Biogen Inc.

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Event Participants

Analysts 1
Paul Matteis

Executives 1
Priya Singhal

Paul Matteis Analyst

Great. Thank you. Good morning, everybody. It's my pleasure to be hosting this panel with Priya Singhal, Head of Development and now also Interim Chief Medical Officer at Biogen. Priya has done this panel with me a couple of years in a row, and there's always a lot to talk about.

So we really appreciate your time, Priya. Thank you again.

Paul Matteis Analyst

Maybe just to kind of kick things off, it would be great if you could just give like a 10,000-foot view of the Biogen pipeline, things have been sort of reshaped, right, with the leadership change at the company over the past, say, 1.5 years. And I guess, maybe on a forward-looking basis, how satisfied are you with where you're at? And what areas or technologies are you looking to kind of increase your exposure to as things continue to unfold?

Priya Singhal Executive

Sure. Thank you, Paul, for having me, and happy to be here. So before we begin, I just wanted to point out that I'm going to be making forward-looking statements. These are based on our current expectations and beliefs. And they are subject to certain risks and uncertainties, and our actual results may differ materially.

I encourage you to consult the risk factors that are in our SEC filings for additional details.

I believe that we've made significant progress over the last year bringing about kind of a new Biogen as we prioritized our pipeline to invest really where we believe we can deliver the greatest return and enhanced value. We've also completed the Reata acquisition. And we

realigned the company's structure and overall cost basis to support the best future growth.

On the commercial side, we see that this is an execution year relative to our new product launches, Alzheimer's, Friedreich's ataxia, postpartum depression. And on R&D, I wanted to focus on the fact that we continue to establish LEQEMBI in the marketplace. We have an opportunity to build on the launch of LEQEMBI with potential subcu formulation, maintenance dosing as well as preclinical AD.

We are also continuing to expand our leadership in Alzheimer's disease with advancing assets targeting tau. And we believe that tau could represent yet another aspect of the future of Alzheimer's disease. So this is our focus on our ASO targeting tau, which is BIIB080. We also think that we have a significant opportunity in lupus, where we've got multiple programs in SLE and CLE with the potential to contribute to revenue in the back half of the decade.

There's a lot we believe to be excited about in the Biogen pipeline. And there are a number of inflection points this year that we can speak about during the session. But I wanted to share that one of our goals is really to continue to increase the productivity of the pipeline to help ensure that we have a regular cadence of drug launches.

And as a leadership team, we understand there's more that we can do on this front. So we also have a very keen eye towards evaluating external opportunities. I work very closely with the Head of Research, the Head of Corporate Strategy. And we think there's a lot more potential to expand beyond neurology into immunology and the rare disease space.

We also think that while we did a very concentrated effort last year on R&D prioritization and it's substantially complete, I expect this to continue to be a dynamic process that is data- and evidence-driven. So that will continue to evolve.

And from a pipeline perspective, we're focused. You've asked about technologies. Well, we have the expertise on small molecules, biologics, ASOs. And Jane Grogan, our new Head of Research, also brings in a lot of expertise on cell and gene therapy. So we'll be continuing to watch and evaluate the potential of all of these spaces as they mature and evolve.

Paul Matteis Analyst

Sorry, taken myself off mute. All right. That's an excellent overview. I naturally have a lot of questions on different programs that you've laid out. I think the one clarification I would love to kind of think through just in your aspirations and business development side is what's your updated thinking on -- within immunology, which areas are adjacent, right?

We can talk about maybe like one of the spectrum, MS, which is just like purely synergistic and, at the other end of the spectrum, mass-market immunology like psoriasis.

So kind of where can Biogen fit within there? And similarly, on the rare disease side, right, we could talk about rare neuro, like you did with Reata, or we could talk about the lysosomal storage disorder space that's completely different. So how do you kind of think about expanding while also sort of overlapping with your preexisting expertise?

