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EDITED TRANSCRIPT

ARCT.OQ - Arcturus Therapeutics Holdings Inc. - Special Call

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PRESENTATION

Operator

Greetings, and welcome to Arcturus Therapeutics Conference Call. (Operator Instructions) Please note this conference is being recorded. I would now like to turn the conference over to your host, Neda Safarzadeh, Senior Director and Head of Investor Relations, Public Relations and Marketing at Arcturus Therapeutics. You may begin.

Neda Safarzadeh *- Arcturus Therapeutics Holdings Inc. - Director and Head of IR/Public Relations & Marketing*

Thank you, operator, and good afternoon, everyone. We are joined today by Joseph Payne, President and CEO; Andy Sassine, CFO; Dr. Pad Chivukula, CFO and COO; Dr. Steve Hughes, Chief Development Officer; and Professor Ooi Eng Eong, emerging infectious diseases program at Duke-NUS Medical School and a member of Arcturus' vaccine Platform Scientific Advisory Board.

Before we begin, I would like to remind everyone that except for statements of historical facts, the statements made by management and any responses to questions on this conference call constitute forward-looking statements that involve substantial risks and uncertainties for purposes of the safe harbor provided by the Private Securities Litigation Reform Act of 1995. Any statements other than the statements of historical facts included in this communication including those regarding the likelihood that preclinical or clinical results will be predictive of future clinical results or sufficient for regulatory approval, the likelihood that the company will obtain clearance from regulatory authorities to proceed with planned clinical trials, the planned initiation, design or completion of clinical trials, the likelihood of success or of the efficacy or safety of the company's COVID-19 vaccine candidate or other product candidates, potential treatment regimen of the company's COVID-19 vaccine candidate, the likelihood that preclinical data or clinical data will be reflective of future clinical results or sufficient for regulatory approval, the ability to enroll subjects in clinical trials and the company's current and future cash and fund financial positions are forward-looking statements.

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Such statements are based on management's current expectations and involve risks and uncertainties, including those discussed under the heading Risk Factors in Arcturus' annual report on Form 10-K for the fiscal year ended December 31, 2019, filed with the SEC on March 16, 2020, and subsequent filings with our submissions to the SEC. Except as otherwise required by law, we disclaim any intention or obligation to update or revise any forward-looking statements, which speak only as of the date they were made, whether as a result of new information, future events or circumstances or otherwise.

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Now it is my pleasure to pass the call to Joe Payne, President and CEO. Joe, please go ahead.

Joseph E. Payne - *Arcturus Therapeutics Holdings Inc. - Founder, President, CEO & Director*

Thank you, Neda. Good afternoon to all. Thank you for joining us today in the heart of the holiday season. As Neda mentioned on the call today, we've got Pad, Andy, Steve and myself, but we're also fortunate to have Professor Eng Eong Ooi from the Duke-NUS Medical School with us. He's an esteemed expert in vaccines, and we look forward to hearing from him later on the call today.

2020 has definitely been a memorable year for all of us, and that's probably an understatement. Messenger RNA science, technology, therapeutics and vaccines are coming of age. We're definitely pleased to see the successes of the mRNA community this year and look forward to more successes and breakthroughs in 2021.

Today, we're going to be providing an update. And just looking at the screen to make sure we're following the same slide as the webcast. It looks like it's loaded. Today, we'll be providing an update on the continued progress in the development of ARCT-021 that's our vaccine candidate, targeting SARS-CoV-2 infection in COVID-19. ARCT-021 is a unique vaccine, utilizes Self Transcribing And Replicating messenger RNA or STARR is our trademark for STARR mRNA as well as our lipid-mediated nanoparticle or LUNAR delivery technology.

We believe the science underlying ARCT-021 may provide meaningful advantages compared to other COVID-19 vaccine approaches. We're pleased to announce today that we've obtained approval of the Singapore Health Sciences Authority to advance ARCT-021 to a Phase II clinical study in up to 600 subjects. This study is supported by a comprehensive clinical and scientific data set that includes our Phase I/II study results as well as extensive preclinical studies.

We plan to provide you with a detailed review of new and updated clinical and preclinical data on today's call. Together, the comprehensive data generated suggest that ARCT-021 result in a highly effective vaccine with a differentiated product profile. As a self amplifying mRNA vaccine, ARCT-021 has been designed to result in substantial immunogenicity even when administered at relatively low doses. Importantly, we believe that ARCT-021 may be effective when administered as a single dose or administration. Such a profile would provide obvious and important logistical advantages compared to the COVID-19 vaccines that are beginning to be used in various countries.

