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KOL Call on NASH, hosted by Altimmune

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PRESENTATION

Operator:

Greetings. Welcome to the Altimmune Incorporated Key Opinion Leader Call on Alt-801 for the Treatment of NASH. At this time, all participants are in a listen-only mode. A question-answer session will follow the formal presentation. If anyone should require operator assistance during the conference, please press star, zero on your telephone keypad. Please note, this conference is being recorded.

I will now turn the conference over to your host Monique Kosse with LifeSci Advisors. Ms Kosse, you may begin.

Monique Kosse:

Thank you Operator, and thank you everyone for participating in today's Key Opinion Leader Call on Alt-801 for the Treatment of NASH. Leading the call today will be Dr. Vipin K Garg, Chief Executive Officer; Dr. Scott Harris, Chief Medical Officer of Altimmune; along with Dr. Stephen Harrison, NASH Key Opinion Leader. After the speakers remarks, we will open up the call for a question and answer session, during which time Dr. Scot Roberts, Chief Scientific Officer, and Dr. John Nestor, Alt-801 Inventor, will be

available for questions. You may also email your questions to questions@lifesciadvisors.com at any time during the call.

As a reminder, this conference call is being recorded and will be available for audio rebroadcast on Altimmune's website at www.altimmune.com. Please click the webcast link on our Events and Presentations page to view the slide presentation.

Before we begin, I would like to remind everyone that remarks about future expectations, plans and prospects constitute forward-looking statements for the purposes of Safe Harbor provisions under the Private Securities Litigation Reform Act of 1995. Altimmune cautions that these forward-looking statements are subject to risks and uncertainties that could cause actual results to differ materially from those indicated. For discussion of some of the risk factors that could affect the company's future results, please see the risk factors and other cautionary statements contained in the company's filings with the Securities and Exchange Commission.

I would also like to direct you to read the forward-looking statement disclaimer in our conference call press release issued November 21, 2019, and now available on our website.

Any statements made on this conference call speak as only as of today's date, Thursday December 5, 2019, and the Company does not undertake any obligation to update any of these forward-looking statements to reflect events or circumstances that occur on or after today's date.

With that, I will now turn the call over to Vipin K. Garg, Chief Executive Officer of Altimmune. Vipin, please go ahead.

Vipin K. Garg:

Thank you Monique, and good morning all. It is my pleasure to welcome you to this Key Opinion Leader Call, where we will be discussing the development of Alt-801, a potent GLP1/glucagon dual agonist for the reversal of metabolic and liver dysfunctions in NASH.

Since acquiring this compound in July of this year, we have grown increasingly excited and optimistic about Alt-801's potential to be a best in class treatment for NASH and other obesity-driven diseases. As our Chief Medical Officer will explain in more detail, this compound is designed to treat the root cause of NASH, obesity, and represents an enhancement over GLP1 receptor agonists currently on the market.

We are very fortunate to have with us today Dr. Stephen Harrison of Pinnacle Research. Dr. Harrison is a world-renowned authority on NASH. He's an author of over 150 peer-reviewed journal articles, and lead investigator in a number of NASH trials. He served as a Professor of Medicine at the Uniformed Services University of Health Sciences, and is currently a visiting Professor of Hepatology at Radcliffe Department of Medicine, University of Oxford. During his Army tenure, he served as the Director of Graduate Medical Education at Brooke Army Medical Center; Associate Dean for the San Antonio Uniformed Services Health Education Consortium, and Gastroenterology Consortium, as well as a gastroenterology consultant to the Army Surgeon General. Dr. Harrison will provide us with an overview of the NASH treatment landscape and also be available for questions at the conclusion of his remarks.

But first, please join me in welcoming Dr. Scott Harris, Altimmune's Chief Medical Officer, who will provide an overview of Alt-801. Scott?

M. Scott Harris:

Thank you Vipin. Good morning everyone.

I will start by providing a brief overview of Alt-801, and then turn the call over to Dr. Harrison for an overview of NASH and the potential role of Alt-801 in the treatment of this disorder.

Here is our Safe Harbor statement.

NASH is a disease of obesity, and fatty liver is identified in up to 90% of obese individuals. NASH is a supply-side disease resulting from substrate overload. The majority of excess liver fats results from free fatty acids released from the breakdown of peripheral fat, not *de novo* synthesis. The accumulation of fat into the liver runs in parallel with the accumulation of fat in other organs. The liver is merely the canary in the coal mine for metabolic sensing, and disease progression in the liver is collinear with disease progression elsewhere. If we don't treat the obesity, the consequences of both liver disease and metabolic syndrome persist. In fact, most patients with NASH die from the consequences of cardiovascular and liver diseases, and not NASH, because the metabolic cause of the disease remains untreated.

Further evidence of the metabolic basis of NASH comes from the fact that 40% of NASH patients who undergo liver transplantation develop recurrence of fatty liver within one year.

The treatment of obesity remains the cornerstone of NASH therapy, but meaningful weight loss is rarely achieved without medical intervention. NASH is a complex disease involving multiple disease pathways, so effective therapies will need to have diverse or pleiotropic mechanisms. Weight loss represents the ultimate pleiotropic mechanism, because weight loss affects multiple metabolic systems, and the disease regresses when patients lose weight.

None of the front-running candidates achieve, in a tolerable manner, the 7% to 10% weight loss necessary to slow down the NASH process, and none have delivered the magnitude of the weight loss achieved through bariatric surgery, a magnitude that is ultimately necessary for the return to normal metabolic function.

While metabolic modulators like GLP1s are the only drugs associated with meaningful weight loss, the level of that weight loss is modest, and falls short of goal. The addition of glucagon activity to GLP1 is critical in achieving significant weight loss, which is the basis of the dual GLP1/glucagon agonist.

