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Presentation

Operator

Hello, and welcome to Regeneron's conference call to discuss Regeneron's Genetics Center and MASH siRNA development programs. My name is Kevin, and I'll be your operator for today's call. [Operator Instructions] Please note that this conference call is being recorded.

I will now turn the call over to Ryan Crowe, Senior Vice President, Investor Relations. You may begin.

Ryan Crowe
Senior Vice President of Investor Relations & Strategic Analysis

Thank you, Kevin. Good morning, and welcome to our Regeneron Roundtable Investor Event, a series of presentations spotlighting key opportunities across Regeneron's pipeline. Today's dual-purpose roundtable will highlight Regeneron's leading genetic efforts through the Regeneron Genetics Center, or RGC, and our MASH siRNA development programs, which are informed by valuable human genetic insights from the RGC.

Before we begin, I would like to remind you that remarks made today may include forward-looking statements about Regeneron, and each forward-looking statement is subject to risks and uncertainties that could cause actual results and events to differ materially from those projected in such statements. A description of material risks and uncertainties can be found in Regeneron's SEC filings. Regeneron does not undertake any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

Let's begin. Today's roundtable will highlight the differentiated capabilities of the Regeneron Genetics Center and our MASH siRNA portfolio, led by the CIDEB siRNA program, which is rapidly advancing into registrational studies.

Today's speaker panel brings together leaders spanning research, clinical development and commercial strategy. First, Dr. George Yancopoulos, Regeneron's Co-Founder, Board Co-Chair, President and Chief Scientific Officer, will provide a quick overview of our RGC efforts and the MASH pipeline. Next, Dr. Aris Baras, Senior Vice President, Head of Regeneron Genetics Center, Co-Head of Regeneron Genetic Medicines, will provide a broad overview of our Regeneron Genetics Center efforts and how it informs nearly everything we do at Regeneron. Then Dr. Gary Herman, Senior Vice President, Clinical Development Unit Head, Regeneron Genetic Medicines, will discuss our portfolio of MASH siRNAs, including the recently presented data for our CIDEB siRNA program. And finally, Josh Adelson, Executive Director, Commercial, New Products, will touch upon our market analysis of MASH and how our CIDEB siRNA has the potential to be paradigm shifting upon clinical validation. We will then use the remaining time for Q&A.

With that, let me now turn the call over to George.

George D. Yancopoulos
Co-Founder, President, Chief Scientific Officer & Co-Chairman

Thanks, Ryan. At Regeneron, we have always focused on genetics to address a major bottleneck in our business, the lack of great targets for diseases where better medicines are still needed. At Regeneron, we have always prioritized genetics, both mouse and humans. Rather than rely on the literature and discoveries of the rest of the world, we chose to build on our initial mouse genetics capability and then decided to invest deeply to create our own human genetics discovery engine that we call the Regeneron Genetics Center, or the RGC, to fuel the next wave of Regeneron targets and therapeutics.

Today, you'll hear a little bit about the RGC and what it can deliver. Almost 15 years later, we have the largest multi-omics database that we are aware of, nearly 4 million individuals with multi-omics data, including DNA sequences and proteomics linked to de-identified, longitudinal health records and other rich human health data. That includes about 3.3 million individuals with data generated internally and about 700,000 from in-licensing. Add to that over a decade of proprietary data curation, advanced analytics and AI, and we have discovered and validated nearly 50 new targets across our pipeline. The impact of the RGC goes far beyond target discovery. We also use human genetics to guide development across as much of our pipeline as possible from selecting additional indications, as we did to help guide Dupixent to 9 FDA-approved indications, to identifying response biomarkers and informing clinical trial design and enrollment.

CIDEB shows the full arc. We discovered the target several years ago and achieved clinical proof of concept in 2026. Lastly, over the last 5 years plus, the RGC has expanded from human genetics into proteomics, developing risk scores and biomarkers for disease,

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clinical outcomes and health traits that have been instrumental in our clinical trials. They also show potential to diagnose and predict disease progression better than existing standards and ultimately, to offer a single test to evaluate risk across dozens and dozens of diseases. Combining our multi-omics database and approaches could reimagine health care management with greater efficiency, lower cost and better outcomes for patients, providers and payers. In short, we are using multi-omics both to discover new drug targets and to revolutionize health care.

Next slide, please. One of Regeneron's early and sustained differentiating approaches has been to focus on large-effect genetics. These include variants that can cause genetic diseases such as CAPS or the otoferlin forms of congenital hearing loss as well as protective variants, such as PCSK9 in heart disease and CIDEB in liver disease, along with dozens of additional protective variants that the RGC has identified across all of our therapeutic areas. We look for what I call super humans from Nature's experiment, people at the genetic extremes, especially those protected from disease that harms everyone else.

