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BHT-II-002: Phase II trial of Live Biotherapeutic Blautix for IBS

Blautix IBS Phase II Results

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Start – Duncan Peyton, Chief Executive Officer, 4D pharma

Slide 1 – BHT-II-002: Phase II trial of Live Biotherapeutic Blautix for IBS

Welcome to another 4D webinar. Today we will be talking about our results from our study of Blautix, which unusually for an IBS study is in both IBS-C and IBS-D patients. My name is Duncan Peyton, I'm the Chief Executive and one of the founders of 4D pharma. With me today from 4D pharma I have Alex Stevenson who is the Chief Scientific Officer and also Glen Dourado, who's our Chief Business Officer. Also, on the call we have analysts from N + 1 Singer, Bryan Garnier & Co, Chardan, Ladenburg Thalmann & Co and Jones Trading.

Slide 2 – Disclaimer

Before we begin, I'd just like to remind you that we will be making forward looking statements relating to 4D pharma's programmes, the marketing and commercial opportunity of our programmes, and the need for additional safety and efficacy data to support regulatory approval. Actual results may differ material, materially, and any forward looking statements made on today's call represent our view as of today only. We may update these statements in the future, but we disclaim any obligation to do so.

So with that I'll hand over to Alex Stevenson, our Chief Scientific Officer, to talk you through what we've seen in this study. Alex?

Dr Alex Stevenson, Chief Scientific Officer, 4D pharma

Slide 3 – Key takeaways

Thanks very much Duncan. Well to start off with what I'd like to do is to talk to you about the key takeaways from the study itself. So in terms of what we set out to achieve in this study, we designed it to generate a meaningful signal of clinical activity in IBS-C and IBS-D and therefore in the combined population and to provide the necessary data for us to develop a pivotal program for Blautix.

What we saw as you'll see is that Blautix demonstrated an effect size relative to placebo that was comparable to pivotal studies of other approved products with both IBS-C and IBS-D, but Blautix also demonstrated activity in the combined cohorts of IBS-C and IBS-D patients as a result. Importantly, Blautix also showed a highly favorable safety profile, which is comparable to placebo. Interestingly, we also saw preliminary evidence of enhanced activity in specific subgroups of patients. We won't talk about that today, but that's subject to further investigation, and we saw a particularly strong signal in overall improvement of bowel habits across both major subtypes of IBS.

So where do we go next from this? Obviously, we are highly encouraged by the data that we've generated. We think it's supportive of progressing the candidate towards pivotal Phase III trials. We think the data we generated shows that Blautix has unique potential to address all subtypes of the disease, including potentially IBS-M [mixed]. As you can see from the quotation at the bottom, you know many in the clinical arena would consider the prospects of having a treatment that could equally benefit both IBS-C and IBS-D with a very strong safety profile as particularly compelling.

Slide 4 – Blautix® – a novel approach to IBS

So moving on, just as a reminder of Blautix itself, Blautix is a single strain Live Biotherapeutic product. It is a purified, freeze-dried and encapsulated formulation of Blautia hydrogenotrophica which is a commensal strain found in the human gut. We manufacture this product in-house, and we have four patent families which provide us with patent coverage out to at least 2036.

Slide 5 – BHT-II-002: investigation of signals in IBS with Blautix®

In terms of the study itself, in the Phase II study, this was a randomised placebo controlled study. Importantly, we got feedback from the FDA and we used their endpoints in this study for both IBS-C and IBS-D, they are the ones that are recommended for registration type studies. We did this obviously because not only did we want to get an idea of effect size, we wanted to also use the correct end points to make sure that the pivotal development phase of Blautix is particularly well informed

In the study we recruited both IBS-C or IBS-D patients as defined by Rome IV criteria. Each of those cohorts was randomised 1:1 to receive either Blautix or placebo, and two capsules were administered twice daily for eight weeks of the treatment period.

Slide 6 – Trial overview: evaluating the efficacy of Blautix®

Now, in terms of the key endpoints of the study, the primary endpoint is based on the overall response rate of patients with either IBS-C or IBS-D. And just to explain the overall response rate in a bit more detail, it comprises of a measurement of pain – so patients have to show improvements in their weekly abdominal pain intensity – and also improvements in either stool frequency for IBS-D or still consistency for IBS-C and the patients have to show that improvement concurrently for 50% or more of the treatment period of eight weeks.

Also, we conducted pre-planned analysis of the primary endpoints including response rates in the combined IBS-C and -D group, and also analysis of bowel habit and pain components independently.

