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Galapagos NV (R&D Update 2016)
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C: Elizabeth Goodwin; Galapagos NV; Head of IR
C: Bart Filius; Galapagos NV; CFO
C: Piet Wigerinck; Galapagos NV; CSO

P: Peter Welford; Jefferies; Analyst
P: Matthew Harrison; Morgan Stanley; Analyst
P: Jan de Kerpel; KBC Securities; Analyst
P: Phil Nadeau; Cowen; Analyst
P: Hugo Solvet; Bryan, Garnier & Co.; Analyst
P: Vamil Divan; Credit Suisse; Analyst
P: Jorn Koch; Rabobank; Analyst
P: Amanda Weyerbacher; inThought Research; Analyst

+++ presentation
Elizabeth Goodwin^ Welcome to all of you. We have a large group here at the Yale Club in New York and we have a large group of folks who are dialed in now looking on our webcast as well. So we're going to try and accommodate all these audiences today, and so I appreciate your patience with some of the technical details. I'd like to ask all the folks in the audience to mute their telephones at this time if they've not already done so.

Wifi codes are available at your table on the card. I'd like for those who are listening in to the webcast to dial in on the following number, 32-2404-0662 and there's a code; 207-496 if you'd like to ask any questions at the end of the presentation. We're going to have a presentation of one-and-a-half hours and we'll have about a 30 minute session for Q&A as well.

Now, during this presentation, we will be making forward-looking statements. Actual results may differ materially from these statements.

Here's the agenda for today. We'll begin with our CFO, Bart Filius, who will give an introduction and talk about the strategy of the Company, and then we will hand over to Dr. Piet Wigerinck, our Chief Scientific Officer, who will walk us through the highlights of our technology platform, our R&D portfolio, and the focus on four key areas. And there you will see some new data today, so that's all very exciting.

I will be alternating at the end with the Q&A; I'll be alternating between the audience and the callers who are viewing the webcast.

With that, I'd like to invite our first speaker, Chief Financial Officer, Bart Filius, to the platform.

Bart Filius^ Thank you, Elizabeth, and good morning everyone here in New York and good morning or good afternoon for those that are listening in to the webcast as well. It's a great pleasure to be here and to talk a bit with you about Galapagos, specifically about our R&D platform and developments therein. I'm Bart Filius, I'm the Chief Financial Officer of the Company. I will give a couple of introductory slides on Galapagos and the background of our company before I'll hand over to Piet Wigerinck.

First of all, at a glance, as is on this slide, Galapagos listed on Euronext in Amsterdam and Brussels. We're also listed at NASDAQ with an ADS program since last year. Actually, as of next Monday, we will be part of the AEX index, the Amsterdam Exchange Index, which is the top 25 companies in the Netherlands, along which other big companies such as Royal Dutch Shell, Unilever and Philips. We're very proud of that achievement as of next Monday as well.

We have a very broad pipeline of novel mode of action drugs, and if there's one message that I'd like you to take away from today's meeting is the breadth of this actual pipeline. And we'll go into quite a bit of detail on how we got there and what the status is of the various programs therein.

It's all been built on our Target Discovery Platform, and in a few minutes, I'll show a short video on what actually the Target Discovery Platform does. But that target discovery platform has led us to find JAK1 in autoimmune diseases and is the basis of our late stage drug, filgotinib, which is currently imminently starting Phase 3.

Another part of the success of the Company that's been founded in 1999 is the partnerships that we've been able to strike with other pharmaceutical and biotech companies, and at the moment, we are very closely working together with Gilead on filgotinib, with AbbVie on our cystic fibrosis pipeline, with Servier in osteoarthritis, and also we have a collaboration with the German company MorphoSys.

Our cash position at the end of the first quarter was more than $1 billion, slightly short of EUR1 billion, which represents roughly $24 per share and makes us a company that is trading at approximately twice its cash position at the moment in the market, giving us an enterprise value of roughly $1.4 billion against the market cap of roughly $2.5 billion.

We've got 440 employees spread out over four different sites. In Belgium, our headquarters in Mechelen, in Paris, France, in Leiden in the Netherlands, and in Croatia. Our mission, really, is to become a commercial stage biopharmaceutical company in Europe. And these are the elements that will be part of that company when we get to that stage. First of all, what it all started with, the identification of novel drug targets in human cells will continue and has already led to the pipeline that we're presenting to you today.

On the basis of that target discovery platform, we designed first in class drugs. We have also in the ability now to start building out a commercial organization; I'll say a few words about that in a second, based on our partnership with Gilead, and also the co-

promotion rights that we have in our cystic fibrosis platform and our alliance with AbbVie. This will allow us to take selective programs to the market ourselves, whereas we have built our company based on partnerships, we will be in the future maintain value in our company and within selected indications, develop selective molecules, and bring those to the market ourselves.

And finally, we'll remain an active company active in partnerships, and we'll make those successful. Two key partnerships are described in a bit of detail on the slide here. So on filgotinib, we have our JAK1, as I said, in autoimmune partnered with Gilead. It's a co-development arrangement, which we signed in December of 2015. In the development phase, which is going to be a huge program, we'll talk about that in a second in a bit more detail, it's going to be huge and Galapagos will be funding 20% of those expenses and we will be participating in researching all the proof of concepts trials therein as well.

In January, Gilead has paid us $725 million of which $300 million was an upfront and $425 million was paid for an equity stake of close to 15% at a stock price of EUR58 at the time. There are milestones still to come; $1.35 billion split out into development milestones, $750 million, and sales-based milestones, $600 million.

On the commercial side, as I mentioned before, this partnership will allow us to start building a commercial infrastructure in the big five countries in Europe as well as in the Benelux, Belgium, the Netherlands and Luxembourg. So eight countries in total in Europe, representing a significant portion of that market, and in those countries we'll have a 50-50 profit split arrangement with Gilead.

For markets outside those co-promotion territories, we have royalties that start at 20% and move higher as the product is generating more sales. So a very powerful and very important partnership with Gilead and we're very, very pleased with the way this partnership has evolved over the last couple of months.

And on cystic fibrosis, also there some news on the partnership front; some of you have seen that last month. The target here, clearly, is to develop a triple combination therapy for class II patients, which represent roughly 90% of the patient population. It's a partnership with AbbVie. We are actually executing the work for Phase 1 until the end of Phase 2, and then AbbVie takes over for Phase 3 and we contribute to the development cost for Phase 3 as well.

This has been expanded recently in terms of milestones. So the milestones now are roughly $600 million and the expansion is $250 million compared to the previous arrangements. This expansion is the result of the fact that we're now working toward a triple combination therapy, which is a much larger development program than we were originally planning. And $250 million increase is associated to work done in the Phase 1 and the Phase 2 period.

There too, even in the smaller territory, there's a 50-50 profit split in the three countries of the Benelux, and we retain the rights for China and South Korea. The royalty rates of

the arrangement with AbbVie have not been changed with the current re-negotiation and start in the mid-teens and go up to 20%. So those two key partnerships are really the start of a very promising late stage pipeline.

But let's get into the science, maybe, in a bit more detail. Because, ultimately, and I mentioned this, we started with our Target Discovery Platform, which is still active and which is still generating novel targets for Galapagos. Now basically, this is based on the collection of adenoviruses with which we are able to knock down over 6,000 different proteins and test these in human cells and evaluate whether it has an impact on the disease state of those cells.

I'd like to show you a small animation to show you how this actually works in the human cells. And after that I'll hand over to Piet Wigerinck, who will take you through the details of our pipeline and take you through the details of the recent developments.

Just looking at the other side of the room if the technology is okay to start the video.

(Video Playing)

Piet Wigerinck^ Good morning, it's good to be back here. For a couple of years we have come over to present to you our research focus, our pipeline and to discuss with you the compounds and the clinical designs, but unfortunately – it's not really unfortunately, but last year was way too busy with all the data sets of filgotinib so that there was really never a calm moment in the year where we say let's take a step back and let's go to New York and discuss the rest of our pipeline. So, very happy to be back here, very happy to have you in the audience.