Alt-801 is a dual agonist that Altimmune is developing for the treatment of NASH and obesity. The GLP1 component has effects that are mediated by depressed appetite and reduced insulin resistance, while the glucagon component evokes increased energy expenditure, adipose browning, and mobilization of liver fats. Unlike GLP1, glucagon has direct effects on the liver and liver fat metabolism. The presence of GLP1 and glucagon activities in a single peptide results in substantial reductions in body weight, liver fat, liver inflammation and fibrosis, while simultaneously regulating blood glucose.

Consequently, Alt-801 is designed to act at the early stage of NASH pathogenesis and disease progression, that is, treating it proximally in the disease and not distally, where treatment is complicated by the multiplicity and redundancy of disease pathways.

Like other compounds, structure is the key to differentiation. Alt-801 is a 29 amino acid peptide that lacks manufacturing issues associated with proteins. The opposite ends of the molecule confer GLP1 and glucagon specificities. The GLP1 component provides the restoration of metabolic function, such as reduced insulin resistance, and the glucagon component improves weight loss by increasing metabolic rates and fat burning. Importantly the potency of these agonists are balanced one to one. It is critical to achieve this balance, so that both effects are expressed simultaneously and one does not dominate. This has been a problem with other compounds in this class.

The proprietary EuPort domain, a long lipophilic side chain attached to the middle of the peptide, drives insulin binding, which along with a modified amino acid residue prolongs its half-life to what we believe will be weekly dosing. The EuPort domain also results in the slow appearance of the compound in plasma, avoiding the rapid surge in concentration that can drive the GI side effects of the GLP1s. This is important because 25% of patients fail to tolerate GLP1s because of GI side effects.

This slide shows the weight loss induced by 28 days of Alt-801 administration in a diet-induced obesity mouse model, compared with the weight loss achieved by semaglutide at similar doses. Animals treated with Alt-801 achieved a 25% reduction in body weight, which was twice that achieved by semaglutide, and this weight loss occurred with relative preservation of lean body mass. The difference between Alt-801 and semaglutide could be attributed to the glucagon component of Alt-801. GLP1 agonists induce weight loss by suppressing appetite. Therefore when animals were pair-fed to the same reduced level of intake, they achieved weight loss in the range of only 5% to 8%, with the other 20% attributable to the glucagon effects.

The Gubra diet-induced obesity model is considered the best animal model of NASH. It is a biopsy proving model, and considered to be most translational to humans. Animals are given a diet high in fat, cholesterol and fructose, and biopsied at 32 weeks for confirmation of NASH, which you can see in the vehicle-treated animal in the upper left. In the DIO mouse, impressive and near-complete resolution of liver fat was observed with 12 weeks of Alt-801 treatment, and this was greater than the effect seen with 12 weeks treatment with either semaglutide or elafibranor.

In the same 12 week Gubra model, greater reductions in fat-driven inflammation in overall NAFLD activity score were observed compared with elafibranor and semaglutide, with all Alt-801 animals achieving a reduction in the NAFLD activity score or NAS of 3, or to a level of less than or equal to 3. Note should be made that these are doses of elafibranor and semaglutide that have been used in other rodent studies in comparable to human doses when allometrically scaled.

In the same model, mean ALT levels fell to below the upper limit of normal and significantly less than either of the two drugs.

Finally these changes in weight, liver fat, and fat-driven inflammation were associated with greater reductions in COL1A1 and galectin-3, biomarkers of fibrogenesis. While not shown here, Alt-801 also efficiently repressed the expression of virtually all fibrotic genes by messenger RNA sequencing.

This final slide depicts the current development plan for Alt-801. We plan to file an IND in the second half of 2020, with the initiation of clinical trials in the fourth quarter of the same year, 2020. In addition we are planning an efficacy and safety trial in obese individuals with fatty liver, with a read-out in the first half of 2021. We believe that the potent effects of Alt-801 on liver fat content, liver inflammation, fibrosis, a weight loss that will be observed in this study, will be key predictors of success in later phase trials.

I'm now pleased to turn the call over to Dr. Stephen Harrison; I've gotten to know Dr. Harrison over the last few months, and he's had a considerable impact on our program. We look forward to his continued involvement as we move our program forward into clinical trials. Stephen?

Stephen A. Harrison:

Hey, Scott, thank you for that great introduction, and for the review of the development pathway so far, and the animal data that you've shown. So, I'm just kind of take it from here, kind of put this in perspective, and then happy to answer any questions, so, next slide?

So, a lot has been learned about the prevalence of this disease, and it's been a special interest of mine since, oh, the early 2000s, back when I published the first prospective liver biopsy-based prevalence study on NASH in *Gastroenterology*, in about 400 patients that we studied here in Texas. Since that time, there have been other data sets that have been done to look at the prevalence and severity of disease.

This is probably the best meta-analysis that's been done looking at this. This was published by Zobair, a good friend of mine from Inova Fairfax in Virginia this past year in *Hepatology*. What we know is that the prevalence is clearly increasing, it's in line with increasing rates of obesity and type 2 diabetes as well as aging population. In the graph on the right you can see the aging population and the increased prevalence in both males and females. I will note that this is a male-predominant disease until females become post-menopausal, and then they rapidly catch up, and they also have more severe disease. If you look around the world, the prevalence rates through cross-sectional analyses of either liver enzymes, imaging studies to include ultrasound or FibroScan, or retrospective liver biopsy analyses show us a prevalence ranging from 14% up to 31%, and a mean of roughly 25% in the general population. What we know is that this varies significantly with ethnicity, with Hispanics having a higher prevalence of both fatty liver and NASH, followed by an equal prevalence in Asians and Caucasians, and a much less prevalence in African-Americans. I will caution though on this slide to tell you that there is yet only one prospective prevalence study with liver biopsies included that have been published, and in that trial the prevalence of fatty liver was roughly 35% and the prevalence of NASH was 15% to 16%. This was in a middle-aged cohort of patients. Next slide?

