Sun Pharma Advanced Research Company Ltd.
Transcript of Update on Baclofen GRS Phase III Topline Results
4.30 PM, October 09, 2017

PARTICIPANTS:

ANIL RAGHAVAN – CHIEF EXECUTIVE OFFICER

SIU-LONG YAO – SR. VICE PRESIDENT, CLINICAL RESEARCH

NARENDRA LAKKAD – VICE PRESIDENT, BUSINESS DEVELOPMENT

CHETAN RAJPARA – CHIEF FINANCIAL OFFICER

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Moderator: Ladies and gentlemen, good day and welcome to SPARC's update on Baclofen GRS pivotal studies. As a reminder, all participant lines will be in the listen-only mode and there will be an opportunity for you to ask questions after the presentation concludes. Should you need assistance during the conference call, please signal an operator by pressing '*' then '0' on your touchtone telephone. Please note that this conference is being recorded. I would now like hand the conference over to Mr. Narendra Lakkad. Thank you and over to you, sir.

Narendra Lakkad: Good evening and a warm welcome for the update on Phase 3 studies of Baclofen GRS.

The call transcript will be put up on SPARC's website soon.

It would be appropriate to mention that the discussion today may include certain forward-looking statements and this must be viewed in conjunction with the risks that SPARC business entails.

During today's call, we will try and answer all your questions, but if time does not permit I request all of you to please send in your questions to me.

I now hand over the call to our CEO, Mr. Anil Raghavan. Over to you Anil.

Anil Raghavan: Thanks Naren.

Good evening everybody. Thank you all for joining this call on such a short notice. As Narendra said, I am joined today by Dr Siu-Long Yao and Mr. Chetan Rajpara. Siu heads our clinical development, and Chetan is our Chief Financial Officer.

We have shared with you the headlines from the top-line results of our Baclofen program last Friday. We are obviously disappointed at the outcome. We think it is important to share with you the results in a bit more detail, offer some direction on

the next steps and discuss the potential impact on our broader portfolio. I will keep this really brief so that we can have sufficient time for our Q&A.

Let me start with an overview of the study data.

Our pivotal study was a placebo controlled, randomized withdrawal study to evaluate the safety and efficacy of Baclofen GRS in Multiple Sclerosis patients with muscle spasticity. In this study, patients are put on a stable dose of Baclofen GRS for 8 weeks before a randomly selected half of patients are titrated down to Placebo. This happens over a four week stretch.

During these four weeks, physicians assess the extent of spasticity and overall well-being of patients using a set of specialized scales. They use something called a Modified Ashworth Scale as a measure of spasticity, and an instrument called the CGIC or Clinician's Global Impression of Change to determine the well-being of patients.

In this study design, it is expected that patients randomized to placebo will fail and do worse on these measures of drug benefit over the 4 week period when drug is withdrawn. Specifically, treatment failure was a composite outcome involving a one point drop in the Modified Ashworth Scale coupled with a rating of 5 or above in the CGIC (ratings of 5, 6 or 7 correspond to categories of Minimally Worse, Much Worse and Very Much worse). So for a patient to fail, he or she had to meet both of these criteria.

We had 293 patients in the trial in the Intent to treat group, 147 on Baclofen and 146 on Placebo. We had 53 treatment failures on the Baclofen arm vs 63 treatment failures on placebo. Even though, we had a lower number of treatment failures with Baclofen, it did not meet the threshold of statistical significance. The p value for the study was approximately 0.2.

This study had a secondary end point called the SGIS. The SGIS or Subject Global Impression of Severity is a patient reported outcome. Patients rate whether his or her spasticity is getting better or worse. The rating is somewhat similar to the CGIC. Here Baclofen fared much better, reaching statistical significance with a p value of 0.0485 on patients rating the outcome as normal or no spasticity. Baclofen also reached statistical significance on several exploratory end points such as Night Time Awakenings, Spasm Frequency etc.

We also had a smaller companion study to ascertain the duration of action of Baclofen GRS over a 24 hour period. Baclofen did not demonstrate a statistically significant difference compared with the placebo arm in this duration of action study.