So today's presentation will be everything outside filgotinib. On filgotinib, if you have questions, I'll try to answer them at the end of this presentation. What I can say is that we are extremely impressed with the way our partner, Gilead, works on this asset. Both the expertise, the number of people, the speed, the decisions they take – we've been very pleased, we are very happy to be part of that program and we look forward to working with them to make it a big success in Phase 3 and in a number of indications.

By the end of this presentation, what I want you to know is: what is our ambition? Where do we want to take this company? To what diseases do we think we can bring novel drugs? How are we going to do that? And finally, what's our pipeline? But more important, how do we plan to tackle novel diseases, and how do we want to be successful in the industry?

We are a novel mode of action company and we will stay a novel mode of action company. Finding novel modes of action is what's most difficult in this industry. So why do we choose this path? We choose this path because it's the way our science can bring most changes, most profound changes, to the lives of patients. So really bring novel drugs to patients that work in a complete different way that are disease modifying, is the way

our science can impact on their life. And that's why we want to maintain being a novel mode of action company, although everybody agrees this is a very difficult thing.

But filgotinib really has proven that even a tiny, small biotech company can be successful. It took us about 12 years from the first assay development up to the start of Phase 3, it has been a long journey, has been a rich journey, full of emotions and full of suspense But it really has shown that as a biotech you can drive your science forward, you can do it. That is my main message to all the colleagues in the biotech industry; be sure you have control of your program, don't count on your partners too early, they will always find excuse to do something else. Keep control, move it forward yourself, and you will find the drugs and you will get them to Phase 3.

For years we've been looking into novel targets by studying primary cells out of patients. And many of you have told me: everybody can do that and in a way, that's correct. We don't have a monopoly of studying primary cells of patients. So over the years we have developed much more complex systems, information richer systems. And that's what I want to show you here as well; rather than work on the simple primary cells out of patients. Over years we have set up much more complex models. An example of here is where from a single patient, we picked two types of stem cells; one out of the gut with a biopsy and a blood sample.

And out of the gut biopsy, we can grow a structure of cells which is organ like; we call it an organoid. And out of the stem cells of the blood, we will grow an immune cell, which is a dendritic cell. And what you can do then is put the two together in a single culture. So a in a single well, we study every component which triggers the disease in patients. In green on the left you see here how the organoid looks like and a bigger picture below. So really, the structure of these are gut-like cells. On your right, you see how the dendritic cell looks like. And in fact, they are in very close contact, so it's the interplay between the immune system and the organoid. It's attacking that we can bring into a single well in which we can study.

So these are much richer systems, much more complex, but that gives us a cutting edge to keep on looking for novel targets in a way nobody has ever done before. So that's the way we take our science forward, that's the way how we are going to keep on looking for novel drugs in the future.

So what diseases do we look on? And here you have four clusters of diseases. I'll start on the left with inflammation. There are two driving forces why you see so many diseases there. One is filgotinib, of course. Really important, Gilead plans to broadly study the drug in multiple diseases next to RA and Crohn's and UC, which we have announced. And by making those plans, we get a better insight in the medical needs and the pathways that are going wrong in patients there.

So, we are setting up animal models and we'll both test field filgotinib as well our novel compounds out of the pipeline. So next to filgotinib, the second driving force is our continued search for novel targets. And I'll show you today two examples, one in the

disease, Lupus, where we have a model with very nice data. w As well in atopic dermatitis, with a complete independent mechanism of action where we start to see nice *in vivo* data with a novel mechanism of action.

Second cluster of diseases is fibrosis. Well known for you is that we work on cystic fibrosis. But as well have a program in Phase 2 on IPF, and we're looking to move a number of assets into the NASH as well over the coming years.

On the long-term, my big belief is with our platform the disease we can impact most is the metabolic diseases. We really should be able of picking up complete novel ways of modifying those diseases. So it's a long-term effort, I won't discuss today, it can take us a couple of years, but it's really one of those diseases, unmet need is huge and where I believe our platform can bring novel insights.

Finally, we have one tactical disease; that's our Hep B effort. Hepatitis B we stepped into because for 40 years people have been doing research and there was no good *in vitro* model that had the full viral cycle. So no new mode has not been discovered; the new assay is a very complex assay. And us, we are really – I have a team which is focusing everyday on the most complex cellular assays. I said to the team: set up a screening assay and let's go for it, because we believe that over the coming 10 years a couple of complete novel cocktails will be put together that finally are going to cure this disease.

So our ambition here is to find a couple of novel ways, novel molecules, bring them to Phase 1, proof of concept, and then find a partner for them. There's no ambition there to go to the market in those diseases; we'll select other partners for that, but we have a pretty competitive Hep B discovery program as well.

Let's look to the pipeline as far as it's in the clinic currently, so dominated by filgotinib, we'll move into Phase 3 any day now. Partner Gilead will announce that. As well we've promised to start of the Crohn's Phase 3 second half of the year, and we'll start the Phase 2 in ulcerative colitis.

Next big chunk there in the pipeline is our alliance with AbbVie for CF; I've told you I'll come to that extensively during my talk. We go for the triple combination for the class II patients, as well our potentiator, we are testing now in a Phase 2 proof of concept study. If data are excellent, we could move this forward as a monotherapy for Class III.

And then we go to our pipeline, which is earlier, and which we intend later to take ourselves into Phase 3 on our own or with a partner. First compound there is autotaxin inhibitor 1690. I have very nice data to show to you today for the first time on '1972. It's in osteoarthritis disease as well; huge unmet medical need, very little has changed over the past 20 years. Very difficult disease, and we believe we have something new there as well. For that molecule, we own the US rights and we will develop clinical studies in the US together with partner, Servier, who will perform studies in Europe.

Inflammation, we have an antibody, the first antibody in Phase 1 with MorphoSys. I won't touch upon that today. But I will show you on our new PCCs, our new clinical candidates, some key data both in fibrosis here and in atopic dermatitis.

So on the long-term, what's our ambition? We think that with those novel mechanisms of actions, and currently we try to start programs on eight novel targets every year. That's yearly on average, three clinical candidates for target plus a backup, which I'm going to call them backups here. But on average, for three targets we find clinical candidates.

Out of those three, if we count every two years; we have six, we count that about four will go to Phase 1, and there we plan to do, on average, two proof of concept studies with those novel clinical candidates. That should give us sufficient compounds to move into Phase 2, and then one compound every two years should move to Phase 3. So that's the ambition to be a European biotech with a commercial force but also with a discovery and a development engine that gives us Phase 3 programs every other year in the mid-term.

We are working hard to this; this is not easy, this does not come from itself. I have a huge team, 200 scientists working the lab every day to do the most difficult thing in this industry; finding novel mechanisms of actions. For discovery, I can show you here how we distribute those scientists. On the left by phase and roughly about half of the scientists work on finding novel disease models, novel targets and novel chemistry. And then the other half of the scientists what they do is optimize them so that we have clinical candidates. Optimizing all the properties so that we feel comfortable that we have what we have into a single molecule, which can move into development.

On the right on this slide, our diseases. About one in three is working on inflammation, and these are not new versions of filgotinib, no, these are complete novel approaches, novel mechanisms of actions, novel targets we are developing. But one in four on fibrosis? Only a small piece of that is CF, that you will see later. And then we have the metabolic and the Hep B, the smaller efforts in portfolio. But really, we try to stick or to keep people focused around these four major clusters in the Company.

Let's now go to couple of key areas and let's start with inflammation. So, you see the picture here of Jeff, who is a patient diagnosed with RA. He visited the Company, talked with him for hours about his life, impact of the disease on his life, impact of drugs that improves his life. Currently his disease is well under control with an antibody, but from the first meeting he saw he me he told me: look, I can't wait for the day an oral pill is there, I really want to have full control over my life and I count on the oral medications to give me back that full control.

And so Jeff is one of our biggest supporters, as well I'll explain what it is to live with RA. For inflammation, I'll keep it quite top line in this way in the center we have filgotinib. Filgotinib blocks the adaptive immunity. Adaptive immunity is a part of our defense system that is activated as soon as an intruder enters the body. Next to that we have other ways of defensing our body. We have the innate system and that is more driven by cytokines like IL-4 and IL-13 and we have the B cells. So on the left you'll see

a GT code, this is a target code; we are inhibiting there an enzyme that is essential in the development of antibodies by plasma B cells. So I'll show you some nice data for a series we will try to move into Lupus over the coming years on the next slide.

