with Dr. Nezam Afdhal, who I've spoken to and hosted a call with back in September. He presented the first release of the data, the Phase III studies, and it was a packed audience. I think it

went really well. The studies were run over 3 years. They examined Promacta and Hep C with an underlying Thrombocytopenia to not only initiate anti-viral therapies but to achieve Sustained Viral Response or SVR, which as you all know is the primary end point.

But at this point, I'm going to stop talking and let the experts do that for you. Tonight we have two principal investigators as you know, Dr. Afdhal he's the Chief Hepatologist at Beth Israel Deaconess and Dr. Edoardo Giannini, from the, hopefully that's right, at the University of Genoa in Italy. Both of these gentlemen are highly recognized by their peers in the area of hepatology. And are major thought leaders in thrombocytopenia. Both understand Promacta extraordinarily well and its role in alleviating thrombocytopenia, so we really couldn't ask for two better experts to take your questions.

So with that, let's get the program started. Dr. Afdhal, could you start us off with the review of the data? He'll start with it, and then afterwards, I'll start with a few questions of my own and then get the audience involved. And hopefully we'll have a great interactive discussion. With that, let's get started.

NEZAM AFDHAL:

Thanks Chris. Okay, I don't want to go in great detail over what we presented, but I want to point out things that it's impossible to discuss in 10 minutes. You know, you have to present 3 years of work and actually 8 years we've been involved in developing this for liver disease, and you have 10 minutes. I went 11.5 minutes and the lights were flashing quite a bit.

So, the first thing is that this is the first ever trial undertaken in this population. And it's the first ever trial of this magnitude undertaken in this population. And traditionally, you can't get into any type of trial if your platelet count is less than 75,000. Usually the cut off is actually 90,000, in many cases it's 100,000. And the patients that are enrolled in this study are all people with significantly advanced liver disease and portal hypertension. So they have developed already the first major complication of cirrhosis, which is portal hypertension. So this is the population that was studied in both ENABLE 1 and ENABLE 2, so the information that we get from this, from our perspective, is phenomenal because this is an opportunity to look at how patients with advanced liver disease respond to interferon based treatments.

The second thing that's worth understanding is that the study design has built into it multiple points at which we evaluate patients for safety. As you know, the study design has first of all a completely open label phase where patients get Promacta to raise the platelet count. Promacta was phenomenal at doing this, 95% of patients in this trial were able to enter the second phase, which was the interferon treatment phase.

During the open label phase there are no thrombotic events. Nothing, happens. The platelet counts go up and they go up significantly, and nothing bad happens. For those of you who remember our presentation at ELEVATE, the procedure study, that's a completely different study. It's actually a sicker population, but it's different because you do something to the patients. But here patient's platelets go up nice and high nothing

happens. The second phase starts, which basically is a withdrawal phase of Promacta in a third of the patients and then the other two thirds go on to stay on Promacta and they all go on Alpha 2A and ribavirin.

At every time point in the study the patients are evaluated for thrombotic events. They start off with a baseline ultrasound. And we have all of this data, which we haven't even looked at even for ENABLE 1. Ultrasounds with Doppler's, flow rates, everything that you do to evaluate people's portal and splanchnic circulation. Then every six months, irregardless of what's happening to them, they have another ultrasound that's done to look at the portal vein, the portal blood flow etc., etc. until the end of the trial.

The trial goes on for either 24 or 48 weeks and then we follow them for another 24 weeks. The patient's involvement in the trial is somewhere around the range of 20 months. So during that time period, patients are followed and anybody that's in the trial, if any events happen to them during that time point it's captured. They may or may not be on treatment. Many events occur off treatment. Because you're following sick patients for a long period of time, alright? The open label phase is phenomenally successful, 95% of patients go on treatment, stopping at very low doses of Promacta it's not difficult to get the platelets up in these patients. It didn't take a lot of treatment.

They then go on and they go on to treatment. The primary end point for successful completion of the study is SVR, the primary end point is completely met. They, in both trials and I showed you the ENABLE to date as well, overwhelmingly at every time point the primary end point is met. So if you're looking to say did the study hit its target primary end points the answer is, yes emphatically and without doubt for both, for both drugs. So there is no doubt about the efficacy. Alright? None, whatsoever. It hits its endpoint because it does what it's supposed to do, keeps the platelet count high. If you look at this slide, the important thing to look at is the number of patients that are on treatment. There are many, many more patients on treatment Eltrombopag throughout the study than there are on the placebo. The reason for that is the placebo patients drop out of treatment because they either can't stay on because their platelets are too low or they fail to have a biological response because they're not getting enough interferon, alright?

