Investor Meeting - Key Opinion Leader *(Corrected version)*

Event Details

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Company: Gain Therapeutics, Inc.
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Company Participants

Gene C. Mack - Gain Therapeutics, Inc., President, Chief Executive Officer & Director
Roy Alcalay - Tel Aviv Sourasky Medical Center, Chief of the Movement Disorders Division
Peter Lansbury - Harvard University, Professor of Neurology
Jonas Hannestad - Gain Therapeutics, Inc., Chief Medical Officer

Other Participants

Jay Olson - Analyst
Raghuram Selvaraju - Analyst
Thomas Shrader - Analyst
Jason Wesly McCarthy - Analyst
Maanasa Sangeetha - Analyst

MANAGEMENT DISCUSSION SECTION

Operator

Good morning, everyone. I want to welcome you to the Gain Therapeutics Parkinson's Disease KOL event. At this time, all attendees are in a listen-only mode. A question-and-answer session will follow the formal presentations. Before we begin, I would like to remind you that Gain Therapeutics management may be making certain forward-looking statements in their presentation today. Please refer to this slide about forward-looking statements, which describe disclaimers and risk factors related to such statements and consult Gain Therapeutics public filings made with the Securities and Exchange Commission that can be found on Gain Therapeutics website or at www.sec.gov.

Now, I'll turn it over to Gene Mack, President and CEO of Gain Therapeutics, for opening comments.

Gene C. Mack

Thanks, Tara. Hello, everyone. Welcome and thank you so much for taking the time to join us today where we will provide additional detail on the exciting biomarker evidence further elucidating GT-02287's therapeutic potential that we have observed in Part I or the first 90 days of our ongoing Phase 1b study.

As we announced earlier this morning, patients who completed the first 90 days of treatment experienced an average improvement of 2.2 points on the MDS-UPDRS Part II and Part III combined scores. Previously, we reported a slightly greater improvement from the first 9 patients that completed 90 days. However, the 2.2 point improvement in MDS-UPDRS scores from the 15 patients evaluable from the total cohort is more in line with what we would expect at this stage given GT-02287's mechanism of action. It's important at this point to keep in mind that Parkinson's is a slow moving assault on the brain that remains persistently on the attack for decades after symptoms begin.

Over the course of a year, the bar for clinically meaningful improvement on the combined MDS-UPDRS score is approximately 6 points versus placebo or no intervention. We believe at the 90-day mark in the Phase 1b – in our Phase 1b study, we are witnessing the manifestation of GT-02287 weakening and halting that attack over time, leading to a significant clinical improvement in those scores over the duration of treatment. Our confidence in this outcome is far greater given the biomarker evidence we are about to explain in further detail today, and the stabilization of MDS-UPDRS that we appear to be getting (00:02:20) to witness.

Before I review the agenda, we hope you will take away from this discussion is a better understanding of what we believe is clear evidence that GT-02287 does indeed modulate GCase activity in the brain with now new never-before produced evidence that GCase modulation in the brain leads to a downstream effect and reduction of an important substrate, glucosylsphingosine that is highly implicated in the pathophysiology of Parkinson's, as well as GalCer (00:02:50), which is not currently part of our clinical development plans, but remains another potential route to expanding the clinical development of GT-02287.

Given the stabilization of MDS-UPDRS scores that we are achieving at 90 days, with no changes in dopamine administration for any of the subjects, we believe the biomarker evidence around glucosylsphingosine supports our hypothesis that GT-02287 will lead to a significant and clinically meaningful stabilization of Parkinson's progression that will continue to mature through the duration of the Phase 1b study.

We have a packed agenda today, so here's a quick look at what's ahead. We'll start off with a quick introduction for our speakers. I'll give a quick overview of Parkinson's disease and the breakdown between GBA and idiopathic Parkinson's. And then after that we'll share a high level look at the design of the Phase 1b study. I'll mention a little bit more about the MDS-UPDRS scores and then we'll get to hear from Dr. Roy Alcalay, who will walk us through the importance of glucosylsphingosine in Parkinson's disease. And then next Dr. Peter Lansbury will discuss the utility of glucosylsphingosine in Parkinson's and its implication along with other GCase substrates in Parkinson's disease, biology and broader drug development. From there we'll dive into some of our recent Phase 1b biomarker data with Roy and Peter's context in mind. And finally we'll open up for a live Q&A with our covering analysts and submitted questions if time permits.

So, let's start with a quick introduction of our speakers. We are thrilled to be joined by Dr. Roy Alcalay, Chief of Movement Disorders Division at Tel Aviv Sourasky Medical Center (00:04:28) and a Professor of Neurology at Tel Aviv University. He previously spent many years at Columbia University, where he continues to be involved in research and education. His work focuses on the genetics and biomarkers of Parkinson's disease and he plays a leading role in major initiatives, including the Michael J. Fox Foundation's PPMI study and the Parkinson's Foundation PD GENEration program.

Also with us is Dr. Peter Lansbury, a Harvard neurologist who spent over 30 years studying what goes wrong in neurodegenerative diseases like Alzheimer's, Parkinson's and ALS, and how to turn those insights into real treatments. His lab was the first to work out key properties of alpha-synuclein and he has led several major Parkinson's research centers at Brigham and Women's Hospital. Alongside his academic work, he has also founded and led biotech companies that were later acquired by AstraZeneca and Bial.

Before we dive into the science, let's just take a quick overview of the Parkinson's disease landscape. As you may or may not know, just to set everybody's market knowledge of Parkinson's, Parkinson's remains the second most prevalent neurodegenerative disease in the United States, with about a million patients nationwide. Approximately 15% of those patients carry a GBA1 mutation, which we think has special significance for GT-02287's development pathway given its targeting of glucocerebrosidase which is the gene – which is the enzyme coded for by the GBA1 gene.