So, a lot of interest has been focused on the diabetic population, and I would argue that fatty liver, to a large degree, is due to the metabolic milieu. As Scott has mentioned, it really is the canary in the coal mine. The liver is the first thing to sense metabolic processes going awry. When you fix them, it's also the first thing that tends to get better.

So it makes sense to look at this prevalence of fatty liver in diabetics, and we know again a very similar meta-analysis done by Zobair's group showed that roughly 50% to 60% of diabetics have fatty liver, and when you look at the prevalence of NASH amongst these type 2 diabetics it's roughly a third of these patients. So that's the low-hanging fruit, if you will, looking at type 2 diabetics with fatty liver, where up to a third of them have NASH. Next slide?

Now, I think this is an important point to make. This idea of liver cancer prevalence increasing, in our country and around the world, is very real. In fact, I would argue that NASH is now the fastest-growing cause of liver cancer among any liver disease out there. We see that highlighted by the city of McAllen, Texas, where the county that McAllen sits in, I have been told, has the highest rate of liver cancer in the U.S. It's clear there that the prevalence of fatty liver disease is significantly elevated.

So, not only in targeting NASH are we aiming to reduce the inflammation and the fibrosis, but we're hopeful that we drive down the rates of liver cancer as well. Next slide?

Okay. So this gets me to the pathogenesis slide. A lot of you have seen this, we published this a couple years ago now. I think it's simplistic enough but complicated enough to explain kind of the conundrum that we live in in the setting of NASH. That is: there are multiple pathways by which you can affect stellate cell activation and inflammatory processes that drive lymphocytes and neutrophils into the liver, giving you the hepatitis, and ultimately the ballooning degeneration cell death that drives stellate cell activation.

If you look on the left hand side, the metabolic processes, this is where we've seen the biggest benefit in NASH trials that have been done to date: drugs that modify metabolic processes, such as resmetirom, the FXR class of drugs, potentially the FGF-21 class of drugs, and really any drug that modulates weight loss. We saw, even data from many years ago, I published a paper with orlistat, showing that the drug was effective in improving NASH if you were able to lose up to 9% of your body weight.

So it's clear that there are drugs that, if you can modulate weight loss in the setting of NASH, you'll have a profound impact on the underlying metabolic processes that drive NASH.

So again, ideas, drugs, that focus on that metabolic pathway, that decrease insulin resistance or improve insulin sensitivity, and that reduce the rate of free fatty acid flux into the liver, will ultimately, in my opinion, be very beneficial in this disease. Obviously you can target *de novo* lipogenesis as well, there are drugs that you guys know that do that; you can go after mitochondrial health, as well, there are drugs that are working on that. You can improve insulin resistance through modulating mitochondria, pyruvate carrier complexes, and you can also go after anti-inflammatory and antifibrotic pathways. My one caveat to that, the last two, is that they are more downstream or more tangential, and they don't have direct impacts on the drivers of this disease. They're kind of midstream or downstream effectors. Unfortunately to date we haven't seen any of these drugs that have met the primary endpoint on either NASH resolution or fibrosis improvement. Next slide?

So, there are a lot of drugs that—and you guys, I think, have heard me talk about this; when we think about liver disease and NASH in particular, there are roughly five different buckets we could put these drugs. We could put them in drugs that modulate insulin resistance, drugs that modulate lipotoxicity and oxidative stress, anti-inflammatory drugs, antifibrotic drugs, and even drugs that modulate the microbiome.

If you go to the next slide, I think you can see where the majority of these drugs are impactful are on the metabolic side. So here you see the drugs that are currently in development, and the vast majority of them are on the left hand side of this slide, in targeting insulin resistance or lipotoxicity and oxidative stress. I think that that goes without saying. I mean this is where we're seeing the benefit, so it makes sense to study drugs that effect changes and improvement in these underlying metabolic processes. Next slide?

So, I want to shift gears and talk briefly about GLP1s, because obviously that's part and parcel to how Alt-801 works, it has a GLP1 agonist effect in addition to the glucagon effect. So just looking at what we know about GLP1 analogues, they have multifactorial effects, we know that there is data showing that they reduce inflammation, body weight, lipids and glucose, they have effects on energy intake, appetite, body weight, and ultimately they also have effects on diabetes and glycemic control. There is data now showing that there may be effects on cardiovascular disease as well.

So using that as a framework, we'll go to the next slide, and just briefly talk about the LEAN trial, so this is a study published a couple years ago now in *Lancet*, looking at liraglutide in NASH; 52 patients were ultimately randomized to get one year of therapy with 1.8 milligram of liraglutide versus placebo, and you had to have confirmed NASH, with or without diabetes, to get into the trial. The NAFLD activity score was a more modest greater than or equal to 3, we use 4 or greater now in most of our trials. The primary endpoint was proportion was significant improvement in liver histology, which was NASH resolution and no worsening of fibrosis. The caveat here is that inflammation was not taken into account. You just had to have ballooning scores of zero; currently the definition would be inflammation of 0 or 1, ballooning of 0. So there's a little bit of a apples-oranges comparison here, but I think you just need to know that going into the results.

So what you see, I think, that's important is weight loss was approximately 5.5% with the lira-treated patient. That also corresponded to about a 26 unit per liter drop in ALT. Ultimately you see the NASH resolution at least by the modified endpoint of ballooning scores of zero, 39% versus 9% that was statistically significant.