So overall it's a disappointing outcome even though there was a trend favouring Baclofen and statistically significant differences on the secondary end-point and many of the exploratory end-points. In terms of next steps, we received the top line results late last week. We will have the complete data set in the next week or so. We will have to spend some time reviewing the results before deciding on the fate of the program. We may also consult FDA if we determine that there is value in such a consultation after our review of the data.

Please allow me to make a few broad comments before we open things up for the Q&A. As I mentioned, this is certainly a setback for all of us. While it is indeed a dampener, we also realize this is the nature of our business. We need to stay focused and execute on our portfolio. We have several important and potentially valuable programs at various stages of clinical development. We discussed these clinical stage assets recently with you in our annual investor call. We intend to stay the course on our portfolio. At the same time, we also need to learn from this experience. We will reflect on our technology, our protocol, execution and our data to determine the key takeaways from the program and make adjustments to our processes and operating

model if necessary. Some of the broader changes have already been underway in the last couple of years, like strengthening our go-no go decision making for clinical stage assets, increasing the rigour of clinical design etc.

Now from a cash flow standpoint, an outcome like this will certainly impact our ability to prosecute the clinical agenda fully. We may have to make some choices and make changes to the way we were looking at our portfolio at the beginning of this year, primarily because of the revenue challenges an outcome like this will pose. We may have to look at partnering some of our products earlier than our current plans. Expected cash flows from this program were important for us in the medium term – 12 to 18 months. We still have access to a significant part of the preferential issue from earlier this year in addition to our regular royalty revenues. We will review our program priorities and cash flows very closely in the coming weeks to understand our options and take important 'resource allocation' decisions.

Thank you very much for your time today. We look forward to your continued support. We look forward to your questions, comments and suggestions if you have any. Thanks again.

We will now open up the call for the Q&A.

Moderator: Thank you very much, sir. Ladies and gentlemen, we will now begin with the Question-and-Answer Session. First question is from the line of Dheeresh Pathak from Goldman Sachs. Please go ahead.

Dheeresh Pathak: Sir, just to understand better and I don't have good technical background of how to interpret these results, so just bear with me. The Phase-III data in your comment you said 50:50 split between Baclofen and the Placebo and then you said some 53 had fallen back and versus some 63 for the Placebo…some number you shared. That endpoint result, how did that compare to the Phase-II success we had, I am just trying to understand

that in Phase-II did we saw material endpoint success for the drug and then in Phase-III there is no statistical significance, just trying to understand what has happened, how was the data different if you can contrast it to Phase-II data?

Anil Raghavan: Sure, your understanding of the protocol and the way the results pan out was absolutely correct. We have randomized this trial into 50% going to Baclofen GRS and 50% going to Placebo and you accurately captured the failure rate in terms of actual number of patients meeting this composite endpoint, that is a treatment failure. If you look at this rate and we mentioned that it fails because it does not meet the statistical significance even though it has a clear trending. Program did not have a specific Phase-II part. In a reformulated asset like this, what happens is you do a series of pharmacokinetic studies and you get a sense of how the drug distribution pan out before taking a call to do a confirmatory study. In that sense, like you see in NCE program you have a full-fledged Phase-II program and then you try to confirm that with the registration program. Here in a reformulated program, usually what you have is the PK study and that is what we have done in this program. So it does not have data which we can go back and check from a conventional Phase-II program.

Moderator: Thank you. The next question is from the line of Ketan Gandhi from Gandhi Securities. Please go ahead.

Ketan Gandhi: Sir, what is your key learning from this failure?

Anil Raghavan: Thanks, Ketan for that question. I think that is a really-really important question. At this point, it is probably too early to answer that question. As I said, we have the top line results coming in last week and we expect to have the full data on the program sometime towards the end of this week and we need to go through a full analysis of the full data set before we conclude what we could have done differently. There are so many variables to that question. There is obviously the question of whether the technology underperformed. I do not know whether

you assimilate, this program was done on a protocol negotiated with FDA. So there was very little leeway in terms of devising the protocol because of the expectations from the FDA. Protocol per se is something which we need to look at and see whether any changes would have made any difference to the outcome. At a broader process level, we also need to look at our translational process per se in terms of the preparatory study that we do before we actually move assets to the clinical program. So we will actually look at all these factors once we have visibility to the full data set and we hope to take appropriate lessons from this experience.