And now just a quick overview of the Phase 1b. So, again this was a fairly involved trial design. We started off with a 90-day treatment duration and then a voluntary – voluntary open-label extension beyond the 90-day treatment course. So, we continue to follow patients, those patients who choose to stay on therapy and be able to continue to watch their progress on GT-02287.

So, what you'll hear today is exclusively from the Part I, which we completed in November 2025. A portion of the Phase 1b study, so those first 90 days. 21 patients enrolled in that trial. We had 15 of those patients opt to move over to the extension phase.

With that I'm going to – just go into a little more detail about today's press release. Again, a total of 19 patients – participants completed the first 90-day administration of GT-02287. Four participants were excluded from the MDS-UPDRS analysis, two (00:07:21) patients that were alpha-synuclein negative at baseline, and another two that were measured in their off state, which means the time in which dopamine is – or the time in which they have no symptomatic support.

The average improvement that we saw in that 90 days, as is – as it applies to Part II and Part III of the MDS-UPDRS scores, we saw pain improvement of 0.6 on Part II and an improvement of 1.6 in Part III for a combined score of – combined improved score of 2.2 points. However, there are among 13 of the 15 evaluable patients, we saw a much better improvement of around 4 points. So, there are 2 patients in that cohort that could potentially be outliers that we're continuing to watch and monitor. But for the most part, the majority of those patients have maintained the benefit that they achieved or have been able to maintain the benefit that they achieved over 90 days.

So, with that being said, let's turn things over to Roy, and he'll walk through glucosylsphingosine and the GCase metabolic pathway. Thanks, Roy.

Roy Alcalay

Thank you for having me. So, as Gene said, I'm not going to talk about specifically the Gain product but rather about the glucocerebrosidase metabolic pathway. And to highlight what's my, I think, independent opinion about how important glucosylsphingosine is as a biomarker in the GBA pathway.

So just a – this is my disclosures, and just to highlight those in addition to what Gene said. And just a brief overview. Glucocerebrosidase or GBA1 is a lysosomal enzyme that breaks down lipids. Now, it is almost universally thought that the association between the gene and Parkinson's is because of reduced GBA activity, glucocerebrosidase, the enzyme GCase activity. The reason to think – there are multiple reasons to think this way, the most obvious one is that multiple, multiple mutations in GBA have been associated with Parkinson's, and all are associated with loss of function, with loss of the GCase hydrolase function. What is the function that we refer to when we say loss of function? It's the breakdown of lipids into some other lipids into – so it's either glucosylceramide to ceramide or glucosylsphingosine that is not as abundant but is more toxic to sphingosine and in both cases with glucose.

So because ceramide – glucosylceramide is the most abundant lipid that GCase breaks down, a lot of focus has been put on glucosylceramide. And specifically, I would like to show this published data, published in Lancet Neurology by the group from Sanofi, I'm the co-author, where we showed that venglustat is a molecule that did not reach clinical meaningfulness but showed a great target engagement in the GCase pathway this is showing the target engagement. So venglustat is not activating the GCase enzyme, but rather inhibiting the counter enzyme, the enzyme that supposed to synthase the glucosylceramide and glucosylsphingosine. And that where you can see on the left that with venglustat, the level of glucosylceramide in plasma significantly goes down. These two graphs clearly are different between placebo and control. And the same, when you measure glucosylceramide in CSF. So glucosylceramide is a great biomarker to test whether the product works.

However, when – and this is the same study again the published data of looking at the effect of the drug on the UPDRS – on the MDS-UPDRS Part II and III. So these are the clinical markers of Parkinson's. Part II is mostly a questionnaire, Part III is essentially a neurological exam. We see that in purple is the group that is treated. In dotted line, the group that was receiving placebo. We see that among those who had GBA severe mutations, the graphs are completely similar. And with the people with mild mutations, those with placebo, if anything did a little bit better than the group of those were treated.

Take home message is that glucosylceramide, the most abundant lipid that the GBA enzyme, GCase metabolizes is not really associated with outcomes that you're looking for if you would like to treat Parkinson's. And, therefore, it makes a lot of sense to look at the next, yet the more toxic, less abundant lipid, glucosylsphingosine. And indeed in studies of Gaucher disease, when Gaucher doctors would like to monitor how much of the drugs they should administer, they use glucosylsphingosine as a biomarker. They don't use glucosylceramide because its levels can fluctuate and they're not necessarily correlated with severity of Gaucher disease. In Gaucher disease, there's no or there's severely diminished GCase activity.

Now, glucosylsphingosine is so toxic that its levels are very low and it's previously hard to measure it. That is why it wasn't reported in the study in The Lancet Neurology of venglustat. But more recent technology is able to measure it both in plasma and in CSF. And I'm showing here data from my cohort at Columbia that again published data in the journal Movement Disorders, where we tested multiple lipids. But at the top left where you can see glucosylsphingosine and we can see that the levels in GBA carriers are higher than the levels in non-carriers, and we don't have that same association with glucosylceramide.

And at the most right point in the graph, we see the levels in Gaucher patients. And again you'll see that in glucosylsphingosine the levels are 10 fold higher in people with Gaucher disease compared to Gaucher – GBA carriers, heterozygous carriers, and non-carriers with and without PD while within the Gaucher patients do have some overlap with non- Gaucher patients with regards to glucosylceramide.

So in summary, GBA, the gene that has been associated with Parkinson's in over 10% of the patients encodes an enzyme that breaks down lipids, GCase, this enzyme breaks down two key lipids, glucosylceramide and glucosylsphingosine. We've learned from the venglustat study that the glucosylceramide levels are not correlated with disease severity or with any clinical markers of Parkinson's. And therefore, I think the money (00:15:02) is in glucosylsphingosine, and that is something that I would say for all drugs that target this pathway. Thanks.

