Q1 2019 Earnings Call

Company Participants

- Lavina Talukdar, Head of Investor Relations
- Lorence Kim, Chief Financial Officer
- Stephane Bancel, Chief Executive Officer
- Stephen Hoge, President
- Tal Zaks, Moderna, Inc.

Other Participants

- Alan Carr, Analyst
- Cory Kasimov, Analyst
- Geoffrey Meacham, Analyst
- Matthew Harrison, Analyst
- Ross Weinreb, Analyst
- Ted Tenthoff, Analyst
- Ying Huang, Analyst

Presentation

Operator

Good morning, and welcome to the Moderna First Quarter 2019 Conference Call. At this time, all participants are in a listen-only mode. Following the formal remarks, we will open up the call for your questions. Please be advised that the call is being recorded. At this time, I'd like to turn the call over to Lavina Talukdar, Head, Investor Relations at Moderna. Please proceed.

Lavina Talukdar {BIO 19691239 <GO>}

Thank you, operator. Good morning, and welcome to Moderna's first quarter 2019 Conference Call to discuss financial results and business update. You can access the press release issued this morning as well as the slides that we will be reviewing by going to the Investors section of our website at www.modernatx.com. Today on this call we have Stephane Bancel, our Chief Executive Officer; Stephen Hoge, our President, Tal Zaks, our Chief Medical Officer; and Lorence Kim, our Chief Financial Officer.

Before we begin, I would like to remind everyone that this conference call will include forward-looking statements. Please see Slide 2 of the accompanying presentation and our SEC filings for important risk factors that could cause our actual performance and results to differ materially from those expressed or implied in these forward-looking statements.

We undertake no obligation to update or revise the information provided on this call as a result of new information or future results or developments. I will now pass the call over to Stephane.

Stephane Bancel {BIO 15174250 <GO>}

Thank you, Lavina. Good morning or good afternoon. As you know, we believe that MRNA has the potential to become a new class of medicines and since Moderna's inception we have worked hard to be the Company that could become the leader in this field.

We believe our mRNA medicines have a potential to address large unmet medical needs and to treat diseases that are not addressable by recombinant proteins or small molecules. Due to the platform nature of mRNA, we believe our mRNA medicines provide a higher probability of technical success and faster timelines to clinical trials and to the market relative to traditional medicines. We also believe that the manufacturing capital intensity of mRNA is materially lower than recombinant proteins that our cost of manufacturing at commercial scale will be similar to small molecule injectable.

In order to achieve a deliver on our goals, we continue to focus on managing risk, especially technology risk and biology risk. We believe that programs will be in the same modality of similar technology risk meaning that once we derisk the sentinel program they are important breakthroughs [ph]. We believe our Chikungunya antibody program will be an important clinical readout. As it chooses the same formulation technology as our MMA program almost advance a rare disease candidate.

As articulated before, our corporate focus is on three priorities. One, to execute on the development pipeline; two, to move new development candidate in existing modality from the lab into the clinic; and three, to continue to invent new development candidates in new modalities. I will review our progress against our priority one on the next slide in a minute.

On priority two, we are happy to announce today a new development candidate with a potential to address the rare genetic disease Glycogen storage disease type 1a or GSD1a in a systemic intracellular modality. Stephen will provide you with an overview of the disease and our preclinical data.

And priority three, Stephen will give you a brief summary from yesterday annual Science Day presentations where we presented ongoing insights into our mRNA and delivery science, that included the potential delivery of mRNA to white blood cells. While we have additional research to perform in this area, we look forward to being able to bring candidates into development as we continue working to help patients with a wide range of serious diseases. Tal will give you an update about the modality in a minute.

But I would like to focus on three programs. RSV, VZV and GSD1a. RSV first, as you know, our strategy across the portfolio is to create best medicine -- the best medicine we can, taking advantage of mRNA flexibility and the speed with which we can advance new

development candidates. We've also report Merck has been seeing an improved version of its RSV vaccine. We've enhanced preclinical potency and the proprietary formulation developed by Merck. For this new candidate mRNA-1172 Merck has filed an IND. We note that the mRNA-1172 is now reflected in our pipeline along with mRNA-1777, which is now paused in this development. Merck and Moderna believe that mRNA-1172 is an improved development candidate and gives the Company their highest chance of bringing a new potent RSV vaccine to people in need. Tal will show more preclinical data in a moment, but we're looking forward to the start of a Phase 1 study. We will then look at the clinical data from both studies of 1177 -- sorry 1172 and 1777. And decide which development candidates to move into Phase 2.

Now let me come to VZV. Based on assessments of the commercial opportunity, research priorities and other factors, Merck has discontinued preclinical development for mRNA-1278. The investigation medicine for VZV, the virus that causes shingles. Merck has returned rights back to Moderna and the Company will not continue development at this time.

Let me now close by a brief note on GSD1A. We're very pleased with our [ph] development candidate that is moving into GSD [ph] talks in our systemic intracellular therapeutic modality and our team, as we can imagine, are working hard to get these medicines to patient as soon as we can.

With this, let me now turn to Tal to give you more granularity on our pipeline.

Tal Zaks {BIO 19987702 <GO>}

Thank you, Stephane. Let me begin with reviewing our progress by modality. And I am going to start with the prophylactic vaccines. Recapping our mRNA vaccine for respiratory syncytial virus or RSV, one of the most common causes of respiratory diseases in both the very young and the elderly. In collaboration with Merck, we designed our vaccine to encode a membrane anchored version of stabilized pre-fusion F protein, which will listen to neutralizing antibody response.

