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PFE - Pfizer Inc Analyst And Investor Call To Review Data Presentations
At Scientific Conferences During The Week Of June 15th

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OVERVIEW:

Co. discussed the data presented at the American Diabetes Association conference.



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PRESENTATION

Operator

Good day, everyone, and welcome to Pfizer's Analyst and Investor Call to Review Data Presentations at Scientific Conferences during the week of June 15. Today's call is being recorded.

At this time, I would like to turn the call over to Mr. Chuck Triano, Senior Vice President of Investor Relations. Please go ahead, sir.

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Thank you, operator. Good morning, everyone, and thanks for joining us today to review clinical data for our hemophilia A gene therapy program that was presented this morning at the World Federation of Hemophilia Virtual Summit and to also review data from our oral GLP-1R agonist, which was presented this past Monday at the American Diabetes Association Scientific Sessions.

I'm joined today by Mikael Dolsten, our Chief Scientific Officer and President of Pfizer Worldwide Research and Development as well as by several other Pfizer colleagues in our scientific and development areas who Mikael will introduce.

Before we start, I want to remind everybody that we will be making forward-looking statements on today's call, and actual results may differ from those statements. Forward-looking statements speak only as of the original date of this presentation, and we undertake no obligation to update or revise any of these statements.

With that, I'll now turn the call over to Mikael Dolsten. Mikael?



Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you, Chuck. Thank you to all of you who are joining us on the call today.

On the heels of our DMD data presentation a few weeks ago, I am excited to talk to you about the hemophilia A gene therapy data just presented with our partner, Sangamo, at the World Federation of Hemophilia Virtual Summit.

I'm joined today by Seng Cheng, our Rare Disease Chief Scientific Officer, who will share the details of the hemophilia A gene therapy data presented this morning and who will be joined later for Q&A by Dr. Brenda Cooperstone, our Rare Disease Chief Development Officer. You will also hear from Morris Birnbaum, our Internal Medicine CSO. Morrie will share exciting new data on our oral small molecule GLP-1 receptor agonist program, which we just presented at the ADA 80th Scientific Sessions. Aditi Saxena, the clinical lead that was presenting the data at ADA, will be joining us for the Q&A.

These presentations underline opportunity in our pipeline in 2 therapeutic areas, Rare Disease and Internal Medicine, that I believe are underappreciated externally at this point. They also showcase our overall approach to advancing potential next-generation breakthrough science through both partnerships and homegrown efforts.

Both programs break new ground. In hemophilia A, our investigational gene therapy may have the potential to provide a long-term durable response for patients, a vast improvement from the weekly infusion of current standard for hemophilia A. Likewise, a small molecule oral treatment to take on diabetes would also mean an improvement over the injected standard of care for people living with type 2 diabetes and potentially improve the treatment of obesity. I will briefly discuss how we see both programs fit within Pfizer's strategy and the potential opportunity for patients.

First, a few comments and context on gene therapy and where it fits within our strategy based on a question we often get asked. We expect to have 3 Phase 3 gene therapy development programs ongoing by the end of this year in hem A and B and in Duchenne's muscular dystrophy. I believe this will make us the only company in the world with that number of gene therapy programs in Phase 3 of development.

A few short weeks ago, we presented the data from our investigational mini-dystrophin gene therapy program for DMD at the ASGCT annual meeting. We have continued to make robust progress within this program and look forward to starting the pivotal trial for this potential therapy later this year. Pfizer's gene therapy programs will be using drug product manufactured with a commercial process at commercial supply scale. To increase our manufacturing capacity, we have invested approximately \$800 million in 3 manufacturing facilities in North Carolina.

Now I want to share why we're excited about the hemophilia A data that was presented this morning, giroctocogene fitelparvovec, formerly known as SB-525. This hem A gene therapy program from our partnership with Sangamo Therapeutics benefits from our heritage in hemophilia and is one of several potential innovative therapies for patients with hemophilia.

The data presented today in this program demonstrated that 5 subjects receiving the gene therapy have at between 30 and 61 weeks of follow-up sustained robust functional Factor VIII activity without the need for additional factor replacement following an initial use of prophylactic factor. This shows the potential for our gene therapy to be a differentiated one from other hemophilia A gene therapies currently evaluated in the clinic.

Pfizer is currently enrolling subjects in a 6-month Phase 3 lead-in study for the hem A gene therapy program, which will serve as the foundation of the Phase 3 registrational study. And we remain on track to dose the first patient in Phase 3 later this year.

At Pfizer, we have 3 Phase 3 program for the treatment of patients with hemophilia. You will hear more about them soon. More broadly and looking to next year, in 2021, we have the potential to have 5 Rare Disease programs in Phase 3 trials.

I want now briefly to discuss the potential in diabetes and obesity of our oral small molecule GLP-1 receptor agonist, which was homegrown in our Internal Medicine research unit, led by Morrie, who you will hear from shortly in more detail.



Where some of our peers have pulled back from internal medicine, we see great opportunity. Internal Medicine has assembled a novel, science-driven and balanced early and mid-stage pipeline focused on a few key areas: nonalcoholic steatohepatitis or short NASH, cardiovascular, type 2 diabetes and obesity, cachexia or muscle wasting. We have important momentum across our Internal Medicine pipeline with more than 5 ongoing Phase 2b program that, if successful, could enable multiple Phase 3 starts between '21 and '22.