Gene C. Mack

Thanks. Thanks so much, Roy. Next, let's turn over to Dr. Peter Lansbury to talk about glucosylsphingosine or the utility of glucosylsphingosine compared to glucosylceramide, and its role in the alpha-synuclein aggregation.

Peter Lansbury

Yeah. Just to sort of retread some of the things that Roy said, I've shown the reaction here on the left, but I've shown it in this context, which is the biological, the metabolic context of the enzyme, to emphasize one thing I think is really important here is that these metabolite levels are markers of traffic through a pathway. Right. They are not necessarily themselves so important as the entire pathway is important. The way I think about this is it's traffic. Right. So you want to make sure the traffic is flowing smoothly through here. When traffic is not smoothly as we see in the venglustat study, when you disrupt this, you can reduce the amount of metabolites in the pathway, but that has a negative effect, because the effect you're looking for is to normalize the pathway. It's like saying I'm going to solve New York traffic by closing all the bridges. Right. They'll surely reduce the traffic in New York City, but it won't have the desired effect the reason the traffic was there in the first place. So that's what I think a big difference is between GluCer and GluSph. GluSph is a side product, it's only formed in a case where there's not enough GCase enzyme activity.

So on the next slide, I just show some data. Here are some published data showing the levels of GluCer don't correlate with the amount of GCase in the brain, so you would think that the higher GCase activity would be the lower GluCer, you don't see that clearly in the brain. Right. And when you look at patients versus controls, also you don't see these large differences in GluCer. GluCer has a way, that pathway has a way of normalizing itself. The problem becomes when that pathway when there's really not enough GCase, and now you have not enough GCase to process this GluCer to convert it into ceramide. But on the far left, you see now it takes a turn, a wrong turn. This is like a dead end alley that if the traffic stand (00:17:45), may be tempted to take it and your car is just going to sit there and GluSph just sits there.

And when it sits there, it does bad things to a lysosome. It has potentially a lot of toxic effects. So, this is a big difference. GluSph only shows up, it's only there when there's an abnormality. That abnormality in this case is low GCase activity. So, when you increase GCase activity, the GluSph can naturally be processed and removed from the cell. And that's what I think is what we're seeing here.

So, I'll show you some data on to support this idea. So, as Roy said, patients with Gaucher disease have very low GCase and this is showing the level of GluSph. This is in blood. But you see they have very, very high levels of GluSph. Patients who are GBA carriers, meaning they have one mutant gene who have GBA-PD, have elevated levels of GluSph relative to normals. So, that elevation is not linear. This is a severe traffic jam. And this is just a slowdown that causes some traffic to accumulate in certain places.

This other paper shows the same type of thing. That is GluSph seems to accumulate in brain of PD patients. This is a post-mortem brain. And that accumulation is correlated in some way to the accumulation of synuclein, which is something else that you may be familiar with as a marker of Parkinson's disease.

So, I think, the important thing here is GluSph is a signal that something's wrong. If you right that wrong, then you should remove GluSph and the pathway can operate normally and all the things subsequently that depend on the pathway like synuclein metabolism can be normalized.

Gene C. Mack

Great. Thank you so much, Peter for that. Now, just to put – tie this all in a nice bow, with our data, Jonas Hannestad will go through Phase 1b biomarker data and what we know as of right now. Go ahead, Jonas.

Jonas Hannestad

Thank you, Gene. So, I just wanted to first pick up a bit where Gene was talking about the study earlier. So, if we can go to the next slide. I'm supposed to move the slide. Sorry. The study has two parts. So, there is a Phase 1b, open-label safety and tolerability study in people with Parkinson's. In Part 1, as Gene said before, people dose for 90 days. Open-label, everyone gets active GT-02287, and then, after completing Part 1, they have the option of continuing into Part 2, where they would get the same dose for another nine months for a total of 12 months and here you can see the numbers.

So, we screened 27 people, we enrolled 21 of those and 19 completed Part 1 and Part 1 completed back in November of last year. The two people who have discontinued were for a variety of adverse events as shown here at the bottom of the slide. Of the 19 who completed Part 1, 15 of them chose to continue into Part 2. Three of them did not want to go into Part 2, and one of them wanted to but he had some extensive travel plans, so he wasn't able to participate in Part 2. We will not discuss Part 2 further here. That's an ongoing study. It will read out around September of this year, when all those 15 patients complete Part 2.

What we will focus on today are some of the both clinical data and biomarker data from Part 1. So, if we go – Again, sorry, I'm used to other people moving the slides for me. Sorry about that. So, picking up again where Gene was talking about UPDRS score. So, just to contextualize this a little bit because I think this is something I encounter frequently, some – a bit of misunderstanding.

So, in Parkinson's disease, you have kind of two big buckets of trials. You can have trials of symptomatic treatments, which affects dopamine in some way and that have very rapid effects. And then you have trials of disease modifying treatments which require much longer duration because of, Gene said again, Parkinson's is in general a very slowly progressing disease. So, just to give you two examples on the right here, we have a trial of Tavapadon, which is a dopamine D1/D5 receptor agonist.

So, this one will activate the dopamine system in people, in this case in people who are not on any dopamine related treatment. And that leads to rapid symptomatic effect. As you can see here, UPDRS scores in both the active arms dropped significantly, which means an improvement, whereas the placebo worsens a bit stays mostly stable over 26 weeks. So, pretty short study, this is symptomatic effect.

