GT-02287 Phase 1 Study Results Call *(Corrected version)*

Event Details

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Company: Gain Therapeutics, Inc.
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Company Participants

Apaar Jammu - Gain Therapeutics, Inc., Manager-Investor Relations & Public Relations
Gene C. Mack - Gain Therapeutics, Inc., Interim Chief Executive Officer & Chief Financial Officer
Khalid Islam - Gain Therapeutics, Inc., Co-Founder & Executive Chairman
Jonas Hannestad - Gain Therapeutics, Inc., Chief Medical Officer

Other Participants

Jay Olson - Analyst
Thomas Shrader - Analyst
Eduardo MartinezMontes - Analyst
Jason Wesly McCarthy - Analyst
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MANAGEMENT DISCUSSION SECTION

Operator

00:00:14 Good morning, and welcome to the Gain Therapeutics Virtual Webinar. At this time, all participants are in a listen-only mode. A Q&A session will follow the formal presentations. As a reminder, this meeting is being recorded, and a replay will be made available on the Gain website following the conclusion of the event.

00:00:33 With that, I would like to hand the call over to your host, Apaar Jammu, at Gain Therapeutics. Please go ahead, Apaar.

Apaar Jammu

00:00:41 Hey, all. Thank you for attending today's webinar. Before we begin, we just want to draw your attention to the legal disclosures regarding forward-looking statements. During this conference call and webcast, the company will make forward-looking statements regarding future events, including statements about financial, business, clinical milestones, potential future milestone payments and commercialization and plans, and strategies anticipated in the remainder of fiscal 2024 and beyond.

00:01:08 We encourage you to review the company's past and future filings with the SEC, which identify specific factors that may cause the actual results or events to differ materially from those described in the forward-looking statements. You can find the SEC filings in the EDGAR database at www.sec.gov or in the Investor Relations section at the company's website at www.gaintherapeutics.com. Please note that any comments made on today's call speak only as of today, September 30, 2024, and may not be accurate at the time of any replay or transcript re-reading.

00:01:44 We have a great event ahead of us. So, with that said, let's get right into it. We'll hear from Chief Financial Officer and Interim Chief Executive Officer, Gene Mack; Founder and Executive Chairman, Khalid Islam; and Chief Medical Officer, Jonas Hannestad.

00:01:58 And with that said, I'd like to turn the call over to Gene Mack, Interim CEO and CFO of Gain.

Gene C. Mack

00:02:04 Thank you, Apaar, and thank you, all for joining us this morning to discuss the exciting data that was presented from our initial clinical study of GT-02287 this weekend in healthy volunteers and the steps that we are taking to advance GT-02287 further on the back of these results into a Phase 1b three-month dosing study in patients with Parkinson's disease, with or without a GBA1 mutation, that will initiate by year-end.

00:02:28 As you know, Gain Therapeutics is a clinical stage biotechnology company, focused on identifying allosteric small molecule therapeutics for the treatment of neurodegenerative diseases and other areas with significant unmet need. However, today's discussion will focus on our lead candidate, GT-02287, and our future plans for its continued development.

00:02:47 Our initial evaluation of GT-02287 that was presented in full yesterday in a late-breaker session at the International Congress of Parkinson's Disease and Movement Disorders, was meant to establish its safety and overall tolerability, as well as determining the distribution of the compound in the body and if it achieves therapeutic concentrations in the brain that correlate with the findings from our earlier preclinical and animal studies. Finally, we wanted to see if any measurable increase in the activity of the enzyme that is the therapeutic target for GT-02287 could be achieved in healthy volunteers after oral administration.

00:03:24 We are excited to report that in addition to establishing very favorable safety and tolerability profile. For GT-02287, we were also able to detect concentrations in the CSF that were in the therapeutic range from our earlier animal studies. Additionally, we did indeed observe significant increase in the activity of glucocerebrosidase or GCase, which is at therapeutic target among these healthy volunteers whose GCase levels were at normal homeostasis for those individuals at baseline. This observation makes it much more likely that the benefits of broad neuroprotection we observed in our preclinical and animal models of Parkinson's disease will translate over to patients.