Priya Singhal Executive

Yes. Overall, what I can tell you is that we believe that we've been in the immunology space. We have a lot of expertise internally. And we have two very large programs in SLE, one with additionally in CLE as you know. In addition, I would say that we are looking at neurology, specialized immunology as well as rare, not necessarily as individual verticals, but they could also intersect.

And this is where you see us playing with specialized immunology, SLE and also CLE, where there hasn't been a treatment in more than 70 years.

Moving from that, you saw us do the acquisition with Reata, where we are looking at Friedreich's ataxia. That is rare, but it's also neurology. So we are really bringing all our collective expertise. And here, I would say it's not just in the disease area, but it's also to leverage the tools that we believe we've been quite successful in. For example, with advancing amyloid as a surrogate biomarker.

We believe we pioneered that within Alzheimer's disease. And then the neurofilament light chain, which is a very important surrogate biomarker, now accepted with the approval -- accelerated approval of QALSODY for genetic ALS or SOD1-ALS.

But we believe that this has ramifications beyond. And in fact, we recently presented data in SMA from the RESPOND study, where we showed that patients who were on gene therapy, SMA patients who received ZOLGENSMA and wanted to have more additional benefit went on to SPINRAZA, the baseline neurofilament levels were high. And almost all patients -- this is, of course, a small study. But almost all patients, their neurofilament levels went down significantly.

So we continue to pioneer across the diseases, and we're looking at biomarkers. Because just to go back to what I said earlier, Paul, our goal is to pioneer but also kind of to drive the results. So we're looking at what is our expertise, what's the domain, for example, in neurology or immunology, that we're really good at and bringing it all together.

Paul Matteis Analyst

All right, excellent. Appreciate it. So let's kind of go through programs and catalysts maybe one-by-one. I obviously have a bunch of questions on lecanemab. But I thought it'd be interesting to start with Angelman's, given that, that's been an area of super-high interest with the progress Ultragenyx has made and it looks like it may be your next readout.

Do you want to maybe talk about that program?

And I guess, as it relates to this Phase I/II study, it's open label. When you think about clinical endpoints on the neuro behavioral side, there can be an element of subjectivity. How are you planning on analyzing this data? And what would you view as an encouraging outcome that would embolden you to advance?

Priya Singhal Executive

Yes. So just to step back, Angelman's is a rare neurogenetic disorder again sort of in that rare neurology with a genetic basis for disease. It occurs in approximately 1 in 15,000 live births worldwide. If you kind of approximate, there are ranges out there, but it's about 500,000

people worldwide. Now the important thing about this, it's a childhood disease.

It's diagnosed in early childhood.

It's characterized by symptoms like severe developmental delays, speech impairment, problems with movement and balance. And it can also involve seizures, which can be quite a burden of disease. There is no treatment that has been approved so far for Angelman's. And patients and individuals with Angelman have a near-normal life expectancy. But they could generally require continuous care.

They are unable to live independently, which naturally places a huge burden on families, caregivers and society and, of course, the patients.

The biological basis of the disease is that the paternal allele of the UBE3A gene is silenced in neurons, leading to expression -- this is normal. This is a normal individual, leading to expression of only the maternal allele. Whereas in Angelman syndrome, that maternal allele is either absent or is inactivated through genetic mutation, leading to a loss of the UBE3A gene expression. And therefore, there's an impairment of the synaptic connections and brain network activity, which you can see would result in all the symptoms that I described.

And this can also be visualized, and this is important, by an increase in slow brain waves or delta waves when compared to neurotypical individuals. What BIIB121 aims to do is to remove the silencing of the paternal allele to restore the expression of the UBE3A gene. So that's the causal basis of disease and that's how our antisense oligonucleotide aims to act. That's really the mechanism.

Now you're right, the Phase I study that is known as the HALOS study, it is an open-label study. It's a multiple ascending dose study across multiple age groups and dose levels to look at safety and tolerability as you would in any Phase I program and Phase I study of BIIB121 in Angelman's. But what's important is this is in patients. So that's the first point to remember. It's across very important age groups and different doses.

