REFINITIV STREETEVENTS

EDITED TRANSCRIPT

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REFINITIV

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PRESENTATION

Operator

Ladies and gentlemen, welcome to the AB Science web conference. I will now hand over to Alain Moussy, Bruno Dubois, Jeffrey Cummings, Philip Scheltens, and Olivier Hermine. Gentlemen, please go ahead.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Good evening and good afternoon and good morning for our participants in the United States. This is Alain Moussy. Thank you for your presence. We have organized a web call to discuss the results of masitinib in Alzheimer's disease. My name is Alain Moussy, I'm the CEO of AB Science. Along with me for this conf call, I have the privilege to have, first of all, Bruno Dubois, who is Professor of Neurology at the Neurological Institute of Salpêtrière University Hospital of Paris. With me also, Dr. Philip Scheltens, who is Professor of Cognitive Neurology and Director of the Alzheimer Center at VU University Medical Center in Amsterdam; and Dr. Jeffrey Cummings, who is the Director of the Chamber-Grundy Center for Transformative Neuroscience in Las Vegas; and Olivier Hermine, who is Professor of Hematology at Hospital Necker.

The way we are going to organize this web call is that I will deliver a presentation that should last around 30 minutes. And then we will, in the second part, open for your questions. And of course, the key opinion leaders will be able to answer them along with me. Olivier Hermine might join us in the middle of my presentation. He is going to present the science behind masitinib, but since he had some constraints, I will actually interrupt in the middle of the presentation and give it to him so that he can walk you through the fundamental science behind masitinib.

So Laurent who is helping me is going to move the slides. So we can go to the disclaimer, of course, as usual, disclaimer for any presentations. And then we go straight to [clinic] I think, and we'll wait for Olivier to join who will present the science, but later.

So I propose that we start with the Slide 8. Okay. So this is the clinical development program of masitinib in Alzheimer disease. This development program is made of 2 studies, a Phase IIa called 4024 and a Phase IIb, which is called 9004, which is the key points, of course, of this presentation.

Then it's important to understand the positioning of masitinib in Alzheimer's disease. There are different, I would say, categories of dementia as we call Alzheimer's disease. The early stage of Alzheimer's disease is called prodromal, then we have mild and moderate then severe. They are classified according to a score called MMSE. Masitinib is developed in mind and moderate Alzheimer's disease, other compounds in earlier phase of the disease, and it's important to understand the position of its compound.

The products registered were registered in late '90s and beginning of the 2000. There were 4, and they are anticholinesterase inhibitors or NMDA antagonist, which is the memantine. And since then, no product has been registered. What is important is to note that the development program is to test masitinib in combination with those compounds, which are the standard of care.

The next slide. Okay. I'm waiting for the system to move to the next slide.

Olivier Hermine

Hello?

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Olivier is there. Olivier, you are there?

Olivier Hermine

Yes. I was there from the beginning, but I could not talk to you with a computer, and only by the phone, but I can wait.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

So Olivier, we are going -- anyway, I have not started to present the results of the clinical study. So I propose if we can, that we start with the scientific rationale back at the beginning of the presentation. And Olivier, you can start with this Slide #3.

Olivier Hermine

Okay. So hello, everybody, and sorry for the problem, I could not reach with my computer. So as you know, we will present some data with masitinib. And first, I would like to say that masitinib is a kinase inhibitor which is taken by oral route, and its target are both mast cells and microglia. And masitinib is a selective inhibitor of c-Kit, Lyn and Fyn kinases, which are critical for mast cell activation. And in addition, masitinib blocks also the MCSF receptor-1, which is very important for microglia and macrophages activation. So by blocking these 2 cells, we do believe that masitinib is a very good compound, which is taken orally to play a role in various inflammatory and neurodegenerative disease.

Next slide, please. So why we have used masitinib in Alzheimer's disease? Because of this mode of action based on 4 targets, which blocks 2 kind of fats. We strongly believe that masitinib play a role in Alzheimer's disease first by modulate the microglia through the MCSFR-1 inhibition. We believe that we may block the microglia inflammation and the distribution of synapse by these mechanisms. Second, we have shown, and I will show you in mice model that masitinib is able to protect synapses lost in Alzheimer's model. Third, it has been hypothesized that the top protein is also related by the Fyn kinase. And since we do block the Fyn, we may expect to block the phosphorylation of tau and aggregation of tau, which might be toxic for neuronal cells in the nervous system.

And finally, by blocking mast cells, which we strongly believe that they are all in the physiopathology of Alzheimer's disease. We may prevent and reduce the consequences of this mast cell activation in the brain.

Next slide, please. So here is to show you some fundamental basic data, which support our hypothesis. In the classical model of Alzheimer's disease in mice, which is APPxPS1dE9 mice model of Alzheimer's disease. We have studied in the Morris water maze model the acquisition of the mice to get food in the water pool. And as you can see here on the right side, the transgenic mice make more time to find the food when you compare to wild-type mice. And interestingly, when we do treat this mice, you see the time to find the food is similar in the transgenic mice or in wild-type mice or transgenic mice treated by masitinib. So here, we show that the treatment of masitinib, they approve the cognitive function of mice.