Today, we'll be focusing on our oral small GLP-1 receptor agonist, sharing new exciting data on this potential medicine that was all discovered in-house at Pfizer. The data demonstrated a real potential opportunity for patients, and our aspiration is to develop the most efficacious oral therapy for type 2 diabetes mellitus and develop the first small molecule oral GLP-1 receptor agonist for both obesity and type 2 diabetes. In doing so, we hope to help address these 2 growing global epidemics and their devastating impact on patients, society and economies. The GLP-1 receptor agonist class may also show promise as a NASH therapy. More to come on that at a later time.

Now I want to turn over to Seng first to walk us through the hemophilia data.

Seng Cheng - Pfizer Inc. - Senior VP & Chief Scientific Officer of Rare Disease Research Unit

So thank you, Mikael. I'm very pleased with the opportunity to present this morning an update of our hemophilia A gene therapy program that was just shared at the World Federation of Hemophilia Virtual Summit.

As you indicated, Mikael, our hemophilia A gene therapy program is part of a broader pipeline of genetic medicines that we're developing that presently also includes efforts in hemophilia B as well as in Duchenne muscular dystrophy, all of which will be in Phase 3 testing in the second half of this year. In addition, we also have a partner gene therapy program in Wilson's disease that is also poised to enter clinical testing as well as a pipeline of preclinical programs that are at different stages of maturity in 4 therapeutic areas of declared interest in this category. And these being rare hematology, neurology and metabolic diseases as well as in rare cardiology.

Our approach in any of these disease areas as is our normal practice is one that seeks to be comprehensive and that fully addresses all aspects of the patient's disease journey. So for example, we may introduce a first transformational product, but then follow-up with our next-generation product concept that exhibits significantly improved characteristics and that is designed to address aspects of the disease that still remain unmet.

And this is indeed the approach that we're applying to our patients with hemophilia A as well as hemophilia B, where we had initially introduced recombinant factor replacement therapies and are now developing nonfactor replacement as well as gene therapies that, if successful in gaining regulatory approval, will significantly improve the quality of care that we can provide to our patients.

So as you can see in this slide, and many of you are aware, hemophilia A and B are X-linked genetic diseases that impact approximately 35,000 males in the United States and over 400,000 globally. That's caused by mutations in the gene, including Factor VIII in hemophilia A or Factor IX in hemophilia B that involve in blood clotting.

Patients who have a deficiency in these factors suffer from severe bleeding into the joints that leads to pain, subsequent joint abnormalities that can limit their motion and thereby, affect their quality of life. Early treatments that were developed include the use of plasma-derived clotting factors, but that carry the risk of contamination with pathogens. And in part because of these, these medicines were subsequently eclipsed by the availability of recombinant factor therapies such as ReFacto, BeneFIX and Xyntha, among others. And more recently, these therapies have also been supplemented with longer-acting recombinant factors, bypass agents, factor mimetics that reduce the frequency as well as increase the ease of administration.

So if you move to the next slide, at Pfizer, in addition to gene therapy, we've also been researching the potential of a nonfactor therapy, namely an anti-TFPI antibody or marstacimab to reduce the burden of treatment as indicated here. By leveraging the extrinsic clotting pathway of marstacimab, we have the opportunity to address both hemophilia A and B patients with a single agent. And because this is not a factor replacement therapy, it also offers the opportunity to address patients with inhibitors. And this is particularly pertinent for the hemophilia B patients with inhibitors who are not adequately managed by current therapies. And I hope you agree that if this development program is successful, the availability of such an anti-TFPI antibody-based therapy would indeed represent a breakthrough first-in-class therapy for this specific patient population.



So as you can see on this slide, I'm pleased to report that results from our Phase 1b/2 study, an extension study, demonstrated that indeed, weekly subcutaneous delivery of marstacimab led to a reduction in annualized bleeding rates or ABRs ranging from 82% to 96% relative to the 6 months prior to the study entry depending on their respective cohort. Both the 150- and 300-milligram flat dosing regimens that were tested were well tolerated and with no treatment-related SAEs in the 20 patients treated so far in the study, I'm sorry.

Importantly, there were also no indications of excessive pharmacological effects or thrombotic events to date, including in subjects who received up to 15 months of marstacimab prophylaxis. Based on these encouraging results, the program was granted fast track destination, and a Phase 3 pivotal study has been initiated across 24 countries with the 150-milligram dose. If successful, this could support a submission for regulatory approval within the 2023 time frame.

In addition to marstacimab, as I show on the next slide, we've also been developing gene therapeutics for hemophilia A and B using recombinant AAV vectors that offer the potential for onetime long-term solution for our patients. Our Phase 3 hemophilia B gene therapy program, which we will not present today, began recruiting patients in 2019. The lead-in phase has fully enrolled, and we are on schedule to generate data that we hope will support regulatory filing in the second half of 2021.

However, as Mikael indicated earlier this morning, I would like to provide you with an update on our gene therapy assets in hemophilia A, which is being codeveloped with Sangamo Therapeutics and in particular, our findings in the high-dose cohort in the Alta study, which, as you see here, is a Phase 1/2 dose-ranging, single-dose, multicenter study with giroctocogene fitelparvovec or SB-525 that's been used before in adult patients with severe hemophilia A.

And as illustrated on this slide, the gene delivery vector is an AAV6 serotype vector encoding a B-domain-deleted Factor VIII gene that is placed under the transcriptional control of a liver restricted promoter. A B-domain-deleted Factor VIII variant, which had previously been shown to have the same activity as wild-type factor, was selected to allow it to be incorporated into the limiting packaging capacity at the AAV vector.