And importantly, the study also utilizes two key aspects that I want to mention.

One is clinical measures that we can look at, assess to look at therapeutic potential, and the other is EEG assessment. So speaking about the clinical measures, they are the Bayley Scales of Infant and Toddler Development Part 4, which is a direct measure of functioning across multiple domains like cognitive functioning, growth in fine motor skills as well as symptoms of Angelman syndrome, Clinical Global Impression, which is another scale that captures the clinical impression of the patient. We're also looking at EEG. So we're selecting EEG data on all patients.

So we can look at these measures. There is natural history in this disease area because not all disease areas have that. And we can assess whether we are seeing an efficacy signal. So this is a Phase Ib study. The ideal situation would be that we have an idea whether we are seeing a signal or not seeing a signal.

Because that brings us to a decision point and we can opt in. And once we opt in, we would be generally aiming to go to a pivotal trial in this rare disease population.

So we are looking to isolate a signal that we believe is real. And we're going to do that based on clinical measures as well as EEG findings and put it all together to compare it with natural history. We also -- this study, just to remind you, is a multiple ascending dose portion. But we also have a long-term extension of various cohorts. So we'll have the opportunity to examine longer-term data as well.

And overall, thus far, what we've seen is no disturbing trends on safety and tolerability. It looks okay. And EEG data that Ionis had put out a press release early toward a trend towards slowing of delta wave activity. And the clinical-assessed -- clinician-assessed endpoints through a majority of participants demonstrate some level of improvement in overall functioning. So we've seen those very early results.

Now we're in the process of really taking that up and looking at it holistically. And that's when we'll make our decision on go/no-go.

The other important thing is that we are very disciplined. And we, at Biogen, we do design our own go/no-go criteria a priori. And this is in consultation with key opinion leaders and others in the space on what would be clinically meaningful across these different scales. And these are the scales that clinicians use. So we believe while, of course, a lot of work lies ahead, if we truly see a signal, it's achievable and addressable as we go forward.

Because it would be a pioneering effort. There isn't another precedent here.

Paul Matteis Analyst

That all makes sense. I have one follow-up question, Priya. For Angelman's, how variable is the course of disease? And I guess, when you think about in an open-label study, if you saw some level of improvement, do we see some patients continue to get better over time, naturally some patients stable, some worse? Like what's the spectrum of that?

And I guess, maybe to put that into context, like how much better do you need to be the natural history to be confident that an efficacy signal is real in a study like this?

Priya Singhal Executive

Yes, it's a very important question and one that we consider all the time when we look at trials like that in rare diseases with open-label data. So one is we are curating natural history. So we know what that variability is. And we have the opportunity to design our own go/no-go that give us confidence that this is not noise. So that is important.

And we won't be doing this alone. We have external input. We have internal expertise. So we'll be kind of coming up with those holistic criteria that help us get confident that we're seeing the change. The other thing is that we'll be looking at EEG findings as well.

There is variability and there is different variability across different age groups. So that is something we are keeping very much in mind.

Paul Matteis Analyst

Okay, makes sense. Now if you move forward here, how do you think about a pivotal study and an endpoint in a pivotal study? Do you need to create a new scale? I think others have

talked about that. Or do you feel like the endpoints that you're currently looking at in this Phase I/II, one or multiple of them could actually be suitable?

Priya Singhal Executive

Well, currently, based on our engagements with experts in the space, we believe that these are the scales that they use. These are the scales that could be used to design what is a clinically meaningful difference from natural history. So we believe they're going to be very important. It's not the scales. So I think that where we are is we believe these have objective components that will be important for the endpoint.

We think these could serve as endpoints.

But of course, we will be engaging with regulatory authorities to really make that call on what is the appropriate endpoint. But at this point, I think EEG as well as the Bayley and the Vineland assessments and CGI change are all going to be important components, if not potentially individual scales, that we would include in a pivotal trial. But we haven't come to that point yet.