In the inset, we show the intended design of the -- kind of the mRNA formulated in an LNP. We worked with Merck to identify and advance improvements to the RSV vaccine, which has led us to the identification of mRNA-1172. This second vaccine, has an improved RSV antigen resulting in enhanced potency in preclinical models, as well as a proprietary formulation developed by Merck.

On the right, we have outlined data from a preclinical study in African green monkeys comparing serum neutralization titers of mRNA-1172 to mRNA-1777. In this study mRNA-1172 was shown to be significantly more potent that mRNA-1777. As Stephane mentioned, the IND for this new vaccine was filed earlier this month and mRNA-1777 will not move forward into the planned Phase 2a study at this time.

Let me now turn to the rest of the prophylactic vaccines. Overall, to date approximately 1,000 healthy volunteers have been enrolled across seven Phase 1 trials at doses of up to

400 micrograms. The emerging safety and tolerability profile remains consistent with that of marketed adjuvanted vaccines.

We've shown promising data from five Phase 1 programs within the prophylactic vaccines modality and we continue to make progress. For CMV, the first three dose levels are now fully enrolled and healthy volunteers have started to being dosed at 300 micrograms of 4th dose level in that study. And VZV, based on an assessment of the commercial opportunity, research priorities and other factors as Stephane has discussed, Merck has discontinued preclinical development of mRNA-1278. Merck has returned the rights back to us and we will not continue development at this time.

Turning to our cancer vaccines, we announced that we will present Phase 1 updates for personalized cancer vaccine at the upcoming American Society of Clinical Oncology meeting or ASCO. As a reminder, our personalized cancer vaccines are being studied as a single agent in patients with resected tumors and in combination with pembrolizumab in patients with unresectable solid tumors. The National Cancer Institute will also present data from its Phase 1 study of PCV, NCI-4650, a monotherapy for patients with advanced metastatic cancers. The abstract titles and presentation times can be found in the press release that went out this morning.

In addition, we are continuing enrollment for our PCV trial and preparing for the randomized Phase 2, while the team at Merck is gearing up to enroll patients on the KRAS Phase 1 trial.

For intratumoral Immuno-oncology, we continue to enroll our OX40 ligand and Triplet trials and prepare for the OX40 ligand Phase 2 cohort in ovarian cancer. Also at AACR, our partner AstraZeneca shared preclinical data that supported advancing MEDI1191 or the IL-12 program into a Phase 1 trial. AstraZeneca will lead an open label, multi-center study of intratumoral injections of IL-12 alone or in combination with a checkpoint inhibitor.

Finally, the local regenerative therapeutic modalities, which includes AZD8601, our mRNA encoding for VEGF A, AstraZeneca recently obtained clinical trial authorization to open a clinical site in the Netherlands. As a reminder of the Phase 1 study showed that AZD8601 was well tolerated and led to the translation of functional VEGF A protein, which caused a dose-dependent increase in blood flow was injected.

Moving next to our systemic secreted therapeutics, let me provide some context on our first program in this modality mRNA-1944 including for Chikungunya antibody. As we were assessing the biology risk for systemic secreted therapeutics, we began the development efforts by encoding a monoclonal antibody with the goal of inducing transient passive immunity in the recipient. An antibody would represent a complex protein as it requires the co translation of two separate mRNAs and the correct intracellular folding and eventual secretion into the bloodstream. From a safety perspective, you would expect an anti-viral monoclonal antibody to be safe, and pharmacologically we should be able to easily measure it's blood levels. This would then allow us to quantify the PK/PD relationship. In other words, how much mRNA is required

to produce how much protein in a relatively straightforward manner. The lipid nanoparticle delivery system used for chikungunya antibody or mRNA-1944 is shared with our sentinel rare disease program methylmalonic acidemia.

The Phase 1 design for this study is shown on Slide 18, we're conducting it in healthy volunteers, so it should give us a read on the safety and tolerability of this formulation, the pharmacological goal, as I mentioned is to determine how much antibody we can produce as a result of systemically administered mRNA and whether we may be able to offer people passive immunity against infection by this virus, which today has neither a vaccine nor specific therapy is available.

We recently completed enrollment of all eight subjects in the second dose cohort in healthy volunteers treated at 0.3 milligram per kilogram in this Phase 1 study. And I look forward to sharing more once we have a complete picture of the data. Also our chikungunya antibody preclinical data was just accepted for publication in the Journal of science immunology. We are continuing to move our Fabry and Relaxin programs towards clinical trials and look forward to providing you with an update at a later date.

Finally, let me turn to our systemic intracellular therapeutics. For methylmalonic acidemia or MMA, we are currently in the process of initiating sites for the Phase 1 trial. We have 45 patients enrolled in our MaP Natural History Study for methylmalonic acidemia and propionic acidemia. 26 of these are MMA patients and 19 are PA patients. In addition, the European Commission has adopted the recommendation from the Committee of Orphan Medicinal Products for orphan designation for mRNA-3927, our PA development candidate further supporting its advancement. We continue to progress mRNA-3927 for propionic acidemia and mRNA-3283 for phenylketonuria, with the goal of bringing them to the clinic.