Now, in Parkinson's we have a lot of symptomatic treatments and those are very important, obviously, for these patients. However, these symptomatic treatments do not stop the underlying progression. So, even if they treat the symptoms and do it well for several years, the underlying biology and the disease progresses and over time they will get worse. So, what is really needed is a medication that can slow disease progression and that's what was attempted in the middle graph with Exenatide which is a GLP-1 agonist. This was a Phase 3 study. They failed to show that it slowed disease progression, but the design is what you need. So, basically here, if you look at the horizontal scale here, the time is here is almost two years. So, this is, I think 90-week study, where they compare placebo and Exenatide. And as you can see those two lines, they barely diverge. What you want to see is that they diverge, so that the placebo gets worse over time and the active gets less worse over time. But with a disease modifying treatment, you do not expect a acute benefit, as you see with the Tavapadon or other dopaminergic agents. So, just putting that for context.

So, our drug, GT-02287, from what we know falls into the category of Exenatide. We think it has disease-modifying potential if dosed over a long period of time, which is why we don't expect to see an acute symptomatic treatment. And that is, as you can see in the graph here, again, on the left in our 90-day study,

there was perhaps a slight improvement in UPDRS scores, but obviously nothing like symptomatic treatment, right? We don't expect that. So, to test the hypothesis that this drug is disease modifying, after the current study, we will have to go into a much longer study, 12 months, potentially 18 months, kind of like the Exenatide study to show that the placebo and the active arm diverge over time. So, it's just some background on the UPDRS.

Now, what we can get from the short study is biomarker evidence that the drug has the intended biological effects that you can measure much faster than changes in the UPDRS.

So, again, to summarize what – what both Dr. Lansbury and Alcalay were talking about, this is – my slide is a bit simpler than theirs. This is how I conceptualize it. So, when you have reduced GCase activity, you cross this traffic jam that Peter was talking about, you have an increased, and you have accumulation of glucosylceramides, in the cell. And then, some of that glucosylceramide is then eventually when you lead – when you reach a certain excess, it's converted to glucosylsphingosine. And glucosylsphingosine doesn't really have a physiological role in the cell, as far as we know, it's a kind of a toxic byproduct that shouldn't be there.

When it accumulates in the cell. First of all, it's difficult to get rid of, because GCase can convert glucosylsphingosine to sphingosine, but it's not very efficient at doing that, unlike converting glucosylceramides to ceramide. So, when it accumulates, it has these toxic effects. It impairs mitochondrial function, it impairs lysosomal function, and it increases the aggregation of a-synuclein. And as you know, in Parkinson's disease, all of these three pathways are thought to be implicated in pathobiology, basically, right? So, mitochondrial dysfunction, lysosomal dysfunction, and the aggregation about synuclein.

So, it's very possible that glucosylsphingosine accumulation in the brain and specifically in dopaminergic neurons will lead to those neurons not functioning well, and thus to symptoms of Parkinson's disease and progression, right?

Now, what we'll show in the next slide is that our drug appears to decrease glucosylsphingosine, which we assume is due to an increase in GCase activity. So we're increasing GCase activity, we're unclogging, we're emptying this bathtub full of glucosylceramides so that we have less glucosylceramides being promoted into glucosylsphingosine and then eventually this is catabolized and gotten rid of and you have less glucosylsphingosine. So that's, we think, will have a therapeutic effect in the long term.

But now I want to point out also the what Dr. Alcalay was talking about before is that glucosylsphingosine is a much better biomarker of this biological effect in glucosylceramide for the various reasons stated. And in Gaucher disease, glucosylsphingosine in plasma is used both as a marker for disease activity and treatment response.

Now, Gaucher disease is, at least Type 1 Gaucher disease, is in essence a peripheral disease. It affects your liver, your spleen, your bone marrow, but there's very little implication in the brain, right? So, measuring something in plasma makes sense when the disease is peripheral. However, Parkinson's is a brain disease. So you have to measure something ideally in the brain, which you can't do, so CSF is kind of the closest you get, and that's why we have focused on measuring glucosylsphingosine in CSF and we'll also get to it in a second.

So the – what measuring glucosylsphingosine does is, one, it's a biomarker for a treatment response; and two, it's an indication that you're getting rid of a toxic substrate that could lead to clinical benefit over time. So, just to reiterate the point that measuring something peripherally in a CNS disease like Parkinson's, may not be useful. So, here's the correlation between plasma and CSF, glucosylsphingosine in our data. And this is this has been also extensively published and this is well known. But they don't correlate. So, whatever's

happening in peripheral organs, doesn't track (00:29:55) what happens in the brain. Therefore, measuring something in plasma, is generally not a good indication of what's happening in the brain. So when you're doing CNS drug development, you want to get closer to the brain, hence, you want to measure things in CSF.

And when we do that, we see that in CSF, in people who have elevated level of glucosylsphingosine, so this toxic metabolite, that's a biomarker for GCase activity, when you have high levels of that, it decreases after 90 days of treatments. 90 days of treatment too short for UPDRS scores, but it's long enough to show this biological effect. So you can see here, every subject who had elevated levels at baseline, decreased substantially. The people who had lower levels in the – in what we presume is the normal range, didn't have any change, because they have levels that are presumably with, sort of, within the physiological range and there's no need to decrease those levels.

So, what does this mean? That means two things again. One, it's a biomarker of an effect. So, this means that the glucosylsphingosine that we measure in CSF, presumably correlates with glucosylsphingosine in the brain. So, it shows that glucosylsphingosine in the brain has decreased, which means that we've unclogged that traffic jam, those New York bridges that Peter was talking about, by increasing GCase activity. So the biomarker of a central, of a CNS target engagement effect, right?