Paul Matteis Analyst

Okay, okay, great. Last question here before we switch to lecanemab and the kind of key subcu question. Just on Angelman's from a competitive perspective, we've done our own analysis of comparing across programs, across mechanisms, preclinical data. And at least our high-level conclusion between your molecule and the Ultragenyx molecule is that there are some key mechanistic differences in how they actually bind to the target.

It looks like Ultragenyx' molecule may be more potent but may have a more narrow therapeutic index. I don't know what your reaction to kind of that at least view would be, if you agree or disagree. But do you want to at least talk a little bit about how your molecule is similar and how your molecule is different and, I guess, your level of confidence that it may be the best program here?

Priya Singhal Executive

Yes. So the BIIB121 ASO, it has a 2-methoxyethyl structural backbone. This is similar to SPINRAZA. That is really how we have developed the -- Ionis has developed the ASO. The Ultragenyx ASO has an LNA backbone, which is similar to rugonersen, which was discontinued by Roche last year, when they saw the efficacy from their Phase I.

We have done internal studies. And we believe that there's a different response curve between the two backbones.

And we think and we believe that the 2-methoxyethyl structural backbone is the better backbone to have in the ASO. So that's one point to note. And we have done internal studies. The second point I think here that's important is we have not seen safety signals with BIIB121. And thus far, patients are tolerating the highest dose in the current HALOS trial, which differs in comparison to the Ultragenyx GTX-102, which did have adverse events under higher doses.

And ultimately, they have resumed after clinical hold at much lower doses. So we think there are several things, that there's potency, there's ability to go to the right dose and there's also the dosing frequency. There again, our assessments have shown us internally that the way we dose BIIB121, which is for the first 2 months and then every 3 months, is important because this is based on our PK/PD data that suggests that Q3 administration is required to see the clinical benefit in Angelman's.

This is different from Roche's rugonersen, which also has the LNA backbone where they did it every 6 months. So we think there are significant differences. And I also want to say that when rugonersen was discontinued, the way we kind of practice internally, if we see that as an external trigger for our own portfolio and we go back and relook at all our data and we confirm or say that our assumptions don't hold anymore. So we believe that this is differentiated. It has the potential to deliver, so we wanted to see it through.

So that's an important point as well.

Paul Matteis Analyst

Okay, great. I look forward to that data. Let's switch gears to lecanemab. I think the key question here that you've probably been asked many times but will going to continue to get asked probably until the PDUFA is really whether or not we have enough safety data for the subcu to derisk approval. What's your kind of latest on your level of conviction that the sBLA filing here is derisked and that you and Eisai are aligned with the FDA?

Priya Singhal Executive

Yes. So just to clarify a couple of points, one is that the subcutaneous Eisai has communicated, this will be a BLA, not an sBLA. That's one point to communicate. The second is that we also have an IV maintenance filing that's going in and in planning. That is an sBLA.

So there's two filings we're talking about. We're talking about a subcutaneous maintenance filing and we're talking about an IV maintenance filing. There is a difference in one being a BLA and the other being an sBLA.

Coming back to the subcutaneous data, I think when we -- when Eisai presented this data at CTAD, what was really, really important about that data was that the 6-month data with the 720 milligrams with subcutaneous sub-study of LEQEMBI in Clarity AD Phase III OLE showed comparable results across PK/PD and safety compared to the IV formulation. We believe that this data supports bioequivalents with IV. And there is a potential viability of a subcutaneous formulation of lecanemab. Thereafter, there have been multiple engagements, Eisai has spoken about them, with the FDA on the data. So that's one piece to kind of keep in mind.

A big focus of the subcutaneous sub-study data was plaque removal. So what we were looking at for bioequivalence on PD was plaque removal. We saw this. We saw this in the treatment-naive individuals, the cohort of 72. But I do keep reminding audiences that we also collected data in Clarity AD in more than 300 patients, who received IV LEQEMBI and then switched -- during the study and then switched to subcutaneous formulation after 6 months of IV treatment.