So based on that I think we can shift gears, go to the next slide, and talk about what happened more specifically with some of the histology. So, if you look on the left hand side, it's basically a bar graph showing what I showed you on the previous slide, which is resolution of NASH, 9% versus 39%. But then when you break down the component parts of the NAFLD activity score, you see again bigger improvements in ballooning over a placebo, and then not as much of an effect on inflammation. When you pivot to fibrosis, you see 26% of patients improved fibrosis versus 14% for placebo, but maybe just as importantly it's nice to know that this class of drug was preventing progression of disease, where you see placebo 36% of people progressed, versus 9% for the drug group. Next slide?

So, as you guys know, liraglutide is on the market, it's not currently being studied any longer in the setting of NASH. Its sister drug semaglutide is being studied in NASH currently in an 18 month trial. I think what's in the public domain is they're expected to read out sometime in 2020.

So, looking at the sema obesity trial, which has been published in *Lancet*, I think you can draw some inferences here. So I presented this data at EASL; 957 participants in eight countries were enrolled; there was a multiplicity of different dosing strategies, there's dose escalation, there's fast escalation. But ultimately what I want to just speak to is these five arms that you see highlighted here, in kind of a *post hoc* analysis setting. So, next slide?

So, when you look at the different dosing strategies for sema, which was 0.05, 0.1, 0.2, 0.3 and 0.4, and you look at weight loss relative to placebo, you see that, when using the higher dose of 0.4 milligram, you approach approximately 14% body weight reduction at 52 weeks. As you know and from what Scott mentioned earlier, 7% to 10% body weight loss has been linked to and associated with improvement in histopathology in the setting of NASH. So, that portends a positive prognosis for the potential to use sema in the setting of fatty liver disease. Next slide?

Now I think just as importantly, ALT normalization is one of the surrogates that we have to show that liver cell health may be improving. You see that again there appears to be a dose response relationship with dosing of sema and the proportion with normal ALT at the end of treatment. That again correlates with the weight loss that was seen, where you have 14% weight loss approximately with the 0.4 milligram, and 46% of those patients ended up having normalization of ALT.

So this is with sema, but I think it speaks more to the GLP1 class of drugs in general, that there is promise here, whether you look at kind of the first generation, liraglutide, where we actually have biopsy data, albeit not using the current endpoint as we define it today, but still a positive impact at 52 weeks, or 48 weeks. Now you have the sema data; while we don't have NASH data, we have weight loss data and we have correlatory improvement in ALT data. So, let's go to the next slide?

So I think you guys have seen this as well. Hit the slide one more time and you'll see the dash line come up at 30%.

So there's been a lot of talk about MRI-PDFF, and I think clearly this has become the gold standard for fat quantification in our field. It's much better than CAP on a fibrous scan, at quantifying the degree of fatty liver, it's much better than liver biopsy at quantifying overall degrees of fatty liver. Now there is growing data linking at magnitude of effect change of at least 30% relative fat reduction with improvement in histology. I'll refer you to the *Lancet* paper with resmetirom that was recently published, that highlights, at least with that mechanism of action and that drug, very positive impacts of correlatory change in PDFF with improvements in histology.

So, it doesn't—I think—the other thing we've learned is that it's probably mechanism-specific. If you're a drug that doesn't modulate triglyceride in the liver very well, you're probably not going to move PDFF, and

we would need to look at other surrogate markers of improvement, whether that's ALT, potentially ProC3L for MRE, it's yet to be determined for some of the compounds that are being studied.

When you look at this slide you can kind of see where the bar is set. So, whether you look at NGM's FGF19, where you see 48% relative reduction in fat with the 3 milligram dose, or up to 58% of liver fat reduction with the 80 milligram extension data that I presented at AASLD about 2½ weeks ago, and then you have Viking way out on the right, where you have the 10 milligram dose showing about a 59% reduction. Those are the current frontrunners at least on MRI-PDFF. What do we have histology for? Well we don't have any for Viking; we do have the data from resmetirom, again, that's been published now in *Lancet*, and we do have the data with NGM, at least 12 week data, and that was published in *Hepatology* last year as well. With NGM you have the 24 week study that is currently ongoing, looking at paired liver biopsies and liver fat as well, and that should potentially read out in 2020.

The FDF21 compound, we don't have a lot of data there, BMS has some data from their Phase 2A study that was 16 weeks in duration. As you know they're doing a paired liver biopsy study in both F3 and F4 patients. We should get the atlas data soon with Gilead's ACC inhibitor, and as you can see here it kind of gets close to the 30% relative fat reduction, but not quite, and so we're anxious to see how that correlates to histology with the ACC class, and then you see the liraglutide data at 31%, and you know the correlatory improvement in histology that have already shown. Next slide?

So, I think I'll—two more slides. This is on NASH resolution. I broke this up just to make it clear for those in the audience. On the left is NASH resolution as it's currently defined, which is ballooning of zero, inflammation of 0 or 1 with no worsening of fibrosis, with baseline NASH fibrosis stage of 1 to 3, and ultimately you see the data from obeticholic acid, elafibranor, aramchol and resmetirom, with the comparative placebo response rates highlighted. On the right hand side, you see a prior definition of NASH resolution, which was essentially ballooning scores of zero but included fibrosis stage of 0 to 3, and you see here that this was a weight loss study, there was also the liraglutide trial, and then there was the PIVENS trial.

So, go to the next slide, and we'll just highlight summary, I think it's important to note that the NASH prevalence is increasing in the world, not just in our country; it's been linked to obesity, and it's particularly prominent in diabetic patients; and it's been linked to the rising prevalence of liver cancer. As you guys know, there are multiple targets for therapeutics, the ideal candidate would be pleiotropic in mechanism and include multiple metabolic pathways. I think for some drugs in development ultimately that is going to be achieved by combining therapy. Data with GLP1 agonists look promising in NASH. Ultimately we will know more in the coming year on histology at 18 months of treatment with GLP1 semaglutide.