And so the Eltrombopag patients get significantly longer treatment. This is important because one of the side affects that occurs during treatment is an increase in liver related events. And it's proportional to the exposure of interferon the patients get. So have you to understand that the patients on Eltrombopag are more at risk because they're on treatment longer. It works, they don't have to reduce the interferon. And we show very nicely that it works. You don't have to reduce it.

The adverse event profile, when you look at it by a standard table of adverse events it's totally similar, there's no difference here, alright? There's no difference in any AE, any SE, any fatal AE any drug related AE, any AE leading to medication discontinuation or withdrawal. So the AE profile, if you're to look at it, is exactly the same in the two arms. And the adverse events that we're talking about are interferon adverse events. Alright? They're what people get on interferon, if you don't know interferon there's nothing on this slide that doesn't occur on every single slide that you see in patients on interferon. This is the special interest adverse events alright? Of course thromboembolic events

are special interest to us for two reasons. One, it is a recognized side affect of Eltrombopag, and it's reported in their label, a 1 to 2% increase in thromboembolic events. So we know that it's there. Two, we had ELEVATE, which is a very different study, but in which we saw an increase in thrombotic events, it's a minimal increase it's six in one arm versus two in the other. But it was enough to make us worry because these were highly symptomatic thrombotic events. So in other words patients had portal vein and (inaudible) vein thrombosis that resulted in liver failure, and bad outcomes and all sorts of things. So we were well aware of this and so was the DSMB and this is the overall thing. There is no different, alright? There is truly no difference. If you wish to see the individual thromboembolic events, I didn't show them at the meeting because they were in the backup slide deck, but I can happily show you what type of events they were.

The issue with progressive liver disease events was related to the fact that they're on interferon longer. These are adjudicated by a special panel that sees no difference in the outcome. The liver parameters for safety throughout the study are identical. I said this in the presentation, INR, bilirubin, albumen, are all the same across both study groups, at the end of the study the, the (inaudible) score, the CPT score, and all of the parameters of liver disease are the same, for those people that were on Eltrombopag versus those that are on placebo. So we don't see anything there. We do see more cataracts. Alright? There is an increase in cataracts, again a special interest for these patients.

The ENABLE two results, exactly the same profile. This we know because this is what you get first out of the printout. This data appeared with GSK about 3 or 4 weeks ago and they, in discussion with me we decided that we would present this data. It's not usual to present a second study at the time you're presenting a first study, but it was decided to do this predominantly not just to show that it works just as well, but predominantly for the safety reasons and the safety reasons are because we have not evaluated all of the thrombotic or thromboembolic events which are imbalanced and we'll go through that imbalance in a second. And the last thing that we want to do is have everybody leave the conference today where there's 5000 people listening to you, to go back and put people on eltrombopag where we don't have the entire data.

And you know, as you know this drug is available on the market and there are already people using it. Not just in the U.S. but in Europe for this indication. And we did not want to appear in any way to say oh, our results show that it's okay and safe to go out there and use it, which could have been interpreted by the audience when they saw the results of ENABLE 1. The difference in thrombotic and thromboembolic events is real here. What is really unusual is there is none in the placebo. This is extremely unusual alright? We've seen in all of these studies about a 2% rate. Cirrhosis is a pro-thrombotic disease state. So we find that unusual. We're seeing a slightly higher rate in the patients on eltrombopag.

I cannot show you because I do not know the full details of all of the thromboembolic events in ENABLE 2, but I can show you the backup table for the presentation of thromboembolic events in ENABLE 1. Alright? As you can see, there's only one severe fatal event on placebo, which I mentioned is a patient with liver cancer that invaded the portal vein. The rest of the events that you see here are not in any way particularly of

any major branch or any, any particular pattern. They are the typical types of things you see in a sick population. The retinal vein thrombosis occur because we do eye exams every 6 months, these are not blindness, these are transient retinal vein thrombosis.

The DVT, we have one, we have a stroke, we have portal vein thrombosis that's well balanced between the two arms. All of it except for the patient with cancer was detected by ultrasound screening, alright? These patients didn't present with portal vein thrombosis because we screen them with ultrasound, we see them. You can see the platelet counts, the platelet counts have no relationship to these events. These are not related to very high platelet counts.

Dr. Giannini did the analysis for ELEVATE and showed that the risk of thrombosis was proportional to the platelet count. I can't show you anything for ENABLE 2, but the pattern as far as I've seen it is very similar to this, alright? So this slide can be shown because it's a backup for our presentation.