Two, if you reduce glucosylsphingosine in CSF, presumably it means that you have reduced glucosylsphingosine in the brain so you have less of this toxic substrate that interferes with mitochondrial function, lysosomal function, and that increased aggregation of alpha-synuclein. So in people with Parkinson's, those effect could have long term benefit if you continued dosing. And that's what we're hoping that this biological effect over a longer period of time than 90 days will lead to clinical improvement or rather clinical slowing of progression.

I also want to measure, though, that from a sort of a biological point of view, we see a similar effect in blood. And we don't think that what's happening in the blood is not a reflection of what happens in the brain. But it is a reflection of what the drug is doing, right? So the drug may be doing the same thing in brain and peripheral organs. The peripheral organs is not very important in Parkinson's but it could be important in say Gaucher disease, if that's a disease that we – that again a therapeutics wanted to pursue in the future.

But what we see is the same thing, in saying glucosylsphingosine in the blood also goes down in cases where the levels are elevated. There's one exception to this and this is interesting from sort of a scientific point of view is this is a certain mutation and that is believed not to be responsive to this mechanism of our drug. And that one does not change. Whereas the other ones, the other mutations do change. So that's an interesting fact that we'll explore further.

Now lastly, just going back to the UPDRS scores again. As I said, we don't expect much of – much change over a 90 day period because it's not a symptomatic effect. But we do see that there is – there appears to be a correlation, again, small numbers, but there appears to be a correlation between change in the – changes in the UPDRS scores, so improvement in UPDRS scores and decreases in glucosylsphingosine in the brain. So the people have decrease in glucosylsphingosine in CSF rather which indicates the brain had improvements in UPDRS scores and the ones who didn't have decrease in glucosylsphingosine in CSF did not have improvements in the UPDRS scores.

So does that mean that this is a symptomatic effect? No, it's probably more likely that this is a – that this unclogging and reduction of this toxic substrate may have a slight sort of short term benefit on the function of these neurons, right? But that is a possibility. But I think this is something that will – we will have to wait and see us as part two of the study continues. We'll have to these patients longer and see if this potentially

promising finding holds up that the glucosylsphingosine will actually do predict and correlate with improvements or less worsening of the UPDRS over time.

Gene C. Mack

Thanks so much, Jonas. So with that backdrop, we are hoping that you can start to appreciate is that we have a very, very, what we believe solid biomarker evidence of a biological effect of GT-02287 is having in the brain via the GCase metabolic pathway or the GBA metabolic pathway. We are excited to watch this play out and are looking forward to continuing to follow the patients in our Phase 1b study.

Over the next year, what you can expect out of Gain is continue the analysis of the Phase 1b study extension. And we are going to continue to look at safety and tolerability. We'll continue to find other evidence of target engagement and biomarker activity. But importantly, we're looking forward to see any evidence of disease stabilization that is already, in our view, beginning to materialize. The final results from the Phase 1b study are expected in the second half, probably around September, so likely towards the end of the third quarter, beginning of the fourth quarter. But we will be able to hopefully provide updates throughout the year.

We have filed our IND with the FDA and have begun a very productive dialogue with the agency already. So we're looking forward to putting in place all the commitments that we need to initiate a Phase 2 study, hopefully in the second half, early part of the third quarter of this year. And again, looking forward to more insights from the mechanism of action and the continued clinical developments. We also will have some news from our pipeline as well as we're expecting to make some progress there. So stay tuned. Gain is expecting to achieve a lot in 2026 and move GT-02287 into Phase 2.

So I think, with that, if I'm not missing anything off the agenda, Tara, maybe we can open it up to questions.

QUESTION AND ANSWER SECTION

Operator

Awesome. Yes. Thanks, Gene. So at this time, we will be conducting a question-and-answer session with our speakers. Please hold for a brief moment while we poll for questions. So our first question comes from Jay Olson at Oppenheimer. Please go ahead, Jay.

Analyst: Jay Olson

Question – Jay Olson: Oh, hey, congrats on these impressive results and thank you for providing this exciting update. Can you talk about the correlation between glucosylsphingosine reduction and UPDRS stabilization or improvement at the patient level?

Answer – Gene C. Mack: Jonas, maybe...

Answer – Jonas Hannestad: Yes. Yeah. Thanks, Jay, for the question. So I think, as I said in the previous slide, these are small numbers. So, I think we have to be very cautious about drawing any conclusions. But it appears that people who had a reduction in glucosylsphingosine in CSF also had symptom improvement on the UPDRS. And the people who didn't, didn't. So whether that holds up in the larger sample size over time,

we don't know. But it could indicate that there are some sort of subacute effects of benefits of clearing glucosylsphingosine in the brain that helps these dopaminergic neurons function better, potentially.

Question – Jay Olson: Okay. Understood. Thank you for that. And then I guess, what's the – how should we think about variations for baseline glucosylsphingosine levels in Parkinson's patients? And do baseline levels correlate with disease severity and GCase activity? And then maybe a related question is, would you expect Parkinson's patients with elevated glucosylsphingosine to gain more benefit from treatment? And will you use that as a biomarker for future clinical trials?

Answer – Jonas Hannestad: Yeah. So again, excellent question. So that's something we have obviously thought a lot about after seeing these results, right? And I think that the challenge is that there is very limited data on glucosylsphingosine levels in CSF because as Dr. Alcalay pointed out earlier, the methods to measure very low levels in CSF have just been developed in the last five years or so. Before that, it wasn't even possible.

So we don't really know much about glucosylsphingosine levels in CSF. The Michael J. Fox Foundation in their PPMI dataset, they're currently measuring that. So how much more data and then we'll be able to do, you know, look at correlations between levels and baseline characteristics, disease progression, et cetera. Our dataset is too small for that. But I think if these data hold up, it is possible that we, in a future study, would have to select patients who have a certain level of glucosylsphingosine in CSF at baseline because those patients may be more likely to respond to this specific mechanism, this drug, right? So then it would be kind of a companion diagnostic or our certification marker.