On the curve on the left, most people sit in the middle. The most useful discoveries are at the end. A protective variant tells us which gene to turn down and what benefit could look like in a person. To find them, we combine 3 approaches. First, large-scale sequencing and proteomics to find the rare variants. To-date, we have access to nearly 4 million sequenced individuals across our collaborations and studies. Second, linked electronic health records because DNA alone is just a code. Tied to years of sample imaging and diagnosis, these health records show what a genetic variant does. And third, AI to analyze all of it at scale. The result, approximately 50 potential novel targets so far across the organ systems on the right from metabolism and cardiovascular and neuroscience and ophthalmology. Targets backed by rare protective variants like these are about 6x more likely to be approved than targets with no genetic support. More programs in the pipeline were either discovered by human genetics like CIDEB, or supported by it, like Dupixent.

Let me show you what one of these 50 targets looks like today. On the next slide. We are highlighting today one of our most recent and exciting stories, a target discovered here at Regeneron by the Regeneron Genetics Center where we now have a therapeutic candidate in the clinic with encouraging results. Less than 5 years ago, the RGC discovered a new protective variant in MASH. On the left, in our analyses of millions of individuals, we found the rare individuals, approximately 1 in 500, who carry a loss-of-function variant in CIDEB have lower serum ALT, a marker of liver injury, less liver fat and a 43% lower risk of liver disease. That is Nature's experiment. The question, can the medicine do to a patient what the variant does on a population level?

Through our collaboration with Alnylam, we developed an siRNA targeting CIDEB and moved quickly into the clinic. Just a few days ago, we simultaneously presented and published the results. On the right, you can see that single doses produced rapid, deep and long-lasting normalization of liver fat in patients with liver disease with reductions of up to 80% from baseline across tested doses lasting for many months. Gary will expand on these results in detail shortly.

This is a full circle moment from a human genetic discovery to clinical proof-of-concept in patients. The clinical benefit we observed with CIDEB siRNA validates our genetics-driven approach and support CIDEB as a potential medicine for the growing MASH patient population. MASH is dramatically under-diagnosed and under-treated today, and we expect that to change as treatment options and diagnosis rates increase.

Now I'll hand it over to Aris Baras to show you how the Regeneron Genetics Center delivers this again and again and how it guides development decisions and with AI and multi-omics supports new diagnostic opportunities as well.

Aris Baras
Senior VP, Head of Regeneron Genetics Center & Co-Head of Regeneron Genetic Medicines

Thanks, George. Moving to Slide 8. We have long believed and seen in our own experience that human genetics evidence improves the probability of drug development success. Recently, we've been able to put some numbers behind that. According to an analysis of databases, tracking drug development success rates, fewer than 10% of programs that enter the clinic reach approval. Several groups have looked at whether human genetics evidence improves those odds, including an independent analysis published in Nature. They reported that programs with any human genetics evidence supporting the target based on analyses of common variants have 2.6-fold higher success rates.

Our analysis of the available data yielded similar results, about 2.8-fold. We extended this analysis to programs with rare, large effect, protective genetic evidence, which is only attainable by sequencing exomes or genomes and found that these programs have about sixfold higher success rates. This supports our approach of prioritizing targets backed by human genetics, especially rare protective variants, which provides the strongest validation and the greatest probability of success.

One major area of focus for the RGC has been large effect genetics, and these variants are almost always rare, requiring very large sample sizes to uncover them. The line here shows our cumulative samples sequenced over time. As we have scaled our databases

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over the last decade, we have repeatedly seen that the more rare variants, the larger the effects are on a trait, disease or phenotype. Increasing scale and diversity allows us to discover more and more incredibly rare therapeutically relevant gene variants, leading to better drug targets. Our data set also includes 1 million participants who are not of European ancestry, which helps ensure our discoveries apply to more patients. Highlighted here are 3 examples.

Next slide, please. One of our earliest MASH discoveries was a protective variant in the HSDB13 gene carried by about 1 in 3 people. This common variant gave a meaningful, but from today's perspective, modest 16% reduction in the risk of liver disease.

Next, please. A few years later, with about 540,000 sequenced samples linked to health records, we found a much rarer protective variant in the CIDEB gene, only 1 in 500 people carry it, but the effects are larger, a 43% lower risk of developing liver disease and 22% lower liver fat. We first published this in 2022 and have recently confirmed the findings in a larger data set of 1 million to 2 million samples in the New England Journal of Medicine.

Next, please. As our capabilities grow, we find even rarer variants with even larger effect sizes. Earlier this year, we published an ultra-rare protective variant in FNIP1, carried by 1 in 5,000 people, which we discovered using more than 1 million samples. On liver fat, the effect is even larger than CIDEB's. Carriers have 68% lower liver fat than noncarriers versus 22% for CIDEB carriers. The protection from cardiometabolic diseases is quite large with a greater than 60% reduction in risk, and we believe it could be a promising therapeutic candidate in that setting. These are just 3 examples.

Next, I'll show you how scale has so far translated into a pipeline of targets. Since 2015, the Regeneron Genetics Center has enabled the discovery or validation of nearly 50 targets. They span metabolism, cardiovascular and renal disease, neuroscience, immunology and more. They've even pushed us into new areas, driven by the strength of the genetics and biology and by unmet need and commercial opportunity. Each tile on Slide 10 is one target labeled with its lead indication and colored by therapeutic area. And its position on the time line is the year it was discovered and entered our pipeline as a new target and program to generate a drug candidate. And the pace has picked up as our scale has grown.