This is important, we're continuing to collect data across both these cohorts.

On the regulatory front, Eisai has announced recently that the regulatory filings for subcutaneous would be split into two separate filings. So Eisai first aims to file -- submit the filing for maintenance subcutaneous with an auto-injector following -- that is following 18 months of biweekly IV treatment. A separate filing is being planned for the subcutaneous auto-injector induction phase, which is the first part before the plaque clearance, 18 months. And we believe that the potential here is for a lower dose of subcutaneous AI in the induction phase, which has the potential to optimize the patient experience and potentially may also have impact on a slightly different rate of ARIA.

But really, the focus here is to optimize the dose for induction based on the 6-month data that we had at CTAD, where we saw that we met bioequivalence. Because that was really the first hurdle. Can a subcutaneous dose actually remove plaque? That's a checked box at 6 months. The question is what's the dose for -- what is the right dose for induction?

And is there a potential that it could reduce it? So we are in discussions. This is requiring additional engagement, and we're continuing to do that. And Eisai has also provided some dates externally very recently that the AI maintenance, they expect in the second half of the fiscal year of 2024, which is their Japanese fiscal year. So it's October 2024 to March 2025.

And then for the auto-injector induction, they expect that by fiscal year 2025, which is March -- by March 2026.

So overall, there's been a number of discussion, number of meetings with the FDA as the data have emerged to really discuss the design of a potential -- what is the right filing strategy, what should be filed first, what should be filed second. Eisai is, of course, the regulatory lead here. They lead these engagements. But Biogen has a seat at the table in all of it. And we review all the documents.

So it would be tough to speculate on what regulators will ultimately decide. But when I look at the data that we generated at 6 months and the patients' unmet need and the importance of this formulation, I think we are going to see progress as we continue to move forward.

Paul Matteis Analyst

I have two quick follow-up questions. So why is it its own BLA? And are there any -- is there anything implicit there on the leverageability or lack of leverageability of the data from the IV? And then as it relates to induction, given this kind of ongoing discussion around the right dose, are you comfortable that you have the clinical data to answer that question and that you're not going to need to generate more clinical data?

Priya Singhal Executive

So the first thing is that it's a BLA because it's considered by FDA as a combination product. It's as simple as that. It is important that it be filed as a BLA because it's not really supplemental. Second question about the clinical data, we believe that amyloid reduction is the right PD endpoint. So we don't believe we need a clinical study.

There may be like PK/PD and all of these types of things that need to be done but certainly

not a clinical outcome study.

Paul Matteis Analyst

Okay. But you might need -- but does that mean you don't think you'll need to treat any more patients with different dose levels, even just...

Priya Singhal Executive

We may need to for the induction piece. So for the maintenance, we believe we have the package and we're working towards submitting that. That's the SC auto-injector maintenance filing. For the SC auto-injector induction, we will have to generate some data, which is why we have communicated the fiscal year 2025 as when they think that, that will be possible. But we're not talking about a Phase III study here.

We're talking about...

Paul Matteis Analyst

You're talking about [indiscernible]. No, it makes a lot of sense. Okay. In your view -- or I guess, look at face, right, the ARIA rate for subcu is nominally higher than was reported at IV. In your view, is the ARIA rate actually higher for the subcu?

Or is this noise? And would you expect the modern requirements for subcu to be different or more burdensome than the IV?

Priya Singhal Executive

Yes. In my personal view, I think it's very similar, very similar. I have said this before. We have a very small sample size that was lecanemab-naive. It was 72 subjects.

It was considered adequate for PK/PD. But of course, it's not the size of a large trial. But what we saw importantly -- so I'll walk you through the incidences.

