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ADXN.S - Addex Pharmaceuticals Ltd Reports Positive Top Line Phase IIa Data for Dipraglurant in PD-LID Conference Call

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CORPORATE PARTICIPANTS

Chris Maggos *Addex Therapeutics - Business Development and Communication*

Bharatt Chowrira *Addex Therapeutics - President, CEO*

Charlotte Keywood *Addex Therapeutics - Chief Medical Officer*

Olivier Rascol *University of Toulouse - Coordinating Investigator, Professor of Clinical Pharmacology*

CONFERENCE CALL PARTICIPANTS

Juan Sanchez *Ladenburg Thalmann & Co - Analyst*

Gregory Wade *Wedbush Securities - Analyst*

Robin Davison *Edison Investment Research - Analyst*

Peter Welford *Jefferies - Analyst*

Samir Devani *Nomura Code Securities - Analyst*

PRESENTATION

Operator

Ladies and gentlemen, good afternoon. Welcome to the Addex Therapeutics conference call. I am Goran the conference call operator. I would like to remind you that all participants will be in listen-only mode and the conference is being recorded. After the presentation, there will be a Q and A session.

(Operator Instructions)

The conference must not be recorded for publication or broadcast.

At this time, it is my pleasure to hand over to Mr. Chris Maggos. Please, go ahead, sir.

Chris Maggos - *Addex Therapeutics - Business Development and Communication*

Thank you, operator. Today, our President and CEO, Dr. Bharatt Chowrira and Chief Medical Officer, Dr. Charlotte Keywood will provide an overview of the promising Phase IIa data on Dipraglurant in Parkinson's Disease - Levodopa Induced Dyskinesia, or PD-LID, that Addex announced last night.

In addition, we are honored to have been joined by Dr. Olivier Rascol, the coordinating investigator and professor of clinical pharmacology at the University of Toulouse. He is one of the world's leading experts on treating Parkinson's Disease, and will join us for the Q and A and make a brief statement.

Bharatt, over to you.

Bharatt Chowrira - *Addex Therapeutics - President, CEO*

Thank you, Chris. Hello, everyone. We are very excited about the Phase IIa data for Dipraglurant, and specifically achieving the primary objectives of safety and tolerability in this study. Equally encouraging, we also started to see promising improvement in Dyskinesia severity in these Parkinson's patients who suffer from this debilitating condition.

As you may know, Levodopa is the gold standard for Parkinson's Disease, but it's often sparingly used in the early stages of the disease due to the fear of inducing Dyskinesia in patients.

There are no approved treatments for PD-LID. We believe an effective anti-Dyskinesia agent, like Dipraglurant, has the potential to change the way Parkinson's Disease is treated because physicians will be able to use Levodopa earlier on in the disease process and more effectively for longer duration during the course of the disease.

With this promising positive data in hand from our Phase II trial, we will accelerate our ongoing partnering activities with the goal of bringing a partner on board before the end of the year.

I would like to now turn the call over to Dr. Charlotte Keywood, Chief Medical Officer, to provide a more detailed overview of the data. Charlotte?

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

Thank you Bharatt. Well, yes, as you've seen the press release the data for Dipraglurant are very promising and we think they demonstrate robust clinical proof of concept. We found that both Dipraglurant doses had good safety and tolerability and, as Bharatt mentioned, demonstrated some early indications of efficacy.

So, just to orientate you a little bit through what was contained in the press release, let me just take you through the study background. We conducted a double-blind, placebo-controlled outpatient study in 25 sites that were split evenly across the United States, France, Germany, and Austria.

Now, this being a first in patient study, the primary objective, of course, was to demonstrate safety and tolerability in this patient population.

Exploratory efficacy was a secondary objective, and measured in two principle ways. The first way was a kind of observer-rated objective score of Dyskinesia severity using the abnormal involuntary movement scale; and secondly, we look at the patient-reported Dyskinesia severity in patient diaries.

Randomization was such that we had 52 in the Dipraglurant group and 24 in the placebo group. The patients had moderate or severe PD-LID. The study treatment duration was four weeks and patients followed a dose titration regimen, receiving 50 milligram doses up to three times a day in the first two weeks of the study until day 14; and then from day 14 to day 28, they escalated to 100 milligram dose regimen, finally ending up at the beginning of week four on 100 milligrams three times a day. The vast majority of the patients in both treatment groups were able to follow the entire dosing regimen and completed the dosing regimen as foreseen in the protocol.

Regarding the safety and tolerability, both dose levels, 50 and 100, were well tolerated and there were no safety concerns arising from any of the safety monitoring parameters. And these include things like heart rate, blood pressure, 12-lead ECG, and of course, blood tests. And in particular, there were no effects on liver function tests with this compound. Everything was completely normal.