But only now just to illustrate, we work broadly on inflammation. We don't focus around JAK, we don't stick around JAK; we have some JAK activities, but we really hunt for novel targets, and when we believe in them we bring forward our PCCs. Let me start with some novel data now. This is a mouse model of lupus. Why do we call it the Lupus model, in fact, what we do is we trigger, we challenge the animals with a chemical, but over time as you can see, in the blood of the mice we see antibodies against double stranded DNA, which is a hallmark of the disease Lupus.

We see them appearing as a consequence of triggering certain pathways. So that is the difference between the grey, the vehicle and then the orange where the animals are triggered. As a positive control in this mouse model we have mycophenolate mofetil (MMF), which is a used Lupus drug. But you can see with this novel drug, novel mechanism of action, we are capable of reducing the number of antibodies against double stranded DNA. So really complete novel science, data I haven't seen too much from our competition. So, difficult project we plan to have a clinical candidate around that this year.

For inflammation I'll go from discovery to the end stage of our pipeline, second new PCCs, or the first new PCC for today, second new target is '2534 as well complete novel mechanism of action around innate immunity. What we do here is an animal model for atopic dermatitis. We going to challenge again the animals with the Vitamin D analogue for about six days and then the innate system is completely activated. As a positive control we use a corticoid dexamethasone here. And you can see that our compound dosed orally is as good as an oral corticoid.

Again, a selective inhibitor of another mechanism of action. So in this model here we measured the ear thickness, which is a measure of the inflammation as well we typically follow the gene patterns and the proteins, and all of those end points move into the right direction. So as well in the field of atopic dermatitis over the coming years you will see a number of our compounds moving.

Let's now go to osteoarthritis. Osteoarthritis is a huge unmet medical need; if you think, you look back for 20 years. What was new to this field were Cox 2 inhibitors with at the best very mixed success, and for the rest nothing really novel. What we brought as novel therapies is really re-formulation of old drugs, has been a very good attempt with MMP 13 inhibitors, which failed. Still ongoing attempts with NGF antibodies, but all in all it's a field with not that much of competition.

We've been trying hard with novel targets, it's sometimes very difficult, as we said, the most difficult thing in this industry. But out of six novel targets we tried, finally one we have in Phase 1 what I call excellent biomarker data. So what you will see over a couple of slides is we measured the breakdown of cartilage in healthy volunteers. So in this

program we have shared that with partner Servier, partner Servier willdevelop outside the US; we have the US rights, we plan to file an IND with this data and open studies in the US early next year.

Let me first show you the PK data of Phase 1; Phase 1 is there to study first safety. Second is PK. Now what you can see in here is we have a very nice profile – fast absorption, half-life of 10 hours, really an ideal compound to go into oral chronic dosing. Because for OA, you have to count on chronic dosing in patients. So we have a half-life of 10 hours, we come to steady stage within three days, which is excellent as well. But more important, what we did during the Phase 1 was measure the cartilage breakdown. All of us, even the healthy volunteers, and I'll show you the data in a minute now. All of us even – we have healthy, have a natural turnover of cartilage. So it's normal that we build new one and that we lose some.

Now, what you see in here is the data. In orange for the placebo group, the solid line is on day one. The dashed line, or the light orange, is on day fourteen and you don't see a difference. You see day one, the healthy volunteers dosed with the active compounds you don't see difference, so it's a quite stable biomarker. We were surprised about that because of the variability between those three groups is quite low. Therefore, each of the three cohort groups here, what we see here, is after two weeks only. We see more than 50% reduction of the breakdown of cartilage. That's what we measured here. Do we stop the breakdown the cartilage? The answer is yes.

Within two weeks already, we see that for all of the dosages tested. In the field of OA, I haven't seen many groups showing a decrease of cartilage breakdown. That's really exciting data I can tell you, the lab that performs this testing is doing it for years and on the day it comes, You have to watch your PC; I'm going to send you data, we haven't seen before, but what you do here in healthy volunteers is really the best we have seen ever here. So exciting data, we look forward to come and do studies here in the US with these compounds.

To close our pipeline in inflammation, we have filgotinib, we have over a thousand years patient experience now with the long-term extension plus the Darwin Program has shown, as you all know, high efficacy. To my opinion, still the only selective JAK inhibitor in the field, and to that discretion, if you want to judge yourself the data simply look which of the JAK inhibitors allow a full rebound, and then I mean a rebound of hemoglobin to the same extent that you see with an anti-TNF or with an anti-IL6 antibody. You will only find one JAK inhibitor, JAK1 inhibitor; filgotinib does that. And as well, it's the only compound which shown that there is no impact on NK cells.

Looking forward to, start Phase 3 and then a very large Phase 2 program in a number of indications and in a number of combinations with Gilead drugs as well. The overview of our clinical portfolio for inflammation starts Phase 3, starts Phase 2, and then you see now the top lines of Phase 1. So we'll open IND in the US early next year, and then kick off studies over here in osteoarthritis with 1972. And then atopic dermatitis is a new PCC we announced today, I believe, in which we'll only start Phase 1 early next year. But the

message is here; we really look broadly to have a pipeline filled with projects which attack inflammation from a broader angle than JAK1 only.

Now I move to the second cluster of diseases, which is fibrosis, and here you see patient Nikki from the Netherlands, suffers from CF for many years, is a Class III patient. Was lucky to get on Kalydeco. This drug completely changed her life. Finally, she's full time back in school for the first time in years, she's never sick anymore. As well, a huge impact on her family; before the whole family was organized around the patient, now the patient has a normal life.

The family as well picks up a normal life. So just an illustration how novel drugs or novel mechanisms of actions impact broadly on lives. Let me first start with the other fibrosis indications; IPF and NASH. So we currently have two programs in clinical development; '1690 in Phase 2 and '2938 in pre-clinical. Both work in a complete different way, but both lipid mediators, '1690, I'll show in the next slide, is blocking the synthesis of LPA species. '2938 blocks receptors through which a lipid mediator has signaled. By blocking these triggers or decreasing the amount of these triggers we want to have an impact on fibrotic diseases.

What's essential always is that we use an animal model to confirm our hypothesis. And I'll show you some data as well today. Autotaxin is coming more and more on your agenda so a few words of explanation here. It's an enzyme. It's an enzyme that is responsible for 80% of LPA synthesis in the blood. There are a number of LPA species – I won't give you details, but it's more than five. And they signal through a number of receptors; LPA1 to LPA6. For LPA1 to LPA2 there are solid data, that they are involved in the formation and initiation of the fibrosis.

So what we've seen is that we can block the synthesis of LPA1 species in both the blood and in the BALF. BALF is the liquid layer in the lungs of animals and that there in those lungs of mice, which are used in/for fibrotic disease, we see a vast increase of LPA. So we can block that increase, and I'll show you immediately.

So for IPF, unfortunately the animal model is the bleomycin mice model, it's a harsh model and it is what it is, but there is not a better model, so we use it as well. We evaluate both in a therapeutic way and a prophylactic way. In 1690 we see the data here. It scores better than pirfenidone and slightly better than pirfenidone in the prophylactic mode.

I can as well show you the therapeutic data, but for the prophylactic model, we have as well measured the LPA concentration in the BALF for those mice. Now what you can see in orange is what happens in the diseased animals that are not treated. You see an increase of a number in LPA16:18 means it has 18 carbon atoms, 16 carbon atoms and then one or two double bonds there. There's a second number for you, so you have a number of different species there that are all triggered. And we infect by blocking autotaxin, block the synthesis also in BALF in these mice of these triggers of fibrotic diseases.