I think significant opportunity exists to improve on the current late stage product candidates, both for NASH resolution and fibrosis improvement, as you saw highlighted in the previous slide, where we are beginning to move the needle on both NASH resolution and potentially fibrosis as noted from the Phase 3 Regenerate trial, but we have a long way to go, and ultimately opportunity to move forward and enhance the efficacy of NASH resolution exists despite the large number of candidates that are currently in development.

So I will end there.

M. Scott Harris:

Well with that, I'd like to open the call now for questions and answers. Please also note that you can submit your questions to questions@lifesciadvisors.com. Operator?

Operator:

At this time we will be conducting a question answer session. If you would like to ask a question, please press star one on your telephone keypad. A confirmation tone will indicate your line is in the question queue. You may press star two if you would like to remove your question from the queue. For participants using speaker equipment, it may be necessary to pick up your handset before pressing the star keys. One moment please while we poll for questions.

Our first question is from Lisa Bayko, JMP Securities. Please proceed with your question.

Lisa Bayko:

Hi there, thanks for the talk, Dr. Harrison, and thanks for the overview to Altimmune.

Just curious about some of the use of the GLP1s now. I mean that seems to be a pretty good indication that this mechanism is working. Do you sense, and are you using GLP1 in your NASH patients today, and I guess, given its use in diabetics, what sort of impact is it having in that population?

Stephen A. Harrison:

That's a great question, thanks for being on the call today. So, I personally am not using the marketed GLP1s for an off-target indication of NASH resolution, or in my NASH patients. I do see probably a third of my NASH patients present with being on a GLP1. It's hard to say. The way I look at it is about a quarter of patients can't tolerate a GLP1, even if you go back and try to dose modify that GLP1, start them at a slower dose and titrate up, they just can't tolerate it because of the GI side effects. About a—maybe—and that's—so if a third of my patients come in with it, those are the ones that are kind of tolerating it. It's hard to say. We put them in clinical trials if they're on a stable dose of a GLP1 for the preceding six months. So I guess we're kind of self-excluding patients, because if they're on a GLP1 and they're responding, they're probably not being referred to me as a liver doc. So I'm seeing the recalcitrant ones, the guys that, despite being on a GLP1, still have elevated liver enzymes, still have FibroScans that are positive, and liver biopsy, being on a stable dose for six months, they still have disease.

So I guess I'm not really sure how to answer your question in total, because I suspect there are people that are responding that were just not being referred to us, and so I'm a little bit in that sense.

Lisa Bayko:

I understand, that's helpful.

In terms of tolerability, I mean, is that one of the main advantages you see of Alt-801? What other, I guess, attributes do you think this combination could contribute?

Stephen A. Harrison:

I think maybe I'll give Scot a chance to answer that as well, if he would like, but from my perspective, my understanding of this compound is that by adding the glucagon component you're able to dial down some of the GLP effect. To me, and Scot can correct me if I'm wrong here, to me this is a little bit analogous to the FXR class, in the sense that if you dose high enough you're going to get side effects. It doesn't matter what FXR you use, if you dose high enough, you're going to have itching and potentially LDL rise, whereas you get the biggest efficacy with that as well; whereas if you down-titrate that FXR you won't have as many side effects but potentially not as efficacious. I think, to the extent where there's a correlation, with a dual agonist such as this one, if you can still get the beneficial effects of GLP but

mitigate the side effect profile to some degree by dialing down that effect and ramping up some of the glucagon effect, then you can still retain the positive impact of the GLP with minimizing the side effect profile. So at least to my understanding, it theoretically makes a lot of sense. Now we don't have human data yet to verify that with this compound, but in the two animal models you saw it looked very promising. Now, granted, the side effect profile of a mouse does not necessarily translate to that of a human; but theoretically it makes sense to me if we can dial down a little bit on that GLP1 activity we can mitigate some of the side effect profile.

Scot Roberts:

Hey Scott, this is Scot Roberts, I just wanted to add a little bit to that.

In addition to the effect that you talked about, we're expecting improved tolerability because of the design of Alt-801 itself. With the better binding to albumin and the way that it's released into the bloodstream, we really have lower peak-to-trough ratios and very a slower onset of activity. We believe that that is going to allow patients to tolerate the side effects better than the standard GLP1s. So it just comes on slower, the total amount of exposure is going to be very comparable, but it comes on slower and a little bit later. We think that the more gentle onset will make the difference.

Lisa Bayko:

Okay great, that's helpful. And then just another question with Dr. Harrison and then I'll go back into the queue. Just as you kind of look at the landscape, there's obviously oral agents, there's a number of injectables. Some of the oral agents look pretty promising, and I cover Madrigal and maybe I'm a little bit biased there, but that class looks quite promising in terms of the amount of liver fat reduction. What is it going to take and what will drive patients to want to add an injectable agent on? Is it the weight loss? Is it added kind of efficacy, or what specific component (inaudible) would we be looking for to kind of want to layer on an injectable product for this patient population? Thanks.

Stephen A. Harrison:

I think that's a great question. Again, I think ultimately, I saw at clinic yesterday quite a few patients yesterday with NASH. These guys or a lot of them, once you explain the disease, and particularly those with F2 or greater fibrosis, you can show them their prognosis based on data from kind of cross-sectional analyses led by several of my colleagues in gastroenterology, for instance, where at F2 you begin to see increased risk of all-cause mortality and liver-related mortality. These patients are kind of finding out for the first time that this asymptomatic disease is really something that they need to be worried about.

Really, the idea of using an oral versus injectable, a lot of these guys, it doesn't really matter. These are middle-aged patients on average; the mean age for most of these is around 50 to 55 years of age. A lot of them are on multiple other medications to include injectables already, whether that's an antidiabetic therapy, whether it's a PCSK9 or something else, that experience with an injectable has already been had and so they're not necessarily scared of it.

