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Galapagos NV Inaugural Toledo Roundtable Presentation (Virtual)

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PRESENTATION

Elizabeth Goodwin ***Galapagos NV - VP of IR***

Thank you all for joining us today for our Virtual R&D Roundtable Covering the Toledo Program. I'm Elizabeth Goodwin, Investor Relations, also representing colleagues in our IR, R&D and Communications teams who have worked hard to bring you this information today.

This recorded Zoom webcast is accessible via the Galapagos website homepage and will be available for replay later on today. Sell-side analysts and professional investors are invited to post questions at the end of our call. I'm going to give you a dial-in number now. That's 44 for the U.K., 2-071-928-338, that's +44-2-071-928-338, and the code is 3312849. I'll give that number again a little bit later. There will be additional numbers visible on the webcast player screen when we come to that part of the event.

And now moving on to our forward-looking statements. I would like to remind everyone that we will be making forward-looking statements during today's webcast. These forward-looking statements include remarks concerning future developments of the pipeline, the Toledo program, in particular, our company and possible changes in the industry and competitive environment. Because these forward-looking statements involve risks and uncertainties, Galapagos' actual results may differ materially from the results expressed or implied in these statements.

And now, I'd like to go over the agenda for today. Our program will last approximately 1.5 hours. First, we'll start with the talk. CEO, Onno van de Stolpe, will introduce our innovation approach. CSO, Piet Wigerinck, will talk about our innovation with the Toledo program. CMO, Walid Abi-Saab, will discuss our clinical strategy; and then Onno will come back to wrap up. You'll see a PowerPoint presentation on screen during their talk. And again, this will be followed by a Q&A session. You'll get more instructions at that point.

So that's all for our logistics today. Now it's time for us to get into what you've all really been waiting for. I'd now like to hand over to Onno to tell us more about the approach to innovation at Galapagos.

Onno van de Stolpe ***Galapagos NV - Co-Founder, CEO***

Thank you, Elizabeth. Very excited to finally take away the wraps around the Toledo targets and Toledo story. So we are going to highlight that today in this session. Thanks for joining this. It's a very positive session. We're all very excited about sharing this information with you.

Innovation is really in the DNA of this company. We have been focused on innovating, innovating and innovating since the start, 22 years ago. We pushed the scientific boundaries, we are very much science-driven. Science is so crucial for anything we do in this company. We follow the biology along the way. We find a target, develop the drug, and see what areas it can be best used for and the Toledo Group is a

very good one. We are exploring various diseases that potentially could benefit from the Toledo drugs that we are in clinical trials with at the moment.

We're clearly very innovative. We are focusing on new methods there. And always, always focus on new mode of actions. So our approach to innovation, as I said, is novel targets that we identify with our platform, combined with chemistry, always supported by biology with technologies to very rapidly go into clinical trials to identify the target as the right target to treat various diseases. We have a very ambitious path in deliverables. Our objectives are to come up with 6 new targets per year, bring that to 4 -- 3 to 4 preclinical candidates per year, 3 proof of concepts, and then that should lead to 1 Phase III start every year. So it's an ambitious program for a small biotech and Galapagos still is. But we are delivering, and we are getting more and more programs into the clinic.

It all boils down to the target discovery platform that we started 22 years ago, based on adenoviral technology. What we did is putting a small piece of human DNA into an adenovirus backbone that when it enters a cell, a human cell, it will actually stop 1 specific protein being produced in that cell. And by doing that with over 6,000 different genes of the human genome, we can rapidly zoom into those genes in the human genome that are responsible for certain diseases.

And when we identify such a target, a hit, then we can develop a drug that ultimately will do similar to the adenovirus when it enters the cell. When it enters the human body, actually will regulate and stop the specific protein that's overproduced in that specific disease. It's a very robust platform that has delivered many interesting targets so far. And the Toledo group is clearly one of them. If you can see here on the slide on the right is actually the Toledo protein for those chemists, and biologists, you can now identify the target based on this graph.

We can get to the next slide. And clearly, our innovative approach with Toledo is now coming into a state where we are going to get results in patients. And it has been a long way where we initially identified the targets and then got excited because of the dual mode of action. We confirmed that in animal models and also in human Phase I healthy volunteer studies. And we are now launching a broad Phase II program to see how this family of drugs behaves in various inflammatory and fibrotic diseases. So very exciting for us.

And the question is, can we make a difference? And of course, you never know until you're actually in the clinic in late stage trials. It's always in a tough decision in what diseases to go for, but the inflammatory diseases clearly are in need for new classes with better efficacy.

If you look at psoriasis then 20 years ago, it now has much better drugs available for treatment where the majority of -- up to 90% of the patients react very favorable to treatment. However, in other inflammatory diseases, this improvement has not gone as fast as with psoriasis. And there's a clear need, unmet medical need, a need for better, safe and effective treatment options. And that is the difference that we would like to make in inflammatory diseases with the Toledo group.

You all know, we have filgotinib on the market here in Europe and shortly in Japan, which is a very exciting drug as well. But clearly, we would like to go another step into treatment of these inflammatory diseases and we hope to develop the Toledo group of molecules as a next-generation in treatment of inflammatory diseases.

We can get the next slide. Then it's my pleasure to hand it over to my CSO, Piet Wigerinck, to give you the background on the Toledo program before we actually continue with Walid on our path to patient data. Piet, the floor is yours.

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

Thank you, Onno. So we promised to raise the curtain on our Toledo program today and we plan to do much more. I hope that by the end of this presentation, you will share with me our enthusiasm around this novel mechanism of action. We call it a master switch. This is new because Toledo acts in a novel way. It acts in a way which is different compared to current drugs. The novelty is that it has a dual action. It blocks on the one hand side the damage and stimulates the repair. That's I want you to remember at the end.

Our body can only work because it's full of systems that act and control. There is always a balance. That's also true in the immune system. We need cytokines, and they are covered here as the orange ones, that act when we get an infection when a virus infects us, or a

bacteria. Then there is the first phase of the fight.

But when they have done the job, we come into a second phase, and then we need the green ones. These are anti-inflammatory cytokines and players, and they take care of the healing. So when there is an infection, we always have a fighting phase and a healing phase. It's important that those 2 are well balanced. Because in patients, what do we see? The fighting phase that's going well but the healing phase is not there because the balance is lost. And as a consequence, our cytokines, our cells, are going to damage the body. They will cause ulcers, they will erode our bones.

So current therapies all are based on the same principle. They try to damage the access of the pro-informatory cytokine. They take away that access to restore more or less the balance to avoid that the healing can't take place. So they're going to take away and make sure that the small amount of the anti-inflammatories can do the job and can limit damage. With Toledo, we have different ambition, and we've seen those data, and I'll share them with you.

We want to play or replay with Toledo at both ends of this balance. We, on the one hand side, limited damage by decreasing the number of pro-inflammatory cytokine cells. But at the same moment, we increased the anti-inflammatory cytokines themselves. That's what I'm going to show to you today, and that's why we're so enthusiastic about this class.

How do we find this level of existing targets? Well, those amongst you who follow us for a long time know it's a long way, and it all starts with the diseases. So on the left, you see here a cartoon of the guts. And talking about the gut is always fun because while the gut is in the inside of the body, it's in fact the outside of the body. And to protect the bowel, we need a layer. These are these green cell tightly connected, epithelial barrier cells. And you also see there, purple star-like cell which spikes through the barriers. This, in fact, is dendritic cell and they act as sensory. And they're extremely smart sensors because when a bacteria passes, which does not cause harm, they don't act. But when a noxious bacteria passes, they will give an alarm signal and then the whole immune system is activated and recruited.