The incidences with IV in Clarity AD, where the n was 898, it was a large n, right, was 12.6% for ARIA-E, 17.3% for ARIA-H and 8.9% for isolated ARIA-H. In the SC sub-study with 72 patients, we saw 16.7%, 22.2% and 8.3%. So we don't believe these are significantly different. That's number one.

Number two, with ARIA, we have collected a lot of data across so many trials. We really understand how ARIA is characterized, not only in terms of incidents but in terms of frequency in APOE4, non-APOE4, severity, need to discontinue, need to change the clinical dosing, all of that. And from that perspective, the characterization remains the same. The monitoring protocol, the characterization, all of it remains the same. So we don't believe that it is significantly different.

That said, if there's a very significantly different dose in the induction phase, as we are currently evaluating, it is possible it could be different. But I don't expect it to be characterized differently. I think it will fall in a similar pattern because that is what we've seen with ARIA.

Paul Matteis Analyst

Yes, okay, okay. Fair enough. Last lecanemab question, and we have, I think, another 12 minutes, so I want to touch upon the lupus programs, the anti-tau program, which is super interesting. But just on lecanemab, look, I'm saying this as a lecanemab optimist. I think I've been really surprised by the pace of the launch.

I think other people have been surprised, too. We knew about all the logistical impediments.

But it's Alzheimer's, right? Like I thought there would just be more of a push in the neurology community to figure out these things faster. I guess, when you think about subcu, where would you rank order the burden of biweekly IV administration on the impediments to lecanemab uptake? And do you think subcu moves the needle modestly, moderately or really significantly when we think about a launch inflection?

Priya Singhal Executive

I think that the biggest hurdle we are seeing so far across Eisai and Biogen and all the discussions and efforts we are undertaking is really access to a neurologist and getting our patients on the treatment pathway. It's not really the Q2 biweekly IV. That said, I think if we had the option, we have always embarked upon subcutaneous as a convenience option for patients. I think it's going to be important. So it's going to be important.

But is it going to change the inflection of uptake? Maybe modestly.

Because really the problem that we're seeing right now, the bottleneck is getting access to a neurologist. Once you get access to a neurologist and once they are committed and agree on treatment, the rest can fall into place. We know that there's elasticity on the infusion centers. While they can be difficult in the beginning, we've seen several centers, several individual neurologists overcome that hurdle. So we don't see it as a major stumbling block.

Where we, Eisai and Biogen, believe subcutaneous could be really important is in the potential preclinical or presymptomatic space. And this is an important inflection. Because as you know, we have the AHEAD 3-45 study, where we are looking at presymptomatic patients. And in that population, you can imagine that subcutaneous dosing could be important. So establishing it now and continuing to build on the foundation, hopefully, we will see success and optimism at the end of the AHEAD 3-45 trial.

That would be a very good place to land for subcutaneous formulation. Because that's a population that can easily self-administer. Because they really do not have the cognitive unfortunate impairment, right, that patients with early AD do. So if you step back, that's where we think and that's why we continue to believe this is going to be important and also to define the dose for the induction phase.

Paul Matteis Analyst

Yes, okay. All right, makes sense. Appreciate it. So let's talk about the two lupus programs you have in Phase III. And I guess, is it litifilimab and dapirolizumab?

Did I say those right? Okay.

Priya Singhal Executive

Yes, you got it right.

Paul Matteis Analyst

I didn't even have to practice. That's great. How do you look at the strength of the data for each of these? Is there one that you think has a higher POS than the other? And maybe just kind of give us the scope of this program and where you are excited, where we should be a little bit cautious maybe.

Priya Singhal Executive

Yes. So overall, we are excited about these programs. We believe that they deserve to have progressed to Phase III. And we think that this is going to be very important data. SLE is a very heterogeneous disease.

And there are many ways to assess progress and improvement. So I want to first talk about litifilimab because this is really an important Biogen program. As you know, it was born at Biogen. And the Phase II LILAC study, which is really an important point here, met its primary endpoint in both Part A, which was SLE, and Part B, which was CLE.