Programs for 6 of these targets, shown with an outline, are now in the clinic and CIDEB is among the most promising. We see potential for many more to follow CIDEB's clinical validation, and we expect additional targets on this slide to advance into the clinic, and we continue to add new ones.

Genetics also helps guide our development strategy. One way we do that is to identify and validate new indications or indication expansion opportunities. Dupixent proved to be a pipeline in a product, as we like to say, with 9 approved indications. Human genetics has helped us evaluate dozens of possible indications over the last decade for this program. Here, we will summarize efforts where we created a genetic risk score of variants in the target and its pathway. In this case, IL-4 and IL-13 and then used it to identify diseases where the target and pathway are genetically and likely causally linked.

Next, please. In this schematic, we have simplified the genetic pathway score into low-, medium- and high-risk categories, which correspond to low-, medium- and high-pathway activity. The higher the odds ratio, the higher the disease risk. In this example, for asthma, the indication in which this score was initially trained, developed and validated, we can see that people with a low IL-4, IL-13 genetic risk score tend to have the lowest risk of developing asthma. And the opposite is true for people with a high risk score.

Next, please. We observe a similar trend for atopic dermatitis depicted here, the odds ratio across genetic risk score levels follows a distribution similar to asthma.

Next, please. The same is true for almost all other diseases for which Dupixent has since been approved. The correlation between the odds ratio of disease development and risk score is striking. Analyses of these risk scores help inform later-stage Dupixent development with the results that everyone is familiar with today.

Next, please. On the right are negative controls, where there is no association, indicating limited genetic support for pursuing those indications and which are not driven by IL-4 and IL-13. This type of work is now done routinely for most development programs in our pipeline.

Switching gears, we would like to highlight a more recent area of expansion for the RGC, proteomics. It builds on our genetics work and gives us another way to support drug development as well as new diagnostic opportunities. Over the last 5 years, the RGC has built proteomics capabilities that can now process 1 million samples per year and measure 5,000 or more proteins in each sample or narrower target panels that allow better detection of specific proteins or isoforms relevant to disease.

The RGC, given its automation and production capacity, was selected to generate Olink proteomics data for all of the UK Biobank, more than 500,000 samples and also routinely generates large-scale proteomics data in its other proprietary health record linked

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cohorts. One example highlighted here is our proteomic risk score for MASH. It was developed, trained and validated in multiple independent large-scale RGC cohorts, including our Geisinger and UK Biobank cohorts, to identify patients with MASH and to predict disease progression and clinical outcomes.

In the NASH Clinical Research Network, or CRN, cohort with baseline biopsy data and structured longitudinal follow-up, we compared the proteomic risk score as a noninvasive liquid biopsy to the gold standard of liver biopsy in identifying patients with F2 or greater fibrosis stage and then looked at their subsequent rates of clinical outcomes, which included hepatocellular carcinoma, decompensation, transplant, ascites, esophageal varices and encephalopathy. As you can see from the Kaplan-Meier plot, the 2 approaches predict very similar 10-year clinical event rates, approximately 15% in patients identified as having F2 or greater fibrosis. As can also be seen in the Kaplan-Meier plot, the proteomic risk score was equally able to identify patients with lower-risk disease such as those predicted to have F0 or F1 fibrosis stages. The liquid biopsy proteomics predicted F0 and F1 patients, again, followed very similar clinical trajectories as those identified by gold standard liver biopsies.

In a further analysis, we compared the performance of our proteomic risk score with other noninvasive tests for MASH and found that the proteomic risk score performed better on standard measures such as sensitivity, specificity and area under the curve. The development of this proteomic risk score creates multiple potential opportunities, spanning a simple blood draw that could replace invasive liver biopsies, biomarkers for trial screening and enrollment and potential future commercial diagnostics.

Next slide. This pace of discovery has been enabled by the scale of our data, our proprietary curation and enhancement of those data and our long-standing use of advanced AI, analytics and data science. Today, we have access to nearly 4 million sequenced participants, including about 3.3 million generated in-house. Our current platform is, to our knowledge, the largest of its kind with sequenced data linked to longitudinal health record data and enhanced by rich imaging, pathology and proteomic data. We anticipate growing to 10 million to 50 million sequenced participants over the next 5 to 10 years. We have started down that path through a series of health record partnerships, such as with TriNetX and Truveta that give us access to more than 400 million health records and the ability to link those to large biobanks and other sample sources.

The chart on the left shows the gap between RGC and other reported sequenced cohorts. Of the reported sequenced cohorts, RGC's database is the largest at about 4 million. Consumer genetics companies have more people, but not all consent for research. They mostly use genotyping arrays with little exome or genome sequencing to unlock rare large effect variants, and there is limited, if any, health record linked data.