So that is the status of how we observe this. The issue that faces us is, really, what is the benefit and the benefit is clear. We were able to significantly increase the chance of sick patients who would otherwise need transplantation to have a response to interferon, get cured of Hepatitis C.

In ENABLE 1 there is no safety signal, none whatsoever. In ENABLE 2, there is a preliminary safety signal that requires further evaluation. But I, and I really cannot comment any further because I don't know. I'll stop there. I'll ask Edoardo to make any comments he wants to make. And then we'll happily answer the, your questions to the best of our ability.

EDOARDO GIANNINI:

Thank you. I agree with him too, are the most important things regarding this study. The first one is that the study allowed the majority of patients, 95% of the patients who otherwise might have not been treated with anti-viral therapy to be treated, (inaudible) treated with anti-viral therapy. The other option was to sit and wait for these patients to develop disease because these patients might not be treated by their physicians. And that 88% of the patients were able to do so within 4 weeks of starting Eltrombopag so in a very, very rapid time.

And the other point is that as the primary end point of the study stated that the use of Eltrombopag was able to decrease the need for interferon reduction, that's allowing the patients to maintain full dose or at least to have a lower number of dose reduction throughout the whole study and this allowed to reach a greater SVR, as compared to patients on placebo.

And commenting on the SRV rate, the SRV rates are those expected in a sick population's patients with liver cirrhosis. And these SVR rates are comparable to those obtained in patients with advanced liver disease, although we have to say there is no benchmark because studies of this kind with patients with advanced liver disease have never been performed, studies with patients with so very low platelet count. So this is really the largest study, which has been performed as of today in this kind of population.

CHRIS JAMES:

Great, great. I'll start with a few questions. I think before we get into the thrombotic events, I think everyone is going to be, you know, the focus is quickly going to go there. What are your thoughts maybe both of you, oh, and great presentation by the way, on the risk benefit profile of Promacta as a treatment for Hep C, related thrombocytopenia and you know now that the data is out and, and….

NEZAM AFDHAL:

You know, look, you can't ever look at anything in isolation, alright? So this study was commenced at the time where there standard of care was interferon and ribavirin. The standard of care is now ribavirin, interferon, and for most of the world, Vertex's drug, telaprevir. People have done studies in populations better than this, you know, better, high platelets.

There's a huge study from France called the Cupid Study, where cirrhotic patients are enrolled in this. The rate of significant Thrombocytopenia is 25%. And patients are having to stop treatment because of this. The need for this drug is created today because in fact we're treating significantly more people and we're treating people with drugs that cause significantly more Thrombocytopenia. And we're failing because we have to stop those drugs. And we have to stop the use of these drugs and, and there is no doubt that in Vertex or telaprevir causes a worsening of Thrombocytopenia in these patients. So is there a need for this agent today? Yes.

And, and part of this is that this need has become more recognized hence, our conservatism in pointing out the fact that you shouldn't just rush off and use Eltrombopag until it's approved and, and approved for this patient population and that's what we want to wait for. We made this mistake 10 years ago. And I was the culprit, when we did the original Procrit study. And we showed the value of Procrit and ribavirin induced anemia. And we created a 100 million dollar market for Procrit based on one study that I did back in the 1990's and never did it get registered, they just took the benefits of that study and used it to use Procrit throughout treatment of Hep C.

The whole purpose of this is to make sure that, that risk benefit is favorable. Right now it looks favorable to me and we need to put this into perspective and, and see how it moves forward as we get more data from ENABLE 2. But I think that the need is great now. And I think that the benefit is clearly shown.

EDOARDO GIANNINI:

Physicians are getting more and more experienced in treating patients with the more advance disease and also the use of drugs of like ENABLE to reach a greater level, so that might help you to cure more patients. And increasing the number of patients that might be treated. Especially patients with more advanced disease. And also in this patient population, Thrombocytopenia is an issue, it may even be more an issue if you use a new drugs.

And interferon is still the backbone of the new treatment algorithm so we still have to deal with this fact. And that when you take into account the, the efficacy and safety of a drug, you also have to take into account what may be the other options for this patients? Because the majority of patients, I should say all the patients, included in this trial might have not been treated anyway with any anti-viral therapy. So you have a population which isn't able to be treated, who isn't able to reach an SVR. And as a proxy of SVR, we all do know very well that reaching SVR lets the patients have a substantial decrease in liver related events in the future, a decrease in liver related mortality and also significant decrease in the development of hepatocellular carcinoma.

So on the one hand, you are enabling patients to have a better future. On the other hand, if you don't have this drug and you're not able to treat these patients, you just have to wait and monitor the patients during time, waiting for something.