The other -- I mean, I don't know how much time you want to spend. But I think what's really important is that it's a very exciting program because we saw really statistically significant differences in Part A and Part B. And we are using the SRI-4 in our Phase III program. But in the LILAC study, we saw that this was also different. It's because of the lack of multiplicity control and consistent with standards that -- and it was a secondary endpoint.

So we didn't say it was statistically significant. But we saw a very important difference there.

So this is important because it's a first-in-class humanized IgG1 monoclonal antibody. And it works through the BDCA2 pathway, which we believe is expressed on plasmacytoid dendritic cells. And that is what reduces the type I interferon. And type I interferon clinical significance path, kind of working through that pathway has been established in SLE. But we believe that this is going to be an important approach to drug this pathway.

So we think it's a very important candidate. We also think that CLE is a really important opportunity. There have been no treatments in 70 years. In SLE, there continues to be a high unmet need. So we remain very focused on our TOPAZ study, two Phase III TOPAZ studies, and our CLE AMETHYST Phase II/III study.

On dapi, it's another mechanism. It's an anti-CD40L or ligand pegylated Fab. And this is in collaboration with UCB. It's a very important inflection point for us this year. We'll be reading out on the Phase III, on one Phase III.

The underlying assumption is that we would need a second Phase III if it's positive. But we are being very clear about how we proceed with it. So rather than having two, we have one. And here also in the Phase IIb study, the primary endpoint was a dose response in dapi with dapi in SLE patients at week 24 were using the BICLA and prespecified dose response models.

And although this endpoint wasn't met, we saw that dapi was very generally well-tolerated and demonstrated separation -- significant separation versus placebo on multiple clinical and

immunological parameters, so higher proportion of patients with BICLA responders, higher proportions of patients with anti-dsDNA titers lowering as well as complement level lowering as early as week 8. So we think this is going to be important and we're waiting for the readout.

Paul Matteis Analyst

Now I guess, to that point, right, given you're doing one study now, you may need another one, there was also another CD40 ligand strategy here that I think in a slightly different indication, was it lupus nephritis, that didn't work. Is it safe to say that this is the higher risk of the two programs and, as a result, you're proceeding more cautiously? Or is that not a fair depiction?

Priya Singhal Executive

Yes. I think it's a different approach. I think the risk here isn't really about the pathway. We think the pathway is really important causally. But it didn't hit -- it didn't meet its primary endpoint in Phase II.

And we believe that, that's because of the prespecified dose response. So that's our assessment of [indiscernible], but it didn't meet it, versus litifilimab that had met its primary endpoint in both CLE and SLE. So I think that is a distinction.

And so we are being very objective in how we invest in Phase III programs. And that's what you'll see come July here, how are we investing in a Phase III program. But it does not reduce my enthusiasm for the pathway and for our belief that, yes, if we can design the right trial and have the right patients, we can actually see an impact of the pathway.

With regards to the BI failure for CD40L, we think it's distinct. It was lupus nephritis. It's a very -- as you know, it's a very -- lupus overall is a very complex and heterogeneous disease. So ultimately, we'll be looking for a meaningful change on primary endpoint and key secondary endpoints. And I wanted to say that it's not about -- right now, our understanding of a registrational package is we will require two studies.

But we're still being deliberate, we're doing some planning. But we're not going onboard and starting a Phase III. So that's how we're thinking about this. And we think BICLA is a very sensitive and clinically meaningful composite measure that will require modification and improvement across multiple body systems with a moderate or severe baseline and without the need for escalation to background medication.

So we designed the trial to give us an answer in that population. And we saw encouraging results in that population. So what we've taken is our belief from Phase II, translated it to the right design for Phase III. And in that, we feel we will get a very clear answer. But we're excited about the pathway.

Paul Matteis Analyst

Okay, okay. Great, Priya. So as you saw from what I said, right, that there were probably five more programs that I wanted to ask about. But I think of all those, in our last few minutes here, I really want to talk about the tau program. And maybe I'll give a quick preamble of our perspective and this will help hone in our conversation.