We have previously shared the initial findings of this program at the ASH meeting in December 2019, during which we presented Factor VIII expression data up to 36 weeks. Today, I will report on our follow-up observations that include expression data in 5 patients who were treated at the 3E13 vector genomes per kilogram dose, 61 weeks or 14 months. The key exclusions for the study were patients with neutralizing antibodies to the viral capsid or inhibitor to Factor VIII. Anyone who had a history of hypersensitivity to Factor VIII replacement therapy, significant liver dysfunction or in whom steroids were contra-indicated were also excluded. The study primary endpoint was safety and tolerability as assessed by the incidence of adverse events and serious adverse events and by changes in clinical lab assessments, vital signs, EKG and liver imaging.

Changes in circulating Factor VIII levels were also managed in these studies. Secondary endpoints included changes in baseline use of Factor VIII replacement therapy and the frequency and severity of bleeding episodes as well as Factor VIII inhibitor levels.

So on the next slide, from a safety perspective, we observed that infusion of a dose of 3E13 vector genomes per kilogram of giroctocogene fitelparvovec, which is the dose administered in the high-dose cohort in 5 patients, was generally well tolerated. However, one patient did experience a serious adverse event of hypertension and fever of 6 hours post infusion that resolved by 12 hours from onset.

Importantly, with the implementation of additional supportive care guidelines, we have not observed similar severity events in the subsequent 4 subjects who were dosed. Among the 5 patients in this high-dose cohort, 4 received treatment with corticosteroids for liver enzyme elevations. Three of these patients had subsequent ALT elevations, which also resolved following a repeat course of corticosteroids. Four episodes of ALT elevations were controlled with oral corticosteroids, and importantly, with maintenance of sustained functional Factor VIII activity levels.

The next slide shows the rise in Factor VIII activity we have observed over the course of the study in the 5 subjects who had been administered this high dose of 3E13 vector genomes per kilogram, including one at 61 weeks post treatment. And as you can see, patients appear to achieve steady state levels of Factor VIII activity by approximately 9 weeks post infusion, and these levels were sustained and remain undiminished in all the patients through the last data point prior to the data cut.

The median steady state Factor VIII levels was estimated to be 64.2%. This actually represents the median of the patient level geometric mean since week 9 post infusion using the chromogenic assay, which is in the normal range. Importantly, I should say that associated with this expression profile, none of the patients experienced bleeding episodes or required Factor VIII replacement therapy subsequent to the first 3 weeks, including the patient at the 61-week time point.

The next slide, the data for the high-dose cohort is summarized here in a box and whisker plot. It again reflects the rise in Factor VIII levels that we saw, reaching a stable plateau at about week 9 that was then maintained through 36 weeks. We only show data up to 36 weeks here because the number of patients with follow-up beyond that time frame is too low for this analysis. It's important to note that the mean Factor VIII levels calculated for these 5 patients following the 9-week time point, shown here in the dotted blue line, is above the lower bound of what had been specified as a normal threshold, indicated here by the red line at 50%.

So in the next slide, in summary, the new data that we've shared since we've had the last update and now containing the initial follow-up observations, including up to the 61-week time point in one patient, continue to demonstrate that giroctocogene fitelparvovec is generally well tolerated. The same expression of functional Factor VIII levels was achieved with resulting no bleeding episodes or requirements for exogenous Factor VIII in the treated patients.

There was one treatment-related SAE associated with vector infusion that did not have a recurrent sequela. I should add that follow-up for the lower-dose cohorts that now extends up to over 2 years did not show any clinical significant safety as well.

Collectively, the encouraging safety and efficacy data are strongly supportive of further development of the gene therapy concept. And we have consequently initiated a Phase 3 lead-in study with the first dosing of the pivotal study expected to occur later this year.

I should also mention that this program has been granted FDA fast track as well as RMAT designations. With this important milestone, as Mikael indicated, we will become the only company to have 3 gene therapy Phase 3 programs in the clinic this year.

Also, when combined with our gene therapy program in hemophilia B as well as our marstacimab for pan-hemophilia, we are building the next generation of therapies for hemophilia patients and in doing so, we believe, are working to provide meaningful therapeutic options to help patients manage their hemophilia.

So in closing, I would like to say that we're extremely pleased and excited with our having identified a dose for hemophilia A that's well tolerated and importantly, that has demonstrated the ability to confer sustained and undiminished expression of Factor VIII through 61 weeks and the absence of any associated bleeding events and therefore, the potential to be a differentiated hemophilia A gene therapy program. I look forward to the opportunity of providing you with additional updates as the data matures further.

So with that, I will turn it over to Dr. Morris Birnbaum, who will share his insights on our GLP-1 agonist for diabetes.

Morris J. Birnbaum - Pfizer Inc. - Senior VP & Chief Scientific Officer of Internal Medicine

Thanks very much, Seng. As Mikael said earlier this week at the American Diabetes Association meeting, my colleague, Aditi Saxena, presented the data from a Phase 1b study utilizing our first oral small molecule GLP-1 receptor agonist.

This morning, I'm delighted to have the opportunity to briefly summarize those data, but to also give you a sense of where this particular drug fits into the larger context, larger portfolio in Internal Medicine. And of course, I'd be happy to answer questions later.

The Internal Medicine R&D strategy really seeks to build on the long successful legacy at Pfizer for developing cardiovascular and diabetes drugs. In recent years, there's been remarkable success at developing therapeutics for serious diseases, cancer, blood pressure. We've reduced smoking and contributed also by our smoking cessation agent from Internal Medicine, Chantix.