CHRIS JAMES:

And as a follow up do you, do you in your opinion, do you think these data support oh GSK's filing of supplemental NDA and Hep C related thrombocytopenia?

NEZAM AFDHAL:

You know we're just investigators. We're not GSK. You know? We can give an opinion to GSK as to the risk benefit of these agents. And you know right now, I would personally believe that the benefit outweighs the risk with the understanding that there is a risk of thrombotic events that is known with this treatment. And it will have to, like all treatments like this, have a plan in place.

We have, we currently have Procrit which has an increased risk of thrombotic events and, and it has a plan in place for its use. But we're not GSK and you know we can't say you know we're going to, we say you have to go and apply this. I personally think that you know having shown the benefit of this agent I would, I would very much hope that we can use this in our patients so long as we prove that there is safety and as I said this data is preliminary. And you know we need to explore it fully.

CHRIS JAMES:

Let me sneak in two more questions. The placebo, the so-called placebo arm is a bit deceiving. What are your thoughts on the placebo rate versus the SVR because theoretically the placebo rate should be zero because these patients would not have been on therapy so….

NEZAM AFDHAL:

So here's the answer. If you look over here on the panel that says RVR, it's 17%. Those are people that wouldn't have been able to get on treatment. But the Promacta has allowed them to get on treatment. Once you have RVR, you're chances of cure are phenomenal. No matter how little or how much you get. When you pull this RVR group out, we haven't done this yet but obviously we will do this, you'll see that the 14% that have SVR are predominantly the 17% who are exquisitely interferon sensitive who have

RVR. So what you're actually doing is it's not really a placebo. It's really, it's a hangover affect.

So that hangover affect is letting those really sensitive, easy to treat patients get started and they're the ones that end up probably getting cured. So, so I think that it's not really placebo but it's the only way you can design a study like this fairly is by doing this type of withdrawal design. And this was done after significant discussions with the FDA, as to what's the best approach for this type of agent. You know in the first study we did, we had one arm that got placebo right off the bat. And the other arm got Promacta. And guess what? Nobody on the placebo arm ever got started on interferon, so the response rate was zero. So you can't do that, it's so biased. It's impossible you know? So you know the withdrawal design had to be put into place. And there is a benefit and thank God there is, because you know we're able to at least help some of the people on that arm as well.

CHRIS JAMES:

Sure.

EDOARDO GIANNINI:

Because you were able to increase the platelet count in these patients and you were able to test the sensitivity to anti-viral therapy. Because there's a sort of a carry on affect, RVR is the first 4 weeks of treatment so you still have a carry on affect of the Eltrombopag which has been given to the subjects and within that month you're able to test the sensitivity to anti-viral therapy. You select the population who is sensitive and was likely to go on and data and the numbers are similar.

CHRIS JAMES:

Okay. And one final, GSK CEO Andrew Witty made comments about the plans for CLD. And we spoke about that I think in the past. What are you thoughts on the future of a CLD study based off of the thromboembolic events that you've seen now in ENABLE 2?

NEZAM AFDHAL:

By CLD, do you mean a study like ELEVATE? Or what?

CHRIS JAMES:

Like ELEVATE, yeah.

NEZAM AFDHAL:

Yeah. So, so you know, as, as a hepatologist who treats patients with advanced liver disease I still think that there is a tremendous role for an agent in that area to elevate platelets to allow procedures to be done safely. The initial study design had flaws in the height of platelets at which the procedures were done because it was done in conservative fashion. And my hope is that GSK, or in fact, I'm not even fussy about

GSK, that somebody else who has a platelet analog will go forward and explore other ways to use these type of agents in the population. Because again, there is an unmet need to do this. So I hope that we can figure this out. And learn from the ELEVATE trial as to exactly what our goals should be.

CHRIS JAMES:

Okay let's open it up. Questions?

CHRIS RICHARD:

Yes, just a follow up on Chris's question. What would be your ELEVATE 2 design? The ideal kind of, what sort of patients? What sort of steps would you put in place to limit thromboembolic events?

NEZAM AFDHAL:

So the biology of Eltrombopag, or the pharmacokinetics of it, is such that in cirrhosis patients there is a period of time in which the platelets continue to go up. So in a conservative fashion, not knowing what was going to happen, it was a 2 week treatment period and then a procedure within 3 days of that period, actually it should have been a much tighter titration. What should happen is probably a week of treatment, and then wait 4 or 5 days and when the platelet count hits the exact level you want then you do the procedure that you want to do.