Ketan Gandhi: Sir, in your opening remarks you said for cash flow management we have to partner some of the molecules. So just wanted to understand whether it will be late stage molecules or early stage molecules?

Anil Raghavan: If you follow our investor calls in the past, one of the approaches that we have actually pursued in prosecuting our portfolio was we stayed away from the temptation of out-licensing compounds early on in its development cycle. But now as I said this will have very definitive cash flow impact this year and probably next year also because we were expecting milestone payments coming from Baclofen in both FY '18 and also in FY '19. So we may probably look at resourcing our late stage programs while selectively out-licensing some of our early stage programs. But at the same time this is too early to commit to any particular direction. That is one of the options that we have and we want to look at all our options before deciding if we take out a program and out-license early on, because we want to do that in a considered manner.

Moderator: Thank you. The next question is from the line of Manish Jain from Sageone Advisors. Please go ahead.

Manish Jain: Just wanted to understand in terms of near-term or medium-term cash flow opportunities. I was looking at abuse deterrents, DPI and PICN besides the two molecules which are waiting for

Halol or alternate site to come in. So between abuse deterrent, DPI and PICN, roughly when approximately you will get an idea on the go/no-go on the commercial side?

Anil Raghavan: Thanks Manish, as you said, there are two programs which are linked to remediation at Halol which can give us short-term cash flow which as you know is Xelpros and Elepsia and we are also pursuing Plan-B. I will take 12-18-months horizon from a cash flow expectation standpoint. There is no, go/no-go situation here because from a clinical data acceptance standpoint, the complete response letters did not set any ask in terms of additional data. So in that sense as soon as we can have facility shifted they are revenue opportunity and we already out-licensed them and there are incremental revenue opportunities there. On Sal – Flu, we have updated you last time, it is a smaller opportunity but we are going through the regulatory consultation at this point and in the next few months we will have an opportunity to receive feedback and we will have to then decide. The key question there is "Do we need to do any incremental studies?" And then if we need to do incremental studies, then we need to weigh that against other opportunities. We will have information to take the decision in the next couple of months or so. For PICN, we are in full recruitment mode now and that is again a significant opportunity and we will see conclusion of that program from a clinical study standpoint sometime in early first quarter of FY'19. That would be the commercial go/no-go position for PICN. So that is the next level of programs after Xelpros, Elepsia bucket at the top of the list. And then we have several data points now coming in, in the next 12-months or so which will give us multiple opportunities. We will have the pilot human liability study on our first asset on the abuse deterrent platform and our study is now as we speak getting triggered and we will have conclusion on that study this year itself. So that along with the PK outcome that we had earlier this year gives us the validation for the program and the platform. That is a significant go/no-go decision point for abuse deterrent platform. If that is validated, that will trigger the

registrational studies and our hope is that we will be able to complete the registrational program with a stretch target by end of the FY '19 or reasonably by first half of FY '20. And then at the platform validation level, we will also start adding more programs to that portfolio of abuse-deterrent platform. We are doing this validation with one asset and then we hope to add at least two to three more programs to that platform once we have platform validation. So that is an important data point to come. The second program where we expect to have go/no-go data coming in in the next three, four months or so is S597, the Dermatology program. We are now doing proof-of-concept Psoriatic plaque study, the study is being recruited in Germany and we expect to see an outcome from this study coming sometime in December of this year. Third, really significant program is our K0706 CML program. We are currently going through the early stage patient study and by end of this year we will be able to complete that study and we hope to get back to FDA to negotiate our registrational protocol with FDA. Our intent on the K0706 CML program is to get to a registrational study sometime in April. These are the data that we are expecting. And then I also want to talk about a few programs where we already have data and we have an opportunity to start the Phase-III program. First is the program that we discussed when we had our annual investor call, Brimonidine OD. We had a successful Phase-II program and we are actually looking at the possibility of initiating the Phase-III and we are preparing an FDA consultation on the Phase-III protocol. Similarly, another ophthalmic program, we have not disclosed the key asset, but we spoke about this program in our investor call and that is also now Phase-III ready. So there are these two Phase-III ready ophthalmic asset and we also have a couple of more programs in the auto-immune Dermatology area which are getting ready for the clinic and we spoke about Minocycline and also the EDG-1 program which is now going into the Phase-I trial. So as you can see, we have late stage revenue opportunities with the programs at the top of the list and then we also have some licensing options if we want to pursue that as a possible way forward to bridge the cash