00:04:04 These very encouraging results Jonas is about to review in more detail provide more than enough rationale to advance GT-02287 into our next Phase 1b study and observing target activation in healthy volunteers that have no GCase deficiency derisks the therapeutic potential of GT-02287 and provides a reason to believe we will see the same healthy improvement cascade across relevant biomarkers of neuroprotection associated with the motor and cognitive improvement in our earlier studies of GT-02287.

00:04:35 Now, before we hand the call over to Jonas to provide the detailed results of our Phase 1 healthy volunteer study, I want to give our Scientific Founder and Executive Chairman, Khalid Islam, an opportunity to contextualize what the advancement of GT-02287 could mean to patients suffering from Parkinson's disease.

Khalid Islam

00:04:56

Thank you, Gene, and good morning to all of you joining the call. We are indeed very pleased to discuss the results of this important study for GT-02287 in healthy volunteers. As Gene pointed out and Jonas will describe in more detail, these results are very encouraging for Parkinson's disease patients as GT-02287 represents what could be the first approach available to patients that addresses the underlying mechanism and molecular pathways of their disease rather than just the temporary symptomatic improvement offered by current treatment (00:05:28) over time.

00:05:30 If the significant improvement of motor function and cognition that we have observed in our preclinical studies continue to be associated with the oral administration of GT-02287 in our upcoming patient studies, it'd mark a truly significant advance in slowing or even potentially stopping the progression of Parkinson's disease. Such therapies are currently not available. We have also recently generated some really interesting data in preclinical models, which will be presented shortly at upcoming conferences and which strengthens our belief that GT-02287 can be a disease-modifying therapy.

00:06:09 We chose to develop GT-02287 because of its unique allosteric interaction with GCase. This is an enzyme that is responsible for multiple functions related to cellular health. In addition to reducing the stress from toxic substrate accumulation of lysosome that is characteristic of Parkinson's disease, the transport of GCase through other important cellular compartments in addition to the lysosome is critical to achieving broad neuroprotection. By interacting with GCase, GT-02287 protects the enzymes who traffics through these other critical cellular compartments such as the endoplasmic reticulum and mitochondria.

00:06:53 While we are encouraged to see the activation of GCase in healthy volunteers, we're even more excited to see the impact we believe is unique to GT-02287, going beyond the lysosome on overall neuroprotection versus approaches that simply target GCase with the lysosome alone. We believe this differentiation will be the key to generating better outcomes in motor and cognitive functions in patients with Parkinson's disease, and look forward to potentially offering this important advance to patients in the near future.

00:07:27 Before I hand over the call to Jonas, I want to thank the individuals and clinicians who participated in the study and express our appreciation for the significant contribution to our efforts in developing this (00:07:39).

00:07:40 Just a quick background. Jonas is trained in internal medicine, psychiatry, and has a PhD in cell biology. Jonas joined us at Gain as the Chief Medical Officer about six months back. Prior to that, he was a CMO at a biotech company in the Bay Area and previously has had roles of increasing responsibility in privately held biotech and mid-sized pharma. He has spent the last 13 years or so in clinical development in neurology, primarily neurodegeneration, and has worked on multiple programs in Parkinson's, Alzheimer's, and ALS, and has spent over a decade in academic medicine conducting basic and clinical neuroscience research.

00:08:22 And I'll pass the call over to Jonas, so he could review the details of the study being presented today. Jonas?

Jonas Hannestad

00:08:31 Good morning. So, as you may know, mutations in this gene called GBA1 constitute the most common genetic risk factor for Parkinson's disease. If you have a GBA1 mutation, you're at three- to five-fold increased risk of developing Parkinson's disease. And in addition to that, if you develop Parkinson's disease and you carry one of these mutations, your rate of progression is faster. So, both your motor progression and for instance, cognitive decline occurs faster on average in

people with Parkinson's and a GBA1 mutation. So, this is a subset of Parkinson's, about 10% of all Parkinson's patients that have a more aggressive form of the disease, if you will.

00:09:25 Now, the exact mechanisms through which GBA1 mutations increase your risk of Parkinson's are not fully understood. However, what we do know is that GBA1 mutations and the resulting mutated enzyme, GCase enzyme, has effects on multiple pathways that are also abnormal in idiopathic or sporadic Parkinson's disease. And these include things like endoplasmic reticulum stress, lysosomal dysfunction, mitochondrial dysfunction, neuroinflammation, and aggregation of alpha-synuclein, all depicted on the slide. And together, these pathway abnormalities then lead to cell dysfunction and cell death and ultimately to the symptoms that people experience when they have Parkinson's disease.