The RGC, since its inception, has been at the leading edge of data science and technology from statistics and machine learning to more recently large language models and broader applications of AI. We've developed custom LLMs to analyze DNA sequences, proteomics and other health data with a proven track record of improving our discovery yield and pipeline impact. Recent examples include pairing our data with LLMs to outperform leading AI models such as Google DeepMind's AlphaMissense at identifying protein damaging variants. Using AI-assisted coding to rapidly scale our programming needs and analysis tools and pipelines, and exploring ways to train LLMs on our large proprietary data sets to enable AI-driven health care queries and products for consumers and companies.

To wrap up, human genetics is a core capability and a key differentiator for Regeneron. It meaningfully improves the odds of success. And across the pipeline as large as ours, that creates a real advantage. The RGC has delivered nearly 50 actionable targets for our pipeline and 6 programs are at clinical stage with CIDEB achieving the most recent clinical translation and proof-of-concept. This is enabled by our large genomics and health record database, our proprietary data curation and our analytics and AI capabilities.

We also use these multi-omics capabilities, which helped guide Dupixent's indications to guide development across most of our pipeline. And as we add proteomics, risk scores and clinical outcomes predictions, we see opportunities beyond drug development in differentiated diagnostics and health care AI. We are exploring ways in which multi-omics could pinpoint who needs intervention. Shifting care from reactive to proactive to potentially create efficiencies, improve outcomes and lower health care system costs.

Where this goes next? With more scale, RGC could play an important role in health care decision-making. We envision a knowledge base and super intelligence platform for health risk prediction and health care management, a resource that patients, doctors, payers, companies and governments can all use to improve health care. Over time, it could also become a meaningful source of value for Regeneron in addition to drug discovery and development.

To wrap up this section, we wanted to emphasize again that CIDEB siRNA is one of many novel therapeutic candidates with first-in-class and/or best-in-disease potential.

Next, Gary will go over our recent CIDEB siRNA results.

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Gary Herman
Senior Vice President of Clinical Development Unit Head & Genetic Medicines

Thanks, Aris. Let's start on Slide 16. Before getting into our clinical efforts, it is important to highlight that MASH, or metabolic dysfunction-associated steatohepatitis, is an inflammatory and fibrotic liver disease driven by excess liver fat, affecting roughly 13 million U.S. adults. The addressable population is expected to expand as disease awareness improves and more compelling treatments are available, noninvasive testing becomes more widespread and more patients reach specialists to seek treatment. Regeneron's approach starts with human genetics, which discovers and validates these targets.

We will discuss our program shortly, but early clinical results have been impressive with up to 80% liver fat reduction with a single subcutaneous dose of CIDEB siRNA and approximately 50% of PNPLA3 siRNA. These strong clinical results support our hypothesis that liver fat plays a causal role in MASH. And as a result, we have chosen to prioritize the CIDEB and PNPLA3 clinical programs while de-prioritizing our HSD-siRNA program based on comparative genetic and clinical data.

Now let's turn to the disease itself on Slide 17. This slide frames the disease our differentiated siRNAs look to address. MASLD is now one of the most common chronic liver diseases affecting millions of patients. The disease progresses from a healthy liver to MASL when fat builds up in more than 5% of liver cells. It can then advance to MASH, which involves inflammation, ballooning, a histological sign of liver cell injury and death and increasing fibrosis from stages F0 through F3. The most advanced stage is F4 or cirrhotic MASH. Out of the current 13 million Americans that have MASH, less than 10% of addressable patients are diagnosed. And only 20%, 25% of those diagnosed receive advanced treatment, highlighting substantial gaps in both identification and care.

Currently, the MASH treatment landscape is going through rapid change. For patients with F2, F3 fibrosis, there are only 2 approved agents, which include resmetirom, a daily oral small molecule thyroid receptor agonist; and semaglutide, a GLP-1 receptor agonist, which is intended to drive weight loss, and as a secondary outcome, results in reduction in liver fat and downstream improvements in histological measures. Looking ahead, genetics-based siRNAs like Regeneron's and other investigational therapies could broaden treatment options for a large population that remains substantially underserved.

Slide 18. As George and Aris discussed, Regeneron's MASH programs demonstrate our genetics-driven approach using human genetic evidence to identify and validate targets to now anchor our clinical MASH pipeline. This is why we are excited by the CIDEB siRNA data, which showed rapid, deep and sustained reductions in liver fat after a single dose. For MASH, the disease process starts with liver fat accumulation with obesity, alcohol and genetic risk contributing to the accumulation of liver fat. The Regeneron Genetics Center discovered a protective CIDEB variant and validated PNPLA3, establishing the genetic foundation for our MASH pipeline.

Fundamentally, human genetics guides our target selection and development strategy while reinforcing the central role of liver fat in MASH and our focus on reducing it. Our genetic analyses show a clear relationship. Higher liver fat is associated with greater risk of cirrhosis and adverse outcomes, but lower liver fat is associated with reduced risk.

