Biogen Inc.

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Priya Singhal

Umer Raffat Analyst

Okay. Excellent. Well, thank you guys for being here. Pleasure to have Biogen management join us. We're only going to talk about the 10,000 patients by end of March and no other topic.

But in all seriousness, thank you, Priya, for being here. I'll turn it over to you to kick things off.

Priya Singhal Executive

Sure. So delighted to be here. I think we believe we've had a really good year and met all the business priorities that we set out -- Chris set out at the outset of the year. So it was about the launches, the approvals, the R&D prioritization, recruiting a new head of research, and really focusing attention on the new wave of products that we believe we have the ability and capability to bring to patients with high unmet need. And I think that on all of these priorities, we feel we've made significant progress and we are entering 2024 really with a lot of promise and a lot of things to look forward to.

We also have very important inflection points coming up in the pipeline in 2024, and we can talk more about that as well. So yes, we feel good about where we are and what we've achieved. Of course, Reata was another important aspect of building the pipeline and building the product portfolio.

Umer Raffat Analyst

Excellent, excellent. Priya, maybe just to kick things off on the Alzheimer's side just because there is so much focus there and maybe just to get that question out of the way, 800 patients as of October. I know there was a big bottleneck removal. So maybe even backing up further, 800 as of October, the goal is 10,000, what Eisai has communicated by April 1, which means the recruitment really would have to pick up in a pretty substantial way.

There's even investors' opinions that maybe it should be around 3,000 or so by early January timeframe to stay on that track. But I also know it wasn't so much that it's a linear growth from July approval to next March, there was a big reimbursement bottleneck removal on the PET scan side in October. Can you speak to that, and if that has accelerated patient entry just broadly speaking?

Priya Singhal Executive

Yes. So I think maybe before that, just to set the stage, really, it was the LEQEMBI data and the traditional approval of LEQEMBI that demonstrated that amyloid is the right surrogate biomarker and can lead to clinical benefit. I think that's the key point here. It's a huge turning point in the treatment of Alzheimer's disease, and we hope it opens the door to a lot more innovation in this space. Having said that, I think what's important to remember is that this is from our experience in market research that we did even before with ADUHELM, and then, of course, now we're seeing more with the LEQEMBI rollout.

This is an immature space in terms of infrastructure. There are several bottlenecks. So CMS, I think, did what they said they would and on the day that LEQEMBI had traditional approval came out and said they were going to reimburse. We don't believe the registry is a bottleneck. We think this is not a difficult point at all.

But there are other aspects, getting to see a neurologist, getting confirmation of amyloid before you start treatment, having access to MRIs and monitoring. All of these, I think, are going to need a lot more work to get established. So that, I think, is the key point. Eventually, we think this is going to be a very important product. We encourage competition as well.

We believe that competition will only enhance the establishment of infrastructure, which is sorely needed. Even the big centers are -- while they have it on their formulary, they're having to put in protocols, put together plans for how they will access MRIs, PET scans, and such. The other piece here, I think, to remember is the blood-based biomarkers. We believe that's going to be a very key inflection point. We're already seeing a lot of momentum, and I'd like to kind of split that into 2.

There's today's blood-based biomarkers that are lab-developed tests. And these aren't scaled, but they can be very valuable in triaging patients, specifically for the negative predictive power because you want to rule out amyloid before you give them an anti-amyloid agent. And that then reduces the stress on the rest of the system. So I want to come back directly to your point of 10,000 patients. That is definitely an aim that I think Eisai has communicated, and it is something that we look forward to seeing.

But we don't think that tells the full story. We think the full story is that this is really a huge paradigm shift for the space, and that establishment of infrastructure is going to be important. And eventually, we think this is going to be a big product.

Umer Raffat Analyst

Priya, maybe just to give you a perspective on sort of some of the investor questions that come in. And some folks are already starting to ask, maybe it doesn't need to be exactly 10,000. It could be off by a bit, but as long as we start to see a much more significant

acceleration. Is it realistic to expect maybe in light of some of that October 13 PET scan changes that there's a bit more of an acceleration happening? Because one question has been maybe docs just want to put one patient through the scan, the reimbursement, if all happens, then 10 more come right behind it.

So do you see scope for that? Or will this be more a gradual step-by-step approach?

Priya Singhal Executive

We think it's going to be gradual and potentially fragmented because of the immaturity of the space. Having said that, we do think there's -- the CMS PET scan removal is going to have an impact. Now, there could be a lag, right? We don't see a problem with patient demand. We don't see a problem with intent to treat, it's just getting patients through the system.