00:10:14 Now, what we have observed with GT-02287, both in, in vitro studies in patient-derived cells, as well as in vivo in mouse models of Parkinson's disease, is that all of these pathway abnormalities are corrected. When we use this compound, either in vitro or in vivo, we see that endolysosomal function is improved, mitochondrial function is improved, neuroinflammation is reduced, the aggregation of alpha-synuclein is reduced, and cell viability increases and ultimately neurodegeneration is reduced. And the purpose of taking this compound into the clinic is obviously to test whether these effects also occur in patients with Parkinson's disease.

00:11:08 So, here is a depiction of the design of this first-in-human Phase 1 study in healthy volunteers. So, this was a single ascending dose and multiple ascending dose study in healthy men and women between the ages of 18 and 65, and the primary endpoint was safety and tolerability and pharmacokinetics. In addition to that, we also measured the ability of GT-02287 to get into CSF and also its ability to modulate GCase enzymatic activity in blood. And the dose levels are depicted here. There were five dose levels in the single dose part, including a food effect cohort, where we tested the effect of a high-fat meal on absorption of the compounds and then four dose levels in the multiple dose part.

00:12:04 Here, you can see some data on the demographics of the participants in the study. So, as is common, the age is in the lower range. However, I think what is unusual in this study is that many Phase 1 studies have a cut-off at 45 years of age. Here, we took it up to 65. So, we have about – 15% of the participants were age 50 or older, and that is important because ultimately, this drug will be tested in people with Parkinson's disease who on average are middle age and older. It was also nicely distributed across men and women. Many Phase 1 studies only enroll men, but here we had about half and half men and women, which is important obviously because Parkinson's is roughly half and half, a little bit more in men perhaps. And then, the racial and ethnic distribution is a reflection of where the study was conducted, which was in Australia, so you have predominantly Caucasian and Asian participants.

00:13:11 Now, with regards to the safety and tolerability of this compound, we observed no serious adverse events. We also observed no adverse events that were categorized as severe or Grade 3 or above, and about – more than 90% of the adverse events were mild in intensity. And we have no subjects who discontinued due to adverse events.

00:13:43 The most common adverse event that we did observe was nausea. And this did appear to be related to GT-02287 and did occur at higher frequencies as we increased the dose. However, again, more than 90% of the nausea events were mild and less than three hours in duration. We have no subjects who vomited and no subjects who discontinued because of the nausea. And this appeared to dissipate over time when you hadn't – people with – who took multiple doses of the drug.

00:14:24

With regard to pharmacokinetics, it was linear across the dose range, which means that as you increase the dose, you have linear increase in the plasma levels of the drug. The half-life was somewhere around 11 hours, and we reached steady state by around day four or five. There was no correlation between the pharmacokinetic parameters and various demographic characteristics as stated here. And the impact of a high-fat meal was what you typically observe with small molecules is that you have a blunting of Cmax and you have a delay in the Tmax because the meal delays absorption, but overall, the exposure or the AUC is the same. In this case, it had a small increase.

00:15:12 Now, I want to draw your attention to the dotted line on this graph. That is the therapeutic thresholds that we believe exist based on data from mice. So, basically, in our mouse models, we see the biological effects that I described earlier on these various pathway abnormalities. We see those occur when you have exposures of about 2,000 of AUC and above. And so, that's the target range we're trying to achieve in humans. And as you can see here in this graph, when you dose at dose levels of about 7 to 8 milligrams per kilogram body weight in humans, you're above that threshold. So, we think that and that's the dose range we want to target going forward so that we know that all of these patients have enough drug in their bloodstream entering their brain obviously to produce these biological effects that we ultimately think will translate into a clinical benefit.

00:16:16 As Gene mentioned earlier, we also have evidence that GT-02287 can enter the brain. So, we measured GT-02287 in CSF. And CSF levels are low, but that is consistent with what we observe in rodents. And the reasons for that is that GT-02287 is not very soluble in water and CSF is mostly water, and it's also highly protein bound. But the important thing from the slide is that the levels in CSF that we observed in humans at this dose level were equivalent to the CSF levels in both mouse and rats at oral doses that in those species produce biological effects in the brain. So, we can infer that the CSF levels in humans reflect similar brain levels to what we see in rodents, and therefore that these levels would have the intended biological effects.