I think it comes down to two things: the severity of the disease in the patient, and whether the compound is effective. I mean at the end of the day, what I've always said with injectables in NASH is, the juice has to be worth the squeeze, the view has to be worth the climb. If you're really knocking the socks off of this thing, an injectable becomes less of a concern. If our patients are achieving significant weight loss with this compound as was shown in the preclinical data, I think the patients will not have an issue with the injectable.

So, I think there's an opportunity for a couple different things here. Whether that's right off the bat, as an inducer agent, as is often talked about with some of the other injectables, or it's a long-term management situation, I think, patients are not necessarily going to be turned off by injectable if the data is incredibly on the positive side with a minimal side effect profile.

Lisa Bayko:

Okay, that's very helpful, thank you.

M. Scott Harris:

Stephen, I have a question for you. As you noted, a read-out on the semaglutide NASH trial is expected in the early part of next year. What impact do you think a positive readout on that trial would have on a dual GLP1/glucagon agonist like Alt-801?

Stephen A. Harrison:

I think it'll be a positive impact. Because again you've got an injectable, and you've got, you know, if you're seeing positive impacts on NASH resolution and fibrosis improvement both, then I think it portends that Alt-801 should do very well. I think what's going to wind up happening is, we'll see the data, we'll see what happens to these patients, both on NASH resolution and fibrosis with 18 months of treatment, and we'll also see the AE profile. So, combining that AE profile with the efficacy of the drug, we'll be able to figure out kind of, you know, are we seeing—is the impact of the efficacy worth the side effects that we're seeing, and if so, then I think it's a prime opportunity for you guys to say, well, we're likely to see very similar type efficacy but potentially less AEs. So I think it would portend well for you guys if that study reads out in a positive manner.

M. Scott Harris:

We have some other questions in the queue, maybe we can move on to those?

Operator:

Our next question is from Mayank Mamtini, B Riley FBR. Please proceed with your question.

Wayne for Mayank Mantani:

Hi guys. This is Wayne on for Mayank. I have a question for Dr. Harrison. Understand that strong metabolic effects should be observed with Alt-801. Could you please comment on the treatment duration required in order to see, in particular, the anti-inflammatory or antifibrotic effect, keeping the NGM-282 experience in mind? How do you believe this could be accelerated through earlier stage clinical testing?

Stephen A. Harrison:

Okay. Well, there's a lot of theoretical there. But I'll give you at least my two cents on it. So, the NGM-282 data really was helpful in my opinion, because we were able to get 12 week liver biopsy data, albeit in an open label population with no placebo control. But we were able to link significant drops in liver fat, significant improvement in ALT, with what's going on histopathologically.

In that trial, I think a couple things stood out to me. One, we were able to move fibrosis very quickly. I'm not saying necessarily that that is solely linked to the mechanism. What I'm trying to drive at there is that this disease in the liver is static, and it can move one way or the other relatively quickly. For years we

thought fibrosis took a long time to improve, right, that's why the PIVENS trial was two years, the FLINT trial was 18 months, and so on and so forth; and then gradually we've learned that it can move much quicker than that.

So I think the good news story here is that if you have a drug that's impactful on liver, that we can begin to see improvements at a much sooner rate than we previously thought.

So, with just again thinking through the development of Alt-801, assuming that the preclinical data is translatable into humans at least as it pertains to the serum biomarkers that were obtained and the weight loss that has been seen, that ultimately we should see a relatively rapid and profound effect on liver fat content as well as liver biochemistries. That potentially we could use noninvasive testing such as PDFF and ALT reduction; again, if you see both moving in the same direction, that correlation is very strong for a positive histopathologic impact.

So I think you could use that to your benefit, if you have a drug that moves the needle quickly, you have a noninvasive test that correlates highly, then you can potentially shorten your early phase development to get to paired liver biopsy studies that are still currently required by the agency.

Wayne for Mayank Mantani:

Okay, thank you. Also have a question for the Altimmune management? So I just want to dig deep into what differentiates Alt-801 from other drugs that are in development. So could you please perhaps talk a bit about the history and the chain of the control of the compound?

M. Scott Harris:

What I can say is that the compound was developed by Spitfire Pharmaceuticals, the inventor was John Nestor, who happens to be on the call here today. The company and the compound was acquired by Altimmune in July of this year. We're fortunate to be moving it ahead now with John's assistance, with the anticipation that we'll file the IND in the third quarter or fourth quarter of next year, and commence clinical trial soon thereafter.

John J. Nestor Jr:

This is John Nestor. I'd like to just mention one thing with respect to differentiation. That is, if you look at the compounds that are listed on Slide 20, so, many compounds being developed, and you're looking at compounds having a number of different effects on the liver histology, one of the important aspects of the GLP1/glucagon dual agonist is the both the direct effect on the liver, reducing fibrosis and reducing the hepatosteatosis. But it also returns essentially all other measures in that Gubra NASH trial to lean normal. Body weight returns to lean normal. The liver weight returns to lean normal. ALT returns to lean normal. Liver histology returns to lean normal.

So the effect of the body weight and the liver weight returning to lean normal has effects throughout the body, not just on the liver, but in the liver we see a dramatic regression in fibrosis and in liver health in general.

So differentiation brought by the glucagon receptor activation directly in the liver, as well as reduction in body weight, atopic fat throughout the body, is the differentiation here.

Wayne for Mayank Mantani:

Okay. Thank you.

Operator:

Our next question is from Jason McCarthy, Maxim Group. Please proceed with your question.

Michael Okunewitch:

Hey guys, this is Michael Okunewitch on the line for Jason McCarthy. Thanks for taking the question.

So you mention that you're targeting earlier-stage disease. I want to get an idea of exactly how early you're looking. Are we talking like F2/F3, or even F1/F2?