And since these are elective procedures there's no reason why you can't do that and, and as I said, Edoardo showed very, very nicely and hopefully we'll have this paper in press very soon that the platelet cut off that predisposed in this, in the ELEVATE study to thromboembolic events was 200. And we did raise platelets that high in some patients and did the procedure and it's a two-prong thing. Platelets can be 200, and if you do no procedure nothing happens. But when you do the procedure you're inside the endothelium you're, you're actually disturbing, you're setting up inflammation. And what does inflammation do? It brings in platelets. And what do platelets do when they come to inflammation? They activate and they clot. And so you know it's a two pronged type of event. Having said that you know cirrhosis is pro-thrombotic to a major degree. So you look at cirrhosis, it's a pro-thrombotic state, interferon is also associated with increase thromboembolic events so you know we're not dealing with easy, easy populations. Alright? We're dealing with tough populations.

CHRIS JAMES:

Keep going. Behind you.

MALE:

Given the way the safety data has come out, does that change at all the next steps for GSK or, or for this drug in terms of getting FDA approval?

NEZAM AFDHAL:

So I'm not GSK but as an investigator, I can tell you right off the bat what it does for us, is it does what we did for ENABLE 1. We sit down, we evaluate the data, we look at it with our statistician colleagues at GSK and we look at all of the events and put together all the announcements, which we already planned. You know? Again this data is so new, it's new to us. You know?

We as investigators have had the opportunity to look only at the top line data on ENABLE 2 and then make recommendations of how we would like to have it analyzed to look for various things. And there are many things that we want to have analyzed out of this data and until that's done, the ENABLE 2 study is still a black box. And that won't come out until I'm sure the next big liver meeting when we'll be able, we'll hopefully have the data before that. But we'll hopefully be able to present it at the next, next big liver meeting. But it, it takes time to get the information that you want here. And we've only, we haven't even fully interrogated the ENABLE 1 data. So what we presented we're very comfortable about for ENABLE 1. What we showed for ENABLE 2 is truly the word preliminary is in there.

MALE:

There seemed also to be a higher, at least numerically higher rate of hepatic decomposition (inaudible) you see in deaths, in the Eltrombopag arm, were those related to the higher thrombotic events?

NEZAM AFDHAL:

No. The, as I said in ENABLE 1, where we have the information, the only thrombotic events to death were the placebo arm, the thrombotic events in the Eltrombopag arm were found on ultrasound and completely asymptomatic. This population has an expected event rate of somewhere between 5 and up to 9% per year,that is the expected event rate. So if you follow a population of patients with cirrhosis and portal hypertension, you can go look this up, look up the (inaudible) trial, the Halsey trial, the (inaudible) trial. Those patients who have portal hypertension have an expected event rate somewhere around that level. The event rate that we see is totally consistent with what we would expect. Events are adjudicated by a panel. The panel looks at every event. In the beginning on ENABLE 1, the event rate was significantly higher than the event rate eventually turned out to be because when it was adjudicated it was felt that these things in the case report form were felt to be events were absolute non-events. So we have to have, we have a panel that's designed in the study to adjudicate this so the number of events is not going to be the same, alright? When it's all said and done, that's just how these trials work.

EDOARDO GIANNINI:

And a very important thing that needs said is that the end of a study, the parameters suggestive of liver function, (inaudible) score and the child-pugh score, which are parameters used to evaluate the severity of liver disease, are the same in both groups.

VAN BRADY:

Yeah, excuse me. Chris suggests in the report that was handed out is a presentation that Eltrombopag could eventually be used by 7% of the 5 million Hep C patients. I just wondered if either of you would care to comment on that?

NEZAM AFDHAL:

I will comment in the most honest fashion I can. The Hepatitis C marketplace is a very dynamic and moving marketplace. What we're talking about today may have an extremely different relevance in 5 or 7 years time. And I think that saying that something will be used by 7% of the Hepatitis C population is a premature estimation by anybody's guess. Eltrombopag has a role in the patient population that we're describing which is a significant proportion and a growing proportion of people with Hep C related liver disease and it has, and it has hopefully if approved, a role in this population. But I don't think we can make, we can support anybody saying it's going to be used in 7% of HCV patients.

MALE:

How much would the eltrombopag treatment add to the cost of treating one of these patients on average?

NEZAM AFDHAL:

Great question. So I don't know if you know what the cost of Hep C treatment is now, it's a bucket load. The addition of Telapavir $52,000 for 12 weeks of treatment is highly significant. My understanding is that Eltrombopag in the U.S. is about $700, correct me if I'm wrong, for a week a treatment. Am I right or wrong on that one?