Next slide. So in other strategy, which I call the navigation strategies, we can see here that the transgenic mice lost its navigation strategies, which is restored by the treatment with masitinib. So here, we show the same thing as I've shown before, that we improve the cognitive function of mice. And in order to understand by which mechanisms, we see this improvement of the cognitive function of mice. We first show that the number of synapse is approved in this model upon treatment by masitinib.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Olivier, sorry, I might interrupt you because I'm not sure, at least on our screen that we see the slide. And I have adopt on the visual.

Olivier Hermine

Okay. I am the Slide 7.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Yes, yes. I know. But we, on our computers, we have a blank slide. And so this is why I ask you just to wait 30 seconds to make sure that we have a visual. Well anyway, Olivier, can you resume the presentation? And...

Olivier Hermine

In 3 bullet points. First, we have shown that masitinib is a transgenic Alzheimer's disease model and prove the cognitive function of this mice. And second, when we look at the mechanism of action, we have shown that the synapse lost is reduced or actually we restore some synapse in the -- in this model by treating the mice with masitinib, which are the key points of the experience that we have done in these models.

And the last experiment, which has been very critical. If we cross this transgenic mice, we develop Alzheimer's disease with mice with no mast cells. And very interestingly, we showed in this cross mice, that in absence of mast cells, there is no development of Alzheimer's disease in this mice, no loss of synapse, no lost of cognitive function.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Thank you, Olivier. Unfortunately, for technical problem -- due to a technical problem, we could not see the visuals, but the message is clear. And the organizers, I would say, of this conference telling us that it will take a little -- a couple of minutes to refresh the presentation so that you have the visual.

So -- but Olivier, thank you. Anyway, I will resume. So we understand why we entered into the front of masitinib in Alzheimer's disease. And we have seen the positioning of masitinib in Alzheimer's disease,in mind and moderate -- in mast cell moderate Alzheimer's disease.

So we -- I said that the clinical development program was made of 2 studies. One study I can describe, even if you don't have the visual because it's the past -- I think the visuals is coming back. So the first study is a Phase IIa, which was published in 2011. And it showed actually, activity of masitinib in 2 variables, which are the key variables to measure efficacy in this disease. The cognition impairment called ADAS-Cog and the daily activity called ADL. And these 2 endpoints are the 2 ones that treatment needs to improve if the treatment wants to be registered. So what we observed in this Phase IIa, which has 34 patients, it was placebo-blinded, is that masitinib was able to control, even improve a little bit the cognitive impairment and the daily active -- sorry, the cognitive impairment and increased the daily activity, whereas the placebo was decreasing as expected.

And on this ground, we entered into a Phase IIb which is the so-called study 9004. Now -- and I'm sorry that you don't have the visuals yet, but still, I'm going to describe the study design. The study design of 9004 was to test masitinib in 3 doses against standard of care, so the anticholinesterase and/or memantine, which were in the 2 arms, and then was randomized masitinib in 3 doses versus their own placebo. So there were control, 1 control, different in each arm. The 3 doses of masitinib were 3 milligram per kg per day, 4.5 milligram per kg per day and the titration up to 6 milligram per kg per day. And the titration arm was randomized 2 to 1, whereas the 4.5 was on the mice 1 to 1. Then what we measured a primary endpoint of Cog and ADL.

And as I said, the inclusion criteria was to include mild and moderate Alzheimer's disease without retraction. MMSE comprised between 12 and 25, so -- which is the definition of mild and moderate. And all standard of care, anticholinesterase and memantine was -- had to be stable. And during the course of the study, the IDMC recommended to stop the 3-milligram arm on the ground of not futility, but less effective, probably, than the other doses and also because it was long to recruit this study. And so that was only that we focus on the 2 other parts.

The statistical test was a -- to say that the study was deemed to be successful if the test on Cog or the test of -- on ADL was statistically significant. So either one or the other, the study was been statistically significant. That means that the risk alpha, which is the risk to have a chance finding was splitted, usually, it's 5%, between the 2 endpoints. So it was to reach a statical significance below 2.5%, was the design of the study. And the population analyzed was the full analysis set. The interim did not consume much alpha.

Then the population analyzed is the following. I'm just going to check if you have the visuals. I fear, no, which is in unfortunate. But still, I'm going to continue. So the -- and anyway, we're going to put the slide through on our Internet site. But just to continue, the population analyzed was for the 3-milligram arm. There were 58 patients which were medically treated. And when we stopped, actually when IDMC has to stop. And the equivalent number of placebo was integrated in the 4.5-milligram per kg arm. The 4.5 milligram per kg arm, at 370 patients in ITT and 358 in the full analysis set. So there were 12 patients that were subtracted from the ITT that I will describe the reasons why.

The titration dose was 278 patients, and the full analysis set was 277. So 1 patient was subtracted. And the reasons for creating this whole analysis set is there were some critical duration of the GCP. Some patients also, 2 patients didn't take treatment. And there were some baseline, which have been reported by the investigators as being actually not consistent with the history of the patients and also some change of caregiver. And they insisted upon the steering committee to not analyze them in the primary analysis, and this is why it was studied from the fast and validated, of course, by steering committee. But we can measure, of course, the impact of those patients in sensitivity analysis. It was multicentric in 21 countries and 51% of the patients were recruited in Europe.