I'm really excited about the opportunity for the new development candidate within our systemic intracellular therapeutic modalities. And we'll now turn it over to Stephen, who will introduce this candidate for glycogen storage disease type 1a or GSD1a.

Stephen Hoge {BIO 17925815 <GO>}

Thanks, Tal. So glycogen storage disease type 1a or GSD1a is a rare inherited metabolic disorder resulting from a deficiency in an enzyme called glucose 6 phosphatase, G6Pase as short. The G6Pase enzymes involved in the metabolic pathway is to allow the liver and to a lesser extent the kidney to maintain the level of glucose in the blood during fasting, And for a couple of hours, in a normal healthy person, most of the glucose from your last meal have been consumed by tissues. So as glucose levels start to fall, most issues in our bodies will convert to using (inaudible) from using glucose for energy to other sources such as lipids or triglycerides. But cells in our brands are unable to make that switch and are dependent upon glucose to survive. So our livers take over responsibility for making and releasing glucose into the bloodstream, to keep the brain alive.

This process involves two different metabolic process. First glycogenolysis or the breakdown of liver stored glucose for release and gluconeogenesis or the conversion of

other substrates into glucose. Glucose 6 phosphatase catalyzes the last step in both of those processes in the ER and liver. And the good news for most of us is that process happens automatically every day, and particularly as we fast overnight, our liver takes over responsibility for keeping our brain alive.

The people suffering from GSD1a are unable to maintain that blood glucose during the fast. As a result, they suffer from threatening hypoglycemia or low glucose, low blood glucose that can often result in debilitating neurologic effects even that over time the lack of the enzyme can also lead to a wide range of severe metabolic arrangements for the hyper -- such as hyperlipidemia from a build up of lipids, lactic acidemia and enlarged and diseased livers. In order to prevent life-threatening hypoglycemia, these patients was -- consumed sugar regularly, almost continuously via complex sugars such as corn starch. Patients need to awake several times a night, every night to consume this corn starch. And some younger patients even need to have gastric tubes placed to facilitate the speeding or be placed on continuous IV glucose drips. Clearly there needs to be an improvement in the standard of care.

As GSD1a occurs in about 1 in 100,000 live births, with a slightly higher prevalence among Ashkenazi Jews. That means that approximately 6,500 patients across the US and EU exist. We believe our platform can address GSD1a or replacing that missing information with liver cells and helping those patients control their glucose.

Just to review a little bit of the preclinical data. We've demonstrated proof-of-concept for G6Pase mRNA therapies in multiple in vivo studies. First looking at the upper left hand panel, we've been able to demonstrate dose-dependent in vivo pharmacology in the animal knockout model, in this case, mice. As you can see at escalating doses from 0.2 milligrams per kilogram up to 1 milligram per kilogram, we achieve a dose-dependent normalization of the glucose of these -- in these animals during fast. It's exciting to see that translates into other markers of activity as well. The panel in the middle to the right shows triglycerides and shows across all dose levels tested here, a normalization of those triglyceride levels.

Lastly, in looking at the liver weight of these animals after -- 24 hours after a dose, we show normalization, partial normalization relative to control of the liver weights in these animals showing broad based metabolic effects. On the far right hand side, we're showing a seven-week study with repeat dosing showing the ability to normalize blood glucose levels during fast in these animals up to five doses. We believe this data supports the development of GSD1a [ph] mRNA-3745 and this proof-of-concept -- in these proof-of-concept studies. And this data was recently presented at ASGCT, and we're excited about the potential for this new development candidate to bring significant clinical benefit to GSD1a patients.

So returning to the pipeline on Slide 25, we've announced GSD1a, our fifth rare metabolic disease into development. We look forward to doing everything we can to help these patients and other patients suffering from these debilitating diseases.

Changing gears, I want to talk a little bit about our Science Day efforts and briefly recap some of the discussions from yesterday. We had the pleasure for doing our second annual Science Day, and we created Science Day to provide a window into our investments in the research platform, and to create new generations of technologies that will enable our future pipeline. I could host the Science Day with Melissa Moore, the Chief Scientific Officer of our platform. Now with over 200 dedicated scientists focusing on advancing technology underlying our investigational medicines, it's impossible to summarize everything. In the last three years we published 25 peer review manuscripts in leading journals with 11 in last year alone.

So for Science Day, Melissa and I tried to select a few vignettes that illustrate the breadth and depth of the basic science we're pursuing at Moderna. These fall broadly into two categories. Our mRNA science and our delivery science. As you can see from the agenda here, we divide the time roughly between the two. But those who are interested in reviewing the Science Day content, I'll direct you to a link either on our website or the PR released this morning. But some of the key highlights are on the next two slides.

So first in the MRNA science space, we demonstrated some of the ways in which we're making our vaccines and therapeutics more potent and safer. We've shared some of the latest in vivo characterization of the nature of the innate immune response and the importance of uridine modification to make an immune silent messenger RNA medicines.

We showed -- we shared advances and how we're using design of our mRNA to maximize potency including several-fold improvements in the amount of protein that were being produced in rare disease animal models. We also showed how secondary structure is being designed into our messenger RNA to create buffer space between ribosomes as they translate it to prevent, what we've been calling ribosomal traffic jams. This can increase mRNA half-life and decrease the need for dosing.

Lastly, we shared some of exciting work we did in physics on nanoparticles, understanding the formulation, their surface characterization and how to make them more potent and effective.