requirement. Before I conclude I want to give priorities on K0706 CML, abuse deterrent platform and the K0706 repurposing on neurodegeneration. These are all game-changing possibilities for us and our intent would be to protect the momentum of these programs even if we have to strategically partner some of the programs on the early stages of this portfolio. That is our current top of the mind thinking, and as I said we need to go through a full analysis of our options before we conclude how we perform.

Manish Jain: Just one question is a little difficult one for you to respond now, but given a choice between licensing a molecule prior to FDA approval and raising more equity, what will you prefer?

Anil Raghavan: I do not want to come to commitment at this point in terms of a specific path that we want to take. Both options are valid options for a company like ours. Even though this is a setback, we have a lot of confidence in the overall set of assets in our portfolio. Raising capital to pursue that fully is an attractive strategic option. At the same time, we can also take a more conservative view and pursue this in a financially prudent from a cash flow standpoint by taking out some of the programs. But it is not just a cash issue, we also need to look at the management bandwidth to manage clinical portfolio of this size. Even before the Baclofen outcome, we had questions in terms of what is optimum size of a clinical portfolio that we can effectively prosecute. It is not just a question of how much cash and capital that we have at our disposal to pursue these assets. We also need to look at how much bandwidth that we have and what we can do with what resources we have.

Moderator: Thank you. The next question is from the line of Sameer Baisiwala from Morgan Stanley. Please go ahead.

Sameer Baisiwala: Anil, a quick question, I am just pulling out from my memory. If I am not wrong, you had launched Baclofen GRS in India a few years back and I remember that you had got a pretty decent market share as well. Is that understanding correct and then how do you explain that the product has been approved and was

allowed in India and has been doing well? I am sure the patients must be getting benefited and then it does not meet the primary endpoint when you go outside.

Anil Raghavan: So we need to go back and look at the study that we have done. In fact, if I remember right, it was actually approved through a bioequivalence route, through PK study.

Narendra Lakkad: Sameer, it was approved through another study which we have designed as per requirement of DCGI in India at that point of time. The current study was designed as per the requirement of USFDA. We do not feel failing on study in the US will have any impact on the product which is in market in India.

Sameer Baisiwala: Anil, this product must have been there in India treating patients for last few years. Would you not be collecting data that sort of mirrors your clinical primary endpoints that you later on plan for the US and the Europe, would you not have access around this data and could have arrived at a decision whether or not this product can meet the FDA hurdle?

Anil Raghavan: It is actually a difficult question, Sameer. The reason why this is difficult is, if you look at the reason for the results that we have is because of set of measures FDA mandated, like the instruments like CGIC or Ashworth Score. In actual practice setting, patients do not go through those kinds of instruments on a daily basis. If you do Phase-IV study in a large number of patients it is not feasible to collect data at that level of depth. So I do not think we could have actually taken Phase-IV opportunity in India to validate the possibility of getting confirmatory set of data from India because of the complexity of the design. Again, just to go back to the question that you had earlier. The real issue in this is, you have unusually strong placebo response and that also varies from study-to-study, in that sense, Phase-II study that passed does not necessarily guarantee clean out come in a Phase-III program because of the variability of the placebo response in indications like this.

Sameer Baisiwala: Anil, can we make the same assumption for your Sal – Flu DPI as well that it has been in the Indian market and it has been selling well, feeding patients, but even that did not cross the primary end point hurdle outside?