Indeed, in many areas of the world, the use of vaccines requiring multiple administrations will be impractical. We expect that the low doses evaluated with ARCT-021 provide additional advantages. We believe that the lower dose level may result in an improved tolerability profile. Also the requirement for lower doses is expected to increase our ability to contribute to the mass of scale of vaccines required across the globe in 2021 and beyond.

Based on the data we have obtained with ARCT-021, we expect to start our Phase II study soon. We've also submitted an IND to the U.S. FDA. And pending IND clearance, we expect to begin activating U.S. clinical sites early in 2021. Our expectation is that we will obtain interim Phase II study immunogenicity data in early 2021. These data are anticipated to enable the selection of a final dose and dose regimen for an ARCT-021 Phase III registrational study, and we expect to begin Phase III enrollment in the second quarter.

Until our human Phase III efficacy study data is in hand, what we do is we employ animal viral challenge studies to help us predict outcomes and to help us understand the probability of success. And I'm happy to report that a single administration of ARCT-021 has now been proven to be significantly effective in 3 separate challenge studies involving mice and now primates, as shown on this slide, number four.

We've previously reported success in a fatal challenge model in mice engineered with ACE2 receptors in their lungs, and these mice are very sensitive to SARS-CoV-2 infection. So much so that their -- the entire control group dies within days after exposure to the virus. But in the vaccinated arm, they were all robustly protected with ARCT-021 vaccination.

Here on this slide, we summarized new primate challenge model data that was included in today's press release. This primate challenge study was sponsored by the NIH/NIAID at Battelle Labs in Ohio. The lead NIH principal investigators were Dr. [Larry Wolfram] and Dr. [Janet Lacy], and we thank them for their contribution.

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As you can clearly see, ARCT-021 vaccination is effective in this Macaque Challenge Model, both single administration and prime boost regimens are significantly effective in this model. Vaccinated Macaques show substantial reduction in lung viral titers. This preliminary data shows that lung viral titers are between 3.3 and 3.81 log units lower in vaccinated primates in both single dose and prime boost groups, respectively.

One week after SARS-CoV-2 virus challenge, geometric mean titers exceeded 1.3x10^4 in non-vaccinated primates compared to the geometric mean titers of less than 10 and and those vaccinated with ARCT-021.

We also announced that ARCT-021 vaccination is protected in now a third animal model in immuno-deficient animals, depleted of B cells, which -- and this suggests that cellular immunity, specifically CD8 T cells plays a critical role in preventing SARS-CoV-2 infection. And Professor Eng Eong Ooi is on the call, as we mentioned, and he's going to be presenting this data in more detail later on the call.

For now, I'd like to pass the call to Steve to review the ARCT-021 Phase I/II clinical results and our clinical plans going forward. After Steve's presentation, we'll be pleased to have Professor Ooi, once again, a leading expert in the development of vaccines, provide additional context on ARCT-021 and the potential for this vaccine to provide high levels of protection against SARS-CoV-2. Steve, I'll turn the call over to you.

Steven George Hughes - *Arcturus Therapeutics Holdings Inc. - Chief Development Officer*

Thanks, Joe. Maybe if we can move on to the next slide after this one. Great. So I'm going to present the results from the interim analysis of our Phase I/II study that's being conducted in collaboration with the Duke-NUS University and Medical School in Singapore. As a recap, this study is testing both single-dose and 2-dose regimens in younger and older adults. The study is fully enrolled with 106 participants, 78 of which received active vaccine and all participants have actually now received all doses with 48 participants receiving 2 doses. The single doses are 1, 5, 7.5 and 10 micrograms, and that the 7.5 microgram single dose we've tested it in both younger and in older adults.

The 2-dose cohorts tested 3 micrograms and 5 micrograms and both of these doses were tested in younger and older adults. At this time, only the 5 microgram data is available. In this presentation, I will focus on the dose levels that we have selected to move forward into our next phase of clinical development, a 5 microgram and the 7.5 microgram doses. We saw emergence of Grade 3 solicited reactions at the 10 microgram dose, so we chose not to progress that dose further.

The primary endpoint for this study is safety and tolerability. Immunogenicity has been evaluated as secondary and exploratory end points and statistical testing has not been performed.

Next slide, please. I'll start with safety. Next slide, please.

Joseph E. Payne - *Arcturus Therapeutics Holdings Inc. - Founder, President, CEO & Director*

Did we lose you say, Steve?

Operator

There seems to be have some technical difficulties. Please stand by.