That is really important. And remember, the doctors aren't in charge of the system. So, in fact, we have examples and anecdotes of where -- in small practices, where doctors are able to treat patients and turn them around from the first point when they come into the clinic to really getting a confirmation in a week. But that's not the typical experience. We think this will eventually get there.

We have so many examples from other paradigm shifts where we've seen it happen. So we believe quite strongly that it will get there. The timing, I think is -- but this is definitely going to be an accelerator. The removal of all barriers will eventually accelerate. It's about getting to the critical mass and the momentum.

Umer Raffat Analyst

Okay. Got it. And has there been discussions between Biogen and Eisai on sort of communicating around this? Again, it's their decision to put that number out, not Biogen's decision. But has there been conversations with them because what we also have now is a week off last week for the most part, again, 2 more weeks like that coming up in December?

And all these things, given how short a time there is between now and end of March, can getting to that 10,000 contribute to lack of neurology appointments, all of the above, neurologists are on vacation, et cetera? Like has there been discussions on how to message around this just heading into the new year?

Priya Singhal Executive

We are definitely very close in our discussions with them. I'm on the joint steering committee and the Chair of that and collaborate with my counterpart who's in Japan. So we're talking to them. We had a CEO-to-CEO meeting. So we're talking to them constantly.

I think it's a little bit of continuing to see the momentum and having all these inflection points, like the CMS PET registry -- PET reimbursement play out. And I think that I'm sure we will communicate at the right time.

Umer Raffat Analyst

Okay. Makes sense. Unless any further -- by the way, I'm certainly happy to take questions from the audience to anywhere you'd like, but unless no more questions on the commercial

side, maybe transitioning then to another aspect of potentially this launch, which hasn't come up yet, which is subcu aspect of the development. Can you speak to how significant that is the way you see it on market development?

Priya Singhal Executive

I think it's very significant. Going into CTAD, I think there was a lot of skepticism about whether a product, an anti-amyloid agent like LEQEMBI can demonstrate bioequivalence in terms of exposure, plaque clearance. And I think that we've demonstrated that with the data that we showed, the 6-month data that we showed at CTAD. So I feel very encouraged about the data. Eisai has communicated on their earnings calls, they've initiated the FDA discussions.

So this is really important because before that, remember, we had examples like gantenerumab and other products where that hasn't worked. So we've demonstrated that we can actually clear plaque, get exposures. Now, I think that whether and how it's going to play into the future still needs to be determined because a little bit of that will be through the filing discussions that we'll continue to have with FDA and other aspects of the data, which will emerge. But the most important thing is that I think that we have demonstrated the bioequivalence. So I think I'm very excited and encouraged by it.

Now, whether in the future, all patients will choose to have a subcutaneous, all prescribers, treating physicians will choose to give their patients. I think these are times where so many variables are at play, that I think we'll have to wait and watch because we have also heard from patients and key opinion leaders that patients like to come into infusion centers with their families. They like to be seen. They like to have that contact. So I think eventually, you could see a mixed population.

But the fact that this provides very key optionality for patients, I think, is very important. The second piece is LEQEMBI, the way we are thinking about the development of LEQEMBI is really for the continuum of Alzheimer's disease. Given that we've shown bioequivalence in this space, I think it will remain to be seen about where all a subcutaneous formulation could be relevant. It could be relevant in the maintenance phase, assuming that goes forward; it could be relevant in a preclinical AD space, assuming that reads out. So what it provides is optionality for us, but optionality for patients.

And I think that we are tackling all these aspects, sort of very systematically. We're looking at the AHEAD 3-45 trial, where, of course, it's IV, but it's less frequent dosing. And then we're looking at maintenance in the Phase II open-label extension, where we're looking at every 4-week dosing. And we're also gathering data there. So I would encourage us to think about the continuum of Alzheimer's disease versus thinking about it as MCI, an early AD and 18 months of treatment because we don't believe that's how this disease continuum is going to play out.

Umer Raffat Analyst

Got it. Can you remind us of the dose used for the subcu in the study shown recently because IV is 10 mg every 2 weeks?

Priya Singhal Executive

Yes. This is 720 mg weekly given by 2 injections, 360 mg each. But we also saw 11% higher AUC, and we saw 14% increased reduction of plaque, which is very encouraging news because, right, you wouldn't want to see it be under what you expected. But that gives us other questions to tackle. So we're having those regulatory discussions really looking across the spectrum here.

Umer Raffat Analyst

Right. So maybe just zooming in on that dose aspect of it. So currently, the dose is 10 mg per kg every 2 weeks, which is the equivalent of 700 mg every 2 weeks for an average person or 100 if it's me. But in any event, so 700 mg every 2 weeks for IV or 720 weekly if it's subcu. But given that 114%, do you think the dose that you would actually file is perhaps a little less than 720 mg weekly?