It terms of the patients recruited, we recruited 353 patients were randomised with eligible baseline criteria. We had 158 patients for IBS-C, 195 for IBS-D. We have clinical sites in both the US and the UK and Ireland and 64% of the patients came from the US. Overall, 75% of the patients were female. The primary endpoint calculations are based on this Full Analysis Set [FAS] of patients [N=353], but we also conducted analysis on the Efficacy Evaluable Analysis Set [EEAS, N=319]. So that [the EEAS] includes all members of the FAS who actually completed the eight-week treatment period and assessment period without major protocol violations deemed to potentially impact the assessment of efficacy, so the efficacy evaluable analysis set is useful because it obviously indicates patients with better compliance and is normally considered to be a better measure of the effect of the treatments.

Slide 7 – Blautix® vs Placebo: combined group

So, moving on now to talk about the results in a bit more detail. I will start by discussing the results that we obtained in the combined IBS-C and -D group. You can see on the slide here that actually we obtained a statistically significant increase in overall response rate of 6.6% compared to placebo.

Looking at bowel habits in terms of bowel habit responders, we obtained statistically significant improvement in bowel habits of 13.1% compared to placebo. And in terms of the pain component, we obtained a statistically significant improvement of abdominal pain responders of 6.5% [compared to placebo], and just to note that given the nature of this Phase II signal finding study, the significance level was set at 0.1 in this study.

In terms of points of interest in the combined group, obviously we're getting indications here that Blautix could be used to treat both IBS-C and IBS-D which is not currently available with approved therapeutics and also potentially as a result, IBS-M. Looking at the Efficacy Evaluable Analysis Set of this population we actually showed, as you might expect, an enhanced response rate at 8.4% [compared to placebo] and reduced P value.

Slide 8 – Blautix® vs placebo: IBS-C

So moving on to look at the different subtypes of the disease. If we look first of all at IBS-C, you can see that in IBS-C in terms of overall response we had an increase over placebo of 7.9%. And looking at the improvement in bowel habits in IBS-C patients we saw an increase in response of 14.1% over the placebo which was statistically significant, and also an improvement in abdominal pain responders of 7.2%.

The IBS-C population was actually the smaller of the two, with 76 patients in total, treated with Blautix, but once again, the Efficacy Ealuable Analysis Set showed a higher response rate overall, 10.1%, and a nominally significant response rate increase to placebo of the P value of less than 0.1.

Slide 9 – Blautix® vs placebo: IBS-D

Then moving onto IBS-D. In terms of the overall response rate, we saw an increase compared to placebo of 5.6%, a statistically significant increase in improvement in bowel habits of 12.2% compared to placebo and an improvement in abdominal pain of 6%. The IBS-D patient population was slightly larger than the IBS-C with 94 IBS-D patients receiving Blautix, and again the Efficacy Valuable Analysis Set showed an enhanced response.

Slide 10 – Comparable efficacy to approved ibs products

So just to put those results into context and looking at the relative risk versus placebo of the results that we obtained in our Phase II study and comparing those to the results that have been obtained from published pivotal studies of other approved IBS products.

You can see that for both IBS-C and IBS-D, we're generating signals of the efficacy that are comparable and within the confidence limits of other approved products of both IBS-C and IBS-D. Obviously with Blautix we have the potential to treat both IBS-C and IBS-D. And it's also worth noting that these comparative studies are typically three to five times the size of the Phase II study that we conducted with Blautix. So, we think this is a very encouraging signal that we've seen here in terms of the ability for Blautix to have efficacy in both IBS-C and IBS-D and very supportive of our Phase III development of this asset.

Slide 11 – Blautix® vs placebo: no discernible difference in safety

Another important feature as I have said is the safety profile of Blautix. Obviously in treating IBS there are a number of products out there that do have significant side effect profiles. With Blautix we saw no discernible difference in safety compared to placebo either in terms of all adverse events [AEs] that emerged in both of the groups, Blautix or placebo, over the course of the treatment period, and also in severe or serious adverse events which were very small in number, equivalent for both Blautix and placebo with none of the treatment related severe or serious adverse events were actually treatment-related themselves.

And if you look actually and compare the treatment discontinuation due to AEs, and you look at the relative risk that we obtained with Blautix and compare that to the other products, you can actually see quite clearly that a number of these products have relative risk which show that they are significantly worse than placebo in terms of the adverse event profile that they generate.

So that concludes the results of the study. I'll now handover to Glenn Dourado to actually give you a bit more of the commercial context of the results and on our plans for Blautix.