Anil Raghavan: Sal – Flu issue is slightly different, the variability in Sal – Flu's case is with the reference product, if you look at the lower dose product where we did not meet bioequivalence, that is primarily driven by the variability of the innovator formulation, in fact, there we have some strengths which are actually playing against us because our device is delivering at a much more consistent level and also at significantly higher level of PK. So the bridging that with a product which is not as is effective in delivering Sal – Flu is the challenge there.

Sameer Baisiwala: Anil, just shifting gears very quickly on the two lead compounds – Xelpros and Elepsia -- what is the status right now -- have you commenced the site switch, I remember in last call you mentioned that you would see which of the two could be faster, so where do you stand on that?

Anil Raghavan: Yes, we did commence the site transfer, so we have now batches being taken from these alternative sites, for one product, it is sourced from within network of our commercialization partner, and in another case we have gone ahead with an external CMO. Both these cases now exploratory batches are being taken. So the plan that we have laid out during our analyst call still holds.

Sameer Baisiwala: So would you say that it is another three to six months away or longer or shorter?

Anil Raghavan: No, it will be longer because the manufacturing per se would be done much earlier, but if you look at the stability data requirement is quite long and that itself needs to be negotiated because if we just go by the letters, regulatory expectation for one product is 12-months of stability data and then we also need to do a clinical bridging for one product, that is we need to do PK study and demonstrate that these two batches are

comparable from pharmacokinetic standpoint. So there is work that we need to do subsequent to taking these batches. The expectations that we set earlier this year was that we will be able to do that sometime in the second half of next financial year, that is where it is headed.

Moderator: Thank you. We have a follow-up question from the line of Manish Jain from SageOne Advisors. Please go ahead.

Manish Jain: Yes, Anil, I was just actually extending to what Sameer was asking to PICN. Given that even PICN has been actually launched in India, I was looking at the reproducibility of those results in the US trial. So what all differences that you potentially foresee vis-à-vis Sal – Flu or Baclofen in PICN study?

Narendra Lakkad: Manish, PICN was registered in India based on a different study. We did head-to-head efficacy study in breast cancer patients comparing PICN with Abraxane and we established similar safety and efficacy to Abraxane. Based on this clinical study, the product got approval in India. In US, registrational study is a bioequivalence study, where we will be doing PK equivalence of Cmax and AUC between Abraxane and PICN. So it is a different study. Similarly for, Sal – Flu, we designed efficacy study in Asthma patients in India. Based on efficacy study, we got the product registered in India. In the Europe, the requirement is based on PK study. So we are doing PK study where we have seen that at a lower strength, we could not establish the PK because the innovator product did not behave the way we expected to behave. So study designs are different, based on the requirements of the regulators in their respective regions.

Moderator: Thank you. We have a follow-up question from the line of Dheeresh Pathak from Goldman Sachs. Please go ahead.

Dheeresh Pathak: Just to understand the placebo arm would have no drug or would it have the IR formulation of Baclofen?

Anil Raghavan: No, the placebo arm would not have drug. So in this case, what happens in the Baclofen study is that the patients will be on steady dose of Baclofen GRS and then they would be dose titrated, that is you bring down the dose on a gradual manner to placebo. So placebo would not have drug, it will have the excipient but it will not have the drug.

Dheeresh Pathak: One arm is getting Baclofen and the other arm is not getting any drug. So at least the benefit that Baclofen IR had, that benefit at least should have shown. So are we seeing it is a grid technology failure. I am just trying to understand where it failed?

Anil Raghavan: No, I would not characterize that way, Dheeresh. What happens in CNS drugs is that there is a significant placebo effect. Usually the study fails because of the duration it takes to wash out the placebo effect, and over a period of time the placebo effect wanes then the actual drug comes back up. There are several design questions which could have led to this outcome. In fact, if you look at the patients on assessment of spasticity, we had statistically significant outcome on that. So in that sense, the patients are actually feeling that they are getting better on these key outcomes. There are several aspects of this design which requires a full analysis to understand what really caused the failure.