Then the baseline characteristic all show that all variables that could impact the primary analysis were balanced. I'm talking about the age. So the age where the median and the mean were balanced between the different arms. And the population was actually included people from 50 to 90 year old, and 20% of the patients had more than 80 years. It was balanced also in terms of MMSE and the population of mild Alzheimer's and moderate Alzheimer's was equivalent. It was 25 in the different arms. And the mean and median of ADL and Cog was also balanced. And so there was no bias on the baseline characteristics.

And unfortunately, you still don't have the visual. But the primary analysis on Cog, as we said in the press release, was statistically significant with a p-value of 0.0003. So three 0 behind -- after the comma, which was highly statistically significant.

Now I'm going to give you the data, even though you cannot see them. The placebo decline at week -- maybe first, I'm going to explain to you how we calculated the change in Cog. There are -- we use the guideline on missing data that actually tells that we need to impute a value at week 24, even for the discontinuation. And the way we should do is to impute a decline, so to speak, using similar set of patients, the so-called cluster. That's what has been done, of course. And so it's not the last observation carryforward that has been used.

So the data shows that the placebo declined at week 24 by 0.63. When I say a decline, it's a worsening of the Cog of 0.63, whereas masitinib improved likewise in the Phase IIa by 1.51. That was the mean. But we calculate the primary analysis in least square mean, which is slightly different. And then we measure the delta in least square mean, and the delta is 2.15. 2.15 is the change in least square mean of the primary analysis, that must be compared to a [standardization], which was around 5.8, 5.4, which gives a p-value of 0.003 extremely strong.

We did a sensitivity analysis of this primary analysis by using what we call a jump to reference methodology. This jump to reference methodology consists in not imputing a treatment effect for discontinuation due to the treatment, like lack of efficacy or toxicity, but instead, imputing a placebo effect. Because you have a penalty if a patient discontinued due to the treatment, lack of efficacy or toxicity. This is a second guideline called interference event. And we use that as a sensitivity analysis of the primary analysis and the change in LS mean is reduced. Instead of 2.15, it becomes 1.89. But the p-value is still statistically significant with 0.00.6 -- 0.0016. And so we can say this statistical test is robust.

The clinical relevance of such data has to be, of course, analyzed by the experts. And I will leave them to -- leave it to them. But bear in mind that we're not comparing masitinib with placebo, but with the standard of care, which are the use of anticholinesterase and memantine.

In terms of the ADL, the daily activity, the test has a p-value as we reported of 0.0381. And the placebo, as expected, actually worsened and a decrease by 1.09 points at week 24. Whereas the masitinib treated arms at 4.5 milligram per kg improved. Likewise, the Phase IIa at 0.51 points, then we calculate it in least square mean and we measure delta of least square mean, which was 1.82, which gives a p-value of 0.0381, still using an imputation model -- method by cluster.

We -- of course, so it's statistically significant, although the design said 1 endpoint was enough to say that the study was successful. And we did the sensitivity analysis on there either and the sensitivity analysis by using the jump to reference already describe shows a change in least square mean of 1.71, which has a p-value of 0.0512, which is slightly above the 0.05, but still very close. So although it's not statistically significant, it's extremely close.

Then we have to measure the impact of the patients who have not been included in the analysis because we're using the full analysis set and not the ITT. You cannot add back the violators, the critical violations by guidelines, but you can add back the 5 patients that I mentioned where it deemed to have actually baseline characteristics that created by us or a change of caregiver. And of course, this has been screened and checked for all sites, and there were only 5 patients that had this problem according to the sites.

So if you add back those 5 patients, doesn't change anything on the Cog. And on the ADL, then we lose significance, and the data shows a 0.07 p-value. So it has an impact of 5 patients on the ADL, but not on the study because, as I said, the study design is to be below 2.5% in 1 of the endpoint but not the 2 together. So that's the impact of those patients that had been excluded from the analysis by protocol and by statistical analysis plan.

Then we have to analyze the secondary variables. The secondary variables are CIBIC-plus and MMSE and CDR and NPI, and we meter the change at week 24 in those variables. From those variables, secondary efficacy variables, the CIBIC-plus change is statistically significant. The CIBIC-plus change measures 3 categories: improvement, worsening and no change. So it's a basic, I would say, interpretation of the change for the patients. And we can see a statistical difference of 71%. The other ratio is improving by 71% in favor of masitinib with a p-value of 0.04. The other secondary efficacy variables do not show statistical significance, although they show a numerical advantage at each time point, in favor of masitinib showing some forms of consistency.

Then we have to analyze the second part of the study, which was already in parallel with the titration 6 milligram, which has its own control. And as we said in the press release, we have not seen statistical significance in this titration arm. And I hope that you will see the data before -- soon. But anyway, I will give it to you again by description. So we can see, instead of a worsening of the placebo in Cog and ADL, we can see an improvement, which is unusual. There is an improvement for -- on Cog for the placebo and an improvement of the ADL. This is one of the reasons why probably we cannot see a statistical significance for the titration dose.

Remember, the randomization of this titration was not 1:1, but 2:1. And so it reduced the number of placebo to less than 100 patients. That might explain why the placebo has an unusual improvement because there were not enough patients maybe to stabilize, I would say, more classic data. But anyway, that's what we observed.