So a lot of them, setting different models, one for the epithelial layer, one for the dendritic cells, one for the macrophages. We decided to go for a more complex model and make our IBD assay, which was bilayer model. And in fact, on top, we have the barrier, where we can measure whether it's really very sticky and nothing leaks through. And below, we put down those sensor cells, the dendritic cells.

And in fact, this is an extremely cool model because if you will add lactobacillus, which is part of yogurt our barrier become stronger. While on the other hand, if we had a dangerous bacteria like E. coli, the barrier get lost. So really, a model which in terms of the relevance and the complexity we hadn't seen before. So in this model alone now to us, to knock out targets in the immune cells and measure the impact of knocking out a target in the immune system on the epithelial barrier is by screening this type of models and assays that we discovered the Toledo.

Early on, we were intrigued and we were lucky that we could find a nonselective tool compound, but as well with the non-selective tool compound early on, we could prove that in fact, the barrier was maintained. We could put in as much as bacteria as we want, if you compensate it with compounds, if you block the target in the barrier stayed integer [intact].

So we start to measure all of the cytokines in these models, and we saw that many were going down and also to our surprise, a few were going up. And this was something we had never seen before. So we wanted to confirm that. And we then set up a macrophage assay, where, in fact, indeed, we could confirm in the second type of immune cells that with an increase of dose, we saw a decrease of the pro-inflammatory cytokines and an increase of IL-10, which is a prototype of the anti-inflammatory cytokine.

So this was the first time that we say, "Wow, this is cool. I don't think anybody ever got this." So this target really, this is something special.

So now I'm jumping 5, 6 years to first give you a bit of the breadth. We've optimized the compounds, we then started to look broadly in all types of immune cells. And to our surprise, in fact, you can see on the left, you see there the macrophages, monocytes. You see a decrease of TNF-alpha, a decrease of IL-12, a decrease of IL-1 beta. And as in our model, we see an increase of IL-10.

When we go to the dendritic cells, you see similar picture but different cytokines. TNF-alpha going down, IL-12 going down and IL-23 going down, IL-10 going. So all of the drugs that we currently have, in fact, they act as well to the Toledo and on top, we increase IL-10.

In T cells, we see a decrease of IL-2 and interferon-gamma. And in B cells on the right, we see again a decrease of TNF-alpha and increase of IL-10. So this is a switch, a master switch, which in many cells of immune system has a similar action. It really does something which we have never seen before. So that's why we call this our master switch in the immune system.

So I'm not going to keep you waiting until the end of the presentation to reveal the target. Let me go into that now. So we call it TOL1, TOL2, TOL3, but behind that code, in fact, and many of you guessed it right, are the SIK1, SIK2 and SIK3. These are named salt-inducible kinases. So what has salt to do with the story? In fact, extremely little. The first member of the family, SIK1 was discovered in '99, when animals were fed a high-salt diet and then one of the enzymes that they showed that was popping up was SIK1. For SIK2 and SIK3, there is no lead at all with salt. So salt-induced kinase is the name, which is of zero link to our story.

We selected 3 -- we are working on 3 clinical candidates currently. You can see GLPG3970. And then is the focus of today, I will only show data of '3970 because that's a component mostly to patients, blocks both SIK2 and SIK3. '4605 has a similar profile, and I will not discuss today. '4399 is a bit of a strange compound. It's selective on SIK3 only. It has a bit of a different profile that's also for a later discussion. So it will not be discussed further today on slides.

We have the movie now. Yes. Okay. So how does SIKs work? As you can see there in the movie, you see the yellow string and green strings. In fact, these are the mRNA's coding for the anti-inflammatory and the pro-inflammatory cytokines. And in an immune cell at rest, they are in balance. This whole system, in fact, is under control of SIK. And SIK controls on the left the HDACs and the CRTCs, give me minute here. So HDACs, in fact, they are blocking NF-kappa B. So if they reach the nucleus where you see the DNA string of the NF-kappa B program, they will block that.

CRTCs, they have the opposite function. If they can get to the cell, they will activate the CREB system. But SIK is a kinase, so it adds a phosphate group to both the HDAC and the CRTC and both stay out of the nucleus and they don't work. And so there is a basal functioning of NF-kappa B and CRTC, and this gives us a kind of balance.

So the next slide now. So where there is an inflammatory trigger, what happens now is that this whole SIK system is biased. And it is a direct activation of NF-kappa B, and you will see a vast increase on the left from the pro-inflammatory cytokines.

So what happens now if you switch off this master switch SIK with Toledo? Next slide, well then, you get 2 opposite functions. So the SIK is blocked, it's not phosphorolating anymore HDACs and CRTC. HDACs go to the nucleus and they block NF-kappa B, so you have a vast decrease of pro-inflammatory cytokines. While CRTCs also go to the nucleus, they activate the CREB cells, and you see an increase of anti-inflammatory cytokines. And this is why this mechanism is so unique that with a single switch of the button, you're going to completely invert what is normally happening during an inflammatory process. You play at both ends and you invert completely the picture. That is the heart of the matter how SIK works.

Next, go back to the presentation. Next slide. So we discovered this target quite a while ago, so it was around 2012. And we will later add to the presentation a number of external references, and you will see the first appear as well in 2012. With those novel mechanism of actions as we are pioneers, in fact, the work is going slow because we don't have any tools to confirm. So it took us a while. But in 2014, we set up an HTS screening. And as soon as we had first hits, in fact, our chemistry team starts to work. And from 2017 onwards, we've been making a preclinical candidates. And up today, we have 4, and we plan to do much more and even increased the speed over the coming months. Because we have those 3 members as SIK1, SIK2, SIK3 and in fact, we want to combine all of them over the coming months.

We have, in fact, set up for our company, a massive effort -- a massive effort, sorry. We've dedicated the largest chemistry team ever. We've dedicated the largest team to understand this mechanism of action. We've synthesized a couple of thousand molecules. We initiated our chemistry work on more than 10 different series. And we're really chasing every selectivity profile that we can think of. So we've been filing patents and more to go. Currently, about 1/4 of the company directly or indirectly in research works on this program and

we really want to put this to the max.

So you can see on the right, we have the different profiles. My ambition is in a couple of years, we'll have plenty of compounds with different profiles, blocking SIK selective in 1 only, duals and triples there.

Next slide. Just to give you an example on how the chemistry worked and what the chemistry did on the left. You see the typical output of the screen. So those orange dots, or only few actives are sitting in the left corner there, meaning they have low potency, and they are not selective because they have the same distance to any axis.

On the right, you see how this chemistry effort, we have grown our series, both in terms of potencies and in terms of selectivities. We have selective SIK3. Duals, we worked on selective SIK2 series, we worked on selective SIK1 series. So this will be a maintained effort. And we will come with whatever profile we believe is sufficiently interesting to be put in patients.

Next slide. Let's now go back to our IBD model. So this is a cartoon of an inflamed colon. And you can see by the fact that the bacteria, the green dots, that are sitting in the lumina as well, they pass a bit through our barriers, which at the moment is leaky. The dendritic cells, they sense the presence, and they activate the whole immune system. They're going to activate the macrophage, the neutrophils and also they will recruit the T cells, TH1, TH2, TH17. And all of them will produce many cytokines to form and to attack those bacteria.