Of course, we did see adverse events in the study and they were a little bit more common in the active treatment group than in the placebo. But, as you can see, they were very common in both treatment groups, being 88.5% in the Dipraglurant group and 75% for placebo.

We did see a few typical mGluR-type adverse events, such as vertigo, blurred vision, and a sort of drunk feeling in the active treatment group, but these were not severe and did not compromise the use of the drug at all.

Looking now at the sort of exploratory efficacy data, as I said, we have two ways of looking at this. And the first one was the in-clinic, objectively observed observation of Dyskinesia severity using the abnormal involuntary movement scale, which is known as AIMS. What you do, you bring the patient into the clinic and you give him their standard dose of Levodopa. And in this study, we asked the patients to choose a dose of Levodopa that they take in the middle of the day that was habitually associated with troublesome Dyskinesia. We sit them down, give them the Levodopa

and then we provoke the Dyskinesia by asking them to subtract serial sevens from 100, which is, actually, once you get past 86, it gets really quite challenging. And this way, it takes their mind off what they're doing and it provokes the abnormal movement.

Then you look at seven body areas - the face, the neck, the trunk, and all four limbs, and you score that from zero, which is obviously no Dyskinesia, through to four, which is severe. So that at any time point you have a total score of 28. We did this every 30 minutes over the three hours during the post Levodopa dosing period so we could construct an entire curve of the evolution of Dyskinesia following Levodopa therapy.

This was done on four occasions. First of all, on day zero, which is before the patient was randomized for study medications. That gave us the baseline of Levodopa Dyskinesia. And then on the first day of study medication, which that was when they received a 50 milligram dose. And then again on day 14 and on day 28. And on those two days, they were taking 100 milligrams of Levodopa. And in that way we could look at some dose responding for the drug.

We were looking to get a 30% reduction in the AIMS - peak dose AIMS - or the AIMS over the three-hour period, the AUC over the three hours in the active treatment group, compared to a 10% reduction in the placebo group.

So, when we looked at the data, we did achieve our target reduction in the whole three-hour period in the Dyskinesia severity. We got a 30% reduction in the AIMS, AUC, and also the peak dyskinesias at day 14 and at day 28. And the reduction over a three-hour period, the AUC from naught to three hours in the Dipraglurant 100 milligram group was statistically significant at day 14.

We also looked at the peak dosings. And this is something that clinicians like to look at when the Levodopa is at its peak of activity, about 60 to 90 minutes after dosing. We like to look at the Dyskinesia severity at this particular time point because that's usually when the patient is most affected. So, again, we looked at that. And on day one we saw a 19% reduction in peak dosings, compared to 4.1% in the placebo group, which was statistically significant. And that shows us that the 50 milligram was already producing effect. On day 14 and day 28, again, we saw this 30% reduction in peak dose AIMS severity. On day 14 the placebo response was 12.6%, so that was statistically significant. However, on day 28, the placebo response did increase to 21.5%, and so we did not achieve statistical significance on that day.

Out of interest in our study, we included deep brain stimulation in patients. These are patients who have severe Parkinson's Disease and have a kind of electronic device implanted in the brain. It's almost like a pacemaker in order to improve their Parkinsonian symptoms. And often, it can improve Dyskinesia. But we had included patients with DBS who continue to have Dyskinesia because we wanted to see whether we could, in fact, have some effect on those patients as well.

When we included those patients in the covariant analysis, it didn't affect the outcome. So, what this means was that, in fact, in this small group of patients that Dipraglurant was as effective in this group as it was in the overall treatment group. So, again, studying DBS patients in the future would be of interest.

For those of you who can remember our previous talks about the MPTP macaque monkey model that we did, when we studied that model, in fact, Dipraglurant had an effect on both components of Dyskinesia, both rapid chorea-form movements, but also the slow, writhing dystonia movements. And in this study we wanted to look to see whether we could have an effect on Levodopa induced dystonia. Now in fact, in patients, Levodopa-induced dystonia is rather more uncommon than the chorea-form movements. So we only had a small sample of patients in which to look at dystonia.

Nevertheless, although we only had a total of seven patients, we were able to build a qualitative view of the effects of Dipraglurant on Levodopa-induced dystonia. We had a look at the peak dose mAIMS and also the mAIMS curves. Qualitatively we could see that, in fact, Dipraglurant was behaving the same way on the dystonia patients as it was on the chorea patients. So, again, this is encouraging. It's not conclusive, but it's quite encouraging that we were mimicking the effects we'd seen in our pre-clinical model it was translating into the patients.

Now, an important feature, of course, of treating Dyskinesia is that you don't affect Levodopa efficacy. So, while we were doing the mAIM scores in the clinic, at the same time we were evaluating the motor function of patients by using the UPDRS part three. And on each of the four testing occasions during the AIM scoring, we could see there was no detrimental effect on the Levodopa efficacy. The UPDRS part III motor scores remained unchanged at all treatment visits.