The masitinib titration is improving, both in Cog and ADL, likewise, the 4.5 milligram, which is consistent. But it's not improving more. Actually, it gives the same mean change in daily activity and less on cognitive function. But we cannot still detect statistical significance for the titrations. But we can already conclude that the titration 6 milligram is not increasing efficacy. And so if there is another study after this study, we should focus on the 4.5 milligram per kg per day.

Because of the divergent effect of the placebo, which occurs sometimes, it was interesting to pool the placebo and to see if the 4.5 milligram per kg dose of masitinib could statistically still maintain an efficacy, statistically significant efficacy on Cog or ADL as protocol. And this is the case. When we pool the placebo, including this unusual effect of the placebo on the titration dose, then we maintain efficacy of a statistical significance of the 4.5 milligram masitinib arm with a p-value of 0.004. So we still have three 0 behind comma, and LS mean change of 1.9, which is close to the

2.15 that we have observed with the proper placebo control of the 4.5. The ADL has a p-value of 0.008. So we are losing some statistical significance here when we pool the placebo.

Then we have another measure, which everybody understands because it's clinically very easy to interpret, which is the percentage of patients which go not to mild and moderate because it's the inclusion criteria, but to severe dementia, which is a threshold of MMSE, strictly less than 10. And severe dementia means that the patients are dependent on people to take care of them permanently, which is a high cost for the society.

And on this criteria, we can see that only 2 patients in the masitinib 4.5-milligram arm have reached this stage, whether the placebo pooled at 15 patients and the statistic is significant with the p-value of 0.004. The add-on ratio 0.19, which means that there are 81% more chance to reach severe dementia with placebo as compared to the masitinib. And we checked, of course, that the low MMSE, the one close to 10. You remember the inclusion criteria started at 12. So we looked at the low MMSE level like strictly less than 14, strictly less than 17. We checked that it was not this balanced and it was not. So we could not explain this is by a bias in low range of MMSE. So this data is interesting, of course, in the context of this study.

Then we move to the safety. And the safety, we had to correct this morning through a press release because the data were not -- were only partially -- fully validated when we attend the first press release, which was focused on the top line of efficacy and which, by the way, is fully validated. Now with a complete validation, we unfortunately detected a mistake. And the correct data has been given this morning through correction, but they are there in these presentations for any of you that could see. But I'm going to give you the numbers.

So what is interesting is the SAE and the severe, of course. And we can see that the percentage of serious adverse events in the 4.5-milligram masitinib arm is 13%. And it is 13% also in the titration arm, and it's 10% in the 3-milligram arm, so not actually strong a difference between the different forms of masitinib. And the placebo percentage of serious adverse event is 5.4%.

The severe -- the percentage of patients with severe AE is 26% for the 4.5, 25% with the titration arm and 19% in the placebo. And you have to know that among the serious adverse events, we have 5%, which are associated with non-severe AE. So they are moderate, but -- or mild even sometimes. But still, there are serious adverse events, which happened in this context in the course of this disease, but it's important to highlight.

Then when we look at the serious adverse events, as per organ class, then you can see this is spread, actually distributed across all organ classes. There is not one category, one organ class, where there are a significant number, a significant increase of serious adverse events as compared to the placebo, including the most frequent adverse events that we know from masitinib, which are the skin tox -- and the gastrointestinal disorders. There is an increase, of course, but it's not significant. For instance, the serious adverse events in the 4.5 milligram arm is 1.6% for skin tox versus 0% for the placebo, 1.6 and the gastro intestinal SAE is 2.2 with masitinib at 4.5 versus 0.4 with placebo. So it's, I would say, distributed across organ class.

Then a few words about the patents. So the patent, as we already reported, has been filed with this data, which could eventually protect masitinib until 2041 in Alzheimer's disease. And the market potential is huge, as you know, in this disease. Unfortunately, Alzheimer's disease affects 2 million people in the United States, the mild and moderate. Mild and moderate Alzheimer disease, 2 million people in the United States and 3 million people in Europe.

The visual is possible. Do you want that we show maybe just the primary analysis, just the primary analysis maybe for the people if they are not been able to see it unfortunately, any -- some slide. It's this one. It's on Slide 17. So -- okay.

So Slide 17, please. So the Slide 17 that we have not been able to see. This is the primary analysis on Cog. So as you can see, a decline of 0.63 at week 24 for the placebo for the mean and an improvement from masitinib 4.5 at 1.51. And the LS mean is slightly different than the mean, the least square mean. The change is 2.15 and the p-value is very strong.

And for maybe just the ADL, can you see the ADL? On the next slide, which is the 18. We'll do -- this is the job to reference. Please, next slide. Yes. Thank you very much. So the ADL, as you can see, a worsening for the placebo of 1.09, an improvement of masitinib of 0.51, a delta LS mean of 1.82 and the p-value, which is statistically significant.

In the course of your questions, I can go back to the slides where, unfortunately, you have not seen the data visually. And I am going to start and open it for questions because those questions -- your questions will be important. And along with the trail, we'll try to answer.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) We have 2 questions. Jean-Jacques Le Fur, you are on live.