So what you see as well on the cartoon, there's only 1 or a few amounts of Treg cells. So what happens now when we block with the Toledo? We're going to block both dendritic cells, the macrophages, and you will see the balance turn. We certainly see a large amount of Tregs, we see certainly the green cytokines appearing, and we don't see any of the pro-inflammatory cytokines anymore. So with the Toledo, you can locally distort, completely revert the interplay, and barrier will restore and the integrity will be restored as well. So bacteria from now on will stay in the guts.

Let's now go to some in vivo data. Today, we only show data of '3970. So the pictures might look very similar to what I've shown before, but that was with different compounds. Today, all data are around '3970. These are 3 IBD models, and the uniqueness of the Toledo family effect that these compounds work in all 3 models. We've seen good activity with JAK inhibitors or other mechanisms of action in 1 or 2 of those models. Never in the 3 models at the same moment.

On the left, you have the DSS, and that's, in fact, a barrier model. In this model, with a chemical, you will damage the barrier integrity, and you see how quickly a compound can restore that barrier integrity. And '3970 scores as much as our internal positive control.

In the middle, you have the T cell transfer model. And in fact, that is more a balance model because you take healthy animals, you're going to infuse a mix of activated T cells, you distort the balance. And as a consequence, you get all of the damage on the colon. Positive reference is a T cell broker abatacept here. Again, you see that '3970 is doing nicely the job to block the damage in the T cell transfer model.

On the right, the MDR 1 model is less used, but it's quite close to the disease. In fact, it's a model where you have sensitive animals, you will trigger them with bacteria and their colon will get inflamed. And even more, the IL-17 antibodies in this model worsen the disease, like we see in the clinic, while IL-23 antibodies will work. So it's a quite relevant model. And also in this model, '3970 has shown nice activity.

Next one. So now, we'll dive a bit deeper into what we've seen in the T cell transfer model in the tissue. So now I'm going to show you really experimental data, and let's start with the macrophages here. What you see here on the left are the activated, the pro-inflammatory M1 macrophages. And upon treatment, you see the number going down.

Same moment on the right. What you see here is that the M2 macrophage, the healing ones, when we induce the disease, their amount is quite low by turning the switch here, we turn on the program and the M2s will increase. So we really have proof, quite relative proof, that we play at both ends of the balance here.

Next slide. So we've also measured locally cytokines. These are now measurements in the colon tissue after treatment. On the left, you see the TNF levels. So we start with the healthy animals, unchallenged. We're going to challenge them with the T cell mix, and you see an increase of TNF in the colon tissue. This is colon tissue, I will stress that. You -- those animals -- or you treat animals with Toledo, and you see a return to almost the healthy levels of before of TNF-alpha. So a very strong blockage of the pro-inflammatory cytokines.

In the middle, the same, but the opposite story for IL-10. IL-10 is the cytokine that's going to induce the healing in the disease state. These levels decrease, they are low. We apply Toledo, and again, we see an increase to almost normal. So we really play -- with all of this data, I'll show you a play at both ends of the balance.

TNF-alpha and IL-10 were only the prototypes of a much broader plan. On the right, you see you see at the top, total panel of the pro-inflammatory cytokines, we measured upon treatment, they all decreased. Below, you see 2 members of the family of the anti-inflammatory cytokines and again, upon treatment, both members increase. So we see across cell types, across cytokines, consistent picture, we play on both ends of the balance.

So Toledo works on multiple immune cells, it's also active in multiple disease models. We've tested, I've shown you the models of IBD. We have done -- I will show you data for psoriasis, psoriatic arthritis, RA. We've tested lupus models, we've tested OA models. It's not everywhere active, like you can see, OA, we don't see activity with our compounds.

Show you the most important one, our next slide first. Next to the anti-inflammatory models, with next in the second area as well starts to be interested in the fibrosis models and also there, '3970 shows nice activity in 2 models of fibrosis. I'll show you the data. But again, we'll concentrate today on explaining the switch and how these molecules work in the fibrotic setting. I promise you to take it as well at the next occasion.

Next slide. Data on psoriasis. This is, in fact, a local model. We are going to inject IL-23 in the ear. And it's a very easy measurement, you just measure how much the ear is swelling, and you can prove then that your compound has an anti-inflammatory activity. You can see that here, '3970 scores as good as our positive control in this model after oral dosing. Its oral dosing compounds penetrate to the body, going to the skin and locally, does its activity there and clearly shows an activity as good as a positive control, which was a TYK2 inhibitor.

Next. Okay. Now 2 models of arthritis. And in fact, on the left here is CIA. On the right, psoriatic arthritis model. And in fact, 2 quite different models, although it's both bone and joint, the CIA model is a model where disease is driven by B and T cells, while the psoriatic arthritis model is driven by other cells.

So -- but as I showed at the beginning, Toledo shows an activity in key B cells, macrophages and dendritic cells. CIA is clearly a check that promise of B and T cells, is that coming through. And you can see over here that '3970 scored as good as Enbrel in this model. So this is a harsh setting. We wait long before we start to dose so that there is good disease. It's the therapeutic setting, as we call it, and then we start to see -- we start to dose, and we see effect in decrease of the disease with these compounds.

The psoriatic arthritis model is a bit of a different model. There, now we inject IL-23, let's say, in a systemic mode. And you get an inflammatory response on the bones and certain of the tendons associated with bones, typical for the disease as well. Again, there, it is becoming a repetitive story, '3970 scores as good as our positive control.

Finally, in terms of animal models. I told that we have shown activity in 2 fibrosis models. On the left, you see the bleomycin. The model is what it is, the windows are small, the '3970 here was even better than nintedanib, which is a positive control. So clearly an indication that there is an antifibrotic activity ongoing here. There's a good rationale. But as I said, I'll keep that for a next roundtable session. On the right, chronic graft-versus-host versus host model where, as well, you can see that the Toledo nicely scores and even better scores than nintedanib.

So next to the autoimmune, which is our start of the program we as well planned later with -- of fibrotic indications, but I'll let -- we'll tell you more about that.

So what do we have today ongoing? We have '3970, SIK2 and 3 starting Phase II. We started to dose patients. Walid will explain the breadth and the thinking behind the program. '4399 and SIK3 selective, we are IND ready. We wait for approval, and we will start Phase I. '4605, very specific as SIK2/3 compound we explain as well later. It's kind of a backup -- it has different properties compared to '3970.

Behind these 3 compounds, we plan to keep on, as I said before, looking selective SIK1s, SIK2s, SIK3s, and then SIK1 combined with 2 and 3. Whatever we can, when we find compounds that show an interesting profile, different of what's out there in the clinic, we will push it forward.

We've put '3970 in preclinical testing and from there, we go to the clinic. So we've performed a Phase I single ascending dose, multiple ascending dose. And in fact, the compounds in terms of PK performed excellently. It's a once-a-day compound, absorption is fast. We see dose proportional exposure. We saw -- and based on the half-life, once-a-day dosing really is our way forward here.

As well what we see with the compound, the chance that it will have drug interaction problem arise later is quite low. But in terms of exposure and dosing, this is an easy compound to move forward.

The more interesting compounds or data came, in fact, from the PD effects that we've been measuring in this Phase I. And you will see now graphs on the left, on the TNF-alpha levels. Day 1 on the left, day 14 on the right. And then IL-10 as well, left day 1; right, day 40. So what we do here is we take blood samples out of those healthy volunteers at specific time points. We're going to trigger the whole blood and then measure whether TNF-alpha is there or not and IL-10.