So very nice data that by blocking the enzyme, we block the triggers and we see an impact on the clinical score in those animals for 1690. We have a much broader data set behind it. 1690 we've taken through Phase 1. All of us make autotaxin; we can block it for a while without any harm and this is, in fact, a textbook example of how you can show target engagement. You see a nice dose response colors correspond to dosages. The lower dosages you will find on the left with low concentration, and after we increase the dosage the colors change, but also the inhibition changes. So there's a very nice illustration on how we inhibit autotaxin. But it is in plasma, our target is to show that we as well inhibit autotaxin in the lungs.

And that's, in fact, the main goal of the ongoing Phase 2 study. We call the study FLORA, FLLORA is one of the animals on the Galapagos Islands. So FLORA, is a 12-week study where we take a small group of IPF patients, there is central reading to include them so that we are sure that they really have IPF. Studies run in the UK, Italy and Ukraine. Patients are dosed for three weeks and we take a BALF lavage, which is a very harsh investigation to do at the beginning and after 12 weeks. And we want to see there a clear impact again of 1690 on the levels of LPA in the BALF of those patients.

Exploratory we're going to measure as well what happens to the lung parameters, but for those amongst you who know anything on IPF, it takes much longer. It typically to see an improvement in clinical science we all know that it takes about a year to see an improvement. So would be first want to see in data through the dose we give here we block LPA, that's sufficient a month that should make a difference or might make a difference and then we going to take this into longer study phase, the Phase 2 study in IPF patients.

So, 1690 is not our only asset in IPF. We have also a new PCC, 2938. As I've said before, works differently. It's blocking one receptor, not on the LPA pathway, another pathway. It's a receptor antagonist that as well has shown nice data in the bleomycin model here. Very low dose; only 3 mg per kg. We have an activity as good as pirfenidone, which is a kind of standard we take as positive control for this model.

And so, little by little, and these are quite harsh models as well to run. We see novel mechanisms of action that show promise, first of all, in the lung model. We, as well, evaluate broadly these molecules and novel mechanisms of action for other types of fibrotic diseases that I can tell you with one it's really – we get a very different picture target by target, compound by compound, some work well on the kidney, some don't work well on the kidney, some show some activity on livers. But for where we have the most solid data today is in the lung fibrosis model.

So giving here the overview of the fibrosis clinical pipeline. So 1690 IPF. So the plan is to recruit all patients this year and that is a 12-week study and some reading. So beginning of next year, we should have the data and share them with you. And then also, next year, we'll kick off the clinical development through Phase 1 for 2938.

But a growing pipeline, really, one of our focus areas in terms of novel PCCs, we really try to grow them extensively this list. Both with other disease – other tissues, kidney and liver and with novel compounds as well.

Let's now move to cystic fibrosis, which probably, is of most interest to many of you in this room. Cystic fibrosis is a terrible disease. It's a disease caused by mutations on a single ion channel, the CFTR, a well-known gene. I personally believe that the medical science is going to change the disease within five to six years. So everybody I meet, family, friends, when they -- when they ask me or they tell me they know somebody with CF, I always give the same message. Go to the University Hospital, sign up for trials as soon as you can because those novel therapies are coming and they're going to have a major impact on your life.

We plan to be part of it. We are working on our own triple combination for Class II together with partner AbbVie, and we will, as well, try to find the better Class III molecule with 1837.

So, for Class III, there is a good drug on the market, Kalydeco, let's be clear about that. Only if you see superior activity, we will move forward there, Class II: lots needs to be done. It's a good outcome that we got Orkambi got approved, but it can only bring improvement for a small portion of patients. Many patients are still not served especially the heterozygous patients, they haven't seen any clinical benefit yet. So we did target both the homozygous and the heterozygous population that I will illustrate with some data.

So what's going on in the disease? On the left here, you see a Class III patient. The blue is epithelial lung layer of the lungs. In yellow, you'll see the ion channel effect in a Class III patient. You have sufficient ion channels. But you – there's a very hard time for the chloride ions in red to pass through.

So you have to add a potentiator and then suddenly the channel opens and you'll see sufficient chloride ions passing through together with the ions, water will come through. If you get the healthy water layer on your lungs, you're able of removing bacteria and all types of dust out of your lungs and you can keep them clean and healthy. CF patients can't do that and get lots of infections.

Class II is on the right. In fact there, the problem is patients make sufficient protein but the protein never gets through the blue layer to the membrane. So that's where you need to add one or more correctors to get sufficient of the synthesized CFTR protein correctly folded on the membrane.

There you see, you only see a few chloride ions on top of it. So most of the time, if you do this trick, your ion channel is there but it’s in a closed conformation, that's why you need to add a potentiator, going to open it, and then you can have a healthy lung layer. So that's why you have to have the triple combination here.

Yet when we started our efforts. I told the team, look, this is a protein folding disease and it's correct. Protein, most of patients, is full length made. Some lack one amino acid, but you need to alter the conformation which is for industry and for science a hard thing to do.

So, in fact, without having a single protein folding expert in the Company, by doing complex screenings, we did find our way to find novel compound that modify the folding and get the folding right.

So for the Class II mutations, what we do there is we have a mix of an early corrector which typically is called a C1 but I rather prefer to call it an early corrector. is a compound that binds at the beginning of a sequence and then we as well add a late corrector which binds according to our science later and at the end stage of the protein and those two will give a correct folding of the protein. And then finally, you have your potentiator to open the channel.

So we're looking here for triple combination therapy. I've been luckily to work in an HIV company. We brought a number of combination drugs to the market, In total we brought three HIV drugs to the market, so I have some experience with combination treatment.

I also worked on some Hep-C drugs as well. There we brought combination drugs to market, but this is novel. It is the first time in history. We have three compounds that affect the folding of the same protein.

So all what you know about combination therapy is right but it's not, per definition, sufficient for this challenge. What we really need to control here is how the three drugs interact with the binding of each other. Because if you have three compounds that bind to the same protein, they affect the binding of each other. And that is the real challenge for the triple combination.

Can you select drugs that bind together strong enough? And as well, why in the development, you can either fix each dose on its own, in a sequence, and that is a correct way of doing but you're in trouble if your third component affects the binding of the first two because then if you fix your dose, you will be in trouble.

That’s why the way we develop these by having flexible dosing during Phase 2 of the three components, allows us to adjust perfectly the dosing of the three. And I can tell you, most of the compounds we've seen in our C2s, they really impact on the binding of the two other components.

So, it's not something that I invent here. No, no. For most of the compounds and we've thrown away many compounds, many C2s we have stopped because because there is too much impact on the binding of the others. So it's really, for us, a cocktail we watch carefully and where we are very stringent, that really the binding of the three together is in sync.

So CF, many of you try to compare. I get lots of questions on how does the data on poster X compare with the data in presentation Y and I'm going to apologize to you because we have really presented a lot to you and you can't always compare them. I'll explain to you why.

So what types of assays do we have? We have on the left, down here, assays on cell lines where we screen libraries. These have little to do with the disease but allow us to massively study these compounds and where we mainly, we don't measure the function, we just measure expression. So we work with a lot of cell surface expression cell lines.

And then moving up, we can do much more complex things as well as cell lines we do band B/C and BD binding and all of that. So then the real hard work happens in the primary cells of CF where we do organoids – I'll show you some of those, Ussing chambers we have TECCs

As well, we have the secondary assays, the surface liquid. I'll show you some data. We have assays on ciliary beating, we have patch clamp assays. So we have lots of different assays and sometimes, we present different – on different compounds, different datasets and they can't always be compared easily.

Another complicated factor is that in this industry, there are different protocols. So many times, people are saying, the Vertex assays look different and this is because they are run a different protocol. So here, we've run in-house in orange our standard protocol. And then in green, when it's considered the Vertex protocol which is, by the way, also used by a contractor we use to verify our data and of which we also have presented some of the data.

So the difference is small with what you see that with the Vertex protocol, is always a higher current. So stop comparing data we published because you can't compare them. You have to be a little bit patience. We have to be as well patience. But stop comparing all those data sets because, honestly, you're wasting your time and the reason is there are different protocols, you'll get different levels of wild type CFTR expression and you get different datasets.

What is for sure is that when we say a compound is better in any of the two protocols, it's always better. There's a huge difference between dual and triple in both protocols. So nobody has a good or a bad protocol, they are just different and their absolute numbers don't match up. That's a message I'd like to give here. It's really – you can't spend your time the way you want, but I don't compare those numbers for myself.