Glenn Dourado, Chief Business Officer, 4D pharma

Slide 12 – Market statistics and us patient pop by subtype

Thank you Alex. So I will now take you through an overview of the IBS market data. So, the first thing to note is that there are three subsets of IBS patients, specifically those with constipation or IBS-C, those with diarrhoea or IBS-D, and those that are mixed or IBS-M, which are patients that fluctuate between IBS-C and D. The three subsets each represent roughly a third of the total market.

The next thing to note is that only IBS-C and IBS-D have approved products, which treat a relatively large percent of the US population per year, but these therapeutics are far from ideal. For example, for IBS-C, the leading agent is linaclotide, which has a mechanism of action that produces significant AEs, including diarrhoea and pain, and for IBS-D rifaximin is an antibiotic with the potential for patients to develop resistance over time.

In contrast, there are no approved treatments for IBS-M, which results in a dilemma for physicians with respect to what to prescribe because these patients that fluctuate from IBS-C to IBS-D or vice versa. So, prescribing a specific therapy can be problematic and often results in discontinuation of treatment.

With the IBS-C and IBS-D markets, the annual instance accounts for roughly 30 to 45 million patients per year in the US alone, with the majority of IBS sufferers being female. The US market in 2024 is projected to be 2.4 billion, but we believe this is an underestimation of the market opportunity because a number of patients discontinued treatment due to adverse effects of existing drugs and because IBS-M is not specifically addressed with current therapeutics. Next slide.

Slide 13 – Globaldata ibs market analysis to 2026: KOL comments

So the key message from KOLs [Key opinion leaders] is that IBS-M remains a significant unmet medical need with no approved therapies to date, but beyond this, beyond IBS-M, currently available drugs for IBS-C and IBS-D don't work perfectly for all IBS patients and many patients end up discontinuing treatment early because of the high percentage of AEs. The Phase II study positions Blautix well to address these concerns, as it can be equally beneficial to both IBS-C and -D patients with a strong safety profile. Next slide.

Slide 14 – Blautix : planning to bring new solution to IBS market

This final slide outlines the three key issues in the IBS treatment paradigm and how Blautix can be used to address these concerns. As previously noted, the IBS-M population does not easily fall into either the IBS-C or -D categories. The Blautix Phase II data demonstrated that the primary endpoint was met in the IBS-C and -D combined group, showing that Blautix can have utility in IBS-M patients. Plus, there were strong trends in the individual subgroups of IBS-C and D.

Secondly, Blautix addresses physicians' concerns with current therapies because its safety profile is comparable to placebo. And finally, poor patient compliance is common due to the debilitating symptoms of inconsistent bowel movements. With Blautix we have seen strong trends in the improvement of bowel habits to even out patients' bowel functions.

So, in conclusion, Blautix is the first therapy to show signals of efficacy in both IBS-C and -D and it has the potential to be the first therapy ever developed for the treatment of IBS-M patients. And finally, we will continue to analyse the Phase II data to guide Phase III pivotal trial designs. And so, with that I will turn it back to Duncan.

Q&A

Duncan Peyton, Chief Executive Officer, 4D pharma

OK, I'd just like to extend thanks to Alex and Glenn for presenting this data today, as well as the team which was led by Louise at 4D pharma for doing an exceptional job in getting this data together for us in a really compacted period of time. But now I'd like to open it up to questions from the analysts on the phone.

So maybe we start with Olga from Bryan, Garnier & Co.

Olga Smolentseva, Bryan, Garnier & Co.

Hi, thank you for taking my questions. The first one would be, could you speak in more detail about Full Analysis Set versus Efficacy Evaluable Analysis Set? I'm just wondering how many patients sort of violated the treatment protocol and for which reasons.

Dr Alex Stevenson, Chief Scientific Officer, 4D pharma

Thanks Olga. Yeah so in terms of the Full Analysis Set compared to the Efficacy [Evaluable] Analysis Set, obviously the patients who violated the treatment protocol were lesser likely to show efficacy. And in terms of the number itself, we're looking at around about 40 patients in total who actually were excluded for the Efficacy Evaluable Analysis Set compared to the Full Analysis Set. So clearly the ones in the Efficacy Evaluable Set are better compliant and they are a better indicator of treatment efficacy.

Olga Smolentseva, Bryan, Garnier & Co.

Great thank you. And maybe a little bit on the pain improvement score. While bowl habit improvement is really encouraging, the improvement in pain seems sort of on the low end in both placebo and treatment groups. Was there anything specific maybe about the recruited patients that could make them sort of less responsive on that criteria?