As you can see, orange is placebo. We don't see any effect on either TNF-alpha, IL-10. The low dose effect already gave an effect on TNF-alpha, not yet on IL-10. But from the second dose effect onwards, we were clearly seeing robust decrease of the pro-inflammatory cytokines and a nice increase as well of the anti-inflammatory cytokines.

In terms of safety, I can be very short. It's all a quite boring Phase I study. So we've seen what you typically see, and we've seen that nothing special, so all lights on green to move forward into the clinic.

And with that, I want to give the word to Walid.

Walid Abi-Saab ***Galapagos NV - Chief Medical Officer***

Thank you, Piet. Good morning, good afternoon, everybody. I hope you can hear me well. I hope we got you very excited about what we've seen so far with this program, and I'm really excited to walk you through the clinical story and our approach there.

So can I have the next slide, please? So when -- this is the slide that you've seen before. And as we've been talking about, the foundation of what we do and what guides us at Galapagos is science. So when we set out to figure out how we want to approach this platform and how we want to learn that we looked at the broad application that we have in inflammation.

And as you can see here, between innate and adaptive immunity, you can see on the left-hand side, these indications that are more close to innate, like psoriasis, UC and CD, in IBD space. And on the right-hand side, you have rheumatoid arthritis, lupus, Sjögren. And in the middle, getting from both worlds, you have psoriatic arthritis. And to a great extent, that colors the way we're going to go forward. But at the same time, we are taking a broad approach so that we can learn from the lead compound so that the follow-on compounds could be better positioned, and potentially could move faster so that we can make these promising SIK inhibitors available to the patients as soon as possible.

If I can have the next slide. So the first step here, and that's the first orange wave, so to speak, the first wave is to cast a wide net in looking at a number of diseases across the innate and adaptive immunity space and in a series of signal detection studies to understand the biology, link that to what we've seen in the Phase I effects as well as in animal studies.

And then the next wave will be to potentially go further in those areas where we have a clear effect in these signal detection studies and go into dose range finding studies. But as well expand into other indications. For example, if you start with ulcerative colitis in the first

wave, we can go into Crohn's disease. If you start with psoriatic arthritis, you can go with ankylosing spondylitis and so on and so forth.

Sorry, staying at the same slide. And then you have that third phase where you can further develop and go into confirmatory program for the studies, the indications where we have effect in the dose range finding studies, but also initiate our fibrosis platform, as Piet described.

So now let's speak a little bit in more details. And I can have the next slide, please. So for to validate this initial space, we started with a psoriasis study. And psoriasis is not really an indication that we plan to continue developing based on the way we think right now. But the reason why we started with it is because it lends itself to very quickly be evaluated and generate clinical data for us to indicate where we need to go next because we can do this in a Phase I setting because most patients are relatively healthy with the exception of some the skin manifestation of their psoriasis.

And then if I can have the next click piece. Then you can see we're going to be casting a white net across that platform that we talked about, looking at signal detection studies in ulcerative colitis and rheumatoid arthritis as well. And then later, which is going to be starting later next year, I'll show you on subsequent slides, we're going to be expanding into more challenging indications, but also very interesting to understand the biology, lupus and Sjögren's syndrome as well.

Next. Then you will have a set of studies where we can go and do those range finding studies in RA and UC. For psoriatic arthritis, I'll talk to you a little bit more further on. That's an indication that we're actually trying to accelerate faster because it promises to make these potential therapeutic agents available to patients as quickly as possible.

And then when we do go into indication expansion, you can see the adjacent indications that I talked about, Crohn's, ankylosing spondylitis. But there are also some others that's why we didn't label that last one. There could be others that we will find out more and learn more around -- along the way and be informed by that first wave of signal detection.

And lastly, you have that Phase III, where you can go into confirmatory studies for inflammatory diseases, but also start exploring the fibrosis indications and other chronic indications that we're going to go after.

Next slide. This digs a little bit deeper on the time line and give you a sense of the parallel set of signal detection proof-of-concept studies, starting with the psoriasis study, which is, again, in additional cohorts in our Phase 1. The ulcerative colitis and rheumatoid arthritis are 2 studies, I'll talk about them in subsequent slides. And then later, we're going to come out with lupus and Sjögren in beginning of 2021. So 3 of those studies are already active and recruiting and the other 2 will be coming up shortly by the end of this year, early next year.

So we have 5 different proof of concepts to investigate a broad mechanism of action to be able to get a good sense of the overall biology and casting a wide net and learning from it. And we expect to have top line from these studies as of the beginning -- as of the middle of 2021.

Now there's a caveat there is that COVID is a bit uncertain. So we're hoping that we're going to be able to move according to the pace that we want to, but there could be some difficulties that we would see along the way.

In the case of psoriatic arthritis, if you remember, I have a picture on the top of the innate and adaptive immunity, and then psoriatic arthritis is there in the middle. And based on the number of studies that we've done preclinically and that Piet has gone through some of them, today, we believe very strongly that the biology supports this indication. We have a very good conviction that we have a good probability of success. So as a result, we decided to prioritize this to take a bet, a bigger bet on this. And instead of waiting until we do things very sequentially, we plan to start immediately into a dose range finding study in psoriatic arthritis in the middle of next year. And then with that, move as fast as possible into Phase III, with the expectation that if our bet is correct, we will make available these potential medicines to the patients in about 1.5 years to 2 years earlier than otherwise.

Now let me take some time to walk you through a bit of the design of these signal detection studies. So you have the first one called

CALOSOMA, which is the psoriasis study. As you will see across the board, those are small signal detection studies. In order for us to be able to cast a wide net and learn, we must do these smaller studies so that we can get initial information and not spend a lot of money at risk. But at the same time, also not take a long time to get the results back.

But with that, also, you have to bear with us when you experiment, there's potential for some studies to have better results than others. So when we start talking to you about them next year, you guys should expect also that some of them will look very good, but maybe some, maybe not as good, and we need to be fully aware of it. And we are going there with eyes wide open.

So this study is essentially -- we're going to have 25 patients, 10 on active -- 10 on placebo and 15 on active, and these are typical patients with moderate to severe psoriasis, with -- have a baseline of at least 12 and above and body surface area coverage of 10% or more. And we will look at, of course, safety and tolerating as we often do, but also at efficacy in the usual PASI scores and so on and so forth to get a sense of the activity. In addition, with those trials, we always look at biomarkers and things of that sort as well.

The next one is the SEA TURTLE study in ulcerative colitis. And that study, again, is a similar design. Generally, it's a 6-week duration. 10 on active [placebo], 20 on placebo [active]. These are patients with moderate to severe UC, who have been exposed to treatment before, of course. And the key outcome is the usual stuff that we look at endoscopy, biopsy. We look at the Mayo score and the partial Mayo score. And of course, we will look at biopsies. And with those, we get a pharmacodynamic endpoint as well to link back to the clinic, linked back to the healthy subjects and learn from this.

And last of the signal detection studies is the LADYBUG study, which is a study in rheumatoid arthritis. Again, it's a study of 15 patients on active and 10 placebo. It's a bit reminiscent of our first study that we've done a long time ago in Moldova with filgotinib, and we're hoping that we're equally going to get some fantastic data with that study that will get us excited about going forward there with this one.

So these are, again, patients who are methotrexate IR, they have moderate to severe active RA. And we usually look at the usual symptoms of RA that you know very well.