Turning to Slide 19, which highlights our MASH clinical pipeline. For PNPLA3 siRNA, a Phase II trial is underway to see if combining our siRNA with GLP-1-based therapy may confer additional efficacy benefits in MASLD patients. We are also initiating additional Phase II studies in MASH patients. CIDEB siRNA has advanced further with registration-enabling trials already underway, which I will discuss in more detail momentarily. Now I will discuss these siRNA programs in more detail, starting with PNPLA3.

Next slide, please. Importantly, PNPLA3 is a precision medicine approach to MASH, targeting patients with 2 copies of the PNPLA3 risk variant. Unlike CIDEB, this is a genetically defined population that has twice the liver fat and up to 4x the risk of cirrhosis compared with noncarriers with a prevalence of up to 30% in Hispanic and East Asian populations. PNPLA3 siRNA can be a precision medicine therapeutic for the millions of MASH homozygous carriers of the PNPLA3 risk variant.

On Slide 21, we previously shared proof-of-concept data last year where a single dose of PNPLA3 siRNA reduced liver fat by up to 50% and with reductions sustained for up to 24 weeks. These results provide early evidence of activity in these genetically defined populations, and we anticipate initiating a Phase II study in F2, F3 genetic MASH next year.

Now let's take a closer look at our CIDEB siRNA program on Slide 22. Unlike our PNPLA3, CIDEB siRNA represents a first-in-class approach with broad applicability in an all-comers MASH population that is also grounded in protective human genetics. Importantly, it is also the only CIDEB targeting agent currently in clinical development.

Turning now to Slide 23. Within MASH, as I previously mentioned, there is substantial need for a well-tolerated therapy that delivers deep, sustained liver fat reduction with the potential to improve liver histology and ultimately reduce liver-related events. This slide addresses an important scientific debate in MASH, whether reducing liver fat is simply a biomarker effect or whether it can translate

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into meaningful histologic and clinical benefits. On the left side of this slide are meta-analyses of previously conducted clinical trials in MASH. These data indicate that the depth of liver fat reduction correlates with liver biopsy response on histological measures. The data show that greater liver fat reductions are associated with higher rates of MASH resolution, including less inflammation and cell injury without worsening fibrosis and greater fibrosis improvement without worsening MASH, which are endpoints in late-stage MASH clinical trials.

Based on this analysis, a 10 percentage point relative decrease in liver fat translated to a 7 percentage point increase in the rate of MASH resolution and a 2.4% point increase in the rate of fibrosis improvement. Collectively, these data highlight the value of looking at liver fat as an early response measure. The right side of the slide shows CIDEB human genetic data that provides complementary evidence. People carrying rare CIDEB loss-of-function variants have lower liver fat, lower markers of liver injury and a 43% chance of developing liver disease. Taken together, these findings support CIDEB siRNA as a therapeutic that reduces hepatic CIDEB mRNA expression, thus mimicking the protective allele, and this treatment has now demonstrated substantial reductions in liver fat in MASLD patients. These encouraging results give us confidence that CIDEB siRNA may have the potential to improve liver histology and ultimately reduce liver-related events.

Now let's highlight our recent data and our clinical development plan for CIDEB siRNA. Slide 24 outlines the proof-of-concept study. This first-in-human study evaluates CIDEB siRNA safety and tolerability as well as biological activity through 2 randomized placebo-controlled parts. Part A tested a single dose in adults with MASLD, which are the results that were just presented Sunday at the AASLD Liver Meeting. Safety and tolerability is the primary endpoint of this first-in-human study and liver fat measurements and markers of liver injury, for example, ALT were secondary. Part B is intended to assess the level of CIDEB mRNA knockdown following treatment and how that relates to levels of liver fat reduction.

Slide 25. Now here are the results from the Part A portion of the study showing what a single dose of CIDEB siRNA can achieve in an all-comers MASLD population. Let me start with the dramatic liver fat reductions that were demonstrated in this trial. After just a single subcutaneous dose, CIDEB siRNA produced rapid, deep and durable reduction in liver fat by up to 80% that were sustained through 36 weeks. At week 12, mean liver fat was near or below the upper limit of normal at every dose level while the placebo stayed well above that. And nearly all treated participants exceeded the 30% liver fat reduction threshold previously associated with histological improvement. Unlike GLP-1-based therapies, which primarily work by decreasing food intake, resulting in weight loss, CIDEB has no effect on body weight, but rather act directly by regulating liver fat.

Next slide. Here on Slide 26, we compare the liver fat reductions observed with CIDEB siRNA with results reported for other therapies in the field. There have been no head-to-head trials, so cross trial comparisons should be interpreted cautiously. At week 24, after a single dose of CIDEB siRNA, liver fat reductions that appear comparable or greater than those reported for approved and investigational therapies, suggesting potential for best-in-disease profile.

CIDEB siRNA speed of response may also be differentiating. It approached its maximum effect by week 12, while some other agents took up to a year to achieve similar or smaller reductions. These results support the potential for improvements in liver histology and clinical outcomes, although those benefits must be established in further studies.