Question – Jay Olson: Okay. It makes sense. And maybe if we could just a few more questions from us. But is it...

Answer – Roy Alcalay: So, Jay, I just wanted to add one more quick point to what Jonas said and that you asked about GCase activity in correlation with glucosylsphingosine. And I just wanted to highlight that I think that glucosylsphingosine is a better – would be – would – we don't know yet, but is expected to be a better marker than GCase activity just because GCase is a hydro – it's – GCase is a lysosomal enzyme. And in CSF, the pH is 7. So it doesn't work in CSF. And that's why I anticipate that GCase activity in CSF is not going to be as useful as glucosylsphingosine. And that's like if – it's a promising biomarker.

Question – Jay Olson: Okay. That's super helpful. Thank you for that. And maybe as a follow up, is it safe for us to think that these reduced levels of glucosylsphingosine would support a disease modifying benefit for GT-02287?

Answer – Jonas Hannestad: I mean, insofar as levels of glucosylsphingosine are detrimental in the brains of these people with Parkinson's, and that over time producing those levels will slow disease progression, then, yes. But again, this is sort of cutting edge biology. So, we don't – we won't know until we do that the actual Phase 2 experiments.

Question – Jay Olson: Okay. All right. Understood. And maybe if I could – thank you for taking all these questions. Maybe if I could just ask one more. Based on these encouraging data that we've seen so far, can you just talk about your target product profile for GT-02287? And I guess what's the ideal patient population that you'd like to treat with GT-02287?

Answer – Jonas Hannestad: Yeah. So I think, in an ideal world, if we could treat anybody with Parkinson's, regardless of GBA variance or glucosylsphingosine levels that would be beneficial, right, for the largest group

of people. But I think as we as we characterize this drug more, we may find ourselves in a situation where we realize that the benefits are likely to be larger in certain sub populations. And this could be GBA1 carriers, it could be people with higher levels of glucosylsphingosine independent of any genetic, right, or combination thereof. And we just – we're just starting to develop those different path – development pathways as we speak.

Question – Jay Olson: Excellent. Well, this is extremely encouraging. And thank you again for providing this update and taking all of our questions.

Operator

Great. Thanks for the questions, Jay. Our next question comes from Ram Selvaraju at H.C. Wainwright. Please go ahead, Ram.

Analyst: Raghuram Selvaraju

Question – Raghuram Selvaraju: Thanks so much for taking our questions and congratulations on all this progress as well as this important information divulged on today's call. I wanted to ask the company how you expect to proceed with regard to regulatory interaction and obtaining regulatory feedback, if any, regarding the use of potential surrogate biomarkers in the evaluation of GT-02287 in Parkinson's disease going forward. And how this is going to dovetail with the purported registrational path in this indication?

I also wanted to see whether there was any expert opinion on the likeliest patients to show a response to the drug based not just on the levels of a specific biomarker in the CSF, but also on the degree of deterioration that has occurred, in the course of the pathophysiology of the disease, because one might expect that GT-02287 would be particularly helpful in those patients who retain some degree of dopaminergic neuronal architecture in the substantia nigra as opposed to those patients with Parkinson's disease who have already deteriorated beyond a certain point. So, I was just wondering, what the evidence indicates would represent the ideal context for a drug like GT-02287 to be applied? Thank you.

Answer – Gene C. Mack: Right. So, there's a lot there. I think the first part of that question was, what we can maybe expect or what we can maybe try to forecast in terms of our interaction with the FDA around biomarkers. I don't know, Jonas, if you want to take that? It's possible that glucosylsphingosine becomes a much more important biomarker if our efficacy continues to be durable. I think, you'll find other sponsors start chasing down what their compounds do in terms of glucosylsphingosine in the CSF now, there's the ability to assay that and also peripherally. So, you may see the emergence of this biomarker more rapidly now that GT-02287 is successful at validating it.

Jonas, maybe you can add or (00:45:57).

Answer – Jonas Hannestad: Yeah, I mean I think, as you know that the question of surrogate biomarkers is something that, FDA is pretty clear that to agree to a surrogate biomarker you have to show that it correlates with or predict clinical outcomes, right? And that's, typically, you can only do that when you do a large Phase 2 or Phase 3 study. So, until such time, my expectation is that FDA at this point would not agree for us to use glucosylsphingosine or any other biomarker as a surrogate endpoint for the purpose of approval, right? It may be that as we get more data in the same Phase 2, they may be open to a conversation at that point that we could get accelerated approval based on that, that biomarker, but I think, it's very early to say.

And in my experience they're generally fairly conservative and then and Parkinson's specifically, they haven't agreed to use other biomarkers such as, dopamine transporter imaging or alpha-synuclein in CSF, where – which we don't really know yet as surrogate markers. So, I think that – so that from a development planning point of view, we are expecting at this time that we will have to do sort of the traditional UPDRS based phase through these studies to get approval for this product.

And then the other part of your question was about what stage of progression in Parkinson's you want to – we want to target? And I think and again, in general, as you pointed out basically in your question, is that, the more neurons you have left in your brain, the better off you are presumably. So, like, treating people as early as possible as in neurodegeneration in general is viewed as better. Now, would this compound specifically have an effect when people are more farther progressed? It's possible. We don't know.

Answer – Gene C. Mack: It might be worth actually hearing from Peter and Roy what their opinion would be on how much evidence the FDA might need in order to validate a biomarker like glucosylsphingosine. Roy, do you care to take a shot at that?