So I hope, I can go to the next slide, that I was able to communicate to you that the approach that we have taken in this program is an ambitious, but also an informed development strategy, where we take first -- the fastest way that we can get clinical data in a psoriasis study in the Phase Ib setting so that we can quickly get that information. We also can take a bet on psoriatic arthritis based on our belief in the biology and also on the data that we have accumulated so far, particularly the pharmacodynamic endpoint from the Phase I study. And that could make the drug available to the patients potentially after 2 years earlier.

Then the learning approach that we take by taking the lead compound and linking back to the biology and translating back to the lab and also to the healthy subjects and have cross learnings will help us to position these follow-on molecules. Giving you an example, the follow-on molecule comes in. And based on preclinical data, we expect it to work in such a, let's say, in RA. The pharmacodynamic profile that we get in Phase I looks very much like what we expected to see in compounds that would work in RA, and it would be different than our SIK2/3. Then we can quickly go into a dose range finding study and not have to do a proof-of-concept study. And again, sort of speed development, but not only that, also positioned for the right indication.

So this is the approach that we're taking. And with every study that we do, our knowledge is going to grow. And ultimately, we will really unleash the potential of this brand-new pharmacology and what it could offer to patients.

And lastly, we're going there with eyes wide open. So we know that this program is early. We are monitoring everything very carefully. We've been monitoring, for example, safety, and we look at the biology at this from the beginning. We have a large group dedicated to monitor safety across all the trials so that we can detect signals very early and so on and so forth. We understand the promise of the novel pharmacology, but we also understand the potential unknowns. And we have all the systems in place to be able to deal with this and solve any issues or if they were to happen, very early on. So I want to tell you that we are going there with eyes wide open, knowing full well about the exciting parts, but also knowing full well that there are certain things that are not known because of the novel pharmacology, and we are going to be watching this very carefully.

And with that, I will turn over to Onno to wrap up this very exciting story today.

Onno van de Stolpe ***Galapagos NV - Co-Founder, CEO***

Thank you, Walid, and thank you, Piet. I hope you all share our excitement with this program. Clearly, we are extremely excited and optimistic regarding Toledo. It is short in its development still, it's early days with all the data, they point into the right direction. And I think it's really the totality of the Toledo data that makes a difference here. It convinces very much. It started with the identification of the target with a very complex assay. We saw in the literature that the mechanism made perfectly sense to focus on this one. For inflammatory diseases. We got the preclinical data in, as Piet has shown to you, where time after time, we saw very good and robust efficacy, something we have never ever seen with a molecule before. And then lately, the Phase I data, where we saw luckily, very good data in healthy volunteers, but we saw also a proof of principle with the fact that we could see a dose-related effect on IL-10 and TNF.

So altogether, we believe that we have a very strong package here that warrants hefty investment in further steps towards the patient.

And if we go to the next slide, it's clear that we potentially have a real master switch for inflammation, different from anything anybody has shown so far, much broader in its application and hopefully, much more effective than anything that is out there at the moment.

We have, of course, with all the work that we have done over the past couple of years, a very broad and strong IP protection, intellectual property protection with the patents. We have confirmation of the mode of action in the Phase I that we did with '3970 with a very, very good safety package. So that gives us a lot of confidence that we have a right window to go into the clinic and into the patient trials.

As Walid has just outlined, we are going into a very smart path in clinical development, which should accelerate to bring this drug to the patient and hopefully, shorten the development time substantially so that we can reach the market much earlier than in other programs that we have been working on.

All this, you could question why we have kept this under the wraps so long, with Toledo as a code name. It's all to not make the competition wiser than needed. Clearly, we have a massive head start on the competition being in Phase II, where, as far as we know, no other molecules for inflammation have been in the clinic based on this set of targets, on the SIK targets. So that competition lead will help us to secure an important market share whenever this actually would get to the market. So a new class that potentially could change the way inflammatory disease and fibrotic diseases are being treated.

Well, what can you expect on the news flow this year? We were very pleased that 3970 finished Phase I. So successfully, we're starting the proof-of-concept studies, the first one underway, the second recruiting. So that's all going in the right direction. Very proud on the teams that worked on this, especially in view of the whole COVID situation that we didn't get delays here.

We're starting the next Phase I for '4399, of which data will come, of course, in '21. But in both, you see in '21, the readouts, which are of course very important of the proof-of-concept studies. 3 proof-of-concept studies will be out in '21, and the rest will be out in '22. So will be a lot of data that hopefully confirm what we are expecting. We -- you see a lot of other stuff happening, Phase I starts, Phase I readouts. But look, in '22, where at the moment, we are planning the first Phase III, which would be a fantastic result if we achieved that.

Then we have really accelerated the speed of this program with a couple of years and it's all possible now for Galapagos to do this, whereas in the past, we were always dependent on partners to finance the road forward. But as you know, with the cash that we received through the Gilead transaction, we can make our own development plan, move forward as fast as possible and decide on the progression of these programs by ourselves, which clearly helps to speed up the programs.

So I truly believe that this is a once in a lifetime opportunity for Galapagos, something all these people that work on this within Galapagos think it is the project of their life. It is something so new, so promising that this can change the way these diseases are being treated. And that as this is happening at Galapagos makes us extremely excited and extremely proud.

Of course, we still need to deliver on it. And it's a risky program because it's early, but all the signals are bright green, and we are looking

forward to sharing more information as we go along the way.

With that, we would like to end the formal part of the presentation. I hand it over to Elizabeth for the Q&A. Thank you.

QUESTIONS AND ANSWERS

Elizabeth Goodwin ***Galapagos NV - VP of IR***

So thank you to our speakers. That concludes the presentation portion of the video webcast. We do invite sell-side analysts and professional investors to post questions. I'm going to give you the dial-in number again. That's 44 for the U.K., 2-071-928-338, and the code is 331289. There's some additional numbers also listed in the webcast player interface, you should be able to access those.

(Operator Instructions) The first speaker is Brian Abrahams from RBC Capital Markets.

Brian Corey Abrahams ***RBC Capital Markets, Research Division - Senior Biotechnology Analyst***

Congratulations on all the innovative work that you guys are doing. Two questions for me. My first is, I'm curious, as you sort of look across -- look at this mechanism. I'm sort of curious what shapes the differences in how you guys are planning to target different compounds towards different indications.

For instance, I noticed that both '3970 and '4605 are SIK2/3 selective, and yet they seem to have different profiles in terms of what diseases they work best in, in the preclinical model. So I'm wondering if you could talk about what explains -- what might explain that mechanistically and what guides your decision on targeting each compound. And then I had a follow-up question.

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

Okay. You can hear me now? Yes. Thank you, Brian. And you guessed the target well many, many months ago. So congrats on that. '3970 and '4605, they are completely different chemical scaffolds, and they behave completely different in the body as well.

So -- and that's probably what's going to help to guide '4605 to a couple of specific diseases because we see a disposition of that compound in higher amounts in certain tissues only, while '3970 is a compound that scores everywhere. So the '4605, it's correct, it's the same as SIK2, SIK3 profile, but the behavior in the body is quite different, and that's due to the chemical scaffolds.

Brian Corey Abrahams ***RBC Capital Markets, Research Division - Senior Biotechnology Analyst***

Got it. That's really helpful. And then maybe a question, if you could...

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

Did we lose Brian?

Elizabeth Goodwin ***Galapagos NV - VP of IR***

Apologies, Brian. That was -- we've lost Brian. Brian, if you can just dial back in, we'll come back to you. I'm so sorry.

So the next speaker is Phil Nadeau from Cowen and Company.