Turning now to Slide 27. As I previously mentioned, meta-analyses of MASH trials show that greater liver fat reductions are associated with higher rates of MASH resolution without worsening fibrosis and fibrosis improvement without worsening MASH, both registrational endpoints. Here, we overlaid the observed liver fat reductions from a single dose of CIDEB siRNA, which produced 58% to 80% liver fat reductions at week 36 with 68% mean reduction across all dose levels. While the definitive clinical trials still need to be completed, the totality of evidence gives us confidence in CIDEB siRNA's potential to deliver meaningful improvements in liver histology and ultimately patient outcomes.

Next slide. Further, Slide 28 shows how quickly CIDEB siRNA lowered serum transaminases in adults. Consistent with the reductions in liver fat, mean levels of alanine aminotransferase, ALT, a marker of liver injury, declined across all doses. The horizontal dotted line represents the mean baseline ALT so that you can more easily appreciate the extent of the reduction of the CIDEB group compared to placebo. A modest reduction of AST, a less specific marker of liver injury, was also observed.

Turning to safety on Slide 29. CIDEB siRNA was generally well tolerated through 36 weeks with similar adverse event rates to placebo. Importantly, there were no nausea or vomiting adverse events reported in the CIDEB siRNA groups, a key tolerability limitation associated with both currently approved and investigational therapies. We also do not see any evidence of elevations in serum triglycerides, or LDL-C.

Next slide. On Slide 30, with these proof-of-concept results in hand, CIDEB siRNA is rapidly advancing into a Phase IIb study in fibrotic MASH and a Phase III noninvasive safety study in MASLD patients is also underway. The Phase IIb study with registrational

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intent targets patients with F2, F3 MASH, where we will assess liver fat reduction as well as MASH resolution and fibrosis improvement via liver biopsy at 52 weeks. We expect final data from this study in 2029. We intend to share our proof-of-concept data with regulators in the coming months to align the registrational pathway for this indication.

Turning to Slide 31. In summary, let me briefly recap the emerging clinical profile of CIDEB siRNA. In totality, a single subcutaneous dose of a first-in-class liver-targeted CIDEB siRNA normalized liver fat and lowered serum transaminases in adults with MASLD. And CIDEB siRNA was well tolerated with adverse event rates similar to placebo. Additionally, the reductions in liver fat and serum aminotransferase levels in these participants mimic the protective effects of those with persons with naturally occurring CIDEB loss-of-function variants, highlighting the power of the Regeneron Genetics approach. The next key step is to establish whether that liver fat reduction translates into better histology and clinical outcomes as we advance this broader development plan. As noted, the Phase IIb fibrotic MASH study and the Phase III MASLD safety study are underway with additional studies potentially initiating soon. We expect a cadence of data readouts beginning in 2029.

With that, let me now turn it over to Josh to discuss the commercial opportunity within MASH.

Joshua M. Adelson

Thanks, Gary. Let's start with the large patient opportunity on Slide 33. For MASH, there is a significant unmet need to improve fibrosis, reverse disease and prevent progression to more severe disease. There is a large prevalent patient population of approximately 13 million U.S. adults or about 5% of the adult population. MASH spans 5 disease stages with diagnosis and urgency to treat increasing as patients progress beyond mild fibrosis. Our initial focus is on the F2, F3 population, which is approximately 40% of the overall population and currently represents 5 million to 5.5 million adults in the U.S.

Currently approved therapies address F2 to F3 MASH, where fibrosis regression is still possible. And as Gary has shown, there is ample room for more efficacious agents with improved tolerability and dosing convenience. It is important to note that approximately 80% of MASH patients are living with obesity or are overweight, making the expanding use of GLP-1 therapies a factor in how this market evolves over time. However, real-world evidence suggests 3 out of 4 patients discontinue GLP-1-based therapies by 2 years. Against this disease backdrop, we see a large patient population with significant unmet need, where our CIDEB siRNA offers a potentially meaningfully differentiated new treatment.

On Slide 34, I will start on the right side of the slide. Currently, the U.S. MASH market is approximately $1 billion in net sales, with significant expansion expected growing to $15 billion or more by 2035, an annual growth rate of more than 30%. On the left side of the slide, we highlight the primary drivers of this rapid growth, which are increasing diagnosis rates and treatment uptake of approved MASH therapies alongside continued modest growth of the underlying prevalent patient population. This significant anticipated expansion of diagnosis and treatment is expected to be driven by increasing use of approved therapies, rising disease awareness as well as Regeneron and others potentially bringing new therapeutic treatment options to address key remaining unmet needs. In total, the addressable patient population could increase from approximately 100,000 to 130,000 patients today to 750,000 to 1 million patients by 2035.

Turning now to Slide 35. Despite recent approvals, substantial unmet need remains in MASH with opportunities for Regeneron's CIDEB siRNA to improve efficacy, tolerability and treatment convenience. Today's treatments represent progress, but the placebo-adjusted improvements in fibrosis shown here are only 12 to 15 percentage points, and there are still no approved treatments for F4 MASH. That leaves meaningful room for therapies that can deliver greater benefit for patients.