The second half of Science Day focused on advances in delivery science, and specifically introducing our immune nanoparticle research program. As Stephane mentioned, this is an effort to deliver messenger RNA broadly in the immune system to a wide range of cell types, including lymphocytes. And we shared some of the translational data we have across species demonstrating progress in that space. The key features of the immune nanoparticle research and program are dose-dependent pharmacology in all major cell types of the immune system, a system-wide effect. As always across all of our efforts in delivery, dose-dependent pharmacology is critical to our success. We also demonstrate how we're transiently expressing proteins that confer cells with new phenotypes and functions and drive responses. How we use mRNA software to show that the cell types in which we express proteins and how we've been driving trafficking of immune cells to new tissues to drive desired cell-to-cell interactions. While this work is still in the research and preclinical phase, we are obviously incredibly excited about the potential it brings to treating a wide range of diseases, including cancer, autoimmune disease and neurodegenerative disease.

So with that I'll now turn over the call to Lorence, who walk through with financials.

Lorence Kim {BIO 18670491 <GO>}

Thank you, Jim. In today's press release, we reported our first quarter 2019 financial results. Please note these results are unaudited. We ended Q1, 2019 with cash, cash equivalents and investments of $1.55 billion and this compares to $1.69 billion at the end of 2018.

Let me highlight two cash flow metrics, which provide a direct view on cash used given -- this is better given the quantity of deferred revenue, stock-based compensation and depreciation that's embedded in our operating income. Net cash used in operations was approximately $144 million in the first quarter of 2019, that compares to $111 million for the first quarter 2018. Please note that Q1 of 2019 and 2018 include $22 million and $25 million respectively of in-licensing payments. Secondly, cash used for purchases of property and equipment was $8 million for Q1, 2019 compared to $32 million for Q1, '18.

Revenue for Q1 2019 was $16 million as compared to $29 million for Q1 ' 18. Note that on January 1st, 2019, we adopted the new revenue recognition standard ASC 606 using the modified retrospective transition method applied to those contracts, which were not completed as of January 1st. The decrease in total revenue was mainly attributable to the decrease in collaboration revenue across all of our strategic alliances mainly -- particularly AstraZeneca and Merck, driven by the adoption of the new revenue standards. Total revenue under the previous revenue recognition standard would have been $38 million for Q1, 2019.

R&D expenses for Q1, 2019 were approximately $131 million compared to $90 million for Q1, '18. The increase was primarily due to an increase in personnel-related costs, including stock-based comp, mainly driven by increase in number of employees, supporting research and development programs, and increase in clinical trial and manufacturing costs, and increase in lab supplies and materials for preclinical studies and clinical trials, and an increase in consulting and outside services costs.

G&A expenses for Q1, 2019 were approximately $27 million compared to $16 million in Q1 of ' 18. That increase was mainly attributable to an increase in personnel-related costs, including stock-based compensation, primarily driven by an increase in the number of employees and consulting and outside services costs, both of which were related to operating as a publicly traded company.

So with that, I'll hand the call back over to Stephane.

Stephane Bancel {BIO 15174250 <GO>}

Thank you, Lorence. To close our remarks, I would like to reiterate that our team is very focused on execution, that are on the three priorities. Number one, advancing development pipeline, number two, investing in new development candidates within the six existing modalities that we just announced this morning on GSD1a, and investing in

new modalities, that is immuno nanoparticles presented yesterday at the Science Day to deliver mRNA to white blood cells.

We are very excited about 2019 and 2020 as we anticipate having a lot of clinical results both in Phase 1 as well as Phase 2 starts and readouts. I believe that Moderna is operating from a place of tremendous strength. I am please with our progress. Enabled by our mRNA platform, our large development pipeline continues to progress based on the data we are generating from now around the 1,000 healthy volunteers and patients enrolled in our trials across all medicines. Three programs in or planning for Phase 2, Six positive Phase 1 readouts, five ongoing Phase 1 trials, three open INDs awaiting phase 1 starts.

If you look at the pipeline by prophylactic area, I'm very proud of where we stand today. We have five immuno-oncology programs, OX40 ligands and PCV, which are being prepared for Phase 2 by our teams. The Triplets which continue to dose escalation in Phase 1 and two open INDs for KRAS and IL-12. We have five rare disease programs; MMA, which is continuing to enroll the natural history study and our teams are currently in progress for initiating sites for Phase 1 with an open IND. PA, which recently got granted orphan disease designation by the EC. PKU, Fabry and now GSD1a in pre-clinical Tox studies.

Three vaccines for major unmet medical needs RSV, CMV and combo hMPV+PIV3. We now have more than 775 employees, who are very committed to change patients' lives through mRNA science. Our Norwood facility, which we believe is a strategic asset to enable companies to scale and ensure high quality medicine as we do our clinical trials and a strong balance sheet.

We know that we have a very special opportunity. And the team is very committed to delivering on the promise of our science and bringing forward the new class of medicines for patients. I would like to end our remarks by thanking the many people who participated in our clinical studies, including obviously all patients, healthy volunteers and the physicians.

With that we're now happy to take the questions. Operator?

Questions And Answers

Operator

Thank you. (Operator Instructions) Our first question comes from Matthew Harrison of Morgan Stanley. You may proceed with your question.