ROB MCKAY:

I'm doing the math real quick, keep talking.

NEZAM AFDHAL:

Okay.

JOHN HIGGINS:

That's about right.

NEZAM AFDHAL: That's about right. So, so significantly less than the amount of Procrit, Neupogen, Incivek, Interferon that we use. And again what you have to realize is there's that, a lot of what you see in the Hep C space is, is marketing. So you have these studies that have phenomenally high response rates and cure rates with the new drugs that are treating people that are essentially completely well, they're not sick. Alright? These people are sick. And the rate of decompensation of 9% per year that means that most of them will either be dead within 3 years or need a liver transplant within 3 years. Therefore what you're doing is you're effectively you get the biggest

bang for you buck for every one of these patients. One of these patients cured in a pharmacoeconomic sense of the word, is worth significantly more than the patients that we're actually curing today, alright? And that's why everybody wants to go get into this population but nobody to date has. Now if we have better, safer drugs we can get into there safer, fantastic. But right now, not one of these patients, not one patient out of this 1600 has ever been on Incivek or teleprevir or any of these drugs.

And the French studies which are putting people that are a little bit better than this, but still sick, they're showing horrendous side affects of these drugs. 25% thrombocytopenia less than 50,000. 42% use of Procrit. 17% of blood transfusion, death and decompensation. So the reality is that you know as you, as you treat the people that need treatment, you pay the price for that with, with your side affects. And Merck launch Incivek and Merck never touched these patients because they didn't want to deal with this.

So if I was to say anything of great value, it's the fact that as a company GSK recognized that this a group of patients with a significant unmet need and wanted to go in there and do something. So I've been involved in this program for 8 years and actually sat down and developed this with John McHutchison and GSK. And I, take my hat off to the fact that they've stuck with this program.

A BERGMAN:

Are these patients appropriate for these drugs?

NEZAM AFDHAL:

They have never been used in these patients. Can they be used? I sincerely hope so. When will we get to them? Very late. You know, you know we're 7 years into the Incivek program. And the incivek and victrelis programs, we started those. I was involved in the phase 1 trial 6 years ago. Not a single patient like this has ever been on treatment. So it just shows you that, that, we develop drugs in a very, very different way to what we actually need drugs to be used for. Alright?

EDOARDO GIANNINI:

And thrombocytopenia might be an obstacle (inaudible) used for an example in Italy we have a planned patient program for the years of (inaudible). That puts 100,000 limit of platelets for the patient to be treated, so the majority of patients were in the need of incivek therapy were sent away. Because of thrombocytopenia.

NEZAM AFDHAL:

So the French are a little bit more liberal. They, they're allowing them in up to 75 I think. But you know they're still, they're still even with the new drugs which are better, you know. You know this picture here, 23 and 14, look at the 23, if you had, if you had Incivek in there or boceprevir safely, it would be 48. Because the relapse rate, the end of treatment response is 48. What these drugs do is they prevent relapse so you would actually be potentially curing half of the patients instead of a quarter of the patients.

You know and this study was obviously designed before those drugs were there, you know?

So I, I think of this as, I think of this in terms of what we can do as a great opportunity. But again, I stress that you know we have to interrogate the safety issues that suddenly appeared out of ENABLE 2, alright? I'm not going to back down on that statement as a investigator, we will be looking at this. And we will be looking at this alright? You know it's not GSK that looks at this, we will be looking at this. We will be getting the data and doing the analysis and seeing what we want to see. Alright?

MALE:

I guess if you could just comment on how these events were treated? I know you mentioned that there….

NEZAM AFDHAL:

That's a great question. Half of them weren't treated and resolved on their own and then some were treated with anti-coagulation and resolved. So let me talk a little bit about what portal vein thrombosis is and what happens when you get it. Now, I'm not including in here the DVT's that occurred and the strokes and the stuff like that. Those thromboembolic events have a, have a life of their own. I'm talking about the one specific to liver disease, alright? So this is the splanchnic events. Alright?

So if you follow a population of cirrhotic patients and we do this all the time, it's part of standard of care. They have an ultrasound for liver cancer every 6 months and a Doppler to look at the portal vein. You pick up what are called partial portal vein thrombosis. The flow in the portal vein is really slow, it's slower than through your leg veins. And when you get cirrhosis the flow is turbulent it goes backwards, alright? And that, that agitation of flow leads to a very low flow rate that results in transient clots.