So, Dipraglurant had effect without having a detrimental effect on Levodopa.

That was the sort of in-clinic observer way of looking at Dyskinesia. But in addition to that, we had some patient-reported outcome looking at diaries. And what the patients did is they collected information in diaries for 48 hours every week for five weeks. So, first of all, in the pre-treatment, the baseline screening period for 48 hours, and then again at the end of week one, week two, week three, and week four of treatment. Every thirty minutes, the patients marked in the diary whether they were asleep (once they'd woken up); whether they were in "off" - and when they're in "off," that means their Levodopa is not working and they're frozen and not moving and they have impaired motor function - and then whether they were in "on." And, if they were in "on" that is, they were able to move, and whether or not they were being troubled by Dyskinesia.

So, from this we could build a pattern of looking at the effects on "off" time to make sure that we weren't compromising Levodopa efficacy, because if we did that, that would increase their "off" time, their frozen time. But also we can get an idea of how much time they were spending in Dyskinesia and whether we can actually reduce the amount of time that patients experience Dyskinesia.

We measured this, as I said, at the end of each week. So, in the first two weeks we were getting information about the efficacy of the 50 milligram dose. And in the second two weeks we could get information on the efficacy of the 100 milligram dosing regimen.

So, the first point about the diary gauge, again importantly, there was no increase in "off" time. So, once again, we were showing that we were not impairing Levodopa efficacy by using Dipraglurant. And in fact, quite intriguingly at week four, the "off" time in the Dipraglurant group actually decreased by 50 minutes per day. So, this may suggest some anti-Parkinsonian effect and actually is consistent with some of the animal data that exists that we and others have done, that also shows that the mGluR5 inhibition mechanism may have some anti-Parkinsonian effect, per se.

So, that is something that is of interest and would warrant further exploration in future studies.

Of course, the other thing we showed was that patients taking Dipraglurant have a greater increase in the amount of "on" time without Dyskinesia. So, the daily burden of Dyskinesia was being reduced by the use of Dipraglurant and to a much greater extent than that of placebo. It was up to a two-fold increase in "on" time without Dyskinesia in the active treatment group compared to placebo.

And, again, we saw an effect in both the 50 milligram the first two weeks of treatment, the 50 milligram dose group, and the 100 milligram dose level as well.

So, this combination - potential decrease in "off" time and having "on" time with a decrease in Dyskinesia potentially could translate into very interesting benefits for patients in the future if these findings are supported in further large scale trials.

And finally, we asked - we had to do a patient and clinician preference. That's the last piece of the jigsaw. We asked patients and clinicians at the end of the study, "Compared with before you started medication, how are your Dyskinesia symptoms now?" And both patients and clinicians tended to prefer Dipraglurant treatment. More patients and clinicians in the Dipraglurant group were reporting improvement in Dyskinesia symptoms in that group.

So, the three pieces of the jigsaw fit together.

So, in summary, I think these data for Dipraglurant are positive and we're pleased to have demonstrated robust proof of concept. Both doses of Dipraglurant had a good safety and tolerability profile, and both have demonstrated efficacy. This increase in "on" time without Dyskinesia, potentially combined with a decrease in "off" time seen at week 4, is very encouraging and certainly warrants further evaluation.

And it's particularly promising that the significant reduction observed in the clinical with Dyskinesia severity on the AIMS is actually mirrored by a patient-reported reduction in Dyskinesia in their daily life in their dairies.

That's the summary of the study. And I'd like to just ask Professor Rascol to make perhaps a few comments about the study.

Olivier Rascol - *University of Toulouse - Coordinating Investigator, Professor of Clinical Pharmacology*

Well, thank you, Dr. Keywood. I'm pleased to be here today to discuss this exciting new approach for treating Parkinson's Disease. As you may know, we have no officially approved drug for the treatment of L-Dopa induced Dyskinesia in Parkinson's Disease. Many of our patients are affected by these adverse response to Levodopa and this can limit the way we are managing the patients. So, this study by Addex, I think that we agree that the proof of concept findings show that a) the primary was met and b) the drug was safe and well-tolerated. And there are also some secondary efficacy proof of concept indications that there is something to work on in the future and that warrants further investigation of Dipraglurant in the treatment of Parkinson's Disease.

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

Thank you. Thank you very much. Bharatt?

Bharatt Chowrira - *Addex Therapeutics - President, CEO*

Thank you, Professor Rascol. We are honored to have you with us today.

As you have heard today, there is a huge unmet medical need for the treatment of PD-LID. In addition, Dipraglurant has broad potential for treating Parkinson's and other diseases. We believe the most direct path to market is the treatment of PD-LID. Regulatory authorities, patient advocacy groups such as the Michael J. Fox Foundation, which by the way has supported this clinical study, and key opinion leaders, all consider PD-LID to be a very debilitating condition that needs to be addressed urgently.