00:17:21 Now, the last piece of data from this Phase 1 study, which I find very encouraging and it was somewhat of a surprise was that we saw an increase in GCase enzymatic activity in healthy volunteers. Also, as Gene stated earlier, in a healthy person, typically you have homeostatic mechanisms that prevent an overactivation of any system or pathway. However, here we see that the compound is able to increase GCase activity by about 30% over the course of this 14 days of treatment.

00:17:54 And as you can see here, GCase activity increases already after the first dose. So, the first time point here is 4 hours after the first dose, and then it continues to increase over the course of 14 days. So, what will be very informative is to see how this looks in patients with Parkinson's disease because they sometimes have lower levels to start with of GCase activity and that is especially true for people with the GBA1 mutation.

00:18:31 So, just to summarize again the findings from this Phase 1 first-in-human study, GT-02287 is safe and generally well-tolerated. We have plasma exposures in what we believe is the therapeutic range at oral doses that are well tolerated, and we have brain exposure, which is obviously important for this mechanism and this indication. And lastly, we have evidence of peripheral target engagement with this compound in healthy volunteers.

00:19:13 So, the next step in development now is to do a study in patients that will start by the end of this year. And this is a study focused primarily on safety and tolerability, three months' dosing duration, and will be a mix of patients with the GBA1 mutation and idiopathic Parkinson's disease, safety and tolerability, pharmacokinetics, and various exploratory biomarkers that are listed here to see if we can replicate some of the effects that we've seen in mouse models in people with Parkinson's

disease. And this study will be run at somewhere six to eight sites in Australia, and it will run through most of next year probably depending on enrollment rates. But we will have an interim readout on biomarker data and also safety and PK data sometime in the middle of next year.

00:20:18 And I think, with that, I will hand it back over to Gene.

Gene C. Mack

00:20:30 Thanks, Jonas. Thank you for reviewing the Phase 1 healthy volunteer study. As Jonas just mentioned, our next steps in the clinical development include initiation of a study in patients who have been diagnosed with Parkinson's disease and expect that this clinical trial could be initiated by the end of the year following regulatory approval. As this trial will be an open-label clinical study, we are looking forward to providing our next clinical data point sometime during the second quarter or middle of next year from a cohort of patients that will be entered in this trial in the early months of next year.

00:21:02 As Khalid mentioned, we have also been invited to present new preclinical evidence that continues to build the case for the disease-modifying potential of GT-02287 and in preclinical models of Parkinson's disease, and supporting the continued development of GT-02287 at additional upcoming scientific and investor conferences during the fall, including next week at the upcoming Society of Neuroscience Conference, which begins on October 5 in Chicago. Soon after, we will begin enrolling patients with Parkinson's disease in our Phase 1b study, and as I said, preparing for the next data inflection point in the middle of next year.

00:21:38 Gain Therapeutics has achieved a critical milestone in the development of GT-02287, advancing into patient studies where the value creation is dramatically accelerated following all of the important and necessary preclinical and early human clinical testing that we have completed. We look forward to updating you on our progress towards the goal of developing a truly disease-modifying treatment aimed at slowing and stopping the progression of Parkinson's disease.

00:22:16 Now, I'll turn the call over to the operator for Q&A.

QUESTION AND ANSWER SECTION

Operator

00:22:25 Thank you, Gene. At this time, we'll begin conducting our Q&A session. With that, our first question comes from Jay Olson at Oppenheimer. Please go ahead, Jay.

Analyst: Jay Olson

00:22:43 **Question – Jay Olson:** Oh, hey. Thank you for providing this update, and congratulations on these results. I had a couple of questions. Do you expect Parkinson's patients to have a greater increase in GCase activity with treatment of GT-02287 when compared to healthy volunteers? And can you talk about what level of GCase activity in Parkinson's patients would translate into clinical benefits? And then, I had a follow-on if I could, please.

00:23:14 **Answer – Jonas Hannestad:** So, as you probably know, Jay, the reduction in GCase activity that we typically observe in people with Parkinson's who have GBA1 mutations is somewhere in the 20% to 50% range because they're missing activity in one allele and the other allele is normally

functioning. So, in those patients specifically, I would expect that increasing the levels back to what you see in healthy subjects would be sufficient. So, that would be somewhere around 50% to maybe 100% increase from their baseline, which would be lower than what we see in these healthy volunteers.