All of these have led to an extension of life span. But at the same time, we're improving the quality of life and extending life span for many in Western societies. And throughout the world, there's also been an adoption of the so-called Western lifestyle, which is defined by overconsumption of calorie-rich meals and a decrease in exercise. The result of all of this has been a worldwide epidemic of obesity, which carries with it the potential for serious disturbances in metabolism.

Now the most widely recognized manifestation of abnormal metabolism is the disease diabetes, which is widely recognized as the major predisposing factor for cardiovascular disease and nonalcoholic fatty liver disease or NASH. All of these syndromes have shared common underlying metabolic abnormalities that really cause the disease. So our goal in the Internal Medicine R&D group is to target those underlying metabolic disorders which cause these related diseases.

So at present, there are 5 Phase 2 studies ongoing in Internal Medicine, each of which has the potential to advance to a pivotal Phase 3 in the '20, '21, '22 time frame. We have 3 trials in NASH in Phase 2, each targeting a different metabolic pathway, each utilizing a small molecule completely developed in Pfizer and each at present a first-in-class target or combination of targets.

Recently, we licensed an antisense oligonucleotide directed against the angiopoietin-like 3 protein, the so-called Vupanorsen. Angiopoietin-like 3 is a genetically validated protein. And we anticipated by reducing its levels in serum we will also reduce the levels of atherogenic lipids that represent much of the residual cardiovascular risk even after correction of LDL-cholesterol levels. We've added cachexia to our portfolio because we see that as a medically important metabolic disease for which there are no approved therapies.

But today, I want to tell you about our GLP-1 receptor agonist, which I'll refer to as PF-2961. Again, this is a small molecule that can be taken orally without any dietary restrictions or fasting. It was developed completely in-house at Pfizer and promises to be the first small molecule of GLP-1 receptor agonist and also the first GLP-1 receptor oral agonist of any kind to be available for obesity. Could I have the next slide, please?

In spite of many drugs that are available for the treatment of diabetes, for most people with this disease, their diabetes is not optimally controlled. In the United States, for example, fully 1/3 of individuals with diabetes go undiagnosed. Of the 2/3 who are diagnosed and under active treatment, less than 50% actually achieve their target hemoglobin A1c levels.

As poorly controlled as this disease is, the opportunities for medical treatment for obesity are even fewer. I think the vast amount of data available now clearly defines the safest and most effective therapy for obesity to be the GLP-1 receptor agonist class of drugs. And yet in spite of this, remarkably few people who are obese or overweight are actually taking this therapy.

We believe the primary factor leading to such a small adoption of such an effective therapy is the resistance of patients and primary care practitioners alike to an injectable therapy. And this is all the more so because this is a largely asymptomatic disease and in fact, is perceived by many not as a disease but as a lifestyle choice. Well, however you view obesity, there is no doubt that obesity predisposes to a large number, over 200 medically serious diseases, including diabetes and cancer. Next slide, please.

So as I said, I'm going to tell you briefly about a Phase 1b study addressing the safety and tolerability of the Pfizer glucagon-like peptide 1 receptor agonist, PF-2961, a small molecule administered twice daily.

This is a 4-week study, randomized, placebo controlled, which is a classic multiple ascending dose design. Now as is true of all members of this drug class, in order to achieve maximally therapeutic drug levels, it's necessary to up-titrate in order to reduce some of the adverse effects.

So like all other GLP-1 receptor agonists, that's the design of this study. In this case, what we did was for all but the lowest doses, there was a 2-week period of titration followed by 2 weeks of stable administration.

The next slide shows that the results of the study showed a safety and tolerability profile that was entirely consistent with prior members of the GLP-1 receptor agonist class. There were no serious adverse effects. There were no deaths. And there are only 2 drug-related withdrawals of the 98 folks enrolled in the study.



The most frequently reported adverse effects were to be anticipated by a GLP-1 receptor agonist, and they were related to gastrointestinal disturbances, nausea, dyspepsia, vomiting and so forth. In addition, there was an increase in heart rate. Again, this is very typical of the GLP-1 receptor agonists, resulting at a level typical of GLP-1 agonists in 4-week studies. It is known that the increase in heart rate tolerates over time. But much more importantly, in longer studies using injectable GLP-1 receptor agonists, it's well recognized that this class of drug actually produces cardiovascular protection. So again, overall, the GLP-1 receptor agonist 2961, PF-2961 has a tolerability profile very, very typical of prior injectable members of this drug class.

The next slide shows you a summary of the type of efficacy we saw in this brief study. Now the participants in the study were all on average afflicted with mild to moderate diabetes. You can see this evidenced by the fasting plasma glucose in the high 100s and a baseline of hemoglobin A1c of 8.3%.

Now as you can see in first row across, administration of PF-2961 led to a dose-dependent reduction in fasting plasma glucose, which was significant at all doses of the drugs administered. Remarkably at the highest doses, in the mid- to highest doses, PF-2961 produced a complete, a near complete normalization of the increase of fasting plasma glucose that these participants had at baseline. And I should note that this decrease in glucose was not associated with any report of hypoglycemia.

Another way of looking at this is by examining the hemoglobin A1c, which this is a very short study to see changes in A1c. And yet, again, at the mid- to high doses, there was both a statistically significant as well as a clinically significant reduction. The hemoglobin A1c placebo-corrected decreased 0.8%, which I should note is on par with many of the widely available and utilized oral antidiabetic agents on the market today.