Steven George Hughes - *Arcturus Therapeutics Holdings Inc. - Chief Development Officer*

Well okay. I think we got cut off. Apologies for that. So starting again from the beginning of this slide, ARCT-021 was generally safe and well tolerated at the 5 microgram and 7.5 microgram doses and no safety concerns have been identified. No participants have withdrawn from the study, and all participants completed all doses.

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All adverse events, except for 2, were mild or moderate, and we only saw a single subject with Grade 3 solicited events. Transient asymptomatic Grade 3 lymphopenia was also reported in one subject, but lymphopenia has been observed with other mRNA vaccines and is not a safety concern.

Next slide, please. I'm now going to move to immunogenicity. This first slide shows IgG antibodies that bind to the spike protein. Similar to what we saw in the mass studies, these antibodies rise over several weeks post dosing and reach a plateau at about day 29 to 36 after the last dose. There was a modest boost effect of about 0.5 log in the time boost cohort. The neutralizing antibody response as measured by PRNT50 is shown on the next slide.

Let me move to the next slide, please. For the single dose cohorts, we have the PRNT50 values at day 29. And for the 2-dose cohorts, we have this data at multiple time points to explore the boost effect. As previously disclosed, the geometric mean titers are within the range of the convalescent serum tested at the same lab.

As disclosed at the last earnings call, we are planning to evaluate neutralizing antibodies using a micro neutralization assay in our Phase II and III clinical trials, and we are testing the serum from the Phase I/II study in this assay as well. However, our lab partner is still optimizing the sensitivity of this assay, so I'm not able to show these results today as we have planned.

I'm now going to turn to cell-mediated responses where we measured T cell responses using both ELISpot and intracellular cytokine staining with flow cytometry. This slide shows the ELISpot responses for PBMCs stimulated with 6 peptide pools spanning the full-length of the spike protein. T cell responses were evident by day 15, and we saw responses in both younger and older adults.

Next slide, please. This slide shows the cytokine staining results. Due to blood volume restrictions, we measured ELISpot and ICS at different time points. So we don't have an ICS values pre-dose. However, the data is placebo-controlled, which controls for lack of baseline to some extent. Here, we see both CD4 and CD8 T cell responses to peptide pool stimulation are evident following both a single dose and prime boost in vaccinated participants.

Next slide, please. This slide shows data demonstrating that we had a Th1 dominant CD4 response. We have plotted interferon gamma responses, which represent Th1 CD4 cells and interleukin 4 responses, which represent Th2 CD4 cells side-by-side for comparison. We can see that the interferon gamma responses are greater than the interleukin 4 responses at all doses, indicating that the CD4 T cell response is Th1 dominant after both the single dose and the prime boost.

Next slide, please. I'm now going to briefly outline our plans for the next studies. Next slide, please. We have submitted a protocol for a Phase II study to be conducted in Singapore and the United States. This has been approved in Singapore, and we are awaiting IND allowance in the USA. This study will enroll 600 older and younger healthy adult participants, with 50% of participants 55 years and older, and 25% of participants older than 65 years.

In this study, we will test 3 different dose schedules for ARCT-021, a 7.5 microgram single dose regiment, a 7.5 microgram 2 dose regiment and 5-microgram 2 dose regiment. All of these will be tested against placebo. The principal goal of the study is to select both for our Phase III registration study, and we are conducting 2 early interim analysis to allow for Phase III dose selection at the earliest opportunity.

The Phase III study will enroll at least 15,000 participants, and we are targeting a steady start in the second quarter of 2021. An interim analysis of the Phase III study is planned to allow an application for emergency use authorization in the United States and conditional approval in Europe in the second half of 2021.

I will now hand over to Professor Ooi, who will discuss how our clinical trial and nonclinical data relates to the prevention of COVID-19.

Eng Eong Ooi - *Arcturus Therapeutics Holdings Inc. - Member of the Vaccine Platform Scientific Advisory Board*

Thanks very much, Steve. So I'll try and integrate the clinical and preclinical data and try and see what -- where this vaccine can go and what it can do.

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Next slide, please. So we know from the news release from Pfizer and Moderna, that they've got some very remarkable results from the Phase III trial. And with both vaccine giving rise to 95% efficacy in preventing COVID-19. This figure -- that these 2 figures taken from one, the publication in New England General Medicine and the other -- the FDA briefing document, both show the intention to treat analysis.

So the blue lines are placebo and red lines are those given vaccine. Although this is a 2-dose vaccine, you can see that the efficacy started to take effect, 12 days, approximately 12 days after the first dose and the line remains flat thereafter. Suggesting that actually the immune response to vaccination from -- and around -- that develops at around a week-or-so sufficient to protect against COVID-19.