Philip M. Nadeau ***Cowen and Company, LLC, Research Division - MD & Senior Research Analyst***

Let me add my congratulations on your progress on this interesting target. I guess two questions for me. The first is that there is a suggestion of SIK dysregulation in cancers. Have you completed your preclinical carcinogenicity studies? And what have they shown?

And then a second kind of a technical question. Are all the compounds that you're developing kinase inhibitors? Or are there other ways to regulate the activity such as interfering with the AMP boundary domain?

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

Phil, thanks for the question. Like any drug that played in autoimmunity, you need to be careful indeed because you're working on balances where, indeed, if you take away too much of pro-inflammatory cytokine, there is a risk for cancer. Those studies haven't started

yet. There are -- we need to -- we typically perform them later during Phase III. But from what we've currently see in preclinical, it's not that we are heavily worried because -- yes, let's keep it to that.

And then the second question. You want to know what all tricks we try to do to block the Toledos? Okay. We are open to novel modality. So if that's -- so we've explained last year at the R&D Day that we will try ASOs and protacs. So if we're successful with one of those, it should not be a surprise that this program will include that. So...

Elizabeth Goodwin ***Galapagos NV - VP of IR***

So our next question comes from Evan Seigerman from Credit Suisse.

Evan David Seigerman ***Crédit Suisse AG, Research Division - VP & Senior Equity Research Analyst***

So a few questions. One -- can you hear me? Hello?

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

Yes. Yes.

Evan David Seigerman ***Crédit Suisse AG, Research Division - VP & Senior Equity Research Analyst***

Is that good?

Elizabeth Goodwin ***Galapagos NV - VP of IR***

Yes, we hear you.

Evan David Seigerman ***Crédit Suisse AG, Research Division - VP & Senior Equity Research Analyst***

Okay. Perfect. Sorry. So looking at the psoriasis indication, there's been -- obviously, the PDE4 inhibitor with Otezla, but there's been a lot of interest in Bristol's TYK2. How do you think your asset compares to these other kind of -- other modalities? And then my second question is, is there any synergistic benefit in combining, say, '1690 with one of your SIK2/3 inhibitors in IPF.

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

Walid, you take the first question.

Walid Abi-Saab ***Galapagos NV - Chief Medical Officer***

Yes. Let me take the first one and then pass it back to Piet for the second one. Our approach for psoriasis, and this will be seen in also other programs that we're developing, is to use them as a signal detection. So for us, to better understand actually how the biology is comparing, we do not know -- I mean if you look at what is the unmet need now on psoriasis, I think we find the bar very high, and we're not necessarily thinking currently about developing our molecules in psoriasis afterwards.

So this is truly to teach us about the biology. And then sort of complete our sort of taking multiple shots across the adaptive and innate immunity that we see in there. And our preclinical studies, as you saw from Piet's presentation, the data looked very good. Now we'll wait to see what will happen in the clinic. Piet?

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

Yes. Thank you. Then on the second question, does it make sense to combine the Toledos with '1690? Well, from a mechanism of action point, they are completely different. So in that sense, indeed, it makes clear sense to, at a certain moment, combine those. So for our fibrosis franchise, we have ambition to bring multiple drugs to the market. And then come with an ideal combo pill at the end so that it completely blocks the progression of diseases like IPF. And from a mechanistic point of view, for sure, this make sense.

Elizabeth Goodwin ***Galapagos NV - VP of IR***

Our next question will be from Dane Leone from Raymond James.

Dane Vincent Leone ***Raymond James & Associates, Inc., Research Division - Research Analyst***

Congrats on the progress with the Toledo program. So maybe I'll keep it to two questions on my end. Just going back through the timeline of the program, the original assay was '3312, which is pan-Toledo. It seems now that your -- the program is avoiding SIK1 specifically. I was just curious where your thoughts on, one, avoiding that target or potential issues running into hitting that target, and maybe selectivity of these next-gen Toledo program assets over SIK1.

And then secondly, I was also interested in SIK2 as the backbone of these compounds. And was curious to get your thoughts in terms of what's been described as maybe pleiotropic activity and expression within tumor cells and how you think about some of these targets in relation to what's been understood within the field of oncology.

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

Okay. So the first question is on SIK1. If you looked carefully to the chemistry slide, you will see that we have families with selective SIK1s. So in that sense, I don't think the conclusion that we have given up on SIK1 is a correct one. So I probably didn't tell, but during when we screen in fact in multiple immune systems, if you check on our data, we've picked up every SIK member in one or another screen. So I'm not going to say that we speak all 3 up in the IBD culture, but we've picked up every SIK in 1 out of 3, so that SIK1 has its place there, that is for sure. Whether you can drag it well and safely, that is a different question. So we are not yet there, otherwise, we would have that profile currently.

For oncology, as I said, so we have -- everybody playing or working in this field is aware. Are we heavily concerned? No. So there are many publications pointing into many directions and when we do the clinical tox, we watch all of those tissues, with special attention. And there is nothing there today to say, "Guys, this is not moving forward." So...

Elizabeth Goodwin ***Galapagos NV - VP of IR***

Our next question comes from Wimal Kapadia from Bernstein.

Wimal Kapadia ***Sanford C. Bernstein & Co., LLC., Research Division - Research Analyst***

Wimal Kapadia from Bernstein. So just -- firstly, just kind of back to -- can you hear me?

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

Yes, yes.

Wimal Kapadia ***Sanford C. Bernstein & Co., LLC., Research Division - Research Analyst***

Hello?

Elizabeth Goodwin ***Galapagos NV - VP of IR***

Yes.

Wimal Kapadia ***Sanford C. Bernstein & Co., LLC., Research Division - Research Analyst***

Okay. Great. So just coming back to an earlier question. When I'm thinking about the outlook for many of the diseases you are targeting, there are now multiple MOAs on the market, and the bar is really only increasing for future molecules. So you know what really gives you confidence that Toledo surpasses that bar so that when the product does come to the market in several years' time, you actually will gain traction?

And just tied to that, how would your plans change should some of the more advanced products in the clinic, such as bimekizumab, also demonstrate great outcomes in indications like psoriatic arthritis, given this is one of the reasons you just mentioned for not pursuing psoriasis? So that's the first question.

And then my second question is just clearly, very exciting in terms of trial outlook. But how should we think about the R&D spend trajectory tied to Toledo? Onno, you just mentioned hefty investment in your presentation. So any additional color on how R&D will be impacted and the trajectory moving forward, would be great.

Walid Abi-Saab ***Galapagos NV - Chief Medical Officer***

Okay. Overall, I think this -- again, we are guided by science and data. So, so far, our preclinical data suggests that this platform could make a big difference and actually be a paradigm changer. That's why we describe it the way we describe it. That's why we're so excited. That's why we've been investing a lot into it.

And we will see how the data look in the clinic, whether our story, which up until now, has been lining up very well, when we take the next step to go into the various diseases, whether we see the same promising efficacy. And in the end, we will base our decision on whether to progress or not on the magnitude of the effect, whether the chance we're going to be making a big difference in the space. As you saw that there's a huge room in inflammatory diseases, whether they are in dermatology, RA, or PsA, but also in IBD where there's a huge room for us to go up like what happened in the psoriasis field 10, 20 years ago. And our hope is that we're going to be in that ballpark.

Now of course, if the landscape changes with new medicines really lifting the bar, then we just have to clear that bar. We cannot be developing -- we have zero interest in developing molecules with minimal incremental change. This is something that we truly, fundamentally believe in at Galapagos. But again, we've let the data guide us, and that's how we will be -- we're looking forward to see what we have, and with that, adjust our way forward.