Lastly, of course, body weight was measured. And again, at the highest dose, there's a striking decrease in body weight, almost 8 kilograms decrease at 4 weeks or about 8% decrease in body weight since on the whole the patient started at about 100 kilograms. Again, this is an impressive early sign of efficacy for a study in which the highest dose, 120 milligrams BID, was administered only for 2 weeks.

Now I should point out also that in the short study, it is very unlikely that either the blood glucose nor the weight loss has reached the maximal effect. We anticipate in longer studies the fasting blood glucose to continue to decrease or to stabilize and hemoglobin A1c to continue to decrease over the next 8 to 10 weeks.

Of course, we don't know yet until we do those studies exactly what the ultimate reduction in hemoglobin A1c will be, but experience with this and other drugs allows us to model it. And when we do submit the mean daily glucose model, it predicts a steady state hemoglobin A1c reduction of about 1.7% or perhaps more. And again, this would put PF-2961 at an equivalent efficacy of injectable GLP-1 receptor agonists.

So next slide. In summary today, what I've done is I showed you evidence that PF-2961 is an effective glucose lowering agent. I've shown you some early signs that it holds great promise as an effective antiobesity drug. And importantly, it can be administered orally without any need for fasting or any other dietary restriction.

In addition, its formulation makes it available for fixed-dose combinations, which historically has been quite important for these individuals with diabetes, especially because of their higher pill burden. In view of the early successes with PF-2961, we're in the process of initiating a Phase 2 study in diabetes, which we anticipate will start dosing next month in July. Later this year, we will also begin a Phase 2 study in obesity which will run in parallel.

Lastly, I should point out that we are cognizant of the success that GLP-1 receptor agonists has had early on in treating NASH. And we look forward to integrating PF-2961 into our already exciting and robust NASH portfolio.

With that, I thank you. I will turn it back to Chuck, and I look forward to answering your questions.

Charles E. Triano - Pfizer Inc. - SVP of IR

Great. Thank you, Morrie, Seng and Mikael, for your prepared comments. At this time, operator, can we please poll for questions? Thank you.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Your first question comes from the line of David Risinger from Morgan Stanley.

David Reed Risinger - *Morgan Stanley, Research Division - MD in Equity Research and United States Pharmaceuticals Analyst*

So I have 3 questions on the oral GLP-1. The first is, could you discuss the very wide Phase 2 dosing range which will include 2.5 milligrams up to 120 milligrams or, I think, 48x the lowest dose? Second, after patients are dosed, how long do they have to wait to eat or drink in Phase 2? And then third, are you working on reformulation efforts? I believe that currently it is BID 4 pills at the high doses.

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Thank you, David. Morrie, please.

Morris J. Birnbaum - *Pfizer Inc. - Senior VP & Chief Scientific Officer of Internal Medicine*

Thank you very much. Thanks. All great questions. I think I'll take them backwards. First of all, yes, we're always in the process of improving formulation. I should point out that the number of pills that were administered in the past study really was just given that way to maintain blinding in such a multi-dose study. And we anticipate ultimately that this will probably be administered by a single pill twice a day.

In reference to your question about how long fasting will be required either before or after administering PF-2961, we anticipate absolutely no restrictions needed at all. This is well absorbed whether taking with fasting or with food, and therefore, there will be no dietary restrictions. But I think for the questions on our choice of dosing, I think I'll turn it over to Aditi and let her answer the question. Aditi?

Aditi Saxena - *Pfizer Inc. - Senior Director and Clinical Lead, Internal Medicine*

Thank you, Morrie. So the dose range that's being assessed in our Phase 2 study, as you mentioned, does range from 2.5 milligrams BID up to 120 milligrams BID because we are trying to assess the efficacy across that broad dose range. Our lowest dose in our Phase 1b study that we administered for 2 weeks was 5 milligrams BID. And our modeling of the, based on mean daily glucose data from that low dose of 5 milligrams BID indicates that it may be at least as, if not more, efficacious than currently available oral agents to treat diabetes, excluding the GLP-1 class. So we're really trying to understand the full range of the efficacy across the range of doses, both for glycemia and for weight loss.

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Thank you. And I thought it was very encouraging to hear that we are projecting to be as efficacious or more efficacious than currently available injectable. And we anticipate no food restrictions, which is different from any reformulated currently.

Operator

Your next question comes from Terence Flynn from Goldman Sachs.



Terence C. Flynn - *Goldman Sachs Group Inc., Research Division - MD*

I guess, again, another question on the oral GLP. Was wondering if you're looking at all at ways to try to optimize the GI profile further. I recognize some of these are class effects. But at least at first pass, when I look at kind of diarrhea and vomiting rates, it looks somewhat higher than oral sema. So that was kind of the first question. Then with respect to the hem A program, can you tell us what percent of patients met the exclusion criteria for anti-AAV6 antibodies? And then how do you think about enrollment of the pivotal trial given kind of the competitive landscape?

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Well, it was terrific with a multiple question on both subpresentations. So Morrie, you start with the oral GLP and the GI and then we have followed then by Seng and Brenda to comment on individually the percentage with preformed antibodies and aspects of enrollment.

Morris J. Birnbaum - *Pfizer Inc. - Senior VP & Chief Scientific Officer of Internal Medicine*

Well, Mikael, as you know, thanks for the question. As you note, the GI disturbances that we saw in this study are very typical of the class. And I really don't think there are any more than have reported with semaglutide. Remember that most of the studies, in fact, all the studies you've seen with semaglutide are very extended studies. And it's well-known that these GI effects tolerate over time. I think if you go back and look at some of the 4-week studies with the injectables, you'll find that the GI effects we're seeing are very comparable or, in some cases, considerably less.