Next slide, please. So with that in mind, if we now take a step back to the Phase I data, you can see that at around day 15 on the left-hand side, this is Moderna's vaccine, Pfizer, of course, in the Phase I, used a different -- slightly different construct than what was eventually tested at Phase III. So for Moderna's data, at day 15, you see high levels of binding antibodies spike -- protein binding antibodies that upon boost, there's some modest gains in terms of the titer.

In contrast, new binding antibody on the right-hand side was relatively low until the boost -- until the second dose. So together -- and the T cell data was not well presented because they only measure at day 29. But nonetheless, from what we know from mRNA vaccines and from T cell biology, that should appear around the second week of -- after vaccination.

So if you take all these data together, it would suggest that either binding antibodies are protective or that you only require low to modest levels of utilizing antibodies. Or the T cells protect against COVID-19.

Next slide, please. So to try and understand this, we then turn back to a mouse model and Joseph Payne had already alluded to this data in his introduction. This is a model that was developed in the lab, where we tested human ACE2 transferring mouse model and to demonstrate efficacy of this ARCT-021. So the mouse -- the mice were given 1 single dose of the vaccine, either 2 micrograms, 10 micrograms compared to placebo. And then 30 days later, we challenged with the wild-type SARS-CoV-2 virus too, which is isolated from a patient in Singapore.

So Panel B shows you the new (inaudible) antibody titers that track with the dose of the vaccine. But whether it was given a high dose of 10 micrograms or the low dose of 2 micrograms at panel C, D and E, you see complete protection, both against disease as well as mortality from SARS-CoV-2 challenge.

In contrast, 100% of the mice that received placebo died from this infection. Panels F and G shows you that this protection was not only against disease, but also against infection, both in a lung as well as dissemination of the virus to the brain. And we tested this by both top assay as well as QPCR.

So with that, then we could ask a question, well, what actually protects against the lethal infection? So next slide, please. So we use the same mouse model. But now before we challenge, we either depleted the B cells or we depleted the CD8 T cell. So how we did that experiment is shown in panel F.

So the isotype antibody, which is not targeted against anything, but of the same IgG construct, this was user controlled. So we depleted the B cells before we vaccinated. And the reason for that is because of the long half-life of IgG antibodies. And then we vaccinated after -- they call it the placebo or they call it the B cell depletion. And then after that, in the panel in green, before we challenge, we either deplete the T cells or give them a placebo, and then followed by the SARS-CoV-2 challenge.

On the right-hand side, you see what happens when you either deplete B cells or T cells or both. So if you deplete B cells, there's nothing changed. There's still complete protection from infection. Both in the lung also brain. In contrast, if you deplete the CD8 T cells or you deplete both, you get breakthrough infection. And this is pretty significance, suggesting that actually in this -- at least in this mouse model and with this COVID -- ARCT-021 that the CD8 T cells will play a very important role in protecting against COVID-19.

Next slide, please. So what I've shown you animal data. Now it -- does this hold true clinically? And we're beginning to see anecdotal data from case reports, suggesting that this may indeed also be the case. This slide shows you patients, 2 patients with excellent agammaglobulinemia, which

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-- there's a genetic deficiency where they do not make any B cells, as can be seen from the red box where you can't measure any B cells in these patients.

They develop SARS-CoV-2 -- they had -- they acquired SARS-CoV-2 infection, developed COVID-19, but nonetheless, recovered from this infection, likely because they all have intact T cell response.

Next slide, please. So we can also draw lessons from other vaccines and other infections. So this is a study of measles, mumps and rubella, or MMR, revaccination. This is carried out in healthcare workers in Singapore because of an outbreak of mumps in the hospital. So the graph -- 3 graphs on the top, basically from left to right, measles, mumps and rubella. And the each graph is split into 3 groups: Group I; II; and 3 in Roman numerals shown at the bottom.

The reason for these 3 groups is that Group I are dosed with antibody titers below the threshold for immunity as defined by WHO. And Group III are those that are well above the threshold. Group II is the one that's interesting, particularly for mumps and rubella, where it's just over the border line of immunity.

But in this -- in Group II for both mumps and rubella, about half of the subjects, developing boost in antibody titer, as shown by the red lines after vaccination. The other half showed no change in antibody titer after vaccination, and those are shown in black line.

If you can ask why did half did not respond to the revaccination? And the answer lies in the graph below. So here, we're comparing gene expression. So this is whole genome -- sorry, this is the immune gene expression taken from the blood at 1 day after vaccination. And so the ratio is by taking non-responders, in other words, the people who are in the black line against those who are in the red line.