Tolerability is another important gap. Gastrointestinal side effects can cause patients to stop treatment for both of the currently approved products. Convenient dosing of every 6 months may also reduce patient treatment burden compared with daily oral therapy or weekly injections and potentially support long-term adherence for this disease that will require chronic lifelong treatment. Physician perspectives as seen on the right side of the slide reinforce these priorities: stronger efficacy, fewer GI tolerability challenges and significantly less frequent dosing. Regeneron CIDEB siRNA has the potential to address these gaps, pending further validation in clinical development.

Turning to Slide 36. As we discussed today, Regeneron's focus is to rapidly advance CIDEB siRNA in the clinic to potentially bring this differentiated liver-directed treatment to an expanding MASH market. As Gary discussed, CIDEB siRNA's emerging clinical profile is compelling. We believe it has first-in-class and best-in-disease potential with rapid onset of action and broad applicability across the MASH landscape. Favorable tolerability, particularly avoiding GI side effects, could also be an important differentiator from existing and emerging therapies, which have GI tolerability issues.

CIDEB siRNA's twice-yearly dosing could also simplify treatment for patients, aligning the administration with routine office visits and may also support better long-term adherence for this disease that will require chronic lifelong treatment. And finally, we see

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potential flexibility in treatment positioning. CIDEB siRNA may be used as a monotherapy or alongside GLP-1 therapies to address liver disease and metabolic needs.

To summarize, the MASH opportunity is substantial. CIDEB siRNA's efficacy, safety and convenient every-6-month dosing could deliver a first-in-class, best-in-disease, broadly applicable treatment for MASH that could set a new standard of care for this disease with a large unmet need.

With that, I will turn it back to George for closing remarks.

George D. Yancopoulos
Co-Founder, President, Chief Scientific Officer & Co-Chairman

Thanks, Josh. Let me summarize today's roundtable discussion. First and foremost, it's very exciting to be seeing our investment in human genetics translating into clinical programs now advancing towards late-stage development. That is the promise of the Regeneron Genetics Center, using human biology to guide which targets we pursue and where we focus our efforts. As Aris described, human genetics and proteomics give Regeneron a significant competitive advantage, helping us discover new medicine, validate research programs and optimize clinical trials. Moreover, we are leveraging longitudinal proteomic data to develop predictive diagnostics with the goal of revolutionizing health care using big data. Powered by the RGC's genomics and proteomics data, multi-omics can optimize health care management, driving greater efficiency, lower cost and better outcomes.

As Gary discussed, our MASH pipeline demonstrates our multi-omics approach in practice, translating genetic insights into therapeutic candidates that are rapidly advancing towards late-stage development in this disease. In addition, you also heard how our multi-omics technologies can also deliver promising new noninvasive diagnostics that can enhance screening for this very same relatively under-diagnosed MASH condition. Based on the data presented today, we are prioritizing CIDEB siRNA to potentially address a broad population with the ambition to deliver a first-in-class therapy with potentially best-in-disease outcomes, pending clinical validation.

As Josh covered, the MASH commercial opportunity is substantial with significant unmet need in a market projected to reach $15 billion over the next decade. We believe for this chronic silent disease, such as MASH, requiring years of preventative therapy, factors such as tolerability and convenience, which will drive compliance are key, CIDEB has the potential favorable profile compared to current therapies to really be game-changing in this disease condition in addition to its potential best-in-class disease profile in terms of lowering the driver of this disease, which is liver fat.

Beyond MASH, we believe that our innovative approaches can extend across many diseases, making genetics, proteomics and the Regeneron Genetics Center an important foundation for future drug discovery and development.

With that, let me turn it back to Ryan.

Ryan Crowe
Senior Vice President of Investor Relations & Strategic Analysis

Thanks, George. This concludes our prepared remarks. We will now open the call for Q&A. Before we take your questions, let me introduce 2 additional colleagues from our MASH clinical team. First, Dr. David Lederer, Vice President and MASH Therapeutic Area Lead; and Dr. Thomas Norton, Executive Medical Director, Clinical Sciences. Both David and Tom were among the key authors on our recent CIDEB publication in the New England Journal of Medicine.
To ensure we are able to address as many questions as possible, we will answer one question from each caller before moving to the next. We also ask that you limit your questions only to the scope of this call, our Regeneron Genetics Center efforts and MASH development programs. Kevin, can we please go to our first question?

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Question and Answer

Operator

[Operator Instructions] Our first question comes from Geoff Meacham with Citi.

Nishant Shailesh Gandhi
Citigroup Inc., Research Division

This is Nishant on for Geoff. One on potential filing time line. So with Phase IIb final data expected in 2029, but the large safety study extending to 2032, what is the earliest realistic filing pathway? Could an interim safety data support an earlier submission?

Ryan Crowe
Senior Vice President of Investor Relations & Strategic Analysis

Why don't we ask Gary to handle that question?