00:23:48 So, to answer your question, if you start at a lower level of GCase activity, you would expect that the compound may be able to increase that activity more in percentage wise than in starting higher up and that's what we see in patient-derived cells. Interestingly, in idiopathic Parkinson's disease, there's a bigger variability and many of those patients do not have decreased GCase activity compared to age-matched healthy controls. So, the question that's very important for us and anyone who works in the GBA field is whether increasing GCase activity in somebody whose – has Parkinson's and whose levels are within that normal range would that translate into clinical benefit? And I think that's an unknown.

00:24:34 **Question – Jay Olson:** Okay, great. Thank you for that. And then, just a quick follow-up. Can you talk about the dose dependency that you observed and which dose levels are you planning to bring into your Phase 1b study? And then, coming back to GCase, what's your thinking about using GCase as a biomarker for accelerated approval in GBA1 Parkinson's and idiosyncratic Parkinson's patients?

00:25:03 **Answer – Jonas Hannestad:** So, the dose levels that we're targeting for this Phase 1b study are in the range of the – as you remember that slide with the dotted line, so doses that will exceed that threshold, right? So, we're somewhere in the between 10 and 15 milligrams per kilogram is what we're targeting in the study. There will be some variability depending on each person's body weight. But the idea is that dose – we are trying to find a dose that is well-tolerated in most subjects, but at the same time has that – reaches that threshold and that increases GCase activity. So, that's the biomarker we'll use internally to understand if we're in the right dose range.

00:25:43 Now, in terms of accelerated approval, I'm skeptical that if they would accept that as the only grounds for accelerated approval in this population and maybe a supportive secondary endpoint. But I don't think they would approve on that alone, yeah.

00:26:00 **Question – Jay Olson:** Okay, great. Congrats again on these results. It's super helpful. Thank you so much for...

00:26:04 **Answer – Khalid Islam:** Hey, Jay, if I can just add one more comment. This is not just a GCase activator. We need to just realize that. This is something that modulates and how GCase go through its function, go past. So, there are multiple effects and multiple components that are involved. I think that's important to keep in mind. So, it's not just the activation of GCase, but also the fact that you're allowing to process through the cell and not do damage to other organelles, which are also doing additional functions. So, you could see how it causes havoc if it's not correct before they start going through that process. So, it's a bit of a wider story than just activation of GCase, just to keep that in mind.

00:26:46 **Question – Jay Olson:** Super helpful.

00:26:49 **Answer – Khalid Islam:** Thank you for your questions.

00:26:51 **Question – Jay Olson:** Thank you very much.

Operator

00:26:51 Thank you for the questions, Jay. The next question comes from Thomas Shrader.

Analyst: Thomas Shrader

00:26:56 **Question – Thomas Shrader:** Hey, good morning. Can you hear me okay?

00:27:00 **Answer – Gene C. Mack:** Yeah.

00:27:00 **Question – Thomas Shrader:** So, the nausea, is – does food make it better? Is that clear? And where does it scale compared to other drugs? A fair number of Parkinson's drugs have some GI side effect, where do you think this would fit?

00:27:17 **Answer – Jonas Hannestad:** (00:27:17) question. So, I think as you said, right, that almost all symptomatic Parkinson's drugs have nausea as their primary adverse event, including levodopa and dopamine agonists. So, in terms of the intensity, it's hard to compare with a small number. But we did see that this was fairly mild in most subjects and well-tolerated and didn't lead to discontinuation. Now, this is something that we'll obviously monitor closely in the patients as we start dosing patients.

00:27:47 And then, with regards to your question about food, it appeared, again, small sample size. But it appear that when people eat food, it sort of attenuates the nausea somehow. But that's to be determined as well.

00:28:05 **Question – Thomas Shrader:** (00:28:03). And then, in terms of biomarkers, is inflammation likely the best PD biomarker? Do you think you can image or look at GFAP? Your thoughts on some sort of PD biomarker for the next study.