Jean-Jacques Le Fur - *Bryan Garnier & Co Ltd, Research Division - Analyst*

Jean-Jacques Laufer Le Fur from Bryan Garnier. I have 2 questions. Unfortunately, Alain, it's difficult to ask question without the data. But I'm a little bit intrigued that the highest -- or there is -- we cannot see any of those effects, perhaps I'm wrong because it's quite difficult to understand that. But it seems this 6 milligram was not superior in efficacy to the 4.5 milligram. So is there any explanation? But I understood the story of placebo, but there -- could there be another explanation?

And my second question is, I understood that masitinib, your trial was more in mild to moderate patients and the competitors like aducanumab were probably on more prodromal. But however, how, perhaps, it's more for your -- for Bruno Dubois, Professor Dubois. How would you position masitinib in this space? And especially compared to aducanumab, for example, for which we already have some data. Many signs?

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Professor Dubois, would you like to take the answer, at least, for the second part?

Bruno Dubois

Yes. Okay. Thank you, Mr. Le Fur, for this important question. I think it's important to have different possibilities because we see the patients at the early stage of the disease, but we see also them at the more advanced stage of the disease. And there is no -- not so many drug to propose. So it's always very interesting to have a new possibility to treat these patients. And I think one of the most interesting results was the fact that apparently, even after 6 months of treatment, there is a slowing down of who are reaching the threshold of MMSE at plan. And I think it's really significant for a clinician to have something, which reduce the entrants in the very, let's say, severe state of the disease.

So it's -- in our portfolio, I think it's -- it may be, if this is confirmed, it may be interesting to us, in addition with treatment which are acting at the early stage of the disease to have some drug that may be effective at a more advanced stage in the disease because, unfortunately, we see patients at this threshold. May I remind you that in general, in France, at least in my country, the MMSE level of those -- of the patients who are diagnosed as having Alzheimer's disease today is around 17, that is very late. And because of that, we see -- most of the case, we see patients at the moderate stage of the disease. So I think it's interesting to have drugs that have developed for this level of dementia.

Philip Scheltens

Can I may add something? Hello? Mr. Scheltens from Amsterdam.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Professor Scheltens, you can go.

Philip Scheltens

Yes. Thank you. I was just listening to Professor Dubois also. I think I totally agree. And just to add to that, I think for the management of Alzheimer's disease in general, we need a larger array of medication in the future. So perhaps, if I ever came to the market in Europe, it will be for the very early patients. There will also be a need to treat these patients in a later stage, as add-on to what we have.

Ultimately, Alzheimer's disease will be treated by a cocktail of maybe 3 or 4 different medications in different stages of the disease and different mode of action, I would say. So yes, we welcome also companies that focus on the later stage of the disease more in symptomatic patients.

Olivier Hermine

Can I add something?

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Yes. Maybe on the (inaudible). Yes, Olivier. Can you...

Olivier Hermine

Okay. Yes, yes, yes. To respond to the question, kinase inhibitor, they may block different kinases, depending on the dose of the treatment. And probably, the kinase that we target like for example, Fyn and Lyn for mast cell activation and MCSFR-1. Using the dose of 4.5 milligram is enough. It's enough to block this target. So if you increase the dose to 6 milligram, you would not block further this kinases. So it is not surprising to not see an improvement of the effect depending on the dose. It contrast when you increase too much dose, you may target other kinases, which might be toxic or potentially toxic or decreasing the mechanical action of the drug. So I think for us, it's not a surprise.

And in addition, as you know, we have some data in MS and in ALS, which show exactly the same pattern of action, is that 4.5 milligram seems to be the optimal dose for this neurodegenerative disease. It may be a different story for a different disease. But here, we strongly believe that 4.5 milligrams per kilogram is enough to block the target the neurodegeneration.

Jean-Jacques Le Fur - *Bryan Garnier & Co Ltd, Research Division - Analyst*

Okay. If I may, may I ask a follow-on question? So it's interesting to see masitinib working on more advanced patients that of the drugs on mild to moderate instead of prodromal. So could we think that masitinib could also work in these earlier stage patients in less than 25 on the MMSE?

Olivier Hermine

Can I -- do you want to respond or can I respond? Or...

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Sure. Sure.

Olivier Hermine

I think that earlier is the better because our drug is not like a regenerative compound, which can use the regeneration of the nervous system, although we may see some new synapse formation in the mice model. So we strongly believe that if we treat the mice -- the human, sorry, as early as possible, we will have a better effect.

Operator

We have another question, Samir Devani from Rx Securities.

Samir Devani - *Rx Securities Limited, Research Division - Research Analyst*

I've got a few, but perhaps, I don't know whether it's possible for you to put that slide deck up on -- I can see it now in our screens. But if you could maybe post that to your website, it would be helpful.

So just in terms of my questions. I guess the first one, just on the clinical relevance of the improvement. I think when you did look at masitinib in the 2011 paper, you looked at doing a responder analysis when with an ADAS-Cog of improvement of 4 decrease of 4. Have you done a similar responder analysis with this data set? So that's the first question. Maybe you want to answer that first.

Bruno Dubois

Philip, do you want to answer about the question about the clinical relevance of ADAS-Cog?

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Yes, Philip.

Bruno Dubois

Philip?

Philip Scheltens

Oh, the question was to me. No, I think the question was actually whether you had done a responder analysis in the current data set. I haven't seen that, but I think that's really relevant to look at. We have to also be mindful that changes in ADAS-Cog, whether it be 2 or 3 points, even with the cholinesterase inhibitors, we have never, as a field, come to the to the sort of real conclusion, is it clinically relevant or not.