Answer – Roy Alcalay: I can't imagine anyone doing it nowadays a study on Parkinson's with GBA without measuring glucosylsphingosine in plasma and in CSF. I think, it's – especially after, I think, the data are strong. Peter would agree with me that glucosylceramide is not a good biomarker for the pathway or at least we know that modifying glucosylceramide isn't a promising way of looking at modifying PD.

Answer – Peter Lansbury: Yeah, I agree with everything Roy said there. But as to whether the FDA would accept it as a surrogate marker, I think, we're in early days. I think, if we have – if the Fox Foundation goes after their entire PPMI database and some correlations emerge that are interesting, that can be followed up on, I could imagine potentially this would be used. But I think, you guys are the ice breakers here and I'm not sure that will happen in the time course that it would be useful for you.

However, I always feel like the FDA looks at data and if you have data that clearly shows there is an effect of GluSph level on response in a large trial, I don't think they're going to ignore it you know, so, I don't think they will conditionally approve a drug if there's no clinical benefit.

But based on that yet, yet but I do think that it should be obtained and you should – because I do think there will be an explosion of measurement. I know that there are a bunch of companies looking now to measure glucosylsphingosine in CSF. I know it's a big active area.

Answer – Roy Alcalay: And it is something that we can get back to about whether glucosylsphingosine is already used in Gaucher trials. I think it is. It is at different levels of glucosylsphingosine. But if that's the case, I can imagine that it will be easier for the FDA to consider it, because at least it shows that there is reliability and validity across labs in measuring glucosylsphingosine.

Answer – Peter Lansbury: Yes.

Answer – Gene C. Mack: So Ram, just as summary, we are off to a really good start with glucosylsphingosine. The likely consequence of that being sort of first here is that while we might go a long way towards establishing it, it probably likely others or maybe in our earlier stage pipeline that we'll receive it (00:51:11).

Question – Raghuram Selvaraju: Thank you.

Operator

Thanks for the questions, Ram. Our next question comes from Tom Shrader at BTIG. Please go ahead, Tom.

Analyst: Thomas Shrader

Question – Thomas Shrader: Hi, everybody. Thanks for all the detail. I thought with all the brainpower, I'd ask some philosophy questions. What is the best data that GCase you could back someone out of established Parkinson's disease? And the question is really motivated by Alzheimer's, where removing plaque was much more profound in its treatment effect than it turned out to be in humans. Are you comfortable the models are better? What's the best data that's driving the biology hypothesis?

Answer – Roy Alcalay: I think the – I can take a stab at the question. When we look at the rate of progression and this is like I kind of hinted to it, but I didn't say it in these specific words. When you look even in the venglustat study on the rate of progression of people with mild mutations in GBA to those with severe mutations in GBA, it's very clear that those with severe mutations progressed faster. So the hypothesis is, that it's not just that the GBA whatever pathophysiology is just causing PD, it's also once it happens it's also contributes to faster progression. So, if you can modify that and bring the severe mutations to the mild mutations, and the mild mutations to bring them to non-carriers, you have modified the progression of PD in a way that you can see even in a one-year study.

Question – Thomas Shrader: So you don't really need to back someone else to have a drug, you could simply just stop them from progressing? The bar is maybe lower.

Answer – Roy Alcalay: Right. I think the – to talk about reversing, I think it's a little early, right. We're not where – this is – but, and there's not a great epidemiological data to support reversing. But I say that even rate of progression, people mentioned earlier the motor progression like which stage of the disease should be affected but people with Parkinson's that have motor symptoms still have quality of life. If you can prevent the cognitive deterioration that happens more frequently with GBA mutations, that will be huge. That is actually – that will be amazing. So even if you don't reverse the motor symptoms or the progression is slower and you're able to develop an intervention that prevents cognition or cognitive impairment that will be great.

Question – Thomas Shrader: And then a quick follow up. Do you think this program is directly competitive with LRRK2 activation? Or do you think LRRK2 activation only works in the presence of robust GCase activity?

Answer – Roy Alcalay: I didn't understand that when you meant initially competitive, what you meant by it. Because it's much easier to do GBA path drug targets than LRRK2 just because there's such a larger population and patients do worse with GBA mutation so they're much more likely to participate in clinical trials. There is a very small subset of people who are dual carriers of GBA and LRRK2 and the data out there is controversial to whether – it doesn't look like there's synergy that which means if both are deleterious in a similar pathway, you would expect that one plus one will be three. So but it doesn't look like this. It doesn't look like those who are dual carriers progressed more worse than carriers of only LRRK2 or only GBA. Some studies actually say that the dual carriers do better than GBA carriers without LRRK2. So I think it's too early to think of a combination therapy of a LRRK2 inhibitor with a GCase enhancer. And I think the lower hanging fruit is targeting the GBA pathway just because it's so much more abundant to the effect within PD.

Question – Thomas Shrader: Okay. Great. Thanks for the thoughts.

Operator

Thanks for the questions, Tom. Our next question comes from Jason McCarthy at Maxim Group. Please go ahead, Jason.

Analyst: Jason Wesly McCarthy

Question – Jason Wesly McCarthy: Hi, guys. Thanks for taking the questions. Nice job on the study outcome. Couple of forward-thinking questions. One, is there any imaging potential for glucosylsphingosine given that ceramides or bioactive sphingosines have been used by MRI or modern MRI, if you would, for things like cognitive impairments and surrogates for drug activity?