We believe that Addex is at the forefront of the effort in developing this potential breakthrough therapy, which could change the treatment paradigm for Parkinson's Disease. Also, based on our market research, the potential market opportunity for Dipraglurant in Parkinson's Disease is well in excess of $1 billion. Further label expansion outside of Parkinson's Disease, such as treatment of non-Parkinsonian dystonia, could more than double the Dipraglurant peak sales potential.

As a result, we think that Dipraglurant is a compelling partnering opportunity. We are now seeking a partner with the vision, expertise and capability to fully exploit Dipraglurant's attractive commercial potential. This data also serve to, importantly, validate our approach to drug discovery and development. We are pioneering the discovery and development of small molecule allosteric modulator based drugs against targets that were previously considered undruggable, such as the mGluR5, which is the target for Dipraglurant. While Dipraglurant is our most advanced product, we also have another product, ADX71149, an mGluR2 positive allosteric modulator, in Phase IIa clinical development for the treatment of schizophrenia.

This study is being carried out in collaboration with our partner, Janssen Pharmaceuticals. We hope to report Phase IIa schizophrenia data from that ongoing study later this year.

In addition, we plan to file an IND for a new clinical program for pain and overactive bladder later this year.

We look forward to continuing to execute on our strategy and look forward to sharing our progress on a regular basis.

Thank you very much for your time. Operator, please open the call for questions.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions)

The first question is from Mr. Juan Sanchez from Ladenburg. Please go ahead.

Juan Sanchez - *Ladenburg Thalmann & Co - Analyst*

Good afternoon, guys, and congratulations. I have a couple of questions for Charlotte. The first one is if you guys difference in adverse events while the patients were taking 50 milligrams versus 100 milligrams? Whether you thought about the dose in terms of future trials? And in the Phase I program, what was the MTD, the maximum tolerated dose?

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

Yes. Well, we're actually still waiting for the full breakdown between the 50 and 100s. So, the AE incidents, I've given you those for the whole treatment period through the whole four weeks. So, the precise breakdown between the two doses has yet to come in. But I think the point was that it was well-tolerated.

And to go on to your question about the maximum tolerated dose. In fact, in Phase I, we didn't go to the full MTD we went up to 500 milligrams in a single dose in Phase I. And for a variety of reasons we decided not to go any further because we went into formulation development activities. And so even up to 500 milligrams the compound was well-tolerated, although up at that dose level we were getting the sort of classic mGluR5 type adverse events, certainly important at that dose although there, again, were no safety findings. So, things like heart rate and blood pressure and ECG were completely unaffected. We were just getting the CNS type side effects.

Juan Sanchez - *Ladenburg Thalmann & Co - Analyst*

And the second question is for Dr. Rascol. If you are familiar with the Novartis drug AFQ056. How would you profile this drug so far against the Novartis drug?

Olivier Rascol - *University of Toulouse - Coordinating Investigator, Professor of Clinical Pharmacology*

Well, that's an important and interesting question. At this stage, it's difficult. You know, they are targeting that mechanism of action which are quite similar. But the elimination half life profile is different. We don't have, I think at this stage, a full understanding of the dose range for either drugs. And I think that it's interesting that in that program to see that on the first day at 50 milligram there was already the signal of an effect and a difference from placebo. So, I know that everybody will be interested in these kind of comparisons. But the data in patients are quite preliminary. There's been a larger study which is in the process of publication and has been released as abstract with the Novartis compound. And still, the dose response is not very clear and to my understanding there will be further work on the dose response by Novartis.

The safety profile is from small numbers and limited follow-up, I don't think that we can separate, really, things at this stage.

Juan Sanchez - *Ladenburg Thalmann & Co - Analyst*

And one final question for Dr. Rascol. Is that 30% reduction in AIMS likely to be clinically meaningful? Or what do you see a clinically meaningful result being? (inaudible - multiple speakers).

Olivier Rascol - *University of Toulouse - Coordinating Investigator, Professor of Clinical Pharmacology*

Well, this is also an important question. Probably you are aware of the fact that the Michael J. Fox Foundation has been funding a study which will try to assess the response of different scale for Dyskinesia in patients with Parkinson's Disease, and also define the minimally clinical important difference. I think that at this stage, 30%, and especially if you notice in that study the baseline score is 12 out of a maximum score of 28. So, these

are relatively, more than moderate, I would say relatively severe Dyskinesia at baseline. If I recall, where in the number of other studies the baseline with the AIMS was something like six to eight at baseline. So, I think these were patients with significant Dyskinesia. And the 30% reduction probably is, in my view, something which is clinically relevant.