Let's now have a look on how triple therapy, *in vitro* affects the healthy state of cells. So we're going to look now to the air surface liquid layer. So what you have in the lung structure, it's in layers and you have a ciliary there and you need a healthy aqueous layer. So if the ion pump doesn't work, there are no ions above the membrane and there is no water layer and then the lungs can't remove the dust and the bacteria.

So what we measure here and this is on the right, this is the well. This is the well, a 12 well system, you have, on the bottom, your epithelial layer and if we have lots of water, water will creep up the border of this well. If you don't have sufficient ions, you have a very low layer and the water layer doesn't go up. So by measuring the thickness of the water, we can measure how close to healthy our cells are or not.

So now some data, on the left, we've taken as control healthy cell line, that's 100%. At zero, we've taken a delta F508 homozygous cell line, with no treatment. And there's a difference. So if you now are going to add dual therapy, if you want corrector plus a potentiator, you'll see some improvement. There is clearly improvement there is no doubt there whether it's – but it's a limited improvement compared to wild type.

That is only from the moment we showed triple therapy we applied triple therapy, C1+C2+ a potentiator, that we came close to the healthy cells. So, really, that's why we are so focused on the triple therapy because we believe you can bring those lungs to a close to healthy state. That's our ambition, that's what we see *in vitro*, and we hope, as well for patients, we can do that and really, this is, how impactful the triple combination can be.

I'm also now going to try to show you some live images on how cells behave under triple therapy. What you see here is a homozygous organoid which is a cell, which is a complex cell structure, many cells together. And if we trigger the ion channel, normally, ions will flow. Water will follow and these cells must swell.

As you can see here, it's already moving everywhere. On the left, you'll see if you don't treat them, there's hardly any swelling although we trigger the cells. We have a dual therapy Orkambi here. We have applied, you see some, but limited swelling.

And then on the right, you'll see again, triple therapy, also in this setting, these cells, massively swelled. So again, a proof that, really, triple therapy for CF is what we hope is going to make a difference. And that's why, honestly, I tell to everybody that knows a CF patient, tell them to go to University Hospital. Tell them to line up because there are really good drugs coming out there over the coming years. The triple therapy you see here live in action, how they – how there is a much bigger impact of the triple compared to dual.

Don't compare number of organoids with current and all of that; it's impossible. The dynamic range is so much smaller but ok, this is different. What is good in organoids is that we can make banks of organoids from different patients. So, currently, we have access to 40 different organoids with different mutations. So that really allows you to test broadly your compound on a number of genetic backgrounds.

As I've said, for CF, heterozygous patients are as well within our scope. Heterozygous patients are the ones that have one delta F508 mutation and another. And unfortunately, for them, early trials with Orkambi from Vertex didn't show any clinical benefit. So they're really within our focus.

This is an assay point on organoid again. So, don’t compare with ion currents, please. I'm going – what I want to show you is that with dual therapy or combi, you'll see some improvement with triple therapy, our triple combo, you'll see much bigger improvement. So, again, there is good hope also for those patients that with triple therapy, we have a chance of improving their lives.

So we will set up studies later to get it as soon as we have triple combination in the clinic for both homozygous and heterozygous patients.

Let's now go and look to the individual components of our CF cocktails. So our C2, currently, most advanced in the pipeline is2737. We selected 2737 for two reasons over 2665. One reason is clearly it has much higher lung penetration which makes sense for this disease. Secondly, it was also a compound that affected less the binding of potentiator and C1. Those two reasons where we said take care before we rush with the suboptimal compound.

2737 really penetrates well and has hardly any impact on the binding of potentiators and C1. What you'll see on the left is testing over a number of patient samples. So different mutation, different donors in the background, and you'll see that between 400 to 600% of dual therapy is a signal we pick up. So if you compare dual to triple, you see four to six fold improvement of ion currents over the membrane.

On the right, you'll see the potency. It’s a quite potent molecule. Double digit, nanomolar on EC50, so really, we only need lower level in lungs and we will be able of achieving those. There’s validation here that we believe this compound will work in a number of patients.

One slide -- or two slides on our C1 corrector, 2222, it's an early binder like lumacaftor and VX-661 from Vertex. The curve is more to the left so it’s a more potent compounds so we hope we'll have to dose less in terms of milligrams but that is not the most essential thing.

What we see as well is that in terms of the maximal efficacy, the Emax, we get here close to the Emax of lumacaftor. Consistently, we see 2222 and lumacaftor being somewhat higher than 661 whether there's going to be a difference, I don’t know, but I'm as curious as you to see the phase 3 data of 661 to see whether they're as good or better or somewhat less good than the Orkambi combination. But there, we might have a slight advantage over our Vertex competitor for triple combination.

2222 went into Phase 1. We did a classic SAD/MAD healthy volunteer, smooth process in Phase 1. Rapid absorption, high levels, no emerging safety signals well tolerated. We really believe this is going to be one of the cornerstones of our triple therapy. We are waiting to add more components to 2222. We'll present more in detail data later in this year at the conference on CF in the U.S.

Then we have two potentiators in the running. 1837, I'll come back to SAPHIRA trials later and 2451. On the left here, you'll see effects on delta F508 homozygous cell lines. They show all a small current. There is no real difference but both are active Vertex compounds as well are active. Whey're not going to claim any difference there. They're all fine candidates for that population.

G551D, we see differences there. You see that 1837, although they are almost semipotent, consistently, our graph gives a higher Emax. So at the top concentration, you see a high current so that mainly that translates to the clinic that patient could have better benefit from 1837 and that's what we currently explore for the first time in the SAPHIRA study: questions how high will the exposure be that we really reach levels. We need to get to that Emax.

There is a potential there that at higher dose levels, we see some higher FEV improvements compared to Kalydeco. We really need to see superior levels to move into Phase 3 there. We're not going to try to equalize Kalydeco.

2451 is a fine compound as well. It's in between the two compounds.

So 1837 went into Phase 1. So there's a data here on the right, day 14 PK/hours. So what you see, there is clearly a compound we need to dose twice a day. So levels rise quickly but dropped quickly as well so by dosing twice a day, we stay above our target exposure that we will have to live with the doses around 120 mg to 250 mg b.i.d., that’s the calculation out of SAPHIRA, we want to get the data to check whether this calculations we currently make are the correct ones.

For the G551D population, we will need the higher dosages there. So the 250 to 500 b.i.d., that is clear.

Let me now switch to the SAPHIRA study. So we have two SAPHIRA studies. SAPHIRA 1, we studied the typical Class III population so patients with one G551D mutation. All these patients still have a G551D mutation. The second mutation is free but probably, is dF508.

What you see here is compared to the mutation in SAPHIRA 2. Actually, this is higher around 370 nanomolar. And as I – as I've said, the Emax we can reach and as the same as on the previous slide is higher. That's – so that's what we want to test in the SAPHIRA 1 study.

So for SAPHIRA 1, we are very pleased in the fact that we've extended the number of patients, so we did find patients. So when I came here two years ago, many of you said you can never recruit a single patient on the study, thank you very much. We have increased our target population because we can recruit those patients.

And last year, many of you told me, yes, but you'll never be able to take patient from Kalydeco and bring them to your study. Thank you very much again, all of the patients

come from Kalydeco and are switched back. So this is all possible. We bring our science with the field. The field is excited about the Vertex drug so don't take me wrong, because the field is as well ambitious and is willing to work to find better drugs and that's what they see in this opportunity, can we test in a safe way other drugs and maybe further improve therapies for these patients. And that's why we have included those patients.

So now over to SAPHIRA 2. SAPHIRA 2 is the Dutch mutation. So it's in our neighborhood. Why did we choose a Dutch mutation? Because, in fact, the EC50 on the Dutch mutation is exactly the same for 1837 as it is on the homozygous delta F508.

So in SAPHIRA 2, we want to see whether the exposure is sufficient to see activity. It will be the same activity as Kalydeco that we see and that we target and that would mean that that dose can be taken forward further. Our dosage around that into Phase 2 dosing. But proof of activity, allowing us then in a triple combo to ensure that people will have some benefit out from 1837 if you take it forward.