And whenever we see these we use anti-coagulants for anywhere from as little as 6 weeks to 3 months and we, the clots usually disappear and then you follow the patients, and then if you have to, they get another one a year later, you do the same thing. Sometimes we do nothing and the clots disappear on their own. Occasionally a patient has a major thrombosis and that presents with symptoms. That's what happened in ELEVATE. A big vein goes and the patient comes in, he's yellow, sick, and all this type of stuff. And that's a major portal vein thrombosis. So when you're monitoring people over time you will see this. We saw four portal vein thrombosis on Eltrombopag. That's four out of 600 patients. Actually all together we saw six if you include the placebo or seven if you include the placebo. That's a less than 1% rate. The reported rate of portal vein thrombosis is between 1 and 2% in people with cirrhosis and portal hypertension. I mean there's nothing, we're not pulling the wool over your eyes, there is nothing out of the ordinary here. There's a disconnect between what was seen in the Eltrombopag arm in ENABLE 2 and what was seen in the placebo, this has to be evaluated.

MALE:

These were, this was an incidental finding?

NEZAM AFDHAL:

In ENABLE 1….

MALE:

Asymptomatic?

NEZAM ADFHAL:

In ENABLE 1 they were found by ultra-sonographic techniques.

CHRIS JAMES:

Were these patients on aspirin or sub-q Heparin?

ADFHAL:

These patients are on, these patients are on many pro-thrombogenic drugs. Some of them are on (inaudible), some of them, most of them are on beta-blockers that slow the blood rate. Look, these are not you and me and healthy people, they are very sick people and they are prone to these type of events. And the only thing that's obvious here and is a definite thing that we have to interrogate, and is a safety signal that I completely agree with, the data we presented this because it was, it was, the decision was mine to present this, not GSK's. This is our presentation. And I totally agreed we should do this. There is a higher number of these events in ENABLE 2 on Eltrombopag than on placebo. And until that is evaluated fully that is a signal that requires full evaluation. That's it.

CHRIS JAMES:

Do they get a filter?

NEZAM ADFHAL:

Oh no, no. They don't have any filters, no, no, nothing happens to these things, this is, this is, the (inaudible) you can't put any filters and you can't do anything like that. You can give anti-coagulants and that's it really. Yeah. Don't be shy, you can ask other questions.

MALE:

I saw two, so between ENABLE 1 and ENABLE 2 there are two things that stick out that are different. Alpha 2A and Alpha 2B and then 90K versus 100K. Are you, could that have contributed to any of these differences in AEs?

NEZAM ADFHAL: Okay, so if we, if we see an imbalance in the platelet count between ENABLE 1 and ENABLE 2 in patients who have thrombotic events. We do

know that Alpha 2A from ENABLE 1 that's Pegasus is a more potent bone marrow suppressor, drops the platelets lower than does Peg-intron. The first thing you see when you see this is, oh my God, this is a Peg-intron effect, your Peg-intron wasn't dropping the platelets down low enough, all these guys have high, high platelets and that's the cause of the thrombosis. That is, this is not the case. Alright?

So, you know it's not the cause of the thrombosis. And so it can, it requires a much greater in depth analysis to figure out what is, what is going on and why there is an imbalance. The first part of the imbalance is why did the placebo group do so well? I mean that's the first part. You know the placebo event is one left branch retinal vein incidental thrombosis (inaudible) ophthalmology. Now that just doesn't make sense. You look at ENABLE 1 and there's a bucket load of thrombotic events in the placebo arm. So you know we saw today right after my presentation Mike Freid stood up and gave the, the, the data for the Pilar trial. In that trial, they had the highest ever reported rate of placebo response to interferon therapy was 65%. It was actually 22% greater than any other trial as reported. Anybody, would tell him there's something wrong with this trial? No, because these things happen. What we have to do is figure out what actually is going on. And it takes time guys, it takes a lot of time and it takes priority, and we're hopefully prioritizing this.

MALE:

You mentioned the addition of the protease inhibitors, Telapavir, Boceprevir hopefully being part of therapy. What overlapping toxicity would you be worried about theoretically between promacta and the PI's, and then the second question is what, how much data would you need to see on the co-administration of promacta and the PI's plus Promacta before you were comfortable using that quad therapy in, in practice?

NEZAM ADFHAL:

You would certainly want to see drug, drug interaction studies, although they don't go through the same metabolic path but you'd still want to see it, as safety drug, drug interaction study for both of those drugs with Eltrombopag, alright? I don't think you need to do a huge trial. I mean the side affect is caused predominantly by interferon and it's exacerbated particularly by Incivek but I don't think you have to do a trial to this. You know just like, just like the approval is, is, is for the treatment of interferon induced Thrombocytopenia that's what you go for, that's the label for utilization, alright? And so interferon induced can be interferon plus something else. It doesn't have to necessarily be (inaudible) but I'm not a regulator, that's just how I would view this utilization.