Onno van de Stolpe ***Galapagos NV - Co-Founder, CEO***

Yes. Well, with regard to the costs associated with it. Clearly, this is a hefty invest, it has been a hefty investment for the last couple of years. However, if in the totality of what Galapagos is spending, these Phase II trials are not going to break the bank. As you know, we are very well capitalized. We got the money from Gilead to invest in innovative new research, and this is clearly right in the sweet spot here. So we believe that it's warranted to continue in this broad Phase II trial. And we'll see if the data justify going into multiple Phase IIIs, we'll clearly do that. It will then be likely in a combination with Gilead.

Gilead has the right to this program after completion of Phase II, and they will have to opt-in per molecule. And after that, costs are shared 50-50. So it's up to them to join, but they are extremely excited about this program, as you can imagine. So I'm not concerned that the cost of this program will go out of control and make our P&L suffer too much. So for now, we believe it's a very doable program financially.

Elizabeth Goodwin ***Galapagos NV - VP of IR***

And our next question comes from Peter Welford at Jefferies.

Peter James Welford ***Jefferies LLC, Research Division - Senior Equity Analyst & European Pharmaceuticals Analyst***

I just have a question, a follow-up really, on the first generation of compound or the first compound, '3312. I wonder if you can give us some more details on why that was deprioritized and what it was that you saw, and whether you think that is chemical specific.

And perhaps, if you could just follow-up there. Could you tell us with regards to the -- I think it was 10 chemical series you said you developed. Are all of these for '3312, '3970, '4399 and I think '4605? Are they all different chemical series? Or perhaps you could just put them for us in terms of chemistry in the various buckets that you've outlined to give us an idea of, I guess, how sort of you've covered that spectrum of drugs so far?

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

Okay. Let me start on the different chemical series. '4399, '3312 and '3970 came from the same family, so -- but that is small variation. So the series going behind, they are much more diverse. So if you want to have selective SIK2, I can tell you, we've tried a number of series. So that is not an easy task. So if you want a selective SIK1 as well, we've tried on multiple series, to get the selectivity right, you need multiple series. So -- but the current, therefore, broader family, you can see the differences. They are especially easy discriminated. But broadly speaking, they come from the same family.

Then on '3312. So '3312 is a pan-SIK compound, so not that selective. And we got where we fool ourselves a bit with early success is that if we targeted this to the colon in the precinical space, this was extremely easy and extremely successful, and we told that as a proof of concept if we can expose the colon only to give our maximal chances of success to validate this target early on.

Unfortunately, when we took in the clinic, we hit one technical problem after the other. And then the program became so terribly slow. That affected '3970, its space -- its internal speed. Took it over and then we decided to progress fast -- program overall slower because I was -- we could have done it firstly with '3312 then the next would have taken again a couple longer runs of optimization. And in terms of speed, this was not going to be competitive and learning so much. So it was an tactic error we made at the beginning.

Elizabeth Goodwin ***Galapagos NV - VP of IR***

So now our next question comes from Jason Gerberry from the Bank of America.

Jason Matthew Gerberry ***BofA Merrill Lynch, Research Division - MD in US Equity Research***

I guess big picture, some of the more high-profile I&I markets where you're moving forward with Toledo IBD, RA. Obviously, there's been a lot of success with oral therapies in the clinic. Is the idea broadly to sort of replicate the efficacy, but achieve that without the systemic safety issues here with the Toledo program?

And then as we think about the program modulating TNF and IL-10, can you talk a little bit about the dual action there, the potential for any offsetting effect, if you dose Toledo too high? Just wondering if you can comment on some of the dosing considerations there.

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

To be balanced -- yes, I can get started there. In a way, I think if the mechanism of Toledo, as you play on both ends should allow us to dose higher on the dose response curve in a safe way. So in that sense, I have a bit of a different vision than the fear that I think I could pick up in your question. That the fact that you play on both ends of that balance, and clearly, you should be able of going higher on the dose response because you will not exhaust the system.

And in that sense, I believe that in terms of both efficacy and safety, there is room there to improve. Of course, if we end up with a profile, which is similar to JAK and -- if a similar safety profile than this is not a success. But intrinsically, this has the promise of being much more better than what is currently out there because we play out at those both ends. Was another question that I missed out?

Jason Matthew Gerberry ***BofA Merrill Lynch, Research Division - MD in US Equity Research***

No. That was it.

Elizabeth Goodwin ***Galapagos NV - VP of IR***

Our next question comes from Emily Field from Barclays.

Emily Field ***Barclays Bank PLC, Research Division - Research Analyst***

I just have a very, very high-level question. I know you touched on this on one of the previous answers. But just -- it would seem that part of the issue with '3312 was a lack of selectivity. And so just thinking about this from a high level, would it be right to assume that as you progress through the next generations and iterations of Toledo that, that would be of increasing selectivity?

And as you go about that, would you still plan to start with the broad indication set? Or kind of as you move through the next generation of the compound, would there be more selectivity also in terms of the relevant indications that you think that those potential assets might be relevant for? Sorry, very high level, but...

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

Thank you. I will take the question on selectivities. So indeed, when I look to the presentation and the history with '3312, you get the impression the way forward here to improve is easy. You just make more selective compound. So we're not doing about 6 years of chemistry here, and it has been a long and an extremely interesting journey with -- a lot of surprises in that sense that as you have 3 players with similar or working around the same activity, it's full of surprise.

So I do not exclude that one day, combined SIK1, 2, 3 will be the best molecule, especially early on when we look to the selective profile, the 2 and the 3s. It is not such an easy picture as it's -- as one might think, just improve your selectivity and you will get there. No, the

picture is quite complex. Anybody who wants to try is welcome, of course. But it is a quite intriguing story, and we learn every day.

So as thinking that only the selective profile has a future here, we are not there today. Walid, maybe you take on the indications that we want to take forward?

Walid Abi-Saab ***Galapagos NV - Chief Medical Officer***

Yes. Sure. Thank you, Piet. Yes. Emily, with regard to the indications, I think the -- our ambition is that the lead compound is going to be generating a lot of information that we can then use to back translate and position the ones that are coming behind. And use essentially, the -- for lack of better word, the pharmacodynamic fingerprint of each molecule to guide us in a given path based on which cytokines are changed and also based on the preclinical data.

So the first one is going to be casting a wide net. The others are going to probably -- are going to be benefiting from that actually, going narrower indications or maybe exploring other indications as well. But it's hard to tell now before we have the data so that we can react to it. But it will be data-driven. That's what it is.

Elizabeth Goodwin ***Galapagos NV - VP of IR***

So now we go to Matthew Harrison from Morgan Stanley.

Matthew Kelsey Harrison ***Morgan Stanley, Research Division - Executive Director***

Great. So I guess two things for me. First, maybe, Piet, can you just talk a little bit about formulations here? And I assume, depending on which disease state you might be targeting, I don't know if you're looking at different formulations for these. So maybe if you could just walk through what you're doing in terms of formulation and bioavailability to different key tissue sets?

And then second thing. I know in the past when you discussed this, you've talked about really wanting to have a significantly differentiated clinical bar. Could you maybe just comment on how you're thinking about that and what you think you'll be able to know from that perspective when you have some of these proof-of-concept studies?