In general, my position is that every improvement or even every sort of stabilization is clinically relevant per se. So -- but a responder analysis can give you a little bit more insight in what kind of patients so -- also the number needs to treat and that sort of configures. But I haven't seen that data yet. But as of now, I see comparable clinical efficacy as we are used to with the cholinesterase inhibitors but with a different mode of action.

Samir Devani - *Rx Securities Limited, Research Division - Research Analyst*

That's perfect answer. So I was just going to just ask because that leads on quite nicely to my second question in terms of -- I appreciate that the acetylcholinesterase inhibitors are used a lot. But would it not be -- do you not expect the regulator to ask you to look at this as a monotherapy as well as potentially in combination with existing standard of care?

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Who wants to take this? Dr. Cummings or...

Philip Scheltens

Jeffrey?

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

And -- or you, Dr. Scheltens, do you want to answer this question? So shall we compare with the standard of care, anticholinesterase, memantine or single agent?

Philip Scheltens

Yes. I think we should do that. We should do that because you have to prove that your drug has an added value compared to the standard of care. So I think it's important to have probably, an arm with the standard of care. I think it's a good point.

Samir Devani - *Rx Securities Limited, Research Division - Research Analyst*

Okay. That's great. And then the third question then just on the drop -- this is probably in the slide deck, but I didn't see anything. Could you just tell us what was the dropout rate in each arm on an ITT basis?

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

I will take it. No, it's not part of the data that we showed today. So -- but of course, it will be in the publications, probably in the conference where our key opinion leader will present the data. So just be patient, and you will have the full set of data. Of course, it's to be shared and analyzed. However, what is important is to note that discontinuation are analyzed in safety, of course, but they are analyzed also in efficacy, in particular, in neurodegenerative disease because the guidelines from the agencies is extremely clear. You should absolutely not use last observation carryforward, and you should impute that are up to week 24, even if there is an early discontinuation. Of course, there are more discontinuation in masitinib-treated arm than in placebo, as expected.

And then you need to distinguish the ones which are at random from the watch, which are not at random, so basically, lack of efficacy and toxicity and -- but you need to impute everything. And in the case where at random, you in future treatment effect. And when it's not at random, the so-called interference event, then to register, to register, I'm not talking about the primary analysis in this particular -- to register, you need to show a significant effect even with the penalty of the discontinuation, not at random, and this is what we call the jump to reference. And in this study, the jump to reference, which is a sensitivity analysis, that might be used by the regulators as the primary analysis is positive. It's positive in a sense, the p-value is very strong. So this is reassuring.

Samir Devani - *Rx Securities Limited, Research Division - Research Analyst*

Okay. And then my final question is on the mechanism...

Jeffrey Cummings

This is Jeff. Can you hear me now?

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Yes, we can hear you. You can comment.

Jeffrey Cummings

Sorry, I just wanted to comment on the last question. The difficulty of performing trials are not on the standard of care. It's very difficult. So that's why it's so important that the drug succeeds in combination therapy.

Bruno Dubois

Yes. Because the reason is that it is very difficult to include patients with no added -- with no regular treatment. So it will be very difficult to do that.

Samir Devani - *Rx Securities Limited, Research Division - Research Analyst*

I totally accept that. I'm just wondering whether there's been any regulatory dialogue in terms of whether the FDA would ask you to look at it as a monotherapy, even in a small group, just to see if there was a single drug effect. But that's fine. I'm quite happy with that response.

My final question is really just on the mechanism of action, which you sort of speculated you have potentially an impact on tau. Did you look at tau in this study?

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Olivier, you wanted to take the...

Olivier Hermine

Yes. I didn't understand the last part of the question. Can you...

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Did we look at tau -- the impact on tau in the studies?

Olivier Hermine

No. No for the patient and no for the mice because there was not a tau [different] model. So I think it is a very interesting question. We should look at the foresaw position of tau in the CNS or even the peripheral one, which is possible now to see if we do reduce, indeed, as the top consolidation. But we haven't got the data yet.

Philip Scheltens

I would just add to that. Philip here. I would just add to that, that it will be really interesting to look at NfL, neurofilament light, also in plasma of these patients. And especially since you are dealing with a drug that is also working in MS and ALS, and in all those diseases, NFL is an important marker of neurodegeneration. So that is something that we can take into the next study as well and perhaps, go back in the study that was just performed.

Operator

Yes. We have another question from [Usan Algodones].

Unidentified Participant

So very quickly, I have 2 questions. So the first, how do you see the Phase III now in terms of patients? And also against whom you will complete, if I may say so. I guess it will not be possible for standard of care, maybe in other treatment. Just a couple of hints about this Phase III, how do you see that?

And my second question is about your sincere view opinion today for these kind of patients. Do you believe MCSFR-1 is -- would be the best you've ever seen so far or not for this -- from this striking score that you have today, 4.5, which is the same, I think, in ALS? Yes. So that's all my 2 questions.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Probably each of our key opinion leader could express themselves on such a question. So who wants to start on the design of the future of Phase III? Of course, it's not done yet. We just discovered this first study, but -- and against what comparator who we compete against. So Jeffrey, you want to start? And then everybody will maybe try to answer.

