(Isabelle Audo) Thank you, Mark! So, thank you very much for this very exciting meeting and the opportunity to share with you some of our data.

Actually, I am just going to give you few examples. And there is a lot of very exciting talks coming up with all other therapeutic developments. So, if you want to have therapeutic approaches, and I am going to talk essentially about retinal disease. I am a retina specialist. So, I am going to talk essentially about the retinitis pigmentosa part of Usher syndrome. If either you want to try to stop the progression of the disease or to restore vision.

To stop the progression of the disease, there were very exciting developments in the past years, aiming at treating the genetic cause. So, that could be gene therapy. Either by replacing the gene, the defective gene by new normal genes or correcting the genes. And you will hear in other talks about oligo and high sense nucleotide, about CRISPR/Cas, about readthrough drugs other things in order to correct the disease.

So, regarding Usher, the problem is: if you want to bring the normal genes to replace the defective genes, you need to have a vector that will deliver the genes to the target cells. So, you usually use viral vectors. And the first

viral vectors that were used are adeno-associated viral vectors, called AAV. And fortunately most of the genes that are mutated in Usher are too large to be packaged in AAV. Or they need to have some special tricks in order to be delivered by AAV.

So, there is one trial in which our centre in Paris is involved which is sponsored by now pharmaceutical company, Sanofi. This trial has been using not AAV, but lentiviral vectors that are able to package larger genes up to 10 kb, which is quite large. Some Usher genes are even larger than that. So, the idea is this virus, this lentivirus vector, it‘s the virus, it‘s called EIAV. It‘s the virus that cause anaemia in horses, and it is not pathogenic in humans, we are not horses. And there were pre-clinical studies that documented the safety of the delivery of this viral vector. And currently, there is two trials, that aim at packaging and delivering a normal gene through this lentivirus.

One is for ABCA4 and it‘s another disease, which is called Stargardt disease, ABCA4 is the long gene. And the other one is MYO7A. As you know, MYO7A mutations cause the most common form of Usher Type I. So, prior to that, there were experiments in animal models and this is a slide as an example of what was performed in monkeys. If you want to use a viral vector, you have to prove that you are indeed able to infect the targeted cells. So, what Sanofi did, is on non-human primates. They delivered the viral, the EA1V viral vector subretinally and then the virus was not expressing gene to be treats, but a gene that made a protein that could then stay in the cells.

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And by doing that, they were able to show that there the EA1V was indeed able to infect cones and rod photoreceptor and also RPE. What they also did, is they performed subretinal injection in non-human primates in one eye. They injected one eye and subsequentially the other eye, or they re-injected the same eye and they could documents that it would not lead to major inflammation. So, that‘s when the trial started.

So, the trial is called UshStat, and is really aiming at one single injection underneath the retina of this viral vector delivering the normal MYO7A gene. This is a trial that is taking place in two centres, Portland, Oregon with the Casey Eye Institute in the US and our centre in Paris. So, this, the design of the trial is dose escalation. So, it started by with vision that had severe disease with the lowest dose, because the first point is to document that it is safe. That it doesn‘t lead to major side effects, because that is not what you want. Although, it was safe in the pre-clinical test.

So, the first patients had very severe retinal degeneration, linked to MYO7A mutations. And then, the dose was increased while we were documenting safety. So, so far 9 patients have been involved in both centres, and with a nice safety profile, which is provided by Sanofi - I have got to say I have no income interest or am payed by Sanofi - and 9 patients involved. And there were several side effects and actually one side effect in the latest patient was panuveitis which means after the surgery, there was inflammation in the vitreous. So, after this inflammation,

everything was resolved and most of the patients recovered. At least, the vision they had prior to the surgery to the subretinal injection. But when the Independent Safety Committee discovered that there was one case of the 9 patients who had developed severe inflammation, they wanted to pause the trials.

Up to now, the trial is on pause, Sanofi did further tests and the safety profile was re-studied with half of the highest dose. And the trial should re-start at the end of 2018. So, the good thing is, we have limited data so far on this patient. As I was telling you, this is mainly looking at safety. But there is some efficacy that are evaluated, based on visual acuity and visual field. And on these slides, I put some results of the visual field for the 9 patients. All the patients that were treated, recovered their baseline visual acuity. And even some of them have after the surgery and after some, you know-in this graph, some patients were followed for 150 days. Some patients are starting to have a difference between visual acuity in both eyes, but very little patients. Yeah, sorry?

(change of speaker) Can you slow down a little bit?

(Isabelle Audo) Ah, excuse me, yeah, sorry, I will slow down. So, these slides were to show you, that the majority of the patients recovered their visual acuity. The visual acuity that they had prior to the injection. And then, we followed these patients and what we would like to document because only one eye has been injected, is to see, what the follow-up- whether the injected eye behaved

better, based on visual acuity and visual field. And, in some patients we are starting to see some differences, but it should be taken with caution. So, again, the trial has been on pause for a year now to have more safety data on the pre-clinical side. And it should resume before the end of this year. So, that was for MYO7A gene replacement and you hear about other gene therapy approaches later on.

So, I wanted to now touch upon few other trials that are either at a pre-clinical stage or will be starting very soon or already started. One is independently of the gene. You want to stop the disease. You know that for the retina, the rod photoreceptors are degenerating first. Then the cones, the cones are more precious photoreceptor because they are responsible for our daylight vision or reading or colour view.