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

I'll take the question on formulation. Well, the formulation, at times, we did was limited to the '3312 at the beginning. We had the idea let's hit it hard in the colon and that failed. So -- but for the rest, '3970 is a relatively easy compound and you can dose it as an oral as a solid and you have a fast absorption. '4399, so in that sense, that [inaudible] and we move forward. Walid, you take the second question on the indications.

Walid Abi-Saab ***Galapagos NV - Chief Medical Officer***

Yes. No, I mean I think these are going to be small segment detection studies. And usually, the way we do this -- and this doesn't apply just for the Toledo program. And for small single detection, you can have 3 outcomes, 1 where there's nothing and then you say, "Okay, well, we went down the wrong path, and we need to go look somewhere else." Or you have data that really knocks the ball out of the park. And you clearly see that you have very promising avenue, then you go and go fast in that direction. Or you have data where it shows you that you have a signal that's worthwhile further pushing in, maybe you need to select your population better, maybe you need to focus with the next study, looking at different endpoints to be able to tease that apart.

But our ambition is that -- and there's a lot of room. I mean let me take IBD, for example. When you have -- looking at these EBS remission rates that we talk about, and you have a difference from placebo, anywhere between 10% to 15% after 10 or 12 weeks induction, the bar is very low right now, and we have huge room for improvement.

And even when you look at maintenance, to look at steroid-free survival at the end of the trial of about 30% and 40%. And we're very excited about this because it's better than anything that has been seen so far. But I'd like to see 90% steroid-free survival. I want none of the patients to remain on steroids longer term.

So there's a huge room for us to do much more. And these initial trials are going to send us to work that, but then we will have to confirm

it with the larger trials. But that is our ambition. Our ambition is to move the needle clearly, visibly, appreciably, clinically, meaningfully, not just small incremental ones.

Elizabeth Goodwin ***Galapagos NV - VP of IR***

Our next question comes from Graig Suvannavejh from Goldman Sachs Group.

Graig Suvannavejh ***Goldman Sachs Group, Inc., Research Division - Executive Director & Senior Equity Research Analyst***

It was a great event. I've got two questions, if I could. The first one was just around the comments around safety. I believe the comment was we're seeing or you're seeing what you typically see. And I'm just wondering if you could just expand on what that means in your mind.

And then second, any initial discussions -- and it might be premature right now, but any initial discussions with Gilead as to what their level of interest is in Toledo? And how should we think about what their level of interest might be in light of what's happening with filgotinib and then the unfortunate disappointing readout for '1972?

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

This one's safe, so we have no volunteers dropping out. We have no events that caused any concern. So -- and there will always be somebody with dizziness, whatever or -- but that is normal. And you always see 1 headache or something that I believe what we saw was really an extremely boring Phase I where we haven't seen anything which is specific to -- so that -- it's funny, it is so difficult to talk about boring details, but okay. Onno, you take a question?

Onno van de Stolpe ***Galapagos NV - Co-Founder, CEO***

Yes. So in this case, boring is very good. So thanks for the Phase I to be boring. Yes, Gilead is clearly very excited about this. The day after the CRL with filgotinib in the U.S., they have expressed their commitment for inflammation long-term, and they see this as the next big thing.

So yes, you don't have to worry about their interest to step on board when the time is there. It will take a while because they have the option after completion of the Phase II studies. But I'm sure they're eagerly following these developments, and we inform them on a regular basis and they will be ready to act when the data are there. And I fully expect them to join, and we'll share the Phase III cost with us when the time is there.

Elizabeth Goodwin ***Galapagos NV - VP of IR***

So our next question comes from Michael Okunewitch from the Maxim Group.

Michael Okunewitch ***Maxim Group LLC, Research Division - Equity Research Associate***

So it seems like TNF is a big part of the dual mechanism. So I'd like to see -- would you expect Toledo to work best in patients with disease phenotypes that are likely to respond to TNF therapy? Or is the dual mechanism likely to expand the population which is likely to respond?

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

What a great question. Well, the Toledo profile, we focus in a slight bit on TNF, but there's a large array of pro-informatory cytokines. We've looked -- asked the same question on IL-12, IL-23. And as I said, I believe that by playing on both ends, we should be capable of showing activity with more patients to start with, I hope, and I think that is the question.

But I know that the slides were around TNF, but you could have made slides on all the cytokines, that is the beauty of this program. It is quite in broad -- it really blocks that whole NF-kappa B program there, which is triggering a large variety of cytokines. So it is not limited to TNF, it's also decreasing IL1 Beta, interferon. So in that sense, we should have a quite broad view on where can play. But it -- my belief that where it is to go far in the end, we should be able ending higher on the dose response, and that will give us a better profile.

Michael Okunewitch ***Maxim Group LLC, Research Division - Equity Research Associate***

All right. And then one more, if you don't mind. I'd just like to touch on -- you have the dual mechanism, which is essentially rebalancing the immune system rather than pure suppression. So would you anticipate that you would avoid many of the side effects associated with traditional anti-inflammatories?

Piet Wigerinck ***Galapagos NV - Chief Scientific Officer***

Yes, that's indeed the anticipation. That's correct.

Elizabeth Goodwin ***Galapagos NV - VP of IR***

Our next question comes from our first question poser today. That's Brian Abrahams of RBC.

Brian Corey Abrahams ***RBC Capital Markets, Research Division - Senior Biotechnology Analyst***

So I think studies have shown that SIK1 may play a role in maintaining muscle health, and I think studies have also shown topical pan-SIK inhibitors may be associated with increased skin pigmentation. So I guess I'm curious specifically about whether you're looking at some parameters along those lines like perhaps, CK or pigmentation in the ongoing studies, and if you've seen anything of note so far.

And then also with respect to therapeutic window. I'm curious where you're expecting to dose in the ongoing proof-of-concept studies relative to the equivalent dose levels at which you saw the impressive activity in the animal models.

Walid Abi-Saab ***Galapagos NV - Chief Medical Officer***

Yes. So thanks. I'll take those. So yes, essentially, as I mentioned, commensurate with the size of our investment, we were also not just looking to understand the biology just in terms of efficacy, but understanding the biology period, with whatever effect that are in humans. So you can imagine, we had a large team dedicated to it, both preclinical and clinical looking at this. And we monitor all of these elements that you mentioned. We're quite aware of the work that's being done with topical use of the SIK inhibitors.

In terms of therapeutic window, the preclinical data -- or I mean I'm sorry, the pharmacodynamic Phase I data that Piet shared with you, showed you very nicely that we do have a very good response both on innate and adaptive immunity and changes in IL-10 and TNF-alpha. And so with those, when we dose in the clinic, we're going to be picking a dose, at least in the signal detection, that will be there targeting both because that's actually what we believe is needed to show the better efficacy. And in those range finding studies, we will have a broader exploration so that we can see the relative impact of the various inhibition of the TNF-alpha, but also other cytokines as well as well as the increase in IL-10 as well and whether more increase is better or how do we characterize the dose response curve. So that's going to be also very interesting data that we will be generating from our dose range finding studies.

Elizabeth Goodwin ***Galapagos NV - VP of IR***

All right. Thanks so much to everyone who's participated. This does conclude the Q&A part of our R&D roundtable. Please reach out to me or to Sofie Van Gijsel. If you still have questions and/or if you'd like to obtain some of the references mentioned during the webcast.

Our next scheduled financial results call will be for the Q3 results at 8 a.m. eastern, 14.00 continental time in Europe on the 6th of November. We'll publish our results the evening before -- after U.S. market close.

We thank all callers for their participation. And please, all of you, stay safe and well. Thank you very much. Goodbye.