And what you see is that the reason why the people did not respond, those lines did not respond to revaccination is because they mounted a very early T cell response, as indicated by the gene expression. So these are T cell activation (inaudible) and genes that are found exclusively in T cells, suggesting that the early T cell response control the MMR vaccine infection because these are live vaccines, and therefore, they need to cause an infection to elicit an immune response, but in this case, the T cells cleared the vaccine so fast that there's no time for the B cells to respond.

Next slide, please. And on the flip side, we can also see that the lack of T cells can be a problem. So this is a case of dengue in Singapore and a patient who had just received a kidney transplant. This is a very young lady who needed a kidney transplant because of autoimmune disease, got a kidney from an unrelated donor and then was on immunosuppressive drops, particularly those that suppress T cells.

Three months after she got the kidney transplant, she acquired dengue. And you can see the graph on the right-hand side that this summarizes this data that I'm going to describe to you. So you see the blue line, this suppress the CD8 T cells, and then she acquired dengue 3 months thereafter. You can see that she had high levels of viral RNA in the blood, as indicated by the orange line. But the unusual thing is that the orange line lasted 5 months. In a healthy person, that line would last about 10 days.

And not only that, but we could find the virus in urine up to 10 months after infection. This is highly unusual in dengue. And this persistence of virus occurred despite the high levels of dengue antibodies, as indicated by the green line, and these are (inaudible) antibodies. She only cleared the virus when, for reasons we still do not understand, her T cells climb -- CD8 T cells climbed to approach the lower limit of normal. And when that happened, the virus disappeared.

So suggesting again that actually, the CD8 T cells play a very important role in clearing infection. And therefore, a vaccine that elicits CD8 T cells could be very beneficial. So I'll summarize in the next slide, that the early protection that we've seen from both the Phase III trials from Pfizer and Moderna's vaccine provides a window into understanding the immunocore and its protection and that the single dose, at least in the mouse model, is able to elicit a full repertoire immune response, particularly the CD8 T cell response that protected against SARS-CoV-2 infection, and that these T cell response learning from other environment infections could be very important in protecting us against COVID-19.

So I'll stop there and I'll hand it back to Joe Payne. Thank you.

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Joseph E. Payne - *Arcturus Therapeutics Holdings Inc. - Founder, President, CEO & Director*

Thank you, Professor. And I think that concludes our presentation. I would like to now turn the time over to the operator to bring forward some questions and some (inaudible).

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question comes from the line of Yasmeen Rahimi with Piper Sandler.

Yasmeen Rahimi - *Piper Sandler & Co., Research Division - Director & Senior Research Analyst*

First question is to the team. Maybe what could be helpful for us is, can you help us, how does your single dose vaccine compared to Moderna and BioNTech immunogenicity data? If you could walk us through and just you provide us color why the single-shot is just as viable as the other mRNA technologies that have been already approved? And then I have a few follow-ups.

Joseph E. Payne - *Arcturus Therapeutics Holdings Inc. - Founder, President, CEO & Director*

Sure. I can start there. Professor Ooi already highlighted the successful efficacy data that's been shared by Pfizer and Moderna and other mRNA vaccines. And you see that very early in the process that you see a clear efficacy. And at those data points, based upon the data that's been shared by the other mRNA. After a single administration, there's low to very low neutralizing antibody titers, even though they're seeing significant success early in the process and the time course.

You asked how we compare. It will be interesting to see how the scientific community compares ours to others. Some people will say equivalent. Some may suggest that our single administration is show superior immunogenicity profile after a single administration. But clearly, the challenge models -- there's proof in the pudding that in multiple challenge models in mice and in primates and even in animals that are severely deficient in immune responses and the ability to create neutralizing antibody titers, we've seen success in all of these models.

So I think that there's a reasonable sense of optimism that our single administration could be efficacious based on the data we've collected. And definitely, to -- in a nutshell, to address your question specifically, yes, I personally believe that after our single administration data is significant and comparatively so as well.

Yasmeen Rahimi - *Piper Sandler & Co., Research Division - Director & Senior Research Analyst*

Maybe just a second question is -- thank you for the impressive preclinical data showing that T cell response drives protection. So do we have any other evidence on time curves for infected patients when T cell response kicks in versus neutralizing titers? I know you shared with us the 2 patients. But if you could elaborate beyond that. I think that preclinical data was very compelling. But if you could share anything else that could be helpful for us. Why neutralizing titers do not drive efficacy beyond what you shared just recently with us on the call?

Joseph E. Payne - *Arcturus Therapeutics Holdings Inc. - Founder, President, CEO & Director*

It's a great question. Professor, you want to address that?