00:28:18 **Answer – Jonas Hannestad:** Yeah. So, we are – so in the next study, we will look at – so, obviously, GCase activity is the sort of the most proximal target engagement biomarkers. But we're – as I think, as Khalid alluded to it, we are very interested in the downstream effects and the acclimation is one of those. So, what we will look at – what we've seen in rodents is that you have reduction in microglial activation and cytokine levels, and we will measure cytokine levels both in CSF and in blood in these Parkinson's patients as a proxy to what is happening in the brain. And I think that is a biomarker that could change fairly rapidly.

00:28:55 **Question – Thomas Shrader:** Got it. And then, I have one follow-up that may be impossible, but the 40% increase in GCase, you're in some sense correcting a natural inefficiency in the complicated process of an enzyme, right, because it already works. Is there any hint as to how much there is there? Is it a – what is the natural inefficiency from, say, cell biology studies? Are you getting all of it? Are you limited by your drug or by just how much GCase there is to begin with? And I say it may be impossible.

00:29:33 **Answer – Jonas Hannestad:** Well, is it? But no, it's a good question now because what you're saying is basically that, yes, there is an inefficiency. Every protein that the cell makes has some propensity to misfold. And it's cell is not a perfect machine. So, there is a dynamic range there that you could increase efficiency to a ceiling, which – and then we don't know, I think for GCase specifically in a healthy cell. We don't know where that ceiling is. So, we don't know if the increase that we saw of about 30% if that is limited because of that cell ceiling or it's our drug. That's, yeah, unknown.

00:30:05 **Question – Thomas Shrader:** All right, congratulations. Looks to me like you got everything you wanted. So, terrific – terrific readout.

00:30:10 **Answer – Gene C. Mack:** And Tom, just to add on to what Jonas was saying, again, with the point that Khalid is making about modulation versus activation, there are direct activators of GCase, but again, that's focusing on the lysosome. And so, by increasing, it's not clear how much activation you actually do need in order to derive broad neuroprotection, which is why our comfort lies in the fact that we are trafficking GCase through each cellular compartment. So, the activation at the level of the lysosome is probably necessary, but in our view not sufficient for broad neuroprotection.

00:30:48 **Question – Thomas Shrader:** Got it. Okay. Thanks, again.

Operator

00:30:50 Thanks for the questions, Tom. The next question comes from Eduardo Martinez from HC Wainwright.

Analyst: Eduardo MartinezMontes

00:30:57 **Question – Eduardo MartinezMontes:** Good morning, thanks. Can you hear me okay?

Operator

00:31:00 Yes, we can.

00:31:03 **Answer – Gene C. Mack:** Yeah.

00:31:02 **Question – Eduardo MartinezMontes:** Great. Yeah, thanks so much for the presentation this morning. I'm speaking on behalf of Ram Selvaraju this morning. And I'm curious kind of what the – I think you spoke a little bit to this, but what is, I guess, the expectation for the relative potential reversal that you could anticipate that the drug versus some of the symptoms of Parkinson's? And would you be able to read it out any of those functional reversals or slowing of progression potentially in the Phase 1b data?

00:31:33 **Answer – Jonas Hannestad:** So, as you may know, Eduardo, in Parkinson's, when you have symptoms of Parkinson's, that's produced by a mix of neurons that have already died in the substantia nigra and neurons that are dysfunctional, but in the substantia nigra. So, presumably, neurons that have already died, depending on how far you've progressed, they cannot be recovered or resuscitated. The neurons that are dysfunctional could be helped to function better, and we've seen that in vitro and in vivo.

00:32:05 So, it's potentially you could see an improvement in function even with this drug in Parkinson's patients and that's something we'll look for. But I think the most promising effect is a slowing of progression, so the preventing those neurons from degenerating further so that you – the slope of decline that you typically see in Parkinson's patients will be altered by the drug.

(00:32:34)

00:32:33 **Answer – Jonas Hannestad:** ...your question.

00:32:35 **Question – Eduardo MartinezMontes:** Yeah. That is really helpful. And is there any stratification or patient selection that's based off of severity of disease that you are going to screen for in the trial design?

00:32:49 **Answer – Jonas Hannestad:** In this upcoming study, no. But as we go forward into studies where we'll be looking more for the clinical benefit, then, yes, we will very likely restrict to early disease. How early, it's to be determined, but early disease for a variety of reasons. One is, the symptom progression is more – is better characterized and you have fewer motor complications and so forth. And also, to the point I was making earlier that you have more neurons that have not already died that you can save. So, you're probably more likely to slow progression. So, sometime – somewhat an early disease is what we'll ultimately be targeting.