Dr Alex Stevenson, Chief Scientific Officer, 4D pharma

Thanks for the question. So as I said, we're looking into some more detailed subgroup analysis of the patients that are coming in. I would say that obviously pain is a slightly less objective measure than stool when it comes to patient reported outcomes, so that's one thing we're looking into. Yes, you're right, the effect on stool consistency with always particularly strong and slightly less than pain, but we've still got a lot of analysis yet to do.

Olga Smolentseva, Bryan, Garnier & Co.

Yeah, thank you again. And if I may just ask one last question. I'm wondering while the etiology of IBS is not fully understood, how should we consider IBS-M? Is it somewhat clinically close to early-stage IBS-C or -D, and maybe are there any additional data that point towards the role of microbiome in IBS-M population specifically?

Dr Alex Stevenson, Chief Scientific Officer, 4D pharma

Yes, it's very good question. So, in terms of you know IBS-C and -D and the drugs that are approved, they are very much approved on the symptoms that are present. In talking to gastroenterologists, it's acknowledged that many of these patients actually do fluctuate from C to D or back again, and in some cases with IBS-M it's pretty hard to actually put a definition of whether it's IBS-C or IBS-D.

Our analysis that we've done in relation to looking at the microbiota of subjects with all different subtypes of the disease actually indicates that there's commonality between those different subtypes, so that what you actually might be looking at is the same indication you just looking at different manifestations in terms of constipation or diarrhoea.

Duncan Peyton, Chief Executive Officer, 4D pharma

OK, maybe if we turn to Edward from N + 1 Singer.

Edward Thomason, N+1 Singer

Hi guys, thanks for having me on the webinar. A few questions if I may. One is probably just talking about the statistics of the trial and particularly why you've used a 0.1's level of significance, and then I'll ask follow-ups on that.

Dr Alex Stevenson, Chief Scientific Officer, 4D pharma

OK yeah, thanks, thanks Edward. So obviously this wasn't a registration study. This is a signal finding Phase II where it's more common to use a higher alpha value and 0.1 is not atypical for this type of study. And what we're trying to do here is actually in relatively small patient groups to see signals that we can then use reliably to help design the pivotal trial. Obviously a pivotal study is likely to be, or will be, larger and will be more stringent in terms of the P value that's applied.

Edward Thomason, N+1 Singer

OK, and then I guess connected to that is probably just why do you think you saw significance for the combined group but not for the response rates for the individual subtypes and is that is that something to do with the effect of the drug specifically for those groups or with mixed biology and it favours that the development path for IBS-M or just a bit of understanding about that would be useful.

Dr Alex Stevenson, Chief Scientific Officer, 4D pharma

Yes, sure. Sorry, just to clarify, we did the combined analysis on IBS-C and IBS-D as part of the prescribed analysis that we're doing on the study and that was really just a combination of the IBS-C and IBS-D results that we'd obtained, so it really reflects I think the fact that we've got obviously an increased number of subjects within that combined group, so it shows you that that actually, in a larger study such as a pivotal study, you are actually going to have a more significant result when it when it comes to those increased numbers of patients, if that makes sense.

Edward Thomason, N+1 Singer

Yeah, follow that. And look two more if I may. I just want to understand the intention after this. Whether you talk about plans for Phase II, would that be again across all subtypes or just for IBS-M or and again, just the corporate strategy for Blautix now and whether you will look to do develop this independently or with a partner.

Duncan Peyton, Chief Executive Officer, 4D pharma

That's a good question, Edward. I think you know we're still going through the analysis as is, working out what the trial would look like, so it's still early days in terms of exactly which path we're going to take. I think, as you know, and I'll let Glenn come on this, we've been talking to a few potential partners as well, so we'll follow all those conversations as well, Glenn?

Glenn Dourado, Chief Business Officer, 4D pharma

Yeah, thanks Duncan. Just to add on tha, we have been in constant contact with all the major players in the IBS space as well as other companies that have expressed interest given the stage that the program is at, and so a number of them were waiting for these Phase II results to be released so we'll certainly follow up with them and see where the interest lies but there is definite interest from major players.

Edward Thomason, N+1 Singer

OK, good to hear, when are we probably going to be expecting the data, the full data from the IBS trial then?

Dr Alex Stevenson, Chief Scientific Officer, 4D pharma

So that will be before the end of the year.

Edward Thomason, N+1 Singer

OK, alright. Thanks for having me.

Duncan Peyton, Chief Executive Officer, 4D pharma

Thanks Edward. Got Sam from Chardan. Sam you got a question?