And would that even open up the possibility of a single shot instead of 2 shots?

Priya Singhal Executive

All these are possibilities. I can tell you we're having a lot of discussions internally with our team at Eisai, and also, we'll be having them with regulators. So we're looking at all those options. I think the most important thing is that we will be data-driven in our approach. So we're looking at everything very objectively.

And yes, those are all possibilities that we're discussing.

Umer Raffat Analyst

So does this mean if there was a base case plan for submission of subcu, let's say, sometime in 1Q, 2Q, would that now be maybe a quarter or 2 out because you'll do some more PK modeling to file a lower dose instead?

Priya Singhal Executive

We're not there yet. I think at this point, we're still guiding towards the Q1 2024.

Umer Raffat Analyst

Okay. Got it. But what -- the thought process on informing what dose you actually file, that wouldn't necessarily involve a new study, it will just be some PK/PD modeling off the existing work?

Priya Singhal Executive

Well, we've already used a lot of modeling in our work. So we'll continue to use the modeling. I think it's hard to speculate about what else it might require. But at this point, our assumption is that we could use modeling.

Umer Raffat Analyst

Okay. Excellent. Mike, anything else on the subcu before we move on?

Michael DiFiore Analyst

Yes. I just want to drill down on the whole content of ARIA. I mean if we look at the subcu naive patients in the study, they actually had lower -- there are lower -- had lower amount of ApoE4 carriers and then a lower amount of homozygous than the IV patients did in Clarity. But yet we saw a higher ARIA. Maybe you can explain that a little bit.

Priya Singhal Executive

Sure. So I'll just pull us back to the cohort that we looked at. It was 72 patients who were lecanemab-naive patients in which we looked at what happened during the 18-month period. And I think that the most important thing here is that the incidence, severity, resolution, and the basic characteristics of ARIA were very similar. We had about 12 reports of ARIA-E in the 72.

If it had been 9 or 10, it would have been exactly the same as Clarity AD, which is more than 890 patients in the lecanemab-treated arm. So overall, looking at the small sample size and looking very deeply at the characteristics of the cases, we believe that this is very similar. We believe it's very similar. The discontinuation rates are the -- are also similar as is actually the incidence in the homozygous, so we drill down. But as you drill down, the numbers get smaller, right?

So it's hard to make very definitive conclusions. But overall, we believe that the characteristics are the same. The one distinction though is that we -- Eisai had communicated that they believe that it was related to Cmax and that is true for IV. However, with subcu, we see a more even distribution and steady state of AUC. So we don't believe it's related to Cmax because it's really pretty flat.

It's not as vertical as it is with IV. So that was the one new piece that we learned when we compared the IV versus the subcu. But we believe that the characteristics and the incidents are not very dissimilar.

Umer Raffat Analyst

Got it. Okay. Now, the other aspect of the subcu, I feel like it's thought about as subcu or no subcu, but I feel like even within it, there's an induction phase, and then, there's a maintenance phase. Can you remind us where are we in terms of understanding what the maintenance IV dose should look like? What's that study?

When do we get an update on that? And then we can think about translating that to subcu regimen.

Priya Singhal Executive

Sure. So right now, we are evaluating subcu -- I mean IV maintenance 4-weekly. So it's a 4-weekly 10 mg per kg dose IV. It's being tested in the Phase II open-label extension, and Eisai has communicated and guided that they would file by Q1 2024 for maintenance IV.

Umer Raffat Analyst

Got it. Now didn't it also have a quarterly, I remember this distinctly...

Priya Singhal Executive

Well, right now, it's just 4-weekly.

Umer Raffat Analyst

And how did that decision get made? Did you see that data?

Priya Singhal Executive

I don't believe they've commented on it. So I won't be saying more on it.

Umer Raffat Analyst

Okay. Got it. But that's fairly something that was initially the plan, either quarterly or monthly.

Priya Singhal Executive

I believe it was, yes.

Umer Raffat Analyst

Okay. And this -- it's reasonable to say this was not entirely made -- this was not a decision made purely on dollars, it was presumably clinical data driving that decision as well.

Priya Singhal Executive

Well, I think they haven't commented, so I would defer to them. But as of now, it's 4 weekly.

Umer Raffat Analyst

Okay. As of now, it's every 4 weeks, it's from the Phase II OLE.

Priya Singhal Executive

That's right.

Umer Raffat Analyst

And you may have, as the CEO of this committee seeing that they'll have...

Priya Singhal Executive

Not the CEO. I'm the chair of the JSC, the joint steering committee.