Q - Matthew Harrison {BIO 17603148 <GO>}

Hey, good morning. Thanks for taking the questions. I guess two from me. So on RSV, can you maybe just clarify a little bit what specifically is Merck hoping to achieve with the new formulation and the new antigen selection relative to what you've achieved so far, and

then, I guess just remind us, when you started a similar point with 1777, how long did it take you to progress to being Phase 2 ready? And then, I have a follow-up. Thanks.

A - Stephen Hoge {BIO 17925815 <GO>}

Sure. Yeah. So obviously, we're pretty excited about that one, the 1172, and we're really pleased that Merck has filed the IND already, and it's moving quickly. You saw the summary of the data in primates. It's been hard to argue with the substantial improvement that we demonstrated there. 1777, and just referencing that slide, shows superior titers to a natural RSV infection, which was there in gray, but 1172 was qualitatively and quantitatively several folds higher. And so, in the face of those improvements, we felt compelled that it makes a ton of sense to move forward.

Now, what are those improvements? Just quickly, I think you hit on them, Matt, but the first is antigen design. This is still a pre-fusion F protein, but it's been further stabilized to improve potency and immunogenicity, and so that's a desirable feature. And then, the second scientific improvement that went into the program, obviously, is the switch from a legacy lipid nanoparticle to a Merck proprietary formulation that has some improved features. Those improved features, I'll let Merck talk about it at a future date, but we think they are a part of what's happening in terms of the improvement here, and ultimately, the combination of antigen and formulation leads to the qualitative improvement you see there.

It does, At this point, mean a pause to 1777 moving into Phase 2a as described, but as talked that our goal is the best RSV vaccine possible with the highest probability of success, and as much as we wanted to see the 1777 data, it's clearly the right answer to look for 1172 first, given the multifold improvement that's been demonstrated in African green monkeys. In general, our experience has translated, and, you know that well. And things that we've been able to see in terms of preclinical species like primates for vaccines has translated into humans. So if this translates in Phase 1 relatively quickly for 1172, which we hope and expect it will, this is the vaccine that we should advance further in development to Phase 2 and Phase 3.

A - Tal Zaks {BIO 19987702 <GO>}

And Matthew this is Tal. In terms of timelines, if you look historically, it typically takes you 12 to 18 months for a Phase 1 vaccine trial that's done in healthy volunteers, so it's a fairly straightforward, simple design. I can't give you a forward-looking guidance here, but I would note that Merck has recently filed its IND, and they will be leading the execution of this trial. Obviously, the team there knows what they're doing in terms of vaccine trials.

Q - Matthew Harrison {BIO 17603148 <GO>}

Okay. Great. That's helpful. And then, the second question is on chikungunya. I know you've entered the second cohort. Do you have any view on how many cohorts you need to get through before you feel like you have enough data to talk about with that modality?

A - Tal Zaks {BIO 19987702 <GO>}

Yeah. This is Tal. The trial is currently designed at four dose levels. That was predicted based on our expectation that translates data from the nonhuman primates that you've seen. I think we're on track with that design, we've been enrolling fairly consistently, and as we said, we're at the second dose level.

Q - Matthew Harrison {BIO 17603148 <GO>}

Great. Thanks very much.

Operator

Thank you. And our next question comes from Salveen Richter of Goldman Sachs. You may proceed with your question.

Q - Ross Weinreb {BIO 20445365 <GO>}

Hi. It's Ross on for Salveen. Thanks for taking the question. Just in terms of mRNA-1172 and RSV and the decision to move forward the more optimized program, is this something that we should kind of think that may occur in other programs going forward as you continue to test new formulations of your current compounds and clinical candidates?

A - Stephen Hoge {BIO 17925815 <GO>}

So we continue with any program we advance. We're always looking at whether there are improvements, and yet there are always there sometimes can be small improvements you can make. I think the question gets more complicated, where you start to see a five-fold improvement is kind of like we're talking here at 1172. Where qualitatively that improvement is so strong and in the background of what's been happening in RSV vaccines more generally, it makes sense to bring the best vaccine forward first and quickly, particularly when you disclose after the lead in this case, 1777. That isn't something that we can't predict happening broadly across many programs or efforts. And in general, as you can see with other vaccines in our pipeline, we haven't been doing this. And so just pointing the history here, it's more of a by exception situation, where this has been happening. And that's probably what we would expect about the future.

A - Tal Zaks {BIO 19987702 <GO>}

This is Tal. Let me just add a couple of points. I think it's one of the fascinating things of beauty of our platform that we have relatively rapid improvements, and that the coding-like nature of mRNA lends itself to those improvements. So if you look at our history, for example, on the first slide's cancer vaccine, we've been able to take it to the next level by increasing the number of neoepitopes from 20 to 34, and as the team works through what that means both in terms of mRNA length and sequence optimization, we've found a way within the clinic to actually introduce that within the current clinical paradigm.

Now, of course, the PCV is a unique type of drug in that regard, and I give the FDA a lot of credit for working with us to enable that. So where we can, we always try to optimize for the best medicine that we can, and it depends on the specifics of the product as to what's the best way to do it.

Q - Ross Weinreb {BIO 20445365 <GO>}

Great. Thanks. And then I just have one follow-up on chikungunya antibody. How can we think about the clinical bar here as we approach the data readout? What are the level, the antibody levels that we should expect to see to confer this passive immunity in humans?