So two similar studies but with different goals. In SAPHIRA 1, seeing do we get to the same level of efficacy? Is exposure high enough? We should get to higher levels of efficacy? That's what we hope for, that's what we will be looking for in SAPHIRA 1. In SAPHIRA 2, it is doing match Kalydeco efficacies and as well as exposure because that's the one we will take forward for our triple combo.

So SAPHIRA is a four-week study. They are short-term studies. So primary endpoint is safety, PK and whether we see side effects. We'll -- especially, we look to sweat chloride. So, sweat chloride is a thing that should move in a couple of days so we should have solid data there. We, as well, will measure FEV but we dose escalate in both studies.

So in SAPHIRA 1, dose escalation is currently twice. Patient starts a 125 b.i.d., go to 250 and then to 500. So it's going to be a little bit of challenge to see the FEV evolution there and we measure blood plasma levels. And so primary focus will be there. Do we see a sweat signal similar or higher than what has been reported for Kalydeco.

This brings me to the overview of our CF portfolio. So we have two potentiators. So everybody asked me which of the two is in the lead? Well, we have two studies ongoing. Phase 1 for 2451 and that will read out of the same month when we'll have a view on the SAPHIRA data and we really went to those data to make decision. We will learn a lot from SAPHIRA.

Do our in vitro models that translate well to clinical efficacy? What are the plasma levels we reach with 1837? What do we see with 2451? And with all that together, we're going to put together our triple -- select one that will move into our triple combo.

So C1 2222, as good as we hoped for. So we have a backup. We will move forward a backup but that's only in case accidents happen or not -- no point there that we're going to make a choice and then C2 is currently, there's 2737. We still work on a backup for

that one as well and another series that is in discovery, I will not comment on those today.

So how does putting our triple combo look like over the coming months in two years? So this is a time view. So, 2222 healthy volunteer is complete. It will do a PK study in patients with 2222 later this year. Then on the potentiator, we have data generated with 1837/ 2451. We select based on Phase 1 data 2451 and SAPHIRA data, the dual, P plus C1. Around the same moment, when 2737 moves in to Phase 1. That's planned beginning of Q4 this year.

And so, there, at the beginning of next year, we can start to combine triples in healthy volunteers and as soon as we have the safety of triples in healthy volunteers, we'll move into patients and then around the middle of next year that we go that we plan to move in patients with our triple therapy.

So we are a bit behind Vertex here, that's clear. Catching up is going to be difficult. So we will do our best to come with an excellent triple combination. There are some elements where we believe data we've published on our C2's look better than what Vertex has published, but you can't compare. So we are hopeful that in the end, we'll have a competitive triple combination therapy and that will be part of the solution for many patients in the future.

Brings me to the overview of the pipeline again, gets so dominated by start of Phase 3 by filgotinib and you'll see many more indications coming over the year. Then the CF program, I extensively explained to you the two potentiators, C1, C2.

Autotaxin gives you the goals of the Phase 2 study, timelines around that and then OA as well, I think, for today and there is most, really, the data that WOW everybody was running around and then saying what are we going to do now? What are we going to do now? It's not an easy disease which we are extremely excited with what we've seen there.

MOR106 I didn't] touch on today, that will be something for next year. So that's in SAD/MAD. So SAD in healthy volunteers. There are those one multiple ascending dose with patients and we'll start in Q4 this year, probably. And then I've shown the animal model data of the two earlier compounds.

Brings me to our clinical news flow of the year. So second half starts Phase 3's by Gilead announcing them probably the design as well at that moment – an ulcerative colitis Phase 2 study also started by Gilead.

So cystic fibrosis, SAPHIRA data, second part of the year, Phase 1 2451 and then start of our 2737, so our C2. At that moment, we should have an idea when – which is going to be our triple combo for C2 and [half] as we can move forward.

And then as well as 1690 when the trial is fully recruited and then probably top line Phase 2 data early next year. So triple combo data of CF healthy volunteers will come

next year and patients will start around middle of the year so that's going to by, hopefully, year end or beginning 2018 when we have some data out of those triple combination.

And then on osteoarthritis, so I've shown – give you the top line is also the biomarker data so Servier has prepared the plan to moving to Phase 2 in Europe and we'll do same and a complimentary program to move into the U.S. into Phase 2.

With this I'm going to complete my presentation and we will open it for questions and answers.

+++ q-and-a
Elizabeth Goodwin^ Okay. Thank you very much, Piet, and Bart, and our audiences for your patience. That was a nice, long talk.

I'd like to have the operator for the conference call explain to callers now how they can pose questions. Operator, go ahead.

Operator^ (Operator instructions) We have our first question from Peter Welford from Jefferies. Please go ahead. Your line is open.

Peter Welford^ Hi. Sorry. It's Peter at Jefferies. Sorry, we have to listen to a little automated thing before we can ask questions.

A couple of questions, if I can do, please. So firstly, can we assume from this then that 2665, that is the other corrector 2 has been discontinued and can you just confirm if that's entirely based on the penetration of the lung and binding that you mentioned for 21 – 2737 or are there other factors as well that led to 2665 being stopped.

And then secondly, I wonder if you'd go into the rationale to why the C1 corrector 2222 is being combined in a Phase 1 with 2451 the potentiator if that makes sense rather than 1837? And, I guess, given you mentioned that 1837 seems to be the lead potentiator, why you're not looking at that as well given that could be presumably the quickest way to move into a triple combo? Thank you.

Piet Wigerinck^ So, Okay. Thank you for the questions. So first question was on 2665 and 2737. So indeed, I can confirm all our resources are focused on 2737. This is, I believe, I mentioned during my talk.

One reason was the lung penetration was – is much better for 2737. Second reason as well as I explained, there are three compounds binding the same protein for 2665. We saw too hard impact on the binding over the others which then is a risk that you need to increase dosages of the other ones. So these are the two reasons why we selected 2737 but we don't have any activities ongoing on 2665.

And then on our potentiator choice, I understand that all of you want to make the choice for me and I want to wait for the data, so all I can say is that we are waiting for the data.

We don’t do SAPHIRA just to be busy now. We really want to learn a lot from SAPHIRA so we'll see how 1837 comes out of SAPHIRA.

2451 is a once a day compound, of course that has advantages for chronic dosing for combination therapy as well but let’s wait for the data of SAPHIRA and the Phase 1 data before we make a final choice.

Time limiting for us is 2737. That’s the third component, we are all waiting for that one so, that's currently in preclinical tox and the moment we get the green light, this moves to Phase 1. At that moment, we need to fix the rest and we'll start to plan the combination piece. That’s really what is the most time critical element in the combination in putting together our CF cocktail.

Peter Welford^ Sorry. Just to confirm then, the Phase 1 with 2451, you wouldn't start until we've got the Phase 1 data, obviously, for 2451 itself and the SAPHIRA results as well in hand?

Piet Wigerinck^ Well, the combination of a P + C1, I believe that's what you mean in healthy volunteers, will make that choice after we've seen in the SAPHIRA and the Phase 1 data of 2451.

Peter Welford^ That's great. Thank you.

Piet Wigerinck^ Okay.

Elizabeth Goodwin^ Okay.. Now, I'd like to take a question from someone in the audience. I see the first hand raised here. Please state who you are.

Matthew Harrison^ Thanks. Matthew Harrison, Morgan Stanley. So two questions, if I may.

Piet, broadly I think you touched on this a little bit but can you just tell us where enrollment is for the SAPHIRA studies and how that’s progressing? And then, second, can you just broadly talk about what work you’ve done on drug -drug interactions? Obviously, these are a lot of compounds you're putting together and what work is ongoing or what you know so far. Thanks.

Piet Wigerinck^ Okay. Recruitment, SAPHIRA, so I guess during the Q1 update that we announced that we are -- that we have increased our target numbers for patients in both studies, so you only increase when the recruitment is on schedule or ahead of schedule. So, important there as well, I think, as a take home message is the way we've designed it where patient that are on Kalydeco have a seven-day washout and is safe to proceed with the experience there is that the way we do it is a safe way and that allows us well as to increase that we are hopeful that SAPHIRA 2 will be recruited any day for the recruiters.