Again, I would say that we have to refine with this compound what is the dose range in terms of efficacy. But for a first proof of concept trial, 30% is, I think, a good signal.

Juan Sanchez - *Ladenburg Thalmann & Co - Analyst*

Thank you guys.

Chris Maggos - *Addex Therapeutics - Business Development and Communication*

Thanks, Juan.

Operator

The next one is from Mr. Gregory Wade from Wedbush Securities. Please go ahead.

Gregory Wade - *Wedbush Securities - Analyst*

Good afternoon. Also, thanks for taking my questions. And congratulations on the results.

Dr. Rascol, could you help us to understand throughout the day of a patient with Parkinson's Disease? How long are they typically "on" and "off?" And then in terms of time, what's the duration of Dyskinesia they usually experience?

Olivier Rascol - *University of Toulouse - Coordinating Investigator, Professor of Clinical Pharmacology*

Okay. It depends on the stage of the disease. It depends also which kind of patients you are selecting. In general, for patients who are in their first year of treatment, it takes time before they get "off" problem in Dyskinesia. So, in the early stage they spend their day quite stable and with a good response. Some 10 or 15 years ago when we have been looking at our patients on Sinemet, the Dyskinesia incidence was about 10% a year. So, that means that after five years of treatment with Levodopa, 50% of the patients get Dyskinesia. And then there is a trend over longer follow ups that the problem will worsen in time of the day spent with Dyskinesia and in terms of severity of the Dyskinesia. In other ways during the early phase of Dyskinesia are just mild, they might be aesthetic, but they do not really have an impact on patients' function and in a (inaudible) of subject. And especially those who are with the younger onset, then dyskinesia can become as troublesome as the "off" problem.

These patients have the problem that it's the same kind of subject who gets at certain time of the day "off" problems, and when they are "on," Dyskinesia. So they are switching from "off" time to back "on" because of Dyskinesia. In the clinical trials when we are looking at these populations overall it's the mean time spent "off" range between five and six hours. So, it's not (inaudible) in terms of time spent "off." and time spent "on" in Dyskinesia it's also something between about five hours. And on the diaries you can also decide if Dyskinesia is considered as troublesome or not troublesome, because when patients have a choice, they rather like to be "on" at the price of Dyskinesia than "off." But if you offer them the option of being "on" without Dyskinesia, obviously it's better to be "on" without Dyskinesia.

And the discussion about the impact of Dyskinesia on quality of life functioning, et cetera, is also a matter of discussion. In the elderly, maybe Dyskinesia might be a lesser problem. But in more active younger patients they become rapidly more disabling with an impact even on cost of care of the patients. It's what we call moderate to advanced patients with Parkinson's disease, most of them get these problems.

Gregory Wade - *Wedbush Securities - Analyst*

Thanks so much. Just a follow-up. The increase of "on" time with Dyskinesia was obviously very notable. Would there be any benefit or is there a potential that the drug could be Levodopa-sparing and would that have any short or longer term benefits to the patients? Thanks.

Olivier Rascol - *University of Toulouse - Coordinating Investigator, Professor of Clinical Pharmacology*

I think it's too early to say. It's a pilot study so there are a number of secondary endpoints, which are just fishing for signals. Obviously, one of the signals I was interested in is that looking at the diaries, at the end of the study there is some reduction in the time spent "off." And of course, it's a small number of subjects for follow-up, so we have to be cautious in extrapolations. But, still, it's considerable that this compound might not just improve Dyskinesia but also might have a positive impact on Parkinsonian symptoms per se.

So, that would be idea if the drug can minimize Dyskinesia when the patients are "on" and minimize or reduce the time spent "off," that's an ideal profile. It has to be explored. And, again, it might be an issue for dosing. It might be that at a certain dose you might have more anti-Parkinsonian response and at another one more Dyskinesia response. But, overall, the first thing that was important to notice is that there is no evidence that adding this compound to Levodopa therapy compromised the benefits of Levodopa on Parkinson's symptoms. And the signal that there is less "off" in the diary might be an indication of the opposite. And if this is true, that would be quite exciting and interesting.

Gregory Wade - *Wedbush Securities - Analyst*

Thank you very much.

Operator

the next question is from Mr. Robin Davison from Edison Investment Research. Please go ahead.

Robin Davison - *Edison Investment Research - Analyst*

Okay. Thank you very much. Congratulations on this excellent data.

First of all, could Charlotte quickly run through the dose titration regimen because it's not clear to me if the patients were all aiming to go up to, let's say, 100 milligrams three times a day, or whether they could, for example, choose to go to 100 milligrams twice a day, for example.