As far as titration schemes, the reality is that in a 4-week study where we're trying to desperately get 2 weeks of stable dosage, the 2-week titration was much faster than we really anticipate we're going to use in the latter studies and certainly, when this drug is ultimately approved. So it's a faster, and I think that increase. I just want to point out that the real advantages of the oral therapy, and we've been told this by a lot of practitioners because unlike the injectables, it really gives you a chance to back titrate. In other words, if you get too much vomiting, you can easily drop the doses of an oral and have an individual with diabetes or obesity respond. One of the issues with using some of the injectables is if you go too quickly and get too much GI upset, the patient has to live with that for a while, a week or 2, and that turns a lot of patients off. So overall, I don't think our tolerability is any worse than the injectables. And I think you'll see it reduce quite a bit as we go into longer studies with slower titration schedules. Seng?

Seng Cheng - *Pfizer Inc. - Senior VP & Chief Scientific Officer of Rare Disease Research Unit*

That number of patients that were excluded because of neutralizing antibodies. I know from the literature that we reported previously for AAV6, that's around the 20% benchmark.

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Thank you, and Brenda, on the recruitment plans?

Brenda Cooperstone - *Pfizer Inc. - Chief Development Officer of Rare Disease*

So the pivotal program is actually in 2 parts. The first is the 6-month lead-in, where patients are assessed on their ongoing prophylaxis, and that has already begun. Actually, it began in 2019. And we have not had an issue with respect to enrollment, notwithstanding COVID. And so we anticipate those new patients coming off of that starting in the second half of this year and don't anticipate that enrollment in and of itself even in this competitive environment will be any issue given that this is a global trial and that Pfizer has a long-standing relationship with the hemophilia patient community and health care providers.



Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you, Brenda. That was a very encouraging answer. And we should note also that durability and a very robust level, well above 50% of normal factor. This is in stark contrast to recent reports by another company where you see number of patients dropping to below detection levels. So I do think, as Brenda summarized, we would expect high patient and physician interest this best-in-class product, and that's what we've seen so far.

Operator

Your next question comes from Louise Chen from Cantor.

Louise Alesandra Chen - Cantor Fitzgerald & Co., Research Division - Senior Research Analyst & MD

First question I had for you is, how do you see the market shaking out for GLP-1s oral versus injectable? There are also these GIP-GLP combos, amongst others. Where do you think you'll fit in here? Second question is on the durability of your hem A drug. Do you expect to see potential decline in Factor VIII level expression like we've seen in other competitive drugs or do you think it will be stabilized? And then lastly, is how deeply do you think gene therapy products will penetrate the market?

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

So Morrie, you start with the aspect of how you see this product penetrate. And maybe you could speak about both the existing GLP-1 injectable and the oral market that is existing, and then we can move to Brenda to share thoughts about durability and the share of gene therapy in the future, particularly for those that are sustainable.

Morris J. Birnbaum - Pfizer Inc. - Senior VP & Chief Scientific Officer of Internal Medicine

Right. Thanks, Mikael. Yes, there's been enormous amount of success with getting the injectable GLP-1 therapy to patients with diabetes, less so getting that same therapy to individuals with obesity. But nonetheless, as I mentioned, still a large percentage of people with diabetes and especially so with obesity are just unwilling to take the injectable or just find it inconvenient. Compliance has not been what one would have hoped with injectable type of therapy. So in diabetes, we think there's a tremendous opportunity for the oral in getting to those patients who are either unwilling to take injectables or are taken care of by primary physicians who are ill-equipped to train patients in terms of injections.

In the case of obesity, I think the opportunity is even greater. We anticipate that PF-2961 will be the first GLP-1 receptor agonist approved for obesity. To our knowledge, the current peptides that are being developed for obesity have not been disclosed -- I'm sorry, which are being developed for diabetes so far, we've not heard anything about them being developed for obesity. So quite possibly 2961 will be the only orally available antiobesity GLP-1 receptor agonist. Right now, less than 1 in 20 people who are eligible for an obesity drug are being treated. And as of that, less than 1 in 20 are being treated with GLP-1 receptor agonists by injection. So really, the potential and the enormity of the untreated patient group is very impressive.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you. Brenda?

Brenda Cooperstone - Pfizer Inc. - Chief Development Officer of Rare Disease

Thank you, Mikael. As Mikael said, we've shown excellent sustained factor levels out through the up to 61 weeks duration. And this is the data that we have available. We think there is hope that this sustained factor levels will continue beyond the 61-week point and that this will be carried into Phase 3.

We also believe that this is a very sophisticated patient population and treating health care providers. And they will wait to see which therapeutic option would be best for the patients themselves. As Seng referred to, we have created a holistic approach to hemophilia so that we have factor replacement as well as nonfactor replacement and gene therapy so that we can cover the entire spectrum of needs of this patient population.

Our market assessment gives us an estimate of approximately 20% of eligible patients who will avail themselves of gene therapy. But as I said, I do believe that we will see that patients and hemophilia specialists will wait to see what the best technology and treatment option will be for their patients given this is a once-in-a-lifetime therapy.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you. And one observation is that some other companies have had need for repeat use of steroids under long time after initial transfusion. And that likely is related to the drop in activity observed as you deplete for liver cells that are genetically transfected. And we have seen mainly during the first early period the need for steroid in general in patients. So I think there is a good rationale why we see a durability that haven't been reported by all companies here.