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Eng Eong Ooi - *Arcturus Therapeutics Holdings Inc. - Member of the Vaccine Platform Scientific Advisory Board*

Yes, I can take that. Yes. Thanks very much. That's a great question. I think the short answer is, I mean, we're still learning a lot about this disease. But the -- at least the clinical trials provide a period of window. I mean, obviously, the immune response in -- naturally infected COVID-19 patient is very much influenced by the virus itself. And we know that this virus suppresses the indifferent responses early on, especially in those who develop severe disease. There's also recent papers that's showing that those who develop disease amount a very -- they have eventually developed very high titer antibodies.

But it's compared to peers later than those with now the disease. So the virus actually modulate a lot of that response. But at least, I think in terms of the timing in which protection appears to be -- to have effect could be mediated by antibodies, triggering other immune processes, including (inaudible) receptor media phagocytosis or complement activation or antibody dependent cellular cytotoxicity or ADCC.

So all these more global effects of antibody-mediated protection have not been properly assessed. We've always just relied on measuring new (inaudible) antibodies. So that's one possibility that actually binding antibodies alone may be good enough. But I think the other emerging set of data that's really exciting is the T cell response to SARS-CoV-2. And then there's a lot of data now that's still emerging such as that actually those with some level of cross reactive T cells that we could have developed against other coronaviruses, seem to be able to protect against severe COVID-19.

So I think there's still a lot to learn. And we are just 1 year on from the time when we first recognized that there's such a new disease that should emerge. So we're still operating with some uncertainty. But I think the Phase III data gives us a lot of hope that what we're seeing is going to be useful.

Yasmeen Rahimi - *Piper Sandler & Co., Research Division - Director & Senior Research Analyst*

And one last question. Has your IND been accepted, can you start dosing your face in Phase II and here in the U.S. and then remind us, why are you doing a Phase II instead of just jumping into a Phase III.

Joseph E. Payne - *Arcturus Therapeutics Holdings Inc. - Founder, President, CEO & Director*

Steve, do you want to take the first part of that?

Steven George Hughes - *Arcturus Therapeutics Holdings Inc. - Chief Development Officer*

Yes, sure. So we submitted our IND right at the beginning of the month. And so as you know, FDA have a 30-day statutory period that review INDs. But they've actually got right up to the end of the month before they need to respond to us. But also FDA have been a little bit distracted with our Pfizer and Moderna emergency use applications.

So we're anticipating hearing from them putting them any day now. In terms of Phase II followed by Phase III rather than just jumping into Phase III. We'd initially actually planned a Phase II/III study, which was a seamless study design. But in terms of the timing of us submitting the application, which we would have been doing instead of the Phase II application, it was falling right in -- flat bang in the middle of the emergency use authorization applications.

And we had feedback from regulatory consultants and also from other sources that there was at least a reasonable probability that the guidance around the design of Phase III studies may actually change in the United States and possibly in Europe as well. And we really saw some risk there in terms of getting hung up with a study design that wasn't going to fit with whatever new designs came out, for instance, what to do with subjects that are on the placebo arm of the subject -- of the study when vaccines start to become available in the country where you're trying to conduct the study.

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That hasn't been fully resolved yet, but I'm sure that it is going to get resolved in terms of guidance very quickly. And we would need to have those kind of things baked into a Phase III protocol. So when we looked at it, we decided to uncouple Phase II from the Phase III. We looked very carefully at the time line as well and actually uncoupling the 2 studies, we didn't lose any time.

And so the approach with the lowest risk, really from a regulatory perspective was to uncouple Phase II from Phase III -- go straight in with a Phase II study, which is going to be unaffected by any changes to the Phase III recommendations. While we continue negotiations with FDA, with the European regulators, the Singapore regulators and other regulators about the fine points of a Phase III study design in the post-COVID vaccine world. Does that answer your question?

Yasmeen Rahimi - *Piper Sandler & Co., Research Division - Director & Senior Research Analyst*

Yes.

Joseph E. Payne - *Arcturus Therapeutics Holdings Inc. - Founder, President, CEO & Director*

Yes, I would just add to that bifurcating the Phase II and III, we can also -- it allows Arcturus to evaluate our lyophilized version of our vaccine in the Phase III trial simply and cleanly. And so that's -- that brings another benefit by uncoupling them.

Operator

Our next question comes from the line of Gena Wang with Barclays.