Umer Raffat Analyst

That's what I meant. That's right. But you've seen the data evolution for the quarterly and monthly. And I'm asking all this because there's -- Lily believes donanemab after a certain amount of time, you don't need to be on any further. But presumably, you guys may be seeing some plaque bounce back and you may need much -- a bit more frequent amount of drug staying on board even beyond the induction.

Priya Singhal Executive

Well, I think that's not quite right. So maybe I can correct that a little bit. So first of all, it's not about us seeing plaque bounce back. This is Alzheimer's disease. We know it's a progressive disease.

From the biological perspective, you can remove plaque, but we have shown through several areas of evidence that while plaque comes back only 3% to 4% annually, what does bounce back much more is the biomarkers, specifically the Abeta 42/40 ratio. And this, we believe, signifies a return of disease. And it is important.

So when you clear plaque, you see clinical benefit. The question is how long can you maintain patients in that phase where they continue to remain in that phase of disease or improve actually, as we showed with lecanemab data at CTAD? So that's really the question.

Now, moving on to how do you drug the target. The targets that all these anti-amyloid agents are targeting are all different. So with lecanemab, we're targeting plaque, which is aggregated amyloid as well as soluble oligomers, which are called protofibrils. And we believe that continuing to target the protofibrils after plaque is cleared is critical to maintaining patients in a stable state of disease. And so it's not really about donanemab, donanemab just simply has exhausted target because it's a pyroglutamate form of aggregated plaque.

It has nothing more, no more work to do in the body, whereas lecanemab actually has a target, which we believe is relevant to progression of disease. So that's what's the biological hypothesis behind pursuing maintenance.

Now, when you pursue maintenance, it's obviously trial and error, right? You don't know -- a lot of this has been evolving now, so we really don't know how much -- how many -- what's the level of biomarkers that are going to return. So that was the trial and error.

And now, we've landed on the 4 weekly, and we believe that's going to be relevant, and that's where we are generating data. So we believe eventually you need that intense phase of plaque reduce -- reduction and clearance, but you can't stop at that point is our current biological hypothesis.

Umer Raffat Analyst

Got it. So if monthly is the regimen for maintenance for IV, is it reasonable to say that -- because in induction, it's every 2 weeks and subcu became weekly, so if maintenance is monthly, then subcu would be every 2 weeks or would it still be weekly?

Priya Singhal Executive

I think we're not there yet. These are the questions that we're trying to assess. And we're looking at the data now that we've generated from subcu to kind of marry all of this up to assess what is the right regimen. So I think we're not there yet. I can't comment further.

Umer Raffat Analyst

I guess said differently, as I think about induction, it's -- currently, as it stands right now, it's weekly, but it's 2 separate shots back-to-back every week. Is it possible that for a monthly regimen instead of doing 2 back-to-back every 2 weeks, you just say, one shot once a week

kind of thing. Is that...

Priya Singhal Executive

It's possible, and we are looking at all permutations/combinations. We have a few things in mind. Number one, what's the data, what's the data going to support? Number two, how do we make it most convenient for patients and provide optionality? So I think we're going in with that.

The good news here is we've demonstrated bioequivalence, which no one else has shown before. So it was the biggest hurdle, and we think we've overcome that. In fact, we have higher clearance.

Umer Raffat Analyst

Got it. Okay. Any questions from the audience on Alzheimer's before we move on from this topic broadly?

Michael DiFiore Analyst

I just have -- curious to see your thoughts on Roche's trontinemab data at CTAD showed a huge Cmax due to the technology platform, but yet very low ARIA. Any thoughts on that?

Priya Singhal Executive

Yes. It's encouraging news because I think it shows that receptor-mediated transcytosis can be effective. And we ourselves, we've got -- we've announced this publicly that we have a transport vehicle that we acquired from Denali, and we're working on this ourselves. And actually, we believe that our ATV has several engineering features that are more advanced than Roche's trontinemab. So we are very excited about what we've seen, and we continue to pursue it.

We'll share more data when that becomes available. It's still preclinical. The thing here is that we did see -- in the trontinemab data, we did see a case of ARIA. And the idea was that can there be no ARIA. So we'll see whether that promise can be fulfilled, I don't know.

But yes, it shows that better exposure, biodistribution can really impact efficacy and safety. So yes, it's exciting.

Umer Raffat Analyst

Priya, remind me, the preclinical Alzheimer's trial that you guys are running, that's 2027 timeframe?