Operator

Your next question comes from Geoff Meacham from Bank of America.

Scott Puckhaber - Bank of America - Biopharmaceutical Equity Research

This is Scott on for Geoff. I have a question on hemophilia A. So any thoughts on how frequently we can expect updates from the Phase 3 trial? Just wondering if it may be beneficial to update to show more durability to alleviate any concerns from the competitor that will already be on the market. And then given what you've seen in the data provided to date, what are the expectations for steroid use in the Phase 3 trial?

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you. Brenda?

Brenda Cooperstone - Pfizer Inc. - Chief Development Officer of Rare Disease

So the expectation, so I can tell you with regard to steroid use, as Seng said, 4 out of the 5 patients did require some steroids, but that their levels were -- the factor were sustained. And we did not see any drop as a result, and they did not require prolonged steroid application.

In terms of Phase 3, the data from our Phase 1 trial will inform the decisions with regard to Phase 3 steroid dosing. As of now, we do not anticipate that we will be using prophylactic steroids, but we will use it reactively as the Phase 1 trial was designed.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you.

Operator

Your next question comes from Steve Scala from Cowen.



Stephen Michael Scala - Cowen and Company, LLC, Research Division - MD & Senior Research Analyst

I also have some questions on hemophilia A program and the LFT elevations. Just to be clear, based on your answer to the last question, the LFTs did not go back up after cessation of steroid treatment. Is that true? And second, have you considered extending the duration of steroid treatment? Also, can you clarify, is the filing in the second half of 2021? That was not clear. So that's on the hemophilia A program. And then on the oral GLP-1, you have 2 programs, one's in Phase 2 and one's in Phase 1. Maybe you could tell us the difference between them.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Yes. I think, Brenda, you want to speak about the hem A, and Seng, if you want to add anything to Brenda's comment, please do that. And then we'll follow with Morrie on why you have explored 2 different GLP-1.

Brenda Cooperstone - Pfizer Inc. - Chief Development Officer of Rare Disease

So of the 5 patients that were discussed in this presentation, 3 of those did have a repeat increase that was well controlled with repeat steroids. One did not have any increase in AST-ALT that required steroids, and one had only a single elevation. So that is the steroid result for all those 5 patients. And again, we will use the data that is generated in the Phase 1 to inform the decision with regard to steroid dosing in Phase 3. And with that, I'd ask Seng if he has anything to add.

Seng Cheng - Pfizer Inc. - Senior VP & Chief Scientific Officer of Rare Disease Research Unit

Let me just add that the resolution occurred very quickly within 2 weeks and that prompt intervention appeared to preserve the therapeutic benefit, and to reiterate that we maintained Factor VIII levels in the follow-up period despite the elevations that we saw.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you very much. Anything about the filing in addition to what you stated in prepared remarks?

Brenda Cooperstone - Pfizer Inc. - Chief Development Officer of Rare Disease

Oh. Yes, excuse me. So the anticipated filing for hem A is in 2023. I believe the date of 2021 was in Seng's presentation was in reference to the filing for hemophilia B.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Okay. As always, we'll keep options for looking for acceleration opportunity, which has been quite successful in our end, but good to have you confirm the plan. And now, Morrie, the oral GLP-1, the additional molecule that you did not speak about today.

Morris J. Birnbaum - Pfizer Inc. - Senior VP & Chief Scientific Officer of Internal Medicine

Right. Thank you, and thanks for pointing out we do have an additional molecule. In addition to 2961, there is another molecule that just completed single ascending dose. And in nonclinical studies, it has very much the same profile as PF-2961. I think right now looks like the major differences, if there are some, will be pharmacokinetic.

I just want to say to make it clear that this isn't backup. PF-2961 so far has looked quite good, and we're determined to take it forward for diabetes and obesity. However, it is notable that the GLP-1 receptor agonism mechanism has shown to be, in early studies, effective for quite a few diseases.

I mean, Mikael mentioned that it's been shown to be effective in NASH. And there are other even more preliminary studies suggesting that GLP-1 receptor agonism might actually help folks with neurodegenerative disease, both Alzheimer's and Parkinson's.

So given what a long time it has been, how difficult it has been for us and others to develop this class of small molecule agonists, we just thought that the best we could do to put ourselves in the optimal position is to have 2 effective therapies going forward. Really, all we're trying to do is increase the range of our opportunities as we bring forward this novel oral therapy.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you very much. And I know that there was a lot of questions on the durability and steroid use. And I think, as I pointed out, the transient and moderate need for steroids in our patients, the robust durability of factor, substantially above 50% of normal, is quite distinct and different from what you have seen with another company reporting recently. And that gives us quite some confidence that we have a unique, best-in-class profile. And of course, we can see that in an area of hemophilia A or B being very important that you don't lock yourself out from the ability of maybe decade-long benefit by using infusion of AAVs that cause significant immune reaction and cross-reactivity for later gene therapies. So we're going to follow how this develops, but we currently have a very positive view from our own and key opinion leaders.

Operator

Your next question comes from Umer Raffat from Evercore.

Umer Raffat - Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research

On the gene therapy first, if I may, there's now the second patient who's dropped off, I believe patient 11. And I know we previously knew that patient 9, which had reported some drop off, had a 50% drop in their von Willebrand factor. Was it the same issue that happened to patient 11 or was it liver inflammation? And I ask because I know you mentioned 3 patients required repeat steroids because of liver enzymes. Was it patients 8, 9 and 11 that was the repeat steroid dose given to?