Huidong Wang - *Barclays Bank PLC, Research Division - Research Analyst*

I have a few regarding the data. First is regarding the prime-based data. Just wondering why after boost, we did not see similar level of mechanic. If we look at the Moderna data, it's more than 20-fold increase in terms of neutralizing antibody. And here, we did not see that much increase after boost. And actually, over time -- that basically decreased over time. I think of the 5-microgram cohort, almost the same as 2019.

Joseph E. Payne - *Arcturus Therapeutics Holdings Inc. - Founder, President, CEO & Director*

Right. Now the professor referred to that a little bit in this presentation. I think it'd be best to elaborate further?

Eng Eong Ooi - *Arcturus Therapeutics Holdings Inc. - Member of the Vaccine Platform Scientific Advisory Board*

Yes. Thanks. So I suspect that -- that's a great question. Thanks very much. And I suspect that the reason why there's not much change in the antibody titer is, again, because of the T cell response. So as you can see from Steve's presentation that we got good T cell response against the antigen. And I suspect that because the -- when you give that in the second dose, the clearance of the cells transfected with mRNA by the CD8 T cells, may be too so rapid that it's not sufficient to provide a boost to the antibody. So however, but that, I think, is a good thing because as you can see from the MMR revaccination data that actually -- that provides solid protection against infection, more so than just antibodies alone.

Huidong Wang - *Barclays Bank PLC, Research Division - Research Analyst*

So I mean related to this question, the -- we do have like -- how many patients are close to 100,000 patients dosed, and we saw clear the prime boost activity and mutualizing antibody clearly correlated with a clinical benefit. If you look at the AstraZeneca, you have one-time convalescent serum, we saw 60% effective rate and while the other 2 show very high. And I think it's unfair to look at their first after prime, because the 4 times

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of convalescent serum after boost that, that certainly we don't know how much actually that play a role to maintain that protection over time throughout the clinical follow-up.

So with -- but potentially, the small numbers anecdotal cases that are supporting T cell versus we have a much larger amount of data showing neutralizing antibody does protect patients from -- subjects from viral infection. So how are we think and rethink about this data set compared to the competitor data?

Joseph E. Payne - *Arcturus Therapeutics Holdings Inc. - Founder, President, CEO & Director*

I don't think that we can conclude from the trial that the antibody's protected against COVID-19 because the (inaudible) protection hasn't been defined in the titer of antibodies that are needed for these, protection hasn't been defined.

I mean they all develop antibodies, which is good. But whether that actually protects has not been defined. So I would disagree with what you just said. Having said that, both if you look at the data that's been published so far from all these front runners, they do not -- at least from the 2 mRNA vaccines. They only measure T cells at day 29, they don't measure any earlier. So again, it's hard to compare between our study and theirs. In terms of the level of T cells and what we can expect.

So of course, given the lack of positive protection that we have to infer, a few things, draw a few lessons from other studies, which is what we're doing now. But I don't think that there is enough data to suggest that (inaudible) antibodies are the ones that actually protect against infection.

Huidong Wang - *Barclays Bank PLC, Research Division - Research Analyst*

Okay. My one last question is regarding the single dose. Just wondering, what is the longer follow-up, the [pre 50] numbers for both 7.5 micrograms and a 5 microgram?

Joseph E. Payne - *Arcturus Therapeutics Holdings Inc. - Founder, President, CEO & Director*

Yes, Steve, you can address that?

Steven George Hughes - *Arcturus Therapeutics Holdings Inc. - Chief Development Officer*

Yes. So within the Phase I/II clinical trial, the single dose cohorts were followed up for 57 days in that study. And then they roll over into an open-label extension study, where they will continue to be followed up for a year. So the first of those single dose patients are about -- within the next few weeks, have their first visit in that open-label extension.

So we have data out to 56 days after their initial injection. That was part of this interim analysis, and then we'll continue to collect data on those participants as they go into the open-label extension.

Operator

Our next question comes from the line of Madhu Kumar with Baird.

Madhu Sudhan Kumar - *Robert W. Baird & Co. Incorporated, Research Division - Senior Research Analyst*

A couple of housekeeping ones and a couple of questions for Dr. Ooi. So housekeeping questions. So first, were the neutralizing antibody titers, from convalescent serum run in parallel with the vaccine samples?

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Eng Eong Ooi - *Arcturus Therapeutics Holdings Inc. - Member of the Vaccine Platform Scientific Advisory Board*

Yes, yes, sorry.

Madhu Sudhan Kumar - *Robert W. Baird & Co. Incorporated, Research Division - Senior Research Analyst*

Okay. That's fine. Second, what were the binding IgG levels from convalescent serum?