From our perspective, right, tau is an excellent target in Alzheimer's. It's a challenging target for monoclonal antibodies because it's largely intracellular and your anti-tau ASO has shown really interesting data on tau lowering that I don't think anyone else has seen before. So that all looks great.

I think the two main questions that we have here are really, one, will knocking down tau at the source be safe? So maybe you can talk about that. And then two, you're embarking on this kind of larger Phase IIb study. When we think about the scope of this program, right, is that -- at this point, do we just kind of have to wait 2 or 3 more years to get a real answer? Or is there any sort of upside to that?

Priya Singhal Executive

Yes. So I think overall, thanks for raising this, I think it's an underappreciated asset in our pipeline. We are very excited. It's really the hallmark -- second hallmark beyond amyloid. And the preclinical data are the most direct evidence for target engagement for BIIB080 or anti-tau ASO.

So we looked at -- I'm going to speak first to really what gives us confidence that knocking down tau won't be toxic.

So just the current understanding of the biology of tau is that there's redundancy in the biological processes that tau participates in such that knockdown has an important impact on pathologic gain of function but not on the physiologic function. This has been published even more recently by Chang in 2021.

In mice, complete knockout of tau is tolerated and animals are viable. But to date, five different tau knockout mouse lines have been generated and phenotypically characterized. In all five lines, no overt phenotype has been reported in adult mice. But age-related older mice or cognitive deficits have been reported in some models, suggesting that complete tau knockout on motor and cognitive functions in animals is inconsistent and inconclusive.

Now moving on from that, we have access to the UK Biobank and we've done -- our translational sciences team has done an extensive amount of work on this particular question, genomic assessment of the loss of function tolerance of tau. So basically, when we look at experiments of nature that are analogous to tau knockdown suggests that if you have heterozygous loss of function of tau in humans, it's likely to be tolerated. And we've seen that pharmacological down-regulation of tau in an adult may not have the same effect on a potential safety state as a long -- lifelong genetic loss of function of tau.

In our study, in our Phase Ib study, we saw about 50% -- 50% to 60%. But we also saw a convergence, as you'll remember, of the fluid biomarkers that are representative of tau many weeks after the last dose, 16 weeks after the last dose, continuing to be sustained. We also saw a reduction from all areas of the brain. And we saw an emerging clinical profile that looks like it's having an effect. So we believe, and we haven't really seen -- I mean, obviously, it's been a very small study.

So we haven't really seen clinical data beyond what we've shown you at CTAD and previously at other congresses in 2023.

But we are very encouraged with where we are. Do we have to wait it out? Yes, because I think from a tau perspective, what we see internally has -- we believe this is the program to invest to lead here, invest to win, invest to lead. So it's a real priority. We are recruiting for the CELIA trial.

It's a large trial. And what we really need to isolate is what's the right dose and what's the right dosing paradigm. Because this is intrathecally delivered. So we're looking at quarterly as well as biannually. And this is based on our understanding from the Phase Ib trial.

And we're looking at three different doses.

So this is important. The primary endpoint is CDR-Sum of Boxes at 18 months. But we'll have a lot of other secondary endpoints. And we always have the provision for an interim. But in this case, we may need to really be very deliberate to get those results and build on them.

So we're looking at all the options and we continue to evaluate this constantly, especially in light of the emerging clinical data we saw from Phase I. But I think it is going to be important to stay the course for a couple of years for sure.

Paul Matteis Analyst

All right. Well, thank you very much. I appreciate all the perspective and for giving us a few extra minutes of your time, Priya. So thank you again for doing the panel this morning. And thanks, everyone, for listening.

It looks like we had awesome attendance on here, and I appreciate those who sent me question. Sorry, I didn't get to everything. But I hope you stick with us for our next broader neurology panel with Steve Paul.