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

The aim was to get all patients to 100 milligrams three times a day. So, in the first week they started off with a single dose of 50. After a few days, they went to 50 twice a day. Beginning of week two, it's 50 three times a day. From week two onwards, they were on three times daily dosing. In week three, then, they were adding in the 100 milligram doses. So, three week, three dividing in - first 100 milligram dose at midday. A few days later they added in a second 100 milligram dose to the 50 they were already taking in the morning. And finally, at the beginning of week four, they were on 100 milligrams three times a day. So, basically, from the beginning of week two onwards, they were on three times daily dosing.

Robin Davison - *Edison Investment Research - Analyst*

Right. And you said the vast majority of patients completed this. I think you said that.

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

Yes.

Robin Davison - *Edison Investment Research - Analyst*

Yes. And the only reason why they might not do that is because of AEs, or something like that?

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

Yes. I mean someone saying I don't think I need this other - in fact, the dose - those patients that didn't take three times daily or didn't take 100 milligrams three times daily, they were tending to drop the morning dose or not escalate the morning dose because they felt like they didn't need it. In fact, Dyskinesia is less important normally during the morning. It tends to come on sort of mid day or as the day wears on. And so some of the feedback we were getting was, "Well, do I really have to do this because I don't think I really need it? I'm getting enough from the two I'm taking later in the day." So, that was quite a lot of the reason for people - for those that didn't, the minority that didn't, that was the reason they were tending to give.

Robin Davison - *Edison Investment Research - Analyst*

Right. On the peak AIMS reduction data which you've got on the press release, and I think you gave a little more detail on the call - so, for example, you said day one it was 19% versus 4.1%. And day 14 - you said what the dipraglurant figure was. The placebo was 0.12%.

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

Sorry. (inaudible - multiple speakers). It was 32.3% on day 14, and 31.4% on day 28 for Dipraglurant. So we hit that 30% we were looking for, just above it.

Robin Davison - *Edison Investment Research - Analyst*

I see. Right. I understand that second part which is the (inaudible) effect you were aiming for. So, I guess the question is the fact that the placebo response increased over time. Is that just an observation we should be concerned about at all? Or is that just noise, really?

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

Well, it's interesting because, actually, the first three weeks the placebo response sort of tended to bobble around and there wasn't this sort of pattern of response that we saw with the active treatment because the active treatment group response increased over time so there was a very clear trend in the active treatment group. In fact, between day 14 and day 28, when you've gone up to the 100 milligram dose, you have a nice maintenance of effect at that dose. Whereas, the placebo response bobbled up and down, and then in week four it ticks upwards. The reasons for that are being discussed it happens in many studies with varied small sample size and short duration. If you repeated this test two weeks later, would the placebo response have gone down?

I think this is an important point, this placebo response, to bear in mind when designing future studies. But you know, it's probably partly inherent to the natural variability of the test that was being done. And I think it's important to note that, in fact, the magnitude of effect with the active treatment response didn't change; it was maintained in spite of the variable placebo response.

Robin Davison - *Edison Investment Research - Analyst*

Okay. You've also got some data on the AUC for AIMS. I think you said you achieved a 30% reduction in that three-hour period at days 14 and 28. Is that correct?

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

That's correct. Yes.

Robin Davison - *Edison Investment Research - Analyst*

But there wasn't a change at day one?

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

Well, there was a 20% reduction at day one. In fact, it's very similar to the peak on day one.

Robin Davison - *Edison Investment Research - Analyst*

I see. Okay. I think this might have been answered a bit, but I'm also interested in the patient diaries. Obviously this "on" time without Dyskinesia appears to be very interesting. It's up to 70 minutes versus placebo. Is that sort of a maximum you got? What was the - I don't know - the average or the amount at day, sort of, 28 that you were getting?

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

It ranged between - the excess of the placebo ranged between 36 and 70 minutes.

Robin Davison - *Edison Investment Research - Analyst*

Thirty-six versus … Right. I mean, how much would the placebo patient have of "on" time without Dyskinesia? Just for that context, you know, that increase.

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

Look at the placebo - we basically had a two to 2.3 average increase in "on" time without Dyskinesia in the active group. And the placebo, the maximum was 1.6 hours "on" time without Dyskinesia. So, you had a good sort of 36 minutes to over an hour difference in "on" time without Dyskinesia between the active and the placebo treatment group. And the active treatment group were going from four hours of "on" time per day with Dyskinesia down to two hours a day with just - they were going four hours a day with Dyskinesia down to two hours a day with Dyskinesia. So, there was quite a big difference.

Robin Davison - *Edison Investment Research - Analyst*

Okay. I think you were measuring mood and sleep. That data has not been analyzed yet?

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

No, they haven't. No, they haven't come through yet.

Robin Davison - *Edison Investment Research - Analyst*

Just finally, yes, just the PGIC and CGIC - I'm presuming the data was blinded at the point that analysis was done, so you're saying the physicians and patients expressed a preference for Dipraglurant because at that point they knew they were taking it?