And then considering the impressive preclinical data in liver fat, is there a potential to use 801 in NAFLD patients before they even actually develop NASH?

M. Scott Harris:

So I would position Alt-801 as actually coming before the FXRs and the other compounds, because the root cause of the NASH is the accumulation of fat in the liver that comes from peripheral sources. Mind you that the other compounds actually act at a step that's distal to that. So I believe that we're proximal.

Regarding the treatment of patients with NAFLD, as you know, only a certain percentage of those go on to NASH and then go on to fibrosis and cirrhosis. But we can't forget about the fact that these patients have metabolic disease elsewhere, and they die predominantly of cardiovascular causes and non-hepatic malignancies. So while this would have to be looked at in a more heuristic sense, there is the possibility of treating those patients with a metabolic disorder independent of NAFLD.

Michael Okunewitch:

Thank you …

M. Scott Harris:

Stephen, would you like to comment on that, further?

Stephen A. Harrison:

I mean I think there's certainly a role for this drug if we're able to replicate similar findings in humans that we see in the Gubra model for instance. I'll use another patient I saw in clinic yesterday, a diabetic with metabolic syndrome obesity, BMI of 46, who had a CAP score of 360; anything above 280 is fat in the liver; it goes to 400; this is a FibroScan CAP. The KPA was 3.6. So anything less than 6 I don't consider as fibrosis or any kind of inflammatory process in the liver. The ALT was mildly elevated, AST mildly elevated. So, by all intents and purposes, this patient had diabetic liver disease, but it was not felt to be advanced enough for me to proceed to a liver biopsy or even consider for a clinical trial. Given the fact that she has obesity, hypertension, hyperlipidemia, diabetes, her A1c is 7.3, and liver disease or at least fatty liver on imaging, I could see a situation where potentially this drug could impact multiple different processes that she has going on in her life. So again, improving the fatty liver, and by improving the fatty liver, again, that's a metabolic sensor for disease. So, if we get rid of the fat in the liver, we can assume that the metabolic processes are improving. Again, if this drug is able to replicate that kind of weight loss, you're going to see dramatic effects across the board on her metabolic profile.

So again, kind of early on, it's hard to say exactly how this is going to play out; but that's a scenario, a real world example where potentially this drug could be impactful.

Michael Okunewitch:

All right, thank you. Then, I have a couple of follow-ups. I'd like to see if you could just give a broad idea, because we're looking a bit down the road, but generally speaking, for targeting earlier-stage patients than we're traditionally seeing, I'd like to see how that could affect the development pathway, in terms of recruitment and finding biopsy-confirmed patients in the earlier stages of disease. Does that pose a challenge?

Then also, is it still going to make sense to use the current registrational biopsy endpoints?

M. Scott Harris:

Stephen, would you like to answer that question?

Stephen A. Harrison:

Yes, sure, I can take that. So, no, it's very easy to find mild patients. In fact it's the number one reason for screen failing in paired liver biopsy studies. So, if we had a study open to take milder patients, it would fill very very quickly.

The bigger question, though, is what's the agency going to pivot to on an approval endpoint. Because with milder patients, we're not necessarily looking at fibrosis improvement per se or even NASH resolution, and so those are surrogates for long-term patient outcomes, right? So we would have to work with the agency on what that is. It may be a CV outcome, it may be something else. But I think one of the things that we're studying very intently is, at least through LITMUS and NIMBLE, these two consortiums that are academically led that are trying to resolve the issue of noninvasive testing using three different contexts of use. One is the diagnosis of those patients with more advanced disease; number two, the therapeutic efficacy marker; and then number three, long-term outcomes. I think what we'll be able to show eventually, at least my fingers are crossed on this, is that we'll be able to have an imaging marker, or a combination of a wet and imaging marker, that we can use in our patients noninvasively to predict long-term negative outcomes.

If we're able to do that, then potentially we can enroll patients, and this is thinking outside the box and maybe a little far into the future, but may be in line with the development of Alt-801 as it proceeds into later-stage development.

Could we have that biomarker that we're able to do in clinic, that then tells me this patient is at risk of developing long-term outcomes, even if they don't necessarily have NASH and fibrosis today, based on a combination of genetic and clinical biomarkers and imaging biomarkers, we're able to then predict that patient will do poorly in the long term, if we're able to enroll them in a trial and reduce that biomarker by whatever magnitude of effect is required, then we're able to show the agency that we've affected how that patient's going to do in the long term.

There's a lot of work that has to be done between now and then, but I think that's where we're headed, because quite frankly liver biopsy is so noisy, at the way we currently use it to define a registrational trial endpoint. I think there will be a shift to find something that is a little bit easier to identify signal, and it's not clouded by as much noise.

Michael Okunewitch:

Thank you, Dr. Harrison.

One last one for the Altimmune team. Let's see if you can give us an idea of how we should view the development pathway for Alt-801. Obviously, you have the Phase 1 first, but after that, there's a number of different routes you can go, including obviously NASH, but obesity and type 2 diabetes as well. All of those are potential markets, some of which actually have like a GLP1 footprint in them already.

I want to know if you're considering pursuing multiple indications in parallel, or if you're planning to focus on NASH initially and kind of go one at a time.

M. Scott Harris:

Well, thank you. Well as we announced, our primary goal at this point is to pursue NASH; however, we're going to let the data drive our decision-making process. We'll have studies that will allow us to identify multiple effects at the same time, both the effects on NASH, the effects on liver fat and markers of inflammation, but also weight loss and diabetic control. If the data shows us that we're having those effects, yes, there is the potential to go down those other avenues.

Michael Okunewitch:

Thank you very much, and looking forward to seeing future updates.

Operator:

Our next question is from Ed Arce, H. C. Wainwright. Please proceed with your questions.