And, you know there are people using Promacta off label right now. You know? And, and you know, we have a response, we have a responsibility as investigators to make sure that people don't do what is wrong. And, and you know where that is a big part of why we show this data. We, we want it to be transparent and safe for our patients. Alright?

MALE:

So we have no sense right now for those 22 patients what the grade of severity (inaudible)?

NEZAM ADFHAL:

We do not.

MALE:

Can I follow up on the previous question? What incremental increase in SVR could you expect with the addition of Promacta to one of the newer DAA's?

NEZAM ADFHAL:

The incremental increase is infinity because the current use is zero.

MALE:

Is zero.

NEZAM ADFHAL:

So if the SVR is zero it's infinity but would we get 75% SVR? No. But could we get 50% of these patients cured? I think so, do you think so Edoardo?

EDOARDO GIANNINI:

Yeah it's quite difficult to provide an answer because these kind of population has ever been treated with triple anti-viral therapy. So there is no benchmark to, to, to counteract the proposal.

MALE:

They already showed today that more fibrosis the lower the SVR rate.

NEZAM ADFHAL:

Oh that's significant. Oh. Yeah that's significant.

MALE:

These weren't these patients that you're talking about here, are actually more ill and have more fibrosis.

NEZAM ADFHAL:

Yeah but did you figure out why that is? It's because it's, it's because, not because they don't have anti-viral efficacy of the drug. It's because they keep having to reduce the drugs because of things like Thrombocytopenia. If 25% of your patients fall to below 50,000 in a trial you are obligated to discontinue treatment. So they have stop rules. So you can't cure somebody if you can't give them medicine.

Promacta doesn't cure Hepatitis C, alright? Promacta enables the current drugs that we use to cure Hepatitis C. That's what we showed. The end of, the end point of the study is that Promacta helps interferon ribavirin therapy cure Hep C. That was shown across both trials. Now as I said we need to further explore the safety.

CHRIS JAMES:

One more question.

MALE:

Okay. A lot of talk about interferon free, where does Promacta fit in, in the future of oral non-interferon based therapies?

NEZAM ADFHAL:

So we haven't seen a lot of Thrombocytopenia with the interferon free therapies. Not one of these combination trials have you seen anybody stand up and show this. In fact the data yesterday from Pharmasset studies specifically pointed out the lack of hematological side affects of combination of PSI9779 plus ribavirin. So we, we could be in a world I don't know how long it's going to take us to get there, where we no longer in any major way need interferon. But that world is quite a ways away. Alright?

A. BERGMAN:

What about interferon lambda? The claim that (inaudible).

NEZAM ADFHAL:

So interferon lambda has to go through the whole evaluation process. It's, it's, the length of time it will take to get interferon lambda through the whole process with the new drugs that are coming out, is about the same time is it will take to get the new oral drugs out. You know? I wouldn't have paid 80 bucks for interferon lambda, not 800 million.

MALE:

Okay.

CHRIS JAMES:

Okay let's wrap it up. I have just one more, you said no relationship between platelet count. Could Promacta be making platelets more active?

NEZAM ADFHAL:

There's not a lot of evidence that, that is in fact true. That you know, that's what, that, that's what happened here. You know the diversity of the thro- you know I showed you the thrombotic events in ENABLE 1 because that's all I have. And, and, and the diversity of the thrombotic events the fact that they were in multiple different areas

suggest that it's, it's, it's more than just you know, oh, that that's taking place. You know whether these people they get this, or predisposed to this or not, I don't know the answer to that either. Again I personally think that, that if we had seen the expected 2% of thrombotic events in the placebo arm we wouldn't be having this conversation. You know?

EDOARDO GIANNINI:

Furthermore there are some experimental data showing that Promacta increases platelets, but it did not activate them.

NEZAM ADFHAL:

Yeah.

CHRIS JAMES:

Well thank you, I think the earnings call is tomorrow so we'll, we'll all be on that and maybe have some more questions.

NEZAM ADFHAL:

I have to go. And I'm going to be in major trouble.

CHRIS JAMES:

Thank you. I'd like to thank again Dr. Afdhal and Dr. Giannini. Really appreciate your patience with the studies and excellent work with GSK. Thanks for all of our attendees. Management will be around for about a half an hour or so, so please enjoy yourselves in reception. Thank you.

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