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

No. Everything was done blinded. Yes.

Robin Davison - *Edison Investment Research - Analyst*

All right. Excellent. Thank you very much.

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

Okay.

Bharatt Chowrira - *Addex Therapeutics - President, CEO*

Thanks, Robin:

Operator

The next question is from Mr. Peter Welford from Jefferies. Go ahead, sir.

Peter Welford - *Jefferies - Analyst*

Hi. Thanks for taking the call. Just a couple of questions left if you can. First, just regards the future plans. Obviously we've got some pretty intriguing data but at the same time there's clearly still some sort of variability in terms of the effect over time and how to (inaudible) the placebo response. Should we infer from this data that it's highly likely there will a further, if you like, more complete dose ranging Phase IIb before we move into Phase III, or where have you got to with regards to your discussions with that?

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

I think Professor Rascol also said this. Identifying an effective dose is crucial. Now, how you do this, clearly, you can go to pivotal efficacy with a dose ranging study so you can actually make a Phase IIb study, a pivotal efficacy study and then you can add on a Phase III study. Or you can decide to do a formal dose range finding study in IIb before you then go to Phase III. And these sort of ways of approaching it were something we would discuss with a partner the best way - clearly we would want to advance this to the market as soon as possible, but also of course, get the most robust data set we can and minimize the chances of late phase failure by having a well constructed Phase II or dose range finding data. We still don't have the full data set on [plasma] concentration from this study which will give us more information about how to do further dose range findings. But as I say, that study can be a pivotal efficacy study if you design it in that way. In which case you can do just one Phase III and the open label safety. Or one can decide to have a stand-alone study.

That's something we would discuss with a partner and work with them. And also there are experts like Professor Rascol and the health authority so that we can, as we say, maximize the chances of success.

Bharatt Chowrira - *Addex Therapeutics - President, CEO*

If I may make a comment. I think that's one thing that we learned from that through study is that on the first day of the smallest dose there was already an effect. So, I think in an overall development program there is a need for defining really what the smallest clinically active dose. And it's true in my experience, especially for CNS and Parkinson's disease development programs, but the definition of the dose is crucial. So, I think in a Phase II program, if it is well conducted, that's going to be the next step.

Peter Welford - *Jefferies - Analyst*

And partnership - you sort of answered this already to a point in the sense that (inaudible) is the safety aspect which is we're obviously going to need more than four weeks dosing in a study significant group of patients here. Is that going to mandate anyway at least two late stage trials to get the database required with sufficient long duration of dosing?

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

Oh, yes. This is a chronic long term indication so you have to have one year of safety information anyway. So, that's a given. You have to do this open-label safety extension to get the safety database. And that's absolutely routine for any medication, regardless of the indication, that's being indicated for chronic treatment.

Bharatt Chowrira - *Addex Therapeutics - President, CEO*

And in Parkinson's Disease the official recommendations from the agencies for adjunct to Levodopa therapy for patients with "off" problems. And Dyskinesia is that the trial should at least be three months of follow-up. The pivotal.

Peter Welford - *Jefferies - Analyst*

Then the last question, if you don't mind, is with regards to the long term and pre-clinical tox, and all that sort of stuff that need investing in doing. Is the pre-clinical tox already ongoing, the long term trials? Or are those trials going to be initiated as well once the partner is on board?

Bharatt Chowrira - *Addex Therapeutics - President, CEO*

Peter, this is Bharatt here. And no. We are in the process of getting ready for that. We're working on the CMC package for the molecule. So, once we have that, then we will be able to start the long term tox program. And so we will in parallel look for a partner. And then together with the partner we'll actually then decide on that CMC package and the [talks] program.

Peter Welford - *Jefferies - Analyst*

That's great. Thank you very much.

Operator

The next question is from Mr. Samir Devani from Nomura Code. Please go ahead.

Samir Devani - *Nomura Code Securities - Analyst*

Just a couple of questions from me. On clinicaltrials.gov it indicates that this study was supposed to enroll 90 patients. So, I was just wondering if you could, firstly, clarify why only 76 were enrolled. And then, secondly, you talked about maintenance of effect in the second two weeks when the doses went up to 100 mg. I was just wondering, was there any indication that it was necessary to go to 100 mg?

Charlotte Keywood - *Addex Therapeutics - Chief Medical Officer*

I can answer both of those. Yes. In clinical trials what we were doing was planning to get 90 screened to have 72 complete. So, the study was always designed about having around 72 patients complete. And in fact, although identifying the patients up front was quite difficult, once they were identified, they didn't drop out of the study. They were good patients. They didn't fail screening and they didn't drop out. So, in fact, in the end we only needed 83 to get 76 complete, so we actually got more completers than we actually needed per the original protocol. So, at some point you have to give some estimates based on industry averages, if you like, for clinical trials, how many you need to screen to get how many complete. But in the end, actually, you could say it went even better than we'd hoped. So, that's the only reason. And we got our target number.