Sam Lee, Chardan

Hi can you hear me OK?

Duncan Peyton, Chief Executive Officer, 4D pharma

Yeah fine.

Sam Lee, Chardan

Great, this is Sam on behalf of Gbola. Congrats on the data by the way. Actually most of my questions have already been answered, but maybe just a little bit outside the box thinking. With the data you've seen so far, is there any indications that you could potentially use this to expand to IBD indications? Namely, all sort of colitis and Crohn's disease?

Dr Alex Stevenson, Chief Scientific Officer, 4D pharma

To answer your question, in actual fact, Blautix has been specifically developed for IBS in the endpoints that we're looking at and the effect that we understand that the bacteria actually has. We have no evidence that it would be suitable for IBD. Obviously we do have other programs that we are, you know, that we have pursued and developed in relation to IBD, but Blautix is specifically for IBS.

Sam Lee, Chardan

Got it, thank you for taking my question.

Duncan Peyton, Chief Executive Officer, 4D pharma

OK, Prakhar you got a question?

Prakhar Agrawal, Jones Trading

Ah yeah, congrats on the data guys. So I had a question on the baseline characteristics of the patients. I know you're going to be presenting the full data set later in the year, but any colour there, specifically, what was the baseline let's say mean abdominal score pain for patients, just trying to see how this patient population compared to some of the other trials for approved drugs, and I had one more question.

Dr Alex Stevenson, Chief Scientific Officer, 4D pharma

OK so, so the patients had IBS-C and IBS-D as defined by Rome IV as well as having moderate or severe IBS symptoms severity score of equal or greater than 175 at the screening visit as defined by IBS-SSS. So in terms of recurrent abdominal pain, on average for at least one day a week in the last three months, associated with two or more of the criteria related to either defecation, changing frequency of stool or associated with changing of the appearance of stool. So, the criteria must have been met for the last three months, with symptom onset at least six months prior to diagnosis. If that makes sense. We haven't actually got out, so we haven't actually got the full breakdown yet of all the data, but obviously that will follow in due course.

Prakhar Agrawal, Jones Trading

Got it. And I guess on the IBS-M opportunity that seems very interesting to me. What's the development plan there? Do you have to, do you have to run like a Phase III do you? Are you running a Phase II right now, or could you just include those patients in the pivotal trial?

Dr Alex Stevenson, Chief Scientific Officer, 4D pharma

Well, the Phase II was specifically designed to give us an indication of the effect size that Blautix has in both IBS-C and IBS-D and it's done that, it's achieved that objective and that will then lead to development of the Phase III design based on those results and we'll also think about ways of potentially looking at perhaps some subpopulations or maybe even IBS-M subjects as well, but that's all for the future and under consideration given the results that we've generated.

Prakhar Agrawal, Jones Trading

Got it, thanks for answering my questions.

Duncan Peyton, Chief Executive Officer, 4D pharma

OK, do we have any more questions?

Edward Thomason, N+1 Singer

Hi Duncan, sorry Edward again. Just one last question was on dose and given the excellent safety profile, is it something that you would look to maybe investigate a higher dose of Blautix?

Dr Alex Stevenson, Chief Scientific Officer, 4D pharma

Well, given the dose in that we're giving is two capsules twice a day, with 10^{10} CFU per capsule. So we've shown in preclinical and now obviously in the clinical setting, that we are seeing an effect there. We don't have from the preclinical data any evidence of a dose response actually with Blautix, so it appears to be very much based around a threshold in the preclinical models, so, you know that's the that's the discussion that we've had with the regulators to date and that's our belief.

Edward Thomason, N+1 Singer

OK, thanks.

Duncan Peyton, Chief Executive Officer, 4D pharma

OK time for one more. Olga?

Olga Smolentseva, Bryan, Garnier & Co.

Yeah, thank you, just I was just wondering basically in the follow up data, you related to the beginning, could we also expect some secondary endpoints, such as fecal microbiota profiles, severity scores, etc.

Dr Alex Stevenson, Chief Scientific Officer, 4D pharma

Yes, so we will be analysing all that data in due course and that will be released.

Olga Smolentseva, Bryan, Garnier & Co.

Thank you.

Duncan Peyton, Chief Executive Officer, 4D pharma

OK guys, thank you very much for listening in. I think it's been another good step forward for 4D pharma. The trail's performed as we wanted it to do in terms of allowing us to develop a pivotal Phase III trial and we look forward to keeping you updated in the future. Thanks very much for your time.