Priya Singhal Executive

We haven't communicated the timeline, but we remain very encouraged by what we showed actually at CTAD in the early tau patients, the low tau patients, and what we showed is that if you get to treat these patients when they have low levels of tau, 76% stabilize, 60% actually show clinical improvement. Now, remember, in this early population, there's a lot of variability. So placebo patients also move in that direction, but it's a very significant difference.

Umer Raffat Analyst

There improvement is on symptoms?

Priya Singhal Executive

CDR sum of boxes. Yes. It's very exciting data and really continues to reinforce our hypothesis that we need to go earlier. Now, eventually, there'll always be a spectrum of patients in all these different stages of disease, but it's very exciting for what the AHEAD 3–45 could tell us.

Umer Raffat Analyst

Got it. So at some point -- this is my last question on Alzheimer's, at some point next year, this is going to be the mainstay Alzheimer's question, I think, by everybody. So let me start by asking you that now. Novo Nordisk will report semaglutide in Alzheimer's in 2025. Since it's a magic drug, it works everywhere.

So I guess my question to you is how do you think about the GLP biology? And in a scenario where that trial comes anywhere close to hitting, how does that change LEQEMBI dynamics or not? Because theoretically, those are complementary mechanisms, but it's a type of question that you probably get a lot more at some point.

Priya Singhal Executive

Yes. It's exciting. So look, when we look at evidence and sources of evidence, we know that there is a higher risk of dementia with diabetes. We know this. It's a multifold higher risk.

But whenever we look at risk, we have to separate association from causality. And we know that 2 trials have previously failed, right? So it remains an important area of inquiry -- scientific inquiry, but trials have failed. Trials fail for many reasons, it's either not the right target or not the right population. So it's a high-risk sort of assessment.

That's one. Second, I think that we also know that glucose transport and glucose metabolism does affect cells, right? It affects cardiac health. It could affect brain health, so it's not -- it's intuitive to believe that there could be some association. Now, whether that's going to be of dementia of all causes or it's going to be dementia, which is Alzheimer's disease and associated with amyloid and tau, that remains to be seen.

In their trial, actually, they allow patients who are on aducanumab. I don't know if you know this, but they do allow that. And eventually, I do believe that if it does hit, it will be very positive for patients all around, and it could be complementary because it's hard for me to imagine or envisage that it could actually remove plaque, you see. So it could promote brain health, but can it remove plaque? So I do believe that removal of amyloid plaque is going to be central for some time, especially when there is a critical mass of plaque...

Umer Raffat Analyst

Do you think it really can reduce plaque?

Priya Singhal Executive

No, I'm saying I don't know that. I don't know that. And that's why they've allowed aducanumab patients to be included in the trial, I'm guessing. I don't know.

Umer Raffat Analyst

And the critical thing you mentioned is there have been 2 trials. So I know the 38-patient liraglutide trial in Alzheimer's. What's the other one?

Priya Singhal Executive

The other one was Takeda, I believe. TOMMORROW -- I think it was called the TOMMORROW trial.

Umer Raffat Analyst

Okay. So they're both smaller trials, but there were no cognitive benefits seen in those studies?

Priya Singhal Executive

Exactly.

Umer Raffat Analyst

Okay. Got it. And there's no -- okay, got it. And there's no buzz from the broader field in general or from Alzheimer's specialists on this.

Priya Singhal Executive

No, I don't know about buzz. I would say that it's an important area of inquiry. We should look at it. It's a very large trial. It's a very large trial.

So I hope it works. I mean I think it's great for patients. I'm just saying from a scientific hypothesis, it's hard for me to understand because there's dementia and diabetes, there's Alzheimer's, which is quite different. And there's several hallmarks of Alzheimer's. So if it doesn't really contribute to removal of that, maybe it promotes brain health in general, that would be a positive.

Umer Raffat Analyst

Excellent. Excellent. Maybe unless there's any further questions on Alzheimer's, I said that 5 minutes ago, let's move on beyond. So let's talk about Reata. I know that EU decision is going to be very critical for you.

In general, I think the investor perception at the time of the deal was given some of the experiences with Amylyx, and again, different drug, different applications. Given the experiences with Amylyx, given sort of even the regulatory back and forth Reata went through in the U.S., Europe is a higher bar, more stringent, so it was nobody's base case that EU would necessarily happen. I know you guys have talked about that there could be a possibility without saying it definitively. So could you speak to what's driving, a little more hope, maybe not definitive, but a little more hope on your end?

Priya Singhal Executive

Sure. So overall, we are really excited about SKYCLARYS and the benefits it could bring to patients. As you know, we did a deep diligence on the product. So we looked at all the FDA correspondents. We look at regulatory correspondents for any diligence we do.