Answer – Peter Lansbury: I'd be willing to give that one a shot because I looked very hard for a few years. I think it's very unlikely that there will be an imaging agent for glucocerebrosidase activity in brain. I think I would say it's ever possibly, but very unlikely in the next five, eight years, it's very difficult. As for directly imaging glucosylsphingosine in the brain, you would have to use MRI for that. And I'm not aware of a signal that I've seen that one could attribute to that particular substrate. It's going to be very difficult because it's such a low-abundance substrate that even if it had a unique, sometimes you get a unique proton (00:56:58) signal that you can key on. It's going to be very low abundance and it's going to vanish into the – into the forest of other protons from other related molecules. So, I think that CSF is probably the best we're going to do, but I did mention in my slides, there is this nice post-mortem brain studies that seem to serve roughly correlate with CSF. So, I do think that CSF is probably a pretty good correlate for what's going on in brain. The (00:57:30) going to do.

Answer – Jonas Hannestad: Is it – I wanted to add to that. I think that, yeah, I agree with Peter that imaging glucosylsphingosine in the brain is probably very difficult because it's present at such low levels. But if you – but there has been a lot of progress in imaging of synuclein, so once that is ready, insofar as reducing glucosylsphingosine will reduce aggregation of alpha-synuclein, you could use that as a sort of a – a proxy imaging biomarker for an effect on glucosylsphingosine.

Question – Jason Wesly McCarthy: Okay. And in terms of the next study, the Phase 2, glucosylsphingosine I'm assuming in CSF would be part of your enrollment criteria, that's something you may discuss with FDA, but also you had mentioned there are certain mutation types that popped up where it may – the drug might not be as effective in terms of lowering those levels, so do you need to screen for these certain mutation types? Is that part of the plan to really try to concentrate your patient population that could potentially benefit from drug?

Answer – Jonas Hannestad: Yeah. So, in the planned Phase 2 study we're not going to exclude people based on these characteristics, but we're going to measure them so that – because I think the data we have at hand is it is too small, the sample size is too small to conclude anything, right. So, what we want to do in Phase 2 is we want to – we will get CSF at baseline, we will measure the glucosylsphingosine and we'll have some – some prespecified hypotheses about high levels of glucosylsphingosine in CSF may do better on XYZ. And similarly we are genetically characterizing all these patients also at baseline and we will include everybody. But then we may have some prespecified hypotheses about such and such mutation in GBA1, may respond better or worse to this mechanism. And then we will see how that pans out in the Phase 2 study.

Question – Jason Wesly McCarthy: Just really quick and I might have missed it, so I apologize. For the 15 evaluable patients for glucosylsphingosine levels, were all 15 elevated at baseline or was there a subset of them only, it was all 15?

Answer – Jonas Hannestad: No, no, no. So, the – I think there's about 6 or 7 who had elevated levels at baseline in CSF and that came down. And the others were – so the other half or a little bit more than half was they had sort of "normal levels".

Question – Jason Wesly McCarthy: Got it. Thank you, guys.

Answer – Gene C. Mack: Thanks, Jason. Tara, do we have time for one more or two more?

Operator

Yes, we do. We have Maanasa Sangeetha from ROTH on. So, Maanasa, please go ahead.

Analyst: Maanasa Sangeetha

Question – Maanasa Sangeetha: Hi, guys. Thank you so much for taking the questions and congratulations on the progress. So, my first question is, so based on the data that was presented today, are you seeing evidence that GT-02287 serves not only as a GCase activator, but it's like participating in downstream events including restoring mitochondrial function and neuronal survival, so what do you think about that?

Answer – Jonas Hannestad: So, we have – we have seen, not in this study (01:01:00) we have seen in vitro and in in vivo mouse models a lot of evidence supporting that. So GT-02287 does not activate GCase directly unlike some of our competitors. It's a chaperone. So, it helps – it helps GCase in the endoplasmic reticulum fold better so that there is less this folding and that then helps the correctly folded GCase to get to lysosomes where it's a hazard as its activity.

We have also seen in in vitro especially that GT-02287 has effects on mitochondrial function. So, improving mitochondrial function. Now, whether that is mediated through GCase and glucosylsphingosine potentially or it's a more direct effect we don't know, because GCase also has been shown recently to have an effect in stabilizing complex one in mitochondria.

Question – Maanasa Sangeetha: Thank you. I have just one more. So, do you think the ongoing Phase 1 open label extension will reveal details about GCSF (01:02:09) biomarkers such as alpha-synuclein and NfL. So, do you have any thoughts on that?

Answer – Jonas Hannestad: Yeah. So – so those are – those are biomarkers that again we think you need longer studies to detect the change, right. So, for NfL, if this – if there is a disease-modifying effect here, we would expect NfL levels to increase at a slower pace in a long duration study like a year (01:02:37). So, we may see some of that in our extension and we dose (01:02:41) these patients for a whole year that NfL levels decrease. Again, the challenge is we don't have a placebo arm, right, so we'd have to compare to historical controls. But in our Phase 2 study we will – therefore we look at both NfL and alpha-synuclein, so seeding amplification species in CSF (01:03:01).

Question – Maanasa Sangeetha: Okay. Thank you so much and congratulations again.

Answer – Gene C. Mack: Thanks, Maanasa.

Operator

Yes. Thanks for the questions, Maanasa. So, this concludes today's Q&A session. I'll now turn it back over to you Gene for closing remarks.

Thanks so much. So, I hope everyone is gaining a better appreciation of how GT-02287's mechanism is being elucidated. And it is very exciting to see the evidence supporting our hypothesis. We know now that we are seeing multiple points at which GT-02287 is aiding in the GBA metabolic pathway. And we can – we expect that to play out in stabilization of UPDRS scores and significant clinical benefit for our patients upon continued dosing of GT-02287.

So, with that we'll close the call. Thank you all for your time and attention and interest. Please feel free to follow up with the company if there's anything we weren't able to address on this call or happy to follow up individually or via teleconference. And look forward to talking to some of you in the future and over the next couple of weeks potentially in San Francisco.