00:33:31 **Question – Eduardo MartinezMontes:** Got it.

00:33:31 **Answer – Khalid Islam:** Eduardo, just to add to that, look, in this current study that's planned, we'll get signal. So, this is looking for changes in sleep, it's looking for neuroinflammation, it's looking at a number of other factors that would help design our future study that Jonas was just referring to, which would allow us to get to more of that much more important markers for disease and for determining efficacy.

00:34:00 **Question – Eduardo MartinezMontes:** Great. That's really helpful. And on the note of the accelerated approval, is there any potential finding – you mentioned GCase, maybe elevation wouldn't be sufficient earlier and it's a much more kind of holistic neuroprotection. You mentioned a couple of the other biomarkers. Would any of those kind of encourage you to pursue accelerated approval with the surrogate endpoint?

00:34:22 **Answer – Jonas Hannestad:** I think the – so my experience so far in Parkinson's with FDA is that there's nothing right now that would be equivalent to what has been done in Alzheimer's, for instance, or ALS. However, I think probably the most promising thing is if you can measure alpha-synuclein with the seeding amplification assay in CSF and make that quantitative, and you see a reduction in alpha-synuclein in the brain, which is what that measures, then that might be sufficient to get accelerated approval. I think the other one is PET imaging of alpha-synuclein, which is currently not available, but there's been a lot of advance in that field. And that would be equivalent to amyloid PET imaging in Alzheimer's, which is what led to, for instance, aducanumab's accelerated approval initially.

00:35:16 **Question – Eduardo MartinezMontes:** Got it. Got it. And just – go ahead.

00:35:18 **Answer – Khalid Islam:** Yeah. And could I just add to that, Jonas? I think the FDA – there was a couple of weeks ago that they were – they started hammering on the seeding assay, and the field's

developing pretty rapidly. So, we'll see what else is coming up over the next period, to be honest. But that was just a couple of weeks ago that the FDA has been saying this is an important marker, et cetera. So, we'll see if that becomes something, which is amenable to accelerated approval.

00:35:45 **Question – Eduardo MartinezMontes:** All right. Thanks so much. Just final question is, if you expect any synergies with existing drugs.

00:35:56 **Answer – Jonas Hannestad:** Not based on what we know because all of the existing drugs or almost all of them ultimately increase dopaminergic neurotransmission, right? So, it's a very specific symptomatic effect. So, I think I wouldn't expect synergy with those drugs. There might be other drugs for neuroprotection or disease modification that could be synergistic, but those are still in development.

00:36:23 **Question – Eduardo MartinezMontes:** Got it. Thanks so much. Those are my questions.

Operator

00:36:27 Thanks for the questions. The next question comes from Jason McCarthy at Maxim.

Analyst: Jason Wesly McCarthy

00:36:32 **Question – Jason Wesly McCarthy:** Hey, guys. Thanks for taking the questions, nice data. As you look towards the outcome of the Phase 1b study, particularly around any biomarkers or suggestive disease modification effects, do you start to look down the road to possibly developing the drug at least in part in the setting of symptomatic PD, but before they go on levodopa and dopamine replacement? I've seen that with some of the – or at least suggested with some of the ABL kinase inhibitors that are out there. They're talking about that, and I wonder if it's something you've thought about.

00:37:12 **Answer – Jonas Hannestad:** Yeah. So, when you do – in clinical development in Parkinson's, it's always – that question always comes up, right? Do you do treatment-naive patients, people who've just been diagnosed with Parkinson's, who have mild symptoms, who are not yet on any kind of medication, right? And do you enroll those and look for disease modification in those or do you go – broaden the criteria a little bit, go a little bit later, and include people who are on medications?

00:37:37 And just as an example, Roche with their alpha-synuclein drug, they started with treatment-naive, now they moved into people on stable dopaminergic therapy. There's an unmet need in both obviously because even once you start these treatments the disease continues to progress and you get worse over time. But there are some nuances in how well you can measure a slowing in progression when somebody is not on medication early in disease versus on medication. So, that's something that we'll discuss over the next year or so.