We looked at all the EU correspondents, and the signs were encouraging. Since that time point, we moved along the cycle. I think this group is very well informed on how that cycle works. We've communicated that we should see an outcome on the CHMP opinion in early 2024 -- by early 2024. So this is important.

The second thing I'll say is that there's a very big difference between Amylyx and SKYCLARYS. Amylyx is going for all ALS. Reata and SKYCLARYS is really going for Friedreich's ataxia in adults, 16 and up. And so it's a very different population, very different dynamics. The Amylyx trial failed its primary endpoint, whereas the SKYCLARYS trial -- MOXIe trial was positive on its primary endpoint, and the secondary endpoints were variable, that's where FDA asked for natural history data going out to 3 years to look at whether this was a chance or a real effect, and they were convinced that this was a real effect.

So that's a very big distinction and that's important for us to remember. The second thing is, as we've progressed along the filing, we haven't seen anything that changes our initial encouragement of where we are on the product. So we'll see what the results are, but we remain optimistic.

Umer Raffat Analyst

Okay. So there's 2 thought chains I want to go down. The first one is you said 1Q '24 for the EU decision. We know the gating factor is day-180 clock stops, they can take, however, long they want. And at some point, the clock starts, and within 30 days CHMP decision comes out.

To the extent you're saying 1Q '24 decision, I'm almost wondering has that clock restarted now, and that's why you feel reasonably confident in 1Q '24 is the decision?

Priya Singhal Executive

We don't comment on specifics, so I can't comment on them.

Umer Raffat Analyst

Okay. But you're obviously very privy to all the back and forth, both at day 120 and at day 180, and everything, there's no surprises per se, I think, is how you describe it.

Priya Singhal Executive

They are no surprises from my end. Yes.

Umer Raffat Analyst

Got it. But the regulatory back and forth at day 120 was done on Reata's clock. But the day 180 is happening on New York. Is that how it's happening?

Priya Singhal Executive

That's how it's working.

Umer Raffat Analyst

Got it. And do you -- would you say FDA and EMA were not necessarily too different in terms of the amount of stringency or the bar they were holding it to because I know we've seen a discrepancy in the past on other applications?

Priya Singhal Executive

It's not stringency. It's about what aspects they believe are most relevant for their regulatory decision-making, their populations. So you'll see sometimes decisions going different ways. So I don't know that it's stringency. I think the most important thing is that this is an orphan population, it met its primary endpoint, was able to demonstrate durability on a 3-year natural history comparison, which I think is very compelling.

Umer Raffat Analyst

Got it. So in FDA review, one of the points FDA was zooming in on -- I will read it how FDA said it, they said, Part 2 is not a highly persuasive study and does not appear to be capable of providing substantial evidence of effectiveness as a single study alone without substantiation, which is why they went into the post hoc of that same trial. And they agreed to use post hoc as sort of that additional evidence, something I had never seen previously. And I always wondered, would EMA be open to that unless EMA doesn't even think that, that initial study was not worthy enough as a standalone. They might think it was perfectly fine, and then, the open-label extension is moved.

Priya Singhal Executive

Well, I think that -- I can't really comment on what EMA is looking at. But remember, all this data is public, EMA and FDA correspond with each other. So I would imagine that all the information is available for EMA to make their decision. And we have certainly been addressing every question that's been raised. So I'm very confident in the responses that we've given, in the data that we've generated, and actually in the just overall product launch.

Umer Raffat Analyst

Got it. So maybe speaking of launch then, my math was that if the drug can do $1 billion in the U.S., it pays for the deal without even having any EU on board. Do you guys still have that opinion that EU is upside to where you did the deal? Or was EU part of the valuation you guys thought about?

Priya Singhal Executive

I don't know that I would comment on that. I might defer to Chris or Chuck to comment on the numbers.

Umer Raffat Analyst

Okay. Okay. Fair enough. Fair enough. Anything else on SKYCLARYS, Mike, number one?

Michael DiFiore Analyst

No.

Umer Raffat Analyst

Okay. Okay. So maybe perhaps let's continue the discussion a little beyond. Sage, can you remind us where we stand now, launch expectations, et cetera?

Priya Singhal Executive

Yes. So we're very excited to be bringing a product for postpartum depression vis-à-vis to mothers in the United States. And so really, Sage teams and the Biogen teams are working very closely. We have all our sales reps. It will be ready and available in December 2023, and we will initiate the launch activities after the holidays in early January 2024, just because of logistics and the holidays.

But we're very excited. Specialty pharmacies are on board. We think that the payer discussions will continue to happen over 2024. Some will do this quickly, some will take their time for their policy and timelines, but we believe that broadly, they'll get there. So we remain very encouraged.