SAPHIRA 1 will take us a little longer. As well there, we should have data before the year ended. So we are not going to keep the trial open until the end there. So recruitment is really ongoing very well.

Then on the combination, treatment and DDI. So one of the reasons to choose AbbVie was, indeed, we want to go for triple combination. AbbVie has the experience to put triple combination, even quadruple combos together. So we have a whole list of DDI studies we do but I have to select the molecule. So we really select the molecules based on the fact that there's an absence of DDI potential so that is part of the selection. We've dropped some compound because they were inducing P450 enzymes. This is as well the most obvious one you can test for, this is never on a complete science but what is the belief in terms of assays we have done and the compounds that – compounds we have selected are clean in that respect. That's all I can say because it's essential for the selection.

Elizabeth Goodwin^ Now, we can take a question from the phone. Operator?

Operator^ Thank you. We'll take our next question from Jan de Kerpel from KBC. Please go ahead. Your line is open.

Jan de Kerpel^ Hello. Thanks for taking my question as well. I've three small ones, in fact.

Piet, could you explain the key reasons why people actually still, from being on Kalydeco and move into a development compound? Secondly, you have NASH being mentioned on you fibrosis slide, how concrete are the plans over there? What kind of molecules do you have and have in place and when could we expect these to progress further on?

And then finally, if you -- if you look at your R&D focus like inflammation fibrosis, metabolic, anti-infectives what kind of – what kind of projects are missing according to you over there that you would like to seek for externally that you could bring internally to have a more complete program? Thanks.

Piet Wigerinck^ Okay, Jan. Thanks for the questions. First question, I believe, why do patients on Kalydeco want to participate in this study? I think the community of CF patients is extremely motivated. I think CF – what the CF foundation did over the years is fantastic work by collecting money, preparing the field, making patients aware of their disease, stimulating research and what we see when we visit the clinical sites. Everybody really wants to -- everybody is targeting the goal, treatment for every CF patient and that's, I think, most impressive effort I've ever seen in this industry.

And so that makes this all motivation to look for novel drugs and we ask the investigators what do you think? Well, first it's the physician that we need to convince but when they see the data, okay, potentially here for novel drugs. Other drugs, even better drugs.

I will talk about it with my patients. And some of them signed up for the study and that's where I know from Vertex that they've told that the recruitment of some of those studies is slower than anticipated and I can understand that but I must say that we really work here in extremely motivated field and then motivated both the research in the industry, the clinical science, and the patients really want to do a lot of efforts to bring treatment to the market for all CF patients and that is I'm pleased to be part of that effort. So that's for the motivation and the efforts of the CF patient.

Second question was on NASH, I believe?

Jan de Kerpel^ Correct.

Piet Wigerinck^ So, the fibrotic diseases, we extend, in fact, our access and in house set of animal models. And so we saw that we have a bleomycin mice model. We have a kidney model running and we are adding and we are testing all the compounds in the area currently starting to transfer those models internally to as well do some NASH type of animal model.

So we own as well, the compounds we have in development, current PCCs or upcoming PCC as well shows up something good in a NASH model and then see how we're going to develop compounds in development. Phase 3 now, so Phase 2, Phase 3, so we are to see that, really, our scientific approach makes sense compared to the competition which we first looked to our animal model data, trying to understand and then decide. But I can't give a data. I can't give the right compound number yet but we are working hard there to add NASH to our focus.

Then the last question, what do you want to add? In terms of disease, it's – we don't want to add because it's already a lot we do so in inflammation, to be honest, filgotinib will further open that box so we'll look into much more diseases and it's going to trigger in the minds of the scientist as well to test all the molecules for more diseases so that's not a contained box, that's a box that will grow.

If you look at externally, we rather look to opportunities where we say, well, this is better than what we currently have in the pipeline. So, it must be novel. It must be better than what we currently have. So we are not really looking to assets in all the diseases. We rather like to find preclinical Phase 1 assets, Phase 2 assets in the list of diseases I have on my slide there.

Jan de Kerpel^ Okay. Thank you very much, Piet.

Very small one coming back on the first question. So the way you explained it is based on motivation, it does not seem that there -- the people patient physicians are not satisfied with how Kalydeco works?

Piet Wigerinck^ No, that's correct. And I hope I didn't try to create that impression. I think it's clear that Kalydeco has been – it's a good drug, caused major change to the

disease of many, many patients. So patients are currently happy. But on the other hand, it this the best we can bring to patient? That's an unanswered question.

And there, the field is ambitious as well. Is it a better drug? They want to know it, they want to test it and they want to decide themselves which drug they are going to use but I hope I did not create the impression that we believe patients are not happy with Kalydeco because – no. Patients are happy and it has changed their life in a fantastic way, honestly.

Jan de Kerpel^ Thank you very much.

Elizabeth Goodwin^ We have a question from the audience.

Phil Nadeau^ Hi. Good morning. Phil Nadeau from Cowen & Company. Two questions. First, on the correctors that you're developing. Vertex has disclosed that preclinically based on some signals and toxicity, some of the second generation correctors and then killed some of the earlier candidates, can you talk a little bit about what you're doing to rule out tox signals, how extensive is your tox testing? And can you also think that these correctors could have propensity for toxicity?

Then second, on filgotinib, when the Phase 3 program was announced by Galapagos and Gilead was mentioned, do you have to do a testicular safety study in males, can you talk a little bit about the design of that study and why do you think the FDA wasn't convinced by your preclinical tests and the Phase 2 data of the safety of filgotinib in males? Thank you.

Piet Wigerinck^ Okay. Preclinical tox on the C2 correctors. Prior to selection, we do extensive tox testing and I must thank partner AbbVie for that. They really have done a lot of tox testing so we frontload our tox de- risking cascade as much as we can. So every PCC that has been selected, went through an extensive, let's say, seven-day tox study at extreme high dosages and exposures to try to rule out. This is not the exact science.

So I can't promise that none of our C2s will never show toxicity but we do a lot of frontload testing prior to the selection. So that's how we try to avoid surprises there.

Then filgotinib, the safety study. We've been always clear and I think as soon as we had a signal, we discussed with both FDA and Europe and it has always been clear that we had to do a testicular safety and that always has been our stand as well. As far -- as soon as you have the signal, as a company, you know you have to do the safety study.

What was unclear, whether this was a healthy volunteer study or a patient study and there, FDA and EMEA have similar view currently for filgotinib that they want a patient study so that the safety study was not a surprise for us. What we've always said is that our safety margin should be big enough to allow patients on the 200 mg. And what we now see is that for RA, patients are allowed on the 200 mg dose. So our safety margin has done what it to do, which was to allow patients and male patients on the 200 mg but

we've always known that in Phase 3, we would have to run a safety study. And so now it's clear. It's a patient safety study.

So that patient safety study will be RA patients on background medication, placebo versus active and then follow up then for a number of weeks. So we believe we can recruit that study, so don't forget there's a high screen failure rate in these studies that patient that are looking for access to novel drug but according to us, don't have all the disease criteria, right, to enter the study and probably amongst those patients, we will find the ones to do the safety study. They get access to the drug in the same way. They get access in the Phase 3 trial and that's what's going to be.

Elizabeth Goodwin^ Okay. Now, we can take a question from the phone again. Operator?

Operator^ Thank you. We'll take our next question from Hugo Solvet from Bryan, Garnier. Please go ahead. Your line is open.

Hugo Solvet^ Hi. Hello. Thank you for taking my questions. I have three.

First two on the SAPHIRA, are all the centers open at the moment? And are there discussions with FDA ongoing, considering that you do not have any U.S. site, if I'm not mistaken. And would that be necessary for Phase 3 combo Phase 2 trials? I would appreciate your view on that.

Second one on SAPHIRA, again, which improvement are you expecting to see to moving to Phase 3? Do you have any idea? Can you give us any color on that?