Eng Eong Ooi - *Arcturus Therapeutics Holdings Inc. - Member of the Vaccine Platform Scientific Advisory Board*

That's a great question. I think it's comparable to slightly higher depending on severity of disease to the -- for our vaccinated subjects.

Madhu Sudhan Kumar - *Robert W. Baird & Co. Incorporated, Research Division - Senior Research Analyst*

Okay. Cool. And then productively, 2 questions. So about the idea related to the T cell activation being what's protected here. So to the best of your ability, you explained biochemically why different messenger RNA vaccines, be it our tourists versus Maderna or Pfizer BioNTech. Why it might have divergent effects on T cells as compared to antibodies?

Eng Eong Ooi - *Arcturus Therapeutics Holdings Inc. - Member of the Vaccine Platform Scientific Advisory Board*

That's a great question. I think I'll answer this in several parts. One, that it's difficult to compare between studies because everyone uses slightly different methods. And then, of course, the antibody, they use stainless cells are also slightly different. It will be great to centralize all of these so that we have comparable data at some point. But there's some caveats here that have to be a little bit careful about reading too much in the data because the methods are slightly different. That's one.

Two is that -- and maybe I can answer this from my own perspective. I mean, I got very excited about this vaccine, at least collaborate with Arcturus on developing self-replicating RNA vaccine because we have been studying yellow fever vaccine for a while now. And one of the drivers of good immune response, yellow fever, as you may know, is arguably one of the best vaccines in the world because the single-shot gives you 10 years or more of protection.

And we've been trying to figure out why this vaccine has been so good. And what we found is that one of the key drivers of a good immune response is how long the infection last. So in the cohort of about over 100 people now that we have received a vaccine and we track what happens in the blood in the first week after they receive the vaccine, and then correlate this to the eventual immune response that they develop. Those who have a longer infection have got a better immune response, which is not surprising because the longer the antigens get presented to the immune response, the better their affinity maturation.

So I think one reason why we are getting such a good cellular immunity is because of the self-replicating mRNA construct that presents the antigen over a longer period for the T cells. And therefore, we get a more robust response set. As one other question earlier asked why the boost is a little bit modest. And I think it's because there's a chance that this could be a single dose vaccine.

Madhu Sudhan Kumar - *Robert W. Baird & Co. Incorporated, Research Division - Senior Research Analyst*

Okay. So following from that, Dr. Ooi, why would that be specific to cellular in T-cell activation relative to B-cell activation? Why would we be kind of chronically pumping out higher and higher doses of antibodies in track with the kind of T cell induction that happens in the self-replicating RNA construct?

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Eng Eong Ooi - *Arcturus Therapeutics Holdings Inc. - Member of the Vaccine Platform Scientific Advisory Board*

Great question again. We're still trying to work out to know -- the what happens in all that, and we see that this will be -- to still to require a bit more experiments. But I suspect that it's part of the safety profile that Steve Hughes presented in our Phase I data, where you get -- when we measured both CD4 and CD8 T cells, you see a lot more interferon gamma secreting cells and IL-4. And as you know, IL-4 is needed to produce to drive the B-cell response.

So I think because of this, the past association between the high IL-4 competitor [different] gamma and the development of immune enhanced disease eventually in the vaccinated animals for SARS and MERS and in children for Respiratory Syncytial Virus or RSV, we -- I think the field and regulators refer to see a TH1 skewed, in other words, high interferon gamma response than IL-4 as a safety readout.

So given that kind of cytokine profile, perhaps that's the reason why we are stimulating a lot more cellular immunity than antibody development.

Operator

Ladies and gentlemen -- Go ahead, Steve.

Steven George Hughes - *Arcturus Therapeutics Holdings Inc. - Chief Development Officer*

Sorry, I just wanted to add this one thing, which is fundamentally the mechanism of the replicon is different to the traditional mRNAs. So we're putting in a construct, which is self-replicating. And part of that self-replication process drives a double-stranded mRNA intermediate before we read off the spike protein. And that double-stranded intermediate drives an interferon response as well.

So the -- fundamentally, we've got a different chemistry or different biology going on inside the cell and outside the cells with a conventional mRNA vaccine.

Operator

And with that, ladies and gentlemen, this concludes our question-and-answer session. And I would like to turn the call back over to Mr. Joseph Payne for any closing remarks.

Joseph E. Payne - *Arcturus Therapeutics Holdings Inc. - Founder, President, CEO & Director*

No closing remarks. Thanks for the time, again, everybody in this busy time of the year. And we look forward to reconnecting and addressing any future questions that you may have. Bye for now.

Operator

This concludes today's teleconference. You may now disconnect your lines at this time. Thank you for your participation and have a wonderful day.

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