And then just a quick one on oral GLP. The baseline weight loss for the 120-milligram BID group, I think that will be very helpful because I believe the baseline for weight was reported across the whole trial across doses. If we could just have the baseline weight for the 120 BID dose in particular or just a confirmation that it's around 92, which was reported for overall?

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you. Great detailed questions here. Seng, you want to comment on what we can learn from the individual patients here?

Seng Cheng - Pfizer Inc. - Senior VP & Chief Scientific Officer of Rare Disease Research Unit

So if I recall, the patient 9, the Factor VIII level indeed has remained stable since week 18. And in patient 11, I'm just -- I kind of remember which one that is. I'm going to try to pull up that data. Brenda, do you remember that patient 11?

Brenda Cooperstone - Pfizer Inc. - Chief Development Officer of Rare Disease

Yes. Yes, patient 11 had a very late elevation in ALT, which we don't believe had any relationship at all to the dosing or the presence of the transgene. And so it is very difficult to draw any conclusions for a single patient experience, but we believe that any changes in ALT, although they were treated with steroids, it was not as a result of the construct itself.



Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Thank you. That was very clarifying. Morris, can you give the baseline weight for that oral GLP high dose?

Morris J. Birnbaum - Pfizer Inc. - Senior VP & Chief Scientific Officer of Internal Medicine

I can't recall, but let me ask Aditi if she has within easy reach the baseline weight specifically for the 120 BID group. Do you remember that, Aditi?

Aditi Saxena - Pfizer Inc. - Senior Director and Clinical Lead, Internal Medicine

Yes, yes. I'm here, and I can answer that question. So as we presented in the ADA presentation, there was differences and there were differences in baseline parameters across the cohorts. This was because there were 12 participants per cohort. There was some variability in the baseline parameters across cohorts, and this did include body weight. So we presented the range of body weight across the cohorts, and they range from about 85 kilograms in one cohort up to 101.6 kilograms in another cohort. And if I remember correctly, the specific baseline body weight for the 120-milligram BID cohort was on the top end. It was around that 100 kg. So the percentage change from baseline would need to be taken into that context. But I would again remind the audience that this is a 28-day study. So we expect with the longer duration of dosing and also a larger study in Phase 2, there would be, of course, much more similarity in baseline parameters across the dosing regimens there, and it's much more clear. Yes?

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

Sorry, Aditi. I thought if you could clarify, when you looked across the 12 patients, so in the 120, did you see a consistent robust weight loss in all of them?

Aditi Saxena - Pfizer Inc. - Senior Director and Clinical Lead, Internal Medicine

Yes. Absolutely, yes. So there was a consistent, robust and significantly and statistically significant weight loss. It's just that when you start from a higher baseline, there can be greater short-term declines. But we saw robust declines. And I say and I should actually maybe mention that the 70-milligram BID cohort, which also saw declines of sort of an average of 4.4 kgs, I believe, had a baseline body weight that was in the range of the mean reported.

Brenda Cooperstone - Pfizer Inc. - Chief Development Officer of Rare Disease

Mikael, this is Brenda. I do want to make a clarification. The patient I was referring to was actually patient 7, who had the late steroid application. Patient 11, which is what your question was about, that patient had a Grade 2 ALT elevation, and his steroid taper was the quickest. And it's very, very difficult to draw, again, any conclusion from that single patient experience, but these levels have been sustained since the point where he stabilized. So we have seen no further drop in levels in that particular patient. Thank you.

Mikael Dolsten - Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical

That's very reassuring. Thank you both of you.

Operator

Your final question comes from the line of Navin Jacob from UBS.

Navin Cyriac Jacob - *UBS Investment Bank, Research Division - Equity Research Analyst of Specialty Pharmaceuticals and Large Cap Pharmaceutic*
Hello?

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*
Yes. Now we can hear you.

Navin Cyriac Jacob - *UBS Investment Bank, Research Division - Equity Research Analyst of Specialty Pharmaceuticals and Large Cap Pharmaceutic*
Operator, we exited the queue.

Operator

That question has been withdrawn.

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Right. This is Chuck again. So we'd like to thank all of you for your attention this morning. I'd like to thank our Pfizer colleagues for the presentation and the Q&A session. Mikael, any closing remarks you want to make?

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

I would think, yes, a similar thought, there were some great questions from our colleagues in the analyst, investor community, and we are pleased to be able to do more regular updates on the type of breakthrough science that we are sustaining.

In this particular discussion today, you could see from 2 areas, Rare Disease, our comprehensive portfolio in hemophilia for multiple patient offerings in hem A and B. We remain very enthusiastic about both our hem A and B gene therapies with potential for best-in-class profile. And as we pointed out in the previous update a couple of weeks ago on DMD, also there we continue to accumulate very encouraging data as we have refined the medical practice in those patients. So we learn across all of our programs, and that's the strength of having such a comprehensive portfolio.

And similar in Internal Medicine, as you noted, there is a great combination and synergy effect of being active in broad aspect of metabolic and cardiovascular disease crossing diabetes, obesity and NASH. And you will hear more about the unique opportunities at Pfizer to combine drugs. And of course, oral GLP-1 could be by itself could have a pipeline in a pill, and look forward to hear more from Morris as we now move swiftly forward. Thank you, everyone.

Operator

Ladies and gentlemen, that does conclude today's conference. We thank you for your participation and ask that you please disconnect at this time.

JUNE 18, 2020 / 3:30PM, PFE - Pfizer Inc Analyst And Investor Call To Review Data Presentations At Scientific Conferences During The Week Of June 15th

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