And we are trying to do this very, very methodically, and sort of systematically, we will scale. So we'll start small, but we'll scale, and we are in total sort of collaboration with Sage.

Umer Raffat Analyst

And what -- I guess, would you have a sense for how much their coverage looks like in January? It sounds like it's a...

Priya Singhal Executive

We haven't commented on that, but I know the teams are working throughout.

Umer Raffat Analyst

Okay. And I feel like I have -- I used to track it much more closely than I have more recently, the scheduling, how did that shake out?

Priya Singhal Executive

That was scheduled for as expected.

Umer Raffat Analyst

Scheduled for as expected.

Priya Singhal Executive

Yes. No surprises.

Umer Raffat Analyst

Got it. And from an abuse liability perspective, has there been any patient or clinician feedback on what if someone takes multiple pills all of a sudden versus not?

Priya Singhal Executive

Not that I'm aware of, no.

Umer Raffat Analyst

Okay. Okay. Excellent. Mike, anything else on this?

Michael DiFiore Analyst

I know with zuranolone -- a lot of work has to be done in terms of changing a paradigm of treating depression. You've been out in the field talking to KOLs, I'm sure you have MSL deployed. What's been the feedback so far? I mean your chart -- I mean the list price is $16,000 for a 2-week course. Number one, have you gotten any pushback from positions on the price front?

And number two, any new updates regarding the attitude toward treating depression with an agent like zuranolone?

Priya Singhal Executive

Yes. I think that people are really waiting is the feedback we've received from both KMEs and from patients. They are really waiting for this drug to be available. It's a very high unmet need, 1 in 8 mothers experiences it. And the under-diagnosis is huge as is the under-treatment.

The fact that it's only a 14-day treatment is being seen as a very big positive. It's also only 1 time, and it can be titrated down as needed. So I think that these are big positives, and the price and all of that was really based on extensive research that was done, inclusive of KMEs and done with a lot of effort. So nothing really that is surprising except that patients are waiting, which is why we're making it available in December, although we are launching officially kind of all the activities in January.

Umer Raffat Analyst

And for the initial launch, are payers requiring that the patient should be on some antidepressant already before this is added on or that's not necessarily the case?

Priya Singhal Executive

Not that I'm aware of, no. It could be a monotherapy.

Umer Raffat Analyst

Okay. Excellent. Mike, anything else on zuranolone before we keep going?

Michael DiFiore Analyst

Any update on plan for the actual MDD indication?

Priya Singhal Executive

Yes. That was a big disappointment. And really, as we've communicated with Sage, we are engaging with the FDA to really consider what are the next steps, whether that is a path forward or not. But we're not -- this is not something that I think we can figure out overnight. So it will take some time to figure this process out.

Umer Raffat Analyst

Got it. As we go beyond, Priya, the obvious, and we just spent a lot of time on obvious, the Alzheimer's, the Reata EU, we talked about zuranolone. There are pipeline programs, which will inevitably get a lot more focus now. There's a BDCA2 in lupus. You have the ASO.

You have the CD40. There's an ALS molecule, and obviously, the oral BTK as well. How are you thinking about prioritizing? Which one is highest on your mind? And we can go down the direction on a couple of those perhaps in the limited time.

Priya Singhal Executive

Yes. We spent a lot of time thinking about how do we prioritize. And I think we landed in a great place in '23. And the way we do this is being very scientific and going to decision points. That's literally how we go about it.

So the top one for me is BIIB080. We shared a very exciting data at CTAD. And you could say it's a very small trial. It's only 47 patients. It's a 1b.

But why is it exciting? It's exciting because of the convergence of the biomarkers and emerging clinical data as well as objective imaging biomarker of tau PET, and it's very exciting because we know that you can tackle amyloid, but you also need to tackle tau. And when you look at amyloid agents that tackle tau and you look at BIIB080, it's orders of magnitude. Small numbers, lots still to come, a lot to prove, but very exciting. So we've doubled down on it.

We are in Phase II. It's a global trial. It's called the CELIA trial. And we are looking at 2 dosing paradigms, 6 monthly and quarterly and 3 doses. We also saw a dose response in this very small trial.

So very exciting, I want to say, footholds that we are trying to confirm in our Phase I trial.

Umer Raffat Analyst

And when is that reading out?

Priya Singhal Executive

We haven't said when it's going to read out, but I think we're looking at multiple ways in which we would think about a readout. So we've got many options. We've got options in our protocol of looking at the data earlier. We've got options -- it's a Phase II trial.

Umer Raffat Analyst

2025 could be a possibility?

Priya Singhal Executive

I can't confirm that. Okay.