Thomas Yip:

Hey everyone. Thank you for taking the questions. This is Thomas Yip asking with a quick question for Ed. Dr. Harrison, on one of the slides, you point out that the evolution of designing what is NASH resolution, are there any other preliminaries that you believe that would be included in that definition in the future, and perhaps any specifically related to Alt-801?

Stephen A. Harrison:

Well, as you know, right now fat is not considered in that parameter. However, one of the first tweaks that we looked at in modifying that current definition was saying, look, we need to minimize placebo response. One of the ways that we did that was by adding a requirement to have a two-point improvement in the NAFLD activity score. What that did was it took that placebo and made it harder to get to negative. Right? Because, if you use an example of an NAS of 4 to get into the trial, and two of those points come from steatosis, one from inflammation and one from ballooning, on follow-up liver biopsy, if the ballooning score goes to zero, by definition, you're cured that patient. To me that seemed a little bit arbitrary and probably not necessarily accurate. If you then layered on top of that a two-point improvement in the NAS, okay great, they had an improvement in ballooning of one point, that got them to zero, but something else has to move by one point, either inflammation or steatosis.

It makes it a little bit more fair that that placebo group actually did something besides just happening by chance alone. What we see when you apply that lens to this is that you minimize placebo response and you optimize the potential for that drug to show a benefit.

So that's currently the way one Phase 3 in development has their pivotal endpoint defined, and I think you might see others begin to pivot that way.

Where we move to in the future, I think, was discussions that came out of AASLD where, as we move I think more towards AI, in artificial intelligence, looking at some of these micrographs of histology, we're able to quantify on a fully quantitative scale the degree of inflammation, steatosis, ballooning and fibrosis, rather than on a semi-quantitative scale or an ordinal scale, which is currently being used by histopathologists. That may allow us to then move forward and take the next step. That's still requiring histology, but I think at a minimum we'll now be able to say, if you have a magnitude of effect change in inflammation or ballooning or NASH or NAS, or fibrosis for that matter, that that would then get you to the point where the agency would give you conditional approval.

Then I think ultimately we move beyond histology into noninvasive, but I think that's probably how we're going to evolve over the next several years.

M. Scott Harris:

Stephen, this is Scott. I have a question here that was submitted to us over the web. The question is, "How should we think about the role of combination therapy with an agent like Alt-801 in treating NASH?"

Stephen A. Harrison:

Well, it's interesting to me. When we first started looking at combination therapy, it was, 'Okay, well maybe my drug's doing something but it has side effects, so let's combine it with another drug that potentially could mitigate those side effects.' Ultimately the original combinations that we've studied, or that have been studied, haven't really shown a positive impact on their own, necessarily. So I think moving forward there is a role for combination therapy, but we just have to take two drugs that work well, put them together and see if they work even better. Where that happens, we—again our thoughts are pivoting a little bit here. We used to think, 'Okay, well we have a metabolic drug. Now, we need to combine it with antifibrotic drug, and maybe even an anti-inflammatory drug,' but I don't think that that's necessarily true. I think you look to see what your drug can do, and you augment it with something that your drug maybe doesn't do quite as well, but yet is still effective. I'll give you an example.

Let's say you have a drug like yours that really does a wonder on liver fat, and improves insulin sensitivity, but doesn't necessarily improve glycemic control. Could you add a drug, then, that improves glycemic control to augment the effects of Alt-801? Again, we don't know all the effects that this drug may have on patients, so I think we need to determine what that effect is, and then you can determine if we need to add an agent to it. But I think that this is—regardless of the fact that it's an injectable, it doesn't mean you can't combine it with other therapy to either enhance the resolution of disease or improve something that your drug isn't covering.

We just have to go back to hep C. With boceprevir and telaprevir, they were certainly better than interferon or ribavirin, but there was still a lot of improvement to be had, not only on the AE profile but on the efficacy of the drug in clearing virus. It wasn't until we got to Harvoni and the DAA therapies, where we were able to tweak those slightly and get to 99% cure rates, but we did that by combining multiple different mechanisms. And I think ultimately that's where we're going to head with Alt-801 and all the therapies, is that there will be few therapies that'll stand alone and treat the majority of the patients. Ultimately, this disease is too heterogeneous for one drug to carry the load.

However, as you noted at the beginning, weight loss tends to cross all modalities, right? If we can achieve and sustain weight loss, then that's a game-changer ultimately in this field.

M. Scott Harris:

Stephen, one final question that was submitted on the web. “What is your impression of the translatability of the animal models of NASH like diet-induced obesity in Gubra models, particularly the Alt-801 studies to human data?”

Stephen A. Harrison:

Well, it’s—I’ll say it like this. If you don’t work in animals, you’re not going to work in humans. If you work in animals, you might work in humans. It doesn’t translate 100% necessarily or the effect size doesn’t necessarily translate, but it is a very encouraging positive piece of data. I would say of all the animal data I’ve seen, particularly as it pertains to what we’ve seen in the Gubra model with Alt-801, it’s highly encouraging, and quite frankly the reason why I’m high on the drug is because of what I’ve seen with the animal model data, and also the mechanism. I think the idea of hitting GLP1 and combining glucagon agonism with that is a very promising model in metabolic liver disease. I think you’ve knocked it out of the park with the first animal study, with a couple animal studies. I think the next phase is to see what we can do in humans and ensure that the AE profile is safe, and that the data generated is positive, and then we’ll just keep rolling.

Operator:

We have reached the end of the question answer session and I would now like to turn the call back over to Vipin Garg for closing remarks.

Vipin K. Garg:

Well, thank you everyone for listening in today. We look forward to continuing the conversation on Alt-801 and our other programs on our future calls. Thank you.

Operator:

This concludes today’s conference. You may disconnect your lines at this time. Thank you for your participation.