And last one, it seems that you are open to outlicense some compounds but considering the ambitious target that you have with the initiation of numerous mid and late stage trial are you considering some bolt-on acquisition and licensing deals, then which area would you like to reinforce? Thank you.

Piet Wigerinck^ Okay. Let me start on SAPHIRA. I think the first question was that there are no US studies part of SAPHIRA which is correct. So we plan to open an IND later this year in a CF program. And at that moment, we will engage with FDA on discussions on how are we going to do combo studies in healthy volunteers and patients.

So I hope I answered with that your first question. So the answer is, yes, there are no U.S. studies currently but we plan to open an IND later this year which then will open the discussion.

Then on the second question, I believe you wanted to know how designs Phase 2 will look and with the combination prior to phase – initiation of Phase 3, let it be clear that FDA has made it clear at the Orkambi advisory board that they don't want to push forward any combo treatments anymore that haven't proved that the combo is better than the single drug.

Honestly, I think the triple combos will only move forward into Phase 3 if they really show a major improvement over Orkambi and that's what we expect as well as -- I think, I, today show sufficient data that underlie our hope while we believe that a combo is going to be much better than the dual combo.

And then we'll have to discuss with FDA there are different ways to prove a triple combination is essential. I hope we can agree that we don't have to do trials that can't bring any benefit to patient. I don't think that's in the advantage of anybody so I don't think we'll have to do monotherapies for all of that and then dual for all and then only triple. I believe there are different ways to show that triple is the way forward and by showing the difference between dual and triple, that's what we have in mind but we'll see FDA -- what we learn from early interactions around that with FDA.

And then what was the third question?

Elizabeth Goodwin^ Do you want me to repeat the third question.

Piet Wigerinck^ Yes. The third question was on the pipeline filling, whether we look for – with our ambitions or long term ambitious indeed to move forward the novel mechanisms of action compounds into Phase 2, proof of concepts and a number of them, one every two years into Phase 3. It's clear that we can't, on the internal effort, that we will supply – we will complement it with compounds from externally. So– there's exercise ongoing externally as well.

We expect whenever we expect a novel target, it's still because we find that our target that we are the only one, we are, in fact, never alone on this world when we work on little targets. We always find groups, company, that have the same focus, the same interest so it's not because we work on novel mechanisms of action that we are the only there. So must be – there are good scientists externally as well and if they have better compounds, why wouldn't we talk to them and try to work together with them in the future.

So it's clear that part of that ambition, we will complement our internal effort with acquiring compounds there. That's correct.

Hugo Solvet^ Okay. Thank you.

Elizabeth Goodwin^ Okay. We have another question from the audience here. Go ahead, Vamil.

Vamil Divan^ Hi. Thanks. It's Vamil Divan from Credit Suisse. So maybe two questions. We touched a lot at the beginning about the different ways you find targets and advancing products and a lot of these mechanism. I'm wondering if you're going to share a little bit of how Galapagos thinks about when and how you look at the commercial opportunity, and simply just assign some kind of finding a target but then what else, you know, the competitive dynamics out there and what the clinical, the commercial hurdles are to advance different products forward?

And then maybe if I could just add a quick one on IPF. You touched on that at the beginning. Aside from 1690 being a little bit further ahead, can you differentiate a little bit more between 1690 and 2938 and what you've seen so far?

Piet Wigerinck^ First, I'll give the floor to Bart now on the commercial testing.

Bart Filius^ Yes. Basically, Vamil, thanks for that question. I think the way we look at that is, first, to assess when we are in the early stage of development whether the molecules are in attractive opportunities per se before deciding on how to commercialize this going forward.

Obviously, filgotinib is a good example. That is in an indication which we would not have commercialized ourselves by the sheer size and by the competitive environments they're in so that's definitely something that we were keen on partnering.

We'll evaluate that based on the different indications we set our autotaxin inhibitor 1690. It could be a good opportunity because it's really an orphan disease. It could be a good opportunity to commercialize that ourselves by the size of that disease and therapeutic area.

So we'll take that on the case by case basis. First, we let the science drive our path forward and take the commercial decisions based on those outcomes.

Piet Wigerinck^ Okay. On the two IPF molecules, so what can I say? So both work on lipid mediators but complete different pathways of lipid mediators. So they have nothing in common in fact, beside the fact that lipid mediators are on -- are on top of the pathways.

So 1690 inhibits an enzyme making LPA species and you'll see the slides or the data so inhibitor we inhibit a range of LPA species, not all of them. There are still longer chain LPA species which we probably don't inhibit. But the focus of what we know in terms of specificity for autotaxin, we inhibit most of that.

So autotaxin blocks plasma-wise, 80% of this is of LPA, that's as well what we've seen in Phase 1. We have blockage for 80%, never fully. So this is a second source there. Most critical there is what -- what happens in the lung.

Then the other 2938, is an antagonist of a receptor, so it's not an enzyme. It doesn't inhibit the synthesis noid 3 the blocking on the cell surface and a specific receptor for another lipid mediator so there is a vast amount of lipid mediator stays there and stays around, but we block the signaling in towards the cell and we then block how the fibrotic processes are engaged.

So with that, we'll go to IPF as well. That's the first model that we'll see also for other diseases. There's also a molecule where we are extensively exploring other diseases.

For autotaxin effect, the whole story is much broader. We picked it up in the screen for RA and then went for all diseases and ended up in the lungs, in fact, where it plays the most role and then selected IPF later so it came by a complete other channel, in fact, than our 2938.

We'll disclose targets later at an appropriate moment and I have to see a bit what I am saying about that.

Elizabeth Goodwin^ Okay. We can take another question on the phone. Operator?

Operator^ (Operator instructions) We'll take our next question from Jorn Koch from Rabobank. Please go ahead. Your line is open.

Jorn Koch^ Yes. Thanks for taking my question. I've only one remaining. I was wondering if you could comment a bit on what you're expecting to see in your own CFTR modulators with respect to the bronchospasm which seems to cost some of the discontinuations Vertex is experiencing and are there any off-target effects that you are currently investigating? Thanks.

Piet Wigerinck^ Okay. Bronchospasms in the CF field. Well, it's well documented that we welcome, indeed with Orkambi a number of patients complain of chest tightness. I believe Vertex commented that with 661, they don't see that. I don't believe anybody has a good explanation on why this happens and how does this trigger. So there's no explanation.

I can only speculate so let's be honest. We hope we don't see that there is no way to say that we are not going to see it so we hope it and -- we will have to live with the data there. So but I don't know – I don't believe the mechanism is known and it's something we can't select molecules on. So those data will come as they come.

So the second question? That's it? Okay. Thank you.

Elizabeth Goodwin^ Okay. We have another question here in the audience.

Amanda Weyerbacher^ Hello. Hi. My name is Amanda Weyerbacher from inThought Research.

Two questions, do you have plans for combining filgotinib with anything? Perhaps one of your compounds or one of Gilead's? And my second question is with the OA data and the cartilage breakdown, the 14 days, was that the furthest time point you looked at or did you looked at anything beyond that?

Piet Wigerinck^ Okay. Thank you. Filgotinib combinations, I'm going to refer to what Gilead said and Gilead really has ambitions combining filgotinib with a number of their molecules. So that is sure on the agenda. And we'll discuss with Gilead how and when we

can combine with our remaining targets. That’s a play where we are not own. Let's say it like that. So we'll discuss that with Gilead.

So the one with OA, it was a 14-day trial. So, yes, the 14 is -- we also had a sample on the 16 and those data were close to day 14 but, okay, it doesn’t add any --. It was a 14-day study so it was the last day of dosing, those data, as you remarked, were very good.

Elizabeth Goodwin^ Okay. We can take one last question from the caller. Operator?

Operator^ There are no further questions over the phone line

Elizabeth Goodwin^ Okay. Then one more question here in the audience? All right. I think that we've asked you all the questions now, Piet.

Piet Wigerinck^ Thank you.

Elizabeth Goodwin^ So, thank you everyone for participating by phone or for real here in the room. So we look forward to speaking with you at our half-year results on July 29th. Thank you very much. Bye-bye.

Operator^ Thank you for your participation, ladies and gentlemen. That does conclude today's conference call. You may now disconnect.