And one other approach would be independently of the genetic cause: Can we save the cones, can we stop the cones to degenerate? And this is some work that was done by my boss, Professor Sahel, for a long, long time. His idea was that not-not always in Usher but in other type of retinal degeneration, the mutation is really carried and expressed only by rod photoreceptors, but the cone degenerates again early.

And his idea was, that not only rods are important for night vision. But they are also able to synthesize to make factors, proteins that are really critical for cone survival. And when a rod degenerates, then a cone degenerates.

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So, there was a huge research going on in our institute to identify this rod-derived conveyability factor. And one was published in 2004.

It was shown in different animal models that it was indeed able to stop in few animal models with rod-cone dystrophy with retinitis pigmentosa. It was documented that the cones could be- the degeneration of the cone could be slowed down or stopped. And even that the structure of the cones, the morphology of the cone was even improved. And there would be a clinical trial initially in a selective genetic group of patients starting in 2020. The group of patients that mirror the pre-clinical studies on the animal models.

But we hope that with the proof of the concept that we are indeed able to deliver- by delivering this trophic factor RdCVF, we can stop the cone to degenerate. Then it should be wide-spreadly tested, including in patients with Usher syndrome and retinitis pigmentosa. So, that was the axis of stopping the disorder. Either by gene editing, gene correction, gene therapy with the current MYO7A clinical trial or protecting the cones. But now you know there is other type of therapeutic approach to restore the vision, when you no longer have photoreceptors and especially the cones to degenerate.

So, professor Zrenner will speak about artificial retina. So, I will just very briefly speak about that. And the idea of artificial retina is: When you no longer have photoreceptors, only photoreceptors are able to be activated by light

to generate an electrical signal at the optic nerve towards the brain. And, so the idea of the artificial retina, and another approach I will mention later on, is to restore the fact that no longer cells of photoactivable and able to send information to the other retinal cells. Other retinal cells, such as the bipolar cells, that are connected directly to the photoreceptor. Or the ganglion cells that are the third neuron forming the optic nerve and sending the vision to the brain. And these two types of cells usually are not degenerating during artificial retina.

So, there is different types of artificial retina, underneath the retina. But underneath the layer of support the retinal pigmented epithelial, or subretinal, or on top of the retina. In our group, especially the group of Serge Picaud in our institute, has been working with Stanford and Professor Palanker to develop a special artificial retina with little diodes here, that are completely independent from each other. And this idea of these diodes is to be subretinally placed surgically. And then with the camera, the camera looking at the environment, coding the information and sending back the information to these micro-diodes by infrared light to encode the vision. And this is something that- So, you see the implant underneath the retina.

This is something that has been tested in primates. And, so this is a bit innovative in a way that there is no connection for this little chip with diodes because it is just activated by this infrared light. And there is currently a trial which is not yet for retinitis pigmentosa. But we hope

it will come in geographic atrophy in two centres: One in Paris, one in Pittsburgh, Pennsylvania on geographic atrophy. And the idea is geographic atrophy in age related macula degeneration. And the idea with this little chip that can reach a thousand electrodes, is to prove, that we are able to restore fine vision in these patients that have only macula involvement. Because if we can do that on patients, who have only macula involvement, then you can also restore that when not only the macula is involved, but also the peripheral retina.

The last trial I want to mention is optogenetics. So, what is optogenetics? So again, when you have retinitis pigmentosa, you lose the only cells that are able to be activated directly by lights into the retina. The idea of optogenetics is not to restore photoreceptors, but to transform the other bipolar cells or ganglion cells that are not affected by the disease and to make them photosensitive. And the idea is: You have some protein in algae, you know, ancient protein, in algae in the sea, that are able to be activated by light and directly open a channel and initiate a signal into the light.

So, there are two types: one is halorhodopsin and one is channelrhodopsin. So, the idea with optogenetics is, it is a sort of gene therapy. It will be injection within the eye, it doesn‘t need to be underneath the retina because you want to target either the retinal ganglion cells or the bipolar cells to inject the genes of this channelrhodopsin, this protein that are able to be activated directly by light and generate the signal. Unfortunately, this channelrho-

dopsin can be activated by natural light, so this type of approach will need to be coupled with specific goggles that will transform our environment and generate light for this. The approach is developed in Paris, this will be red light in order to activate this photo-pigment that will be in the ganglion cells.

So again, the group of Serge Picaud has performed testing on mice showing that they were able to indeed infect ganglion cells and generate an electrical signal by stimulating this channel. It was also performed in macaca, in monkeys. And the intravitreal, it was proven that just injecting inside the curvature of the eyes, not underneath the retina, but inside the eye in the vitreous, the channelrhodopsin was distributed quite widely. So, it could give larger vision.

So, the trial is supposed to start anytime soon. And it has been accepted in France, there will be other trials, other centres in the UK and the US and we just got the approval. And so, the idea was, one single injection in the eye. And testing this device with the goggles to see, if there is any possibility to photoactivate and restore some vision at the cellular level. It is a sort of similar approach than the retinal implant. But you really go directly to the cells, trying to have maybe, hopefully a better refined visual restoration.

So, there is also a very exciting development, in the group with the mathematicians that work in Paris and in Pittsburgh, is to try to combine optogenetics or implants with

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a precise coding of the visual signal by a specific camera in taking into account, how our brain is able to analyse the space with the contrast and the speed. And to try not only to improve the device that is delivered to the retina. But also improve the way, the information is treated by a camera and sent to this different approach. So, this is going to be continued. And I want to thank you for your attention! (applause)