Siu-Long Yao: I just want to add to what Anil is saying. I think with respect to the technology and the placebo effect, I think based on what we know today and the trend in the primary end point as well as the secondary exploratory endpoints, I think you can be pretty confident that the drug is having an effect. As Anil has said, I think part of the issue is some of the ways that the activity is assessed, so for example, we alluded to differences in ways that activity of drugs are assessed in the US versus India and each region has a preference to how they would like the drug proven to be effective. So we have the challenges that one method is different from another method and you can get different results as a consequence. However, I am pretty confident that the drug

works, it is just a matter of demonstrating that activity to the various parties.

Dheeresh Pathak: Earlier when I had asked, you said you did not have a Phase-II study but you had PK study. So in the PK study, you had compared it to Baclofen IR or it was what did you compare it to in the PK study?

Anil Raghavan: It is compared to Baclofen IR.

Moderator: Thank you. Next question is from the line of Krishna Prasad from Franklin Templeton. Please go ahead.

Krishna Prasad: Just a quick clarification; would you continue to sell Baclofen now in India?

Anil Raghavan: Yes, we do not see a reason why we should reconsider because it was actually done on a successful study which was approved by DCGI.

Krishna Prasad: The other question I had was, let us say, when you started off this Phase-III trial for Baclofen, and internally what was your probability of success for this program?

Anil Raghavan: We do not assign individual probability of your success but for a class of programs in a certain stage of development, we have certain probability of success assigned based on historic data set, that was in the range of almost 70%. When I talked about looking at the lessons learned from this exercise and this is also a lesson that we have to go and revisit in terms of reliance on historic data in that class versus making a more specific estimation of the chance of the successes. These are questions that we may have to resolve as we go through this analysis.

Krishna Prasad: Just a follow-up to that, generally at what point do you decide to go ahead with the Phase-III, I mean, in this case, you said it was 70% and you kind of went ahead with it, but typically, where is the tipping point for Phase-III trial?

Anil Raghavan: The decision to go forward with the Phase III trial is not necessarily taken on an assessment of probability of success alone. You look at a set of scientific factors. In this case, let us look at the underlying problems. You have Baclofen IR program with certain level of dosing and it has a certain PK profile and it creates a certain set of compliance issues and also safety issues and we are trying to address those patient compliance issues and some safety issues using a once-a-day formulation by increasing the gastric retention. So there the key question is, "Can we actually achieve PK profile which is comparable to the multiple dose IR product?" In multiple PK studies, we had demonstration of the comparability of the PK profile. That gave us the confidence to go ahead with the strategy because mechanistically that is what matter.

Krishna Prasad: Do you think there is a need to have may be more experienced partners in maybe future programs, companies which have probably taken drugs to the market and who can thereby, help you to navigate some of these issues, is that something that you would probably consider more seriously going forward unlike what we have done so far which is typically partnered with Sun?

Anil Raghavan: There are multiple things to unpack in your question. So the partnership with Sun Pharma was done on these two programs after we completed Phase-III registrational programs, in that sense, that partnership was not aimed at augmenting our expertise level in clinical development. Just to go back to the construct of your original question, we have been saying this consistently, we recognized need for improving and augmenting our competency in clinical development area and we have been doing that consistently in the last couple of years. So we feel that we have come up quite some distance in terms of the maturity of the capability in that area. Once we go through this analysis and if we determine that it is the capability issue, then the argument that the approach that you are suggesting has some value. But it is premature for me to commit, that is the cause of what happened, but independently we are scaling up our clinical capability in line with the growth of our clinical stage portfolio.

Moderator: As there are no further questions from the participants, I would now like to hand over the conference to Mr. Lakkad for his closing comments. Over to you, sir.

Narendra Lakkad: Thank you. Since we do not have more questions we are closing this call. If there are any questions in future, we will happy to take over e-mail or phone. Thank you all for joining today's call.

Moderator: Thank you very much, sir. Ladies and gentlemen, on behalf of SPARC that concludes this conference call. Thank you for joining us and you may now disconnect your lines.