00:38:16 **Question – Jason Wesly McCarthy:** Right. And there was an earlier question or somebody touched on some of the side effects. When you're thinking about other PD drugs and the GI-related effects that they do have, are you planning to do – are you going to have to do a DDI study early on if you're going to be in the setting of even a levodopa or a dopamine replacement therapy for drug-drug interactions and get it out of the way?

00:38:43 **Answer – Jonas Hannestad:** So, we have no – so based on our in vitro data with liver enzymes interactions, we have no potential interactions with any of the approved Parkinson's drugs. So, for

this first study, there's no reason to think that it would have an interaction with levodopa or a dopamine agonist or an MAO-B inhibitor. But there are drugs with which GT-02287 could interact and some of those drugs will be excluded and then, at some point, we may have to do a clinical drug-drug interaction study but not before this first patient study.

Operator

00:39:16 Thank you for the questions. We have time for one more analyst. So, the next question comes from Boobalan Pachaiyappan from ROTH.

Analyst: Boobalan Pachaiyappan

00:39:25 **Question – Boobalan Pachaiyappan:** Hey. Good morning, everyone. Can you hear me okay?

00:39:27 **Answer – Gene C. Mack:** Hey, Boobalan.

00:39:30 **Question – Boobalan Pachaiyappan:** All right, great. So, thanks so much for taking my questions. So, a few from us. So, maybe on the safety front, I know one subject had a transient increase in AST and ALT. So, I'm just curious if you can provide some color on that. I mean, what dose was the patient on and how was the issue resolved?

00:39:50 **Answer – Jonas Hannestad:** So, this was a patient who received 50 milligrams per kilogram, so the top dose in the single dose cohort. This was an increase in ALT and AST after a single dose of GT-02287. This subject, it appeared that they had slight increase from before dosing. So, if you look at the ALT/AST levels, they increased a bit before the dose actually and then they continued to increase after the dose and then they went back down. So, I think it's very difficult to conclude that that is related to the drug. There were no subjects in the multiple dose cohorts with similar levels, drug levels, had any ALT/AST elevations. So, I think it's a – unrelated to drug, but that's unknown at this time.

00:40:44 **Question – Boobalan Pachaiyappan:** All right. Thanks for the color. And then, in terms of the interim safety readout that you're planning to get it at some point middle of next year, so I'm just curious, how do you plan to study or leverage the findings from the mitochondrial health and the ER stress? And how do you plan to integrate these results into developing GT-02287 for GBA-PD? I mean, what is that you're looking for and how are – what would make this a good biomarker for future studies?

00:41:15 **Answer – Jonas Hannestad:** Yeah. So, what Khalid was highlighting earlier, right, is that the – the potential benefit of this drug in Parkinson's is beyond just activating or making GCase more active,

right, by getting to lysosome. So, GCase has many other functions in the cell, including mitochondrial in mitochondria. And what we've shown is that the drug can improve all of those pathways, which are probably involved in Parkinson's to some extent.

00:41:43 So, it's a broader mechanism of action. And the way we will measure that in patients that we have – we have markers of endoplasmic reticulum stress, of mitochondrial function, neuroinflammation as we spoke about earlier, we will measure all of those and then that those data in totality will then give us some understanding of whether this drug works in the same way in mice and in humans.

00:42:13 **Question – Boobalan Pachaiyappan:** All right. That's it from us. Thanks so much.

00:42:15 **Answer – Gene C. Mack:** And Boobalan, just to add on to that too, what's interesting about our observation from the multiple ascending dose study is that we still saw GCase modulation out 14 days. So, we're not sure if that continue – we're not sure if we're at a point of saturation there or if with additional dosing, we get even a healthier profile if that does indeed translate. So, it will be interesting to see what happens at 28 days, 60 days, 90 days.

00:42:44 **Question – Boobalan Pachaiyappan:** All right. Thank you so much.

Operator

00:42:47 This wraps up the (00:43:39) portion of Q&A. I'll now turn the call back to Apaar for any concluding remarks.

00:42:54 Yeah, thank you. Unfortunately, we have to cut the Q&A off. We just want to be mindful of the market open. But the corresponding poster on this Phase 1 data could be found on the Science and Technology portion of the website or in last Friday's press release. I want to thank those – on behalf of the Gain team, I want to thank everyone in attendance for their time, and we look forward to keeping you updated on the progress of GT-02287. A recording of the transcript and of this conference call will be available at www.gaintherapeutics.com. Thank you, everyone.