A - Tal Zaks {BIO 19987702 <GO>}

So, as you will see in the preclinical data that, as we said, has recently been accepted for publication, so it should come out soon. The target expression for this antibody is about 1 microgram per ml in terms of what we think is going to be a therapeutic concentration or a concentration that will -- should prevent from infection based on the totality of the preclinical data, and that was easily achieved within the dose levels that we've cleared for in the toxicology studies and the preclinical studies. So from a target product profile for this application, what we're shooting for is 1 microgram per ml. If you look at where most therapeutic antibodies live in terms of concentrations, if you pull the FDA label for Remicade, the trough levels are between 0.5 microgram per ml and about 6 microgram per ml. So it's within the range of what monoclonal antibodies have achieved for therapeutic levels for many indications.

Q - Ross Weinreb {BIO 20445365 <GO>}

Great. Thank you very much.

Operator

Thank you. And our next question comes from Cory Kasimov of J.P. Morgan. You may proceed with your question.

Q - Cory Kasimov {BIO 3009346 <GO>}

Great. Good morning, everyone. Thanks for taking my questions. I have two of them for you as well. So first one is, I am curious how this RSV decision changes, how you're thinking about your CMV program, if at all, and maybe what the latest in terms of timelines for when we should expect data from that fourth dosing cohort from CMV. And then, I have one follow-up.

A - Tal Zaks {BIO 19987702 <GO>}

Yeah. This is Tal. It does not actually change, in my view, one iota how we think of CMV or what we're doing about CMV. I think if you look at the totality of our data to date, we've shown a pretty consistent safety and tolerability profile across the 1,000 or so healthy volunteers that have been dosed across the various programs. And so, now it's about figuring out the best vaccine and the best dose for any given application. In that regard, CMV, the dose for CMV and the activity for CMV needs to be defined in the context of a CMV clinical trial.

I can't give you forward guidance, obviously, clinical trials are at the mercy of a lot of external factors. But if you look at our past performance and if you see where this trial is, you can sort of connect the dots. And we're at the fourth dose level here. The goal of this

vaccine is really to -- since it's a Phase 1 and you're dose-escalating, we want to make sure we're getting a good sense of what would be a tolerable profile to take forward. And so, as we continue to dose-escalate, at some point, we will say, okay, we think we've reached the bar for what should be tolerable. That's how you define it in the Phase 1, at which point we'll wait and make sure that we understand the immunogenicity, and then we'll share the data.

Q - Cory Kasimov {BIO 3009346 <GO>}

Okay. And then, the follow-up question is on MMA, and curious when we should expect the first patient to be dosed in that program. Can you just kind of give maybe a little overview on what the dose escalation strategy might be there?

A - Tal Zaks {BIO 19987702 <GO>}

Yeah. So as we said, we're -- the IND has been open for a couple months now. It takes you time to talk to sites, initiate the sites. The first cohort here following discussions with regulators is going to be adolescents age 12 to 18. So obviously, we're in active discussion with the sites to get them initiated, get the study ongoing, and at the same time, talking to the investigators and even the patient advocacy groups here to try and identify the patients.

In terms of the dosing regimen that you asked, this is sort of a traditional dose exploration. We're going in from the very first dose in this disease at a dose that can be effective. It's one of the requirements to do a pediatric development, and so even at the initial starting dose, which is 0.2 milligrams per kilogram, we think we -- there's an opportunity to have benefit, and we'll dose escalate from there based on the totality of tolerability and what we see in terms of biomarker effect.

Q - Cory Kasimov {BIO 3009346 <GO>}

Okay. Thanks for taking the questions.

Operator

Thank you. And our next question comes from Ted Tenthoff of Piper Jaffray. You may proceed with your question.

Q - Ted Tenthoff {BIO 1880164 <GO>}

Great. Thank you very much, and thanks for hosting us yesterday up in Cambridge. That was really interesting. I want to pick up on Cory's first question just with respect to CMV development path. Maybe you can kind of outline sort of where you would expect to take the Phase 1 datasets and what next studies would be, and then I just have one quick follow-up, please.

A - Stephen Hoge {BIO 17925815 <GO>}

So I think the Phase 1 -- the goal is to demonstrate, obviously, its tolerability, safety, and immunogenicity. In our case, the critical piece is to be able to demonstrate the

immunogenicity against both components of this vaccine. As you will recall, we both have a complex pentameric protein here, which I think is a unique feature you can do with mRNA and against GP. So we need to figure that out.

Now, in terms of the full development path, I think there's work ahead of us to talk to FDA and other regulators to understand this is obviously a very high unmet need, but it is an unmet need within the context that's obviously challenging to develop, which is trying to prevent maternal transmission to babies in utero is what we're trying to achieve here at the end of the day. Getting there is not simple. Over the years, there have been various discussions of other companies with the FDA, so there is a good body of precedent for what full development looks like. We're just starting down the path of those conversations.

I will say that the effort on our side is led by Wellington Sun. As you may recall, he was the prior Division Director for vaccines for FDA for the past decade before joining our team. So he is very busy these days, actually, putting this together, discussing with other experts in the field, and planning on that next set of conversations to understand what that full development pathway looks like.