So, just remind me of the second question. Oh, yes, yes; 100 milligrams. He's written it out for me. Thank you, Chris.

When we design the dose regimen for this study, we used the animal pharmacology data that we generated. And to estimate the maximum plasma concentration that we needed, the target plasma concentration, we've always found our animal pharmacology data to be rather reliable in predicting affecting humans. This study now even supports that as well. So, in picking the 50 and 100 milligram doses, we were actually bracketing the target plasma concentration that was identified from the animal pharmacology. The 50 milligram dose is a bit below the target; and the 100 milligram is quite substantially above the target plasma concentration. So, we knew we were in the right plasma concentration range to see pharmacology, and that has been borne out by the results of the trial. So, that's why we went up to the 100 milligram dose.

Samir Devani - *Nomura Code Securities - Analyst*

Okay. Thanks a lot.

Operator

The next question is a follow up question from Mr. Gregory Wade from Wedbush Securities. Go ahead.

Gregory Wade - *Wedbush Securities - Analyst*

Thanks for taking the follow up.

Dr. Rascol, the data in the dystonia patients is interesting. Do you think that that's potentially translatable to other movement disorders where dystonia is an issue? And then, Bharatt, could you give us some numbers around the size of (inaudible - multiple speakers).

Olivier Rascol - *University of Toulouse - Coordinating Investigator, Professor of Clinical Pharmacology*

Well, it's an interesting observation. We have to be cautious because the numbers are small. So, again, these are indicative of preclinical findings. But from the clinic and from the animal models, the MPTP treated monkeys, dyskinesia and dystonia, there is some evidence that there might be different mechanisms. It's not always easy to disentangle these different movements, but even in the [rut] some might be more related to the glutamate or the serotonin or the dopamine, or a combination of these mechanisms. So, it's important to look at these. And in some patients

dystonia is more troublesome than chorea because it might be more painful or it might impair function in a more pronounced way than chorea which are just brief and not long lasting movements.

So, it's true that if this can be - and Charlotte will correct if I'm wrong. But I think that this is also something that has been observed in the animal models. So, there is some consistency between the two observations.

Now, saying that this is enough to pretend that this compound will be an effective anti-dystonic therapy for primary dystonia or dystonia from other causes, I think is too early. But I think it is worth testing. And I think that I would encourage in the future development some further exploration of this potential of the compound.

Gregory Wade - *Wedbush Securities - Analyst*

Thank you.

Chris Maggos - *Addex Therapeutics - Business Development and Communication*

And, Greg, you had another question?

Gregory Wade - *Wedbush Securities - Analyst*

The size of the non-Parkinson dystonia …

Olivier Rascol - *University of Toulouse - Coordinating Investigator, Professor of Clinical Pharmacology*

The size of the non-Parkinsonian population it's - it depends because, you know, some are drug-induced. Some are genetic, some are post-lesions. And so it's quite heterogeneous. But it's quite an interesting market if you think about this is the main indication for botolinum toxin in the clinical neurology indications. So, there is a need for orally active treatments. And so that could be quite interesting market from the financial aspect and an important clinical market from the medical need aspect.

Bharatt Chowrira - *Addex Therapeutics - President, CEO*

And, Greg, just to follow up on that, is that in our current approved standard of care for dystonia, especially is the injectable botox. And that can be only used for focal dystonia. Obviously, for generalized dystonia, you can't really use that. So, having an oral small molecule that has the potential to treat dystonia in non-Parkinsonian dystonia would potentially be quite a major advancement. But we'll have to look into that. There are diverse - there are 15 or 16 different types of dystonias.

Olivier Rascol - *University of Toulouse - Coordinating Investigator, Professor of Clinical Pharmacology*

If one thinks about, you know, speculating about other types of indications, you can also include tardive Dyskinesia, which is also a common problem in a number of patients with very little clinically efficacious medication and, indeed, treatment options.

Gregory Wade - *Wedbush Securities - Analyst*

Thanks for taking my question.

Chris Maggos - *Addex Therapeutics - Business Development and Communication*

Thanks, Greg.

Operator

(Operator Instructions)

Gentlemen, there are no more questions at this time.

Bharatt Chowrira - *Addex Therapeutics - President, CEO*

Great. Thank you, everyone, for joining this call. And we appreciate your time and we look forward to providing an update as we get more data.

Thank you everyone. Bye bye.

Operator

Ladies and gentlemen, the conference is now over. Thank you for using the Chorus Call Facility, and thank you for participating in the conference. You may now disconnect your lines. Good bye.