Jeffrey Cummings

Yes. So I'll give a preliminary set of ideas. The most -- the strongest predictor of a successful Phase III is a successful Phase II. So we would try to stay very close to the parameters of the Phase II trial in the Phase III trial. I think the technology of doing trials has improved very significantly since this trial was designed and we'll introduce those new changes.

Bruno Dubois

Yes. I would like to reinforce the point from Jeffrey. And I think that, of course, we will have to introduce the concept of biomarkers in order to make sure the patients do have Alzheimer's disease. So to improve the quality of the improved patients and to probably stick on the 4.5 dose. And also, maybe we can think about based on what Olivier said, probably to try to enlarge a little bit the increase to early stage of the disease. So mostly, this will be the main features of this new trial, if you want to do that.

Philip Scheltens

Yes. Philip here. There's nothing really for me to add. I mean, although the sort of sensible things have been said. I think this is actually the challenge. I think it has to be done probably against a comparator, which is now standard of care with the cholinesterase inhibitors. And I think it's ultimate the proof of the imputing is whether it's better in addition to the cholinesterase inhibitors. And of course, the biomarkers are, as Jeff said, this is now standard. So we have to include them not only for diagnosis but also for a treatment efficacy over time.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Thank you. Shall we take another question?

Operator

For the moment, we don't have any questions online. (Operator Instructions) We have a new question from [Ana Grund].

Unidentified Participant

I have a question on intermediate time points. Did you have a week 12 or week 18 ADAS-Cog and ADL?

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

I will take the answer. It's not part of the design. Of course, we have visit patients, so we can still look at that. But it's not part of the tactical analysis plan. Although -- also keep in mind, we impute all data anyway. So the week -- it's interesting, of course, to see the measure at week 8, at week 12, at week 24 to see the evolution. But all data are imputed anyway at week 24. We'll look at it.

Unidentified Participant

Yes. Normally, we would show the curves over time. And I think curves are also telling the story. So I think I would just recommend to show that as well.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

I think in the publication, we will do. But for this presentation, we -- at this time, just time to release the top line, the primary analysis, the sensitivity, some key secondary and basic safety, which by the way, we didn't have time to analyze properly. So we are just at the beginning. We just received the data and the rest will be done, as usual, with the correct methods, and you can -- you will see what you request, but a little later.

Bruno Dubois

I'm sorry because I have to leave. I have another meeting now. It's Bruno Dubois. So I'm sorry to leave, and I hope the meeting will follow the good way. So bye-bye, everyone.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Professor Dubois, thank you very much for your presence, and thank you from AB Science.

Bruno Dubois

Bye-bye Philip, and bye-bye, Jeffrey. Take care.

Philip Scheltens

Bye-bye, Bruno.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

There are other questions?

Operator

We don't have any questions for a moment. (Operator Instructions)

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Maybe I...

Operator

I'm sorry. We have another question from [Emily Diamond].

Unidentified Participant

I'm not sure why it's not going through on the online platform when I tried to ask a question, but I was just curious how many of the subjects had mutations associated with familial or early onset Alzheimer's disease.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

I'm not sure. Personally, I'm not well understood your questions. Can you rephrase?

Unidentified Participant

In -- how many of the treatment group subjects, in particular, had the mutations associated with early-onset Alzheimer's disease or familial Alzheimer's disease? So mutations in the APP? Or...

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Understood. We don't know because we didn't measure it. When we started in 2012 study, it was not part of the design. And I'm afraid we don't have the samples to do it now. So unfortunately, we don't -- we cannot answer this question.

Jeffrey Cummings

It's highly likely that there were none since those mutations are so rare. But it's possible that in that 10% very early onset patients included that there were maybe 1 or 2.

Operator

We have another question from the number ending by 1-9833.

Unidentified Participant

(foreign language)

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

I would translate in English because our participants are not all understanding French. But I don't understand your question. Your question is when are we going to introduce the first one? I mean, when do we expect to register to have the first registration? Is that -- is it your question?

Unidentified Participant

Yes. Exactly my question.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Okay. So I'll take it. And the answer is we have -- we don't know. And we have different programs. And we said that the confirmatory study in other indications in Alzheimer will come in early 2023 in ametropic lateral sclerosis and mastocytosis.

Now if we focus on Alzheimer, and we try to build a plan ahead, then we can estimate. We're going to restart as soon as possible. But after having carefully designed a new study with the KOL, both Europe -- I just continue. So we're going to restart a complementary study in 2021. We think we could complete recruitment end of 2022. It's a 6-month time point. So we could actually add the results in '23. And then we'll see which one is...

(technical difficulty)

I don't know -- hello? I don't know if -- I may ask the conference operator here. Hello?

Operator

Yes. We can hear you, sir.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Yes, but there is this ringing.

Operator

Yes, I know.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

If you can stop that. Anyway. Let's take another question.

Operator

Yes. [Mr. Intu], you are online.

Unidentified Participant

Yes. So the recent months, you guys generated a positive data in multiple indications. So I just want to know how we're going to prioritize your indication for further studies? And which indications do get approved first? Are you going for ADL first? Or you're going (inaudible) first?

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Again, it was hard to understand you. Can you rephrase slowly?