Q - Ted Tenthoff {BIO 1880164 <GO>}

Great. Ad that's super helpful. And then, one more for you, Tal, if I may. Just with respect to the triplet program for IO for cancer, so I was pleased to see that you guys are expanding to the second dose. I think this thing is going to really carry a big hammer, and safety is going to be one of the primary focus areas. Was there anything you saw to date that gives you any pause here? Or how is that looking from an early standpoint from a safety side?

A - Tal Zaks {BIO 19987702 <GO>}

So look, It's hard for me to comment on a trial that's in progress. The data continues to come in, and we're obviously evaluating it on an ongoing basis. I can tell you that we're at the second dose level. As a reminder, for OX40 ligand alone, for the membrane protein, we've got up to 8 milligram, which was the intended dose, and that seems to be tolerated well. So in terms of the contribution of OX40 ligand itself and the lipid nanoparticle delivery technology, I'm pretty comfortable with their tolerability profile.

I think your question is correct with locally secreted cytokines, do you get to a level that is worrisome? I don't know yet. I would point out that the preclinical data in totality was pretty supportive of going to much higher doses. I think that's the unique ability of mRNA to set up this local paracrine effect within the tumor with minimal spillover into the blood. And these are obviously things we measure, so we will be looking at the expression of these proteins, both in the tumors and systemically, to see if they're detectable. We will be looking at the typical safety parameters, labs [ph] etc. It's frankly too early to say.

Q - Ted Tenthoff {BIO 1880164 <GO>}

Fair enough. Thanks so much for answering the questions.

Operator

Thank you. And our next question comes from Alan Carr of Needham & Company. You may proceed with your question.

Q - Alan Carr {BIO 15355437 <GO>}

Hi. Thanks for taking my questions. One of my early -- which you could -- I'm hoping you can tell us a little bit more about some of these rare disease programs at preclinical programs that you presented just recently. It looks like a bit of a shotgun strategy in terms of the number that you have running in parallel. How do you decide which ones to bring forward? And maybe give us a sense of expectation in terms of when these might move forward into the clinic. And then, a second one -- I'm wondering if you can elaborate a bit more about this proprietary formulation developed by Merck for 1172. To what extent do you, at least, work with Merck on developing new delivery formulations for -- in both those specific programs and how they -- with Merck, and then they translate to other programs that they are not licensed during collaboration with Merck? Thanks.

A - Stephen Hoge {BIO 17925815 <GO>}

Sure. So the two questions -- so first, on the ASGCT abstracts, five of which were presented, the wide range of academic collaborators and institutions, as you saw. We do have a very active research collaborations with academia across a very wide range of rare diseases. What you saw was a sampling of that activity, but it was ready for presentation by many of those academic labs. By participating with those folks, we absolutely commit to them being able to present that data at the appropriate fora, as well as publish it.

And so you will see a steady flow of those sorts of things. That doesn't necessarily translate into our portfolio strategy or programs that we're taking forward into development. I'll point to our own publication record there even over the last couple years, where there's a number of programs that we've published on high-impact journals that are not currently in our development pipeline.

What we choose to take into development is, goes through a different series of filters in terms of prioritization, as well as our view on unmet need and developability. So I can't comment on whether or not you should expect those things to be translating forward, and in fact, I would only say that you should expect to continue to see a large amount of that activity, both in publication and presentation collaborations with academia.

On to the 1172 delivery vehicle, so we've -- obviously, we've had a multiyear collaboration with Merck where we do talk a lot about things we are learning to enable the best development of the programs we're partnered with on them, including the vaccines like RSV. We -- I can't comment specifically on the improvements that went into the 1172 formulation that Merck is developing or is developing, but obviously, we published last year in a paper on our website, Hassett et al, some of the deficiencies with the legacy lipid nanoparticle formulations in terms of local tolerability in the vaccine context.

That underpinned a lot of our efforts to -- several years ago to develop our own proprietary lipid nanoparticle delivery technologies that actually are already in programs

like CMV and HMPPIV. RSV had started before that as an effort, and so as we shared that data with Merck long before we published it, they made their own determinations about what that might mean for that development program. And, as I said, I'll let them, at the appropriate time, sort of talk about any improvements in specific, but obviously, they're aware of all of our work together.

Now, we do share information back and forth. I think part of your question was do we collaborate on these things, and obviously, we do. We were sharing that information with Merck long before its publication, and as they make improvements and steps forward in formulation, that becomes a two-way street, and so, we're excited by it.

Q - Alan Carr {BIO 15355437 <GO>}

Great. Thanks for taking my questions.

Operator

Thank you. And our next question comes from Geoff Meacham of Barclays. You may proceed with your question.

Q - Geoffrey Meacham {BIO 21252662 <GO>}

Hey, guys. Thanks for the question. For the new GSD program, the disease ideology is pretty complicated, with multiple organs involved. I guess the question is just help us with how you're thinking about the regulatory path down the road post-proof-of-concept. I imagine there's been some discussion of endpoints already. And then I have a follow-up.

A - Tal Zaks {BIO 19987702 <GO>}

Thank you, Geoff. This is Tal. It's a great question. This disease is a different one, as you rightly point out. The unmet need here is not just the multiple organs that are affected. If you think about the patient experience and the quality of life, it's the frequent feeding at night, but if you actually meet one of these patients, which I've had the opportunity to sit down. When I sit for a meeting for two hours, I typically take a cup of coffee. A GSD1a patient who sits for a two-hour meeting needs to have a cup of corn starch that they're drinking, and if you think about that day in, day out, your entire life, there's obviously a high unmet need there that's manifested in many dimensions.