Umer Raffat Analyst

No problem. The oral BTK, you have a second one now in Phase I. Can you speak to your confidence on the liver safety on that one relative to the first one?

Priya Singhal Executive

Yes. Before I can get that, I want to address what you raised earlier. We've got very important inflection points in an ALS, ASO, BIIB105, mid-2024 as well as the [indiscernible] product that we have, which we believe is differentiated from the Roche and Ultragenyx BIIB121. And we've got litifilimab and dapi. Dapi will read out its first Phase III mid-2024.

So we've got several readouts in 2024.

Umer Raffat Analyst

And the lupus readout.

Priya Singhal Executive

Yes. For dapi, anti-CD40 ligand. And then you asked about BIIB091.

Umer Raffat Analyst

The BTK.

Priya Singhal Executive

BTK. Yes. So we believe that really the liver toxicity is related to the covalence which, of course, gets you the brain penetrance, but it could also result in liver toxicity, and we've seen this across the class. So we are pretty convinced. As you know, we stopped orelabrutinib, our own -- the one that we had acquired from -- collaborated with InnoCare, which was a brain-penetrant, covalent BTK inhibitor, and we have now pursued forward with BIIB091, which is a noncovalent BTK inhibitor, but we think we've seen a lot of class-related exciting data, and we think our product is differentiated.

Umer Raffat Analyst

Could this be accelerated, a Phase III relatively fast based on some early observations?

Priya Singhal Executive

Well, we've got a lot of ways in which we're thinking about how do we get a readout, which is going to be -- and what's our barometer, is it OCREVUS, is it something else? So we'll be looking at that very closely. As I said, we are being very, very thorough and systematic about what are our readouts and how do we select our go, no-goes, and where will we double down versus walk away, which is why we walked away from orelabrutinib, but then double down on BIIB091.

Umer Raffat Analyst

Got it. So maybe in the last couple of minutes, I know you mentioned CD40 ligand with the Phase III lupus readout, some annexure. I think the dose response and efficacy was not very linear. Can you speak to that, and if that introduces risk into the readout or not, and whether you have any interim data?

Priya Singhal Executive

Yes. So I think what you're referring to is the Phase II did not meet its primary endpoint. But it was related to BICLA as well as dose response. And we saw the dose response across, we thought it was compelling, although the p-value was 0.06. So we thought it was compelling, and that is why we took it into Phase III.

So we'll wait to see the readout, but we think this is important.

Umer Raffat Analyst

Got it.

Priya Singhal Executive

It will need another Phase III if it's positive. That's the base case for filing.

Umer Raffat Analyst

And are you -- has there been any interim data endpoint?

Priya Singhal Executive

Not so far, no.

Umer Raffat Analyst

Got it. Okay. Excellent. Mike, anything else we missed?

Michael DiFiore Analyst

Yes. I just want to touch briefly upon BIIB105 for ALS. A lot of changes to the trial design occurred last year, I mean added some maintenance doses in 2 of the cohorts. You also added the ALSFRS as a secondary endpoint. Maybe talk us through why those were done.

Priya Singhal Executive

Yes. Very good question. I think that just stepping back, BIIB105 is an ataxin-2 ASO. So what we believe in the biological hypothesis is that some patients have an ataxin-2 mutation, and they go on to develop ALS, but we believe that this is relevant and a central node for TDP-43 accumulation in sporadic ALS. And so we've got a small cohort of ataxin-2 mutation patients, but also all comers.

And we learned -- so remember, all this was happening in parallel. We had our readout on SOD1, toferson/QALSODY. We learned a lot about how neurofilament behaves, what are the levels of neurofilament activity that we need to see that could predict clinical activity and

clinical benefit. So we incorporated all of that so that we could get confidence in our go/no-go criteria. That is why we made changes.

We expanded the highest dose cohort, and we made sure that we had all the data that could give us a clean readout. That was the reason because we now have a lot of internal data from our failed C9orf72 trial on neurofilament and positive trial on SOD1. So we believe we kind of have the really important dataset to have neurofilament predict in the BIIB105 trial.

Umer Raffat Analyst

And what do we learn then specifically in mid next year in the readout?

Priya Singhal Executive

We will see whether it's a go/no-go...

Umer Raffat Analyst

And the data specifically is what?

Priya Singhal Executive

It's all the end points. We have clinical endpoints. We have biomarkers. We have everything. It's quite a comprehensive slate.

Umer Raffat Analyst

Fantastic. Well, unless any more questions from the audience, we're going to go ahead and wrap it up. Thank you guys for being here.

Priya Singhal Executive

Thank you for the great questions.