Unidentified Participant

Yes, yes, yes. So because we follow your molecule, we would know you guys had a positive data in several indications, ADL, mild and also other indications. So the question I have is, how are you going to prioritize your future studies? And which indication you are going first? Yes.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Yes. Well, some studies have already started their confirmatory program, which is the case in amyotrophic lateral sclerosis and mastocytosis. Now we have recently received several good news, several positive Phase IIb, and they are asthma, severe asthma, there is multiple sclerosis, progressive forms, pancreatic cancer and now Alzheimer. In 12 months, we received 4 additional Phase IIb, so to speak, positive data, which legitimates your question.

So what are we going to do next? In asthma and pancreatic cancer, we have 2 studies in the program already. So we are going to discuss with the authorities the possibility to file. That's what we publicly announced. If we have the possibility to file, we file. If we do not have, then we will start again. For progressive forms of MS and Alzheimer, it's obvious. We have to do another one. So that's what we're going to do.

Now if you ask me what's the priority, they are very important, each of them. But if we had theoretical, I would say, questioning, to select few, we would focus on the neurodegenerative programs, which is made of what we call the Trilogy internally, ALS, progressive forms of MS and Alzheimer. And why? Because this is where probably masitinib brings an innovation by focusing on innate immune system in unmet medical need, which has deficit for the last 20 years, most, if not all of the programs, okay? So that's our focus, it's neurodegenerative disease. But we are not going to pursue the other ones, we're going to continue them. So that's my answer.

Now maybe what we can do is just speak about the innovation, the mechanism of action, what makes it different. I don't know if Olivier is still there.

Olivier Hermine

Yes, I'm still here. Yes, yes, yes. I'm still here.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Do you want to say a word about the concept, innovation of masitinib in neurodegenerative disorders, which is Alzheimer, progressive forms of MS and ALS? Because we think it's important. This is the third data. We think it's important.

Olivier Hermine

I think which is really important is that because we have 2 questions related to the fact that we do a lot of different studies, but all of them are related to the blocking of mast cells and probably microglia and macrophages. It might be true in [NFPA] in cancer and in neurodegenerative

disorders. And we have shown, and I think it's very important that all of these neurodegenerative disease, these are, in fact, inflammatory disorders associated with innate immune cell activation, including microglia and mast cells. And by doing so, the cells may kill the synapse in the brain or eventually, in the periphery or in the spinal cord to induce Alzheimer's disease and ALS and MS.

So I think we think that all of this is are related to the same mechanism of action, which is blocking some kinases, which play a critical role in all of this neurodegenerative disease at different levels and probably because some abnormal proteins may activate some signaling pathway in mast cells and microglia, which, in turn, may keep these neuronal cells. And so if we block this activation, we may reduce the keeping of neuronal cells.

So interestingly, as we discussed before, as early as we treat this patient, expect there will be the result. So I think it's a very unique mechanism of action in the new development drug that has been shown in previous trials in neuro cell disease.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Thank you, Olivier. I think we'll close soon because it's already more than 1 hour and 15 minutes, unfortunately, extended by some technical problems. But before, I would like that we leave the -- each KOL, their -- Professor Dubois left, but the possibility to say something about their, I would say, insight or the truth, they receive the data very shortly. So they don't have everything, of course, but still to have their opinion about this preliminary data. We'll call it like that.

Maybe, Jeffrey, if you're there, you start and then Philip can talk. I'm not sure, maybe Philip first.

Philip Scheltens

Yes. Let me start. Philip here. I have to go to as well. But I'm -- as always, I'm very happy to see a Phase II properly conducted. I think that's number one. It's also very encouraging that we have some positive results. The safety, we have to look into a little bit better. And I think this is -- this warrants exactly thinking about Phase III with the proper dose and the proper population over a longer time period.

But as of now, I think the mode of action is unique. It's also encouraging to see new modes of action being pursued and doing properly Phase II studies. And so I'm all into seeing the Phase III still being designed and carried out. And in that sense, I'm optimistic.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Thank you, Philip. Jeffrey, do you want to give your insight? Maybe Jeffrey is -- because I know he's there, but maybe has a problem, too, with the connection -- the voice connection. Maybe Olivier, if you are still there, if you want to give an insight or opinion.

Olivier Hermine

I mean, I said before, what I said, but I think we bring some new way and new vision of the physiopathology of the disease, which include the mast cells and microglia activation, and we had a good drug to block this activation. So it's a very good safety profile. And also I think we opened a new way to explore this neurodegenerative disease.

Alain Moussy - *AB Science S.A. - Co-Founder, Chairman, President, CEO & Scientific Director*

Okay. Well, if Jeffrey cannot say something, maybe we'll stop there. I would like to thank you all, the participants, the KOL and the organizer. It's -- we will solve the technical problem by putting the slide show on the Internet site so that everybody can access it and see the data.

We commit to continue developing this drug in the different indications, and Alzheimer is probably a top priority. Of course, we are very happy that masitinib through this targeting of innate immune system might be a response to this health problem. And we'll prepare this space reactively with our care that we think very much again. Thank you, all. And we'll stop there.

Operator

Ladies and gentlemen, this concludes the web conference. We are very sorry for the technical issues encountered. Thank you for your participation. You may now disconnect.