Now, to your point about regulatory path and endpoints, I think it's still early days. This is just the declaration of our intent and our development candidates. There's work ahead of us. We have to go talk to the agency, we have to go figure out the strategy for the Phase 1 first, and then we have to understand what is going to be the development path to bring and demonstrate that we can actually impact not just the basic biology of these diseases you've shown, quite remarkably, I think, the mouse model, but actually, how do we demonstrate that we're able to address all those manifold manifestations of this disease spanning from the biochemistry all through the quality of life, preventing relatively rare, but very severe events, but at the same time, actually changing their day-to-day quality of life in a much more consistent fashion. That's a lot of work that's still ahead of us.

Q - Geoffrey Meacham {BIO 21252662 <GO>}

Got you. Okay. That's helpful. And then on the cancer vaccine and IO programs, I know you're in enrollment ramp at this point, but maybe can you speak to whether we'll see any clinical updates at the upcoming ASCO meeting?

A - Tal Zaks {BIO 19987702 <GO>}

So the -- it's a medical meeting. You like to show the data that you have. I'll point you that the -- to the abstracts once they will be live, I think, in a couple of weeks. So they will describe the content of the data that we will be sharing there.

Q - Geoffrey Meacham {BIO 21252662 <GO>}

Okay. Thanks.

Operator

Thank you. (Operator Instructions) Our next question comes from Ying Huang of Bank of America. You may proceed with your question.

Q - Ying Huang {BIO 16664520 <GO>}

Hi, Good morning, and thanks for taking my questions. I want to ask about the GSD1a program. First of all, I guess, I know you have five rare disease programs in the pipeline. Does that suggest an increase in focus on this modality compared to others?

Secondly, there's a competitor which is conducting trial in gene therapy for this disease, basically. Can you talk about maybe pros and cons versus the mRNA approach, and given the data we have seen recently from that compared to Applied Genetics [ph], what do you think you can improve of? Thank you.

A - Stephane Bancel {BIO 15174250 <GO>}

Yeah. So thank you. It's Stephane. I am going to take your first question, and Stephen will talk about the gene therapy. So as we indicated, since early 2018, rare disease is an important point of focus of the Company, obviously, because of the unmet medical need because of a quick passthrough approval, and also because of what we believe is a lower biology risk, that's are some of the things we're trying to do. So as you know, as we build the pipeline of the Company, as I said in my introduction remarks, we focus very much on managing risk. And so the way we think about our pipeline now in development is we have some very interesting vaccines in infectious disease that got a big unmet medical need, but I think we have a -- if comes to, in fact [ph] any addition to be able to help a lot of people.

With five of our programs now, we think we have a nice portfolio of IO, and what we're looking for is great execution in the clinic to see what we can do for patients with those programs. And given more of the "straightforward" biology of rare disease, we're in our (inaudible) missing instruction for the DNA. And as you have seen in a lot of publication work that we have done, the very exciting preclinical model data, we really want to focus

on rare diseases, and this is consistent with the strategy we're applying now a year-and-a-half ago. And so what you saw at the ASCGT a few weeks ago, there's a lot of work going on there. This is a very important area for the Company. Stephen?

A - Stephen Hoge {BIO 17925815 <GO>}

Yes. And so on just GSD1a and gene therapy specifically or generally, we -- starting with mRNA, our focus is on dose-dependent pharmacology. I think the defining feature of our platform is our ability to have predictable dose-dependent pharmacology. Give a dose today, you get a response; you give it next week, you get the same response. If you need more response tomorrow, you give twice the dose; you should expect to get twice the response. And that's what we mean by sort of dose-dependent pharmacology, functions like a traditional drug.

We focused a lot of our rare disease efforts in metabolic diseases, where you would expect the needs of the patient based on metabolism will change over time, sometimes in a week, sometimes over years as they age. And in particular, as they're growing in young, it can be highly dynamic. And so, we focus on looking at diseases like GSD1a. MMA is another example of this, where we are expecting to need to titrate to the dose response that's desirable to manage that disease.

Now, there are -- as you mentioned, a gene therapy approach going up to GSD1a as we speak, and we really don't view those as necessarily competitive. In fact, we think these are different tools that physicians will use, hopefully in combination for different purposes to help patients manage this disease. We can easily imagine worlds where, sort of analogous to insulin, they are sort of basal long-acting forms, but you're still managing the disease day in, day out with -- by testing blood glucose, or week in and week out by controlling for it. That will give, frankly the physician -- we hope that -- where personally we would hope that they're successful and we're successful, because more tools for clinicians as they're treating patients will be a great thing. So we don't necessarily view it as competitive; we view it as adjunctive, and we're focusing on a different area of the pharmacology.

Q - Ying Huang {BIO 16664520 <GO>}

Thank you.

Operator

Thank you. And I am not showing any further questions at this time. I would now like to turn the call back over to Stephane Bancel for any further remarks.

A - Stephane Bancel {BIO 15174250 <GO>}

Well, thank you very much for joining us today and for your questions. We look forward to talking and to seeing many of you in the coming weeks, including at ASCO around the PCV post trials [ph]. Have a great day.

Operator

Thank you. Ladies and gentlemen, thank you for participating in today's conference. This does conclude today's program. And you may all disconnect. Everyone have a wonderful day.