Gary Herman
Senior Vice President of Clinical Development Unit Head & Genetic Medicines

Yes. So obviously, we're really excited about CIDEB and the potential and the role that liver fat is ultimately going to play in downstream benefits in MASH and on histological endpoints. But at the moment, histological endpoints are the registrational endpoints. And that's what we need to see in this next study. Safety is important in a common population. We're also looking at noninvasive measures. And we're open to talking to FDA about that. There's a lot of excitement. But at the moment, we're going to be relying on those biopsy endpoints.

George D. Yancopoulos
Co-Founder, President, Chief Scientific Officer & Co-Chairman

And as you said, the final data from the Phase IIb study is indicated on the slide to be read in 2029, but there is the opportunity for interim analyses and so forth. So pending discussions with the FDA, timings and so forth could also be potentially accelerated.

Operator

Our next question comes from Joon Lee with UBS.

Joon So Lee
UBS Investment Bank, Research Division

A question on your RGC platform. How do you make sure that altering the gene product in adults would recapitulate the clinical benefits seen in individuals born with it? As an example, Lp(a) was once considered a promising target based on human genetics, but turned out maybe not to be the case. So how do you avoid these pitfalls?

Aris Baras
Senior VP, Head of Regeneron Genetics Center & Co-Head of Regeneron Genetic Medicines

Great question. Genetics is great, it's not perfect. And there's also nuances to it, right? So a lot of times, you have genetics really looking -- giving you a sense of what's happening with risk, right? It may not be perfect at predicting what happens with disease progression. And so oftentimes, we have to look at that as well, not just disease risk, but also disease progression or secondary prevention settings.

The other thing is when you look at human genetics analyses, they are not 100% translatable to a clinical trial setting, right? An example with Lp(a you described, not only is that kind of a secondary prevention setting, not like a primary prevention where really the human genetics comes from, but those trials are also in heavily treated and well-managed patients in that setting.

So we actually take quite a bit of good care at Regeneron to look at -- we've learned those types of tricks and nuances when you bridge from human genetics to clinical translation. But bringing it back to the CIDEB example and multiple of our MASH programs, you can see the care we take in those and to ask those types of sophisticated questions, and you're seeing a very nice translation here and proof-of-concept from those genetic studies.

George D. Yancopoulos

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Co-Founder, President, Chief Scientific Officer & Co-Chairman

Yes. It's often very hard to say, how do you ensure that what you see in the genetics is going to be reproduced by a drug. Obviously, the question is being born with the genetic trait as opposed to putting in a drug that later in life will impact things. In fact, this is why you have to use things, which we deploy all the time, such as genetically humanized mice models that recapitulate the disease setting where we can actually see whether or not a late-life intervention can mimic the genetics. We do that routinely and we did that with CIDEB.

We should also tell you that we're beginning to understand from our large-scale database why perhaps the Lp(a) result was such as -- was seen in terms of the Lp(a) results that we may be talking about in the future. But it should be noted that sometimes, as is the case with CIDEB, the result with a therapeutic intervention exceeds that, that was seen with the genetics. And why might that be the case? CIDEB is so rare that we describe results only from carriers. Those are -- that is people who are heterozygous for the CIDEB loss-of-function mutation. That means that these individuals only have a 50% decrease in this gene and this protein's activity, whereas our siRNA drugs routinely are delivering 80% to almost 100% reduction in the gene product. That is why what you're actually seeing here is the exact opposite of what you're worried about or what was seen with Lp(a), where the effect of the therapeutic intervention is actually far higher than what was predicted by the genetics because in the case of the genetics, we don't have large numbers of homozygous knockouts.

So in this particular case, we were very optimistic about going forward into the human studies because we had animal interventionist approaches using therapeutic approaches to show that we can impact in adult animals, the exact biology that we were hoping to reproduce here. And we had a drug that reduced the CIDEB substantially more than what was known or what we've seen based on the genetic carriers. So this is the case where not only does genetics predict it, but the therapeutics we can drive the CIDEB almost a complete ablation is even higher than what we've seen with the genetics.

Operator

Our next question comes from Tyler Van Buren with TD Cowen.

Tyler Martin Van Buren
TD Cowen, Research Division

So the genetic evidence is strong, of course, but is it primarily greater liver fat reductions that leads you to believe that CIDEB could be differentiated on MASH resolution and fibrosis? Or is there a unique aspect of the biology or the mechanism that you'd like to highlight in this regard?

George D. Yancopoulos
Co-Founder, President, Chief Scientific Officer & Co-Chairman

I think that we should point out that this is probably the first MASH-targeted therapy that directly addresses the mechanism of the disease as defined by the genetics. The other approaches are indirect, trying to indirectly affect things like food intake, which will then affect liver fat, which will then affect MASH. We are directly addressing the mechanism that is driving both liver fat, but the genetics also shows the subsequent inflammation and fibrosis, which is driving the disease. And in fact, the genetics shows all of that. Not only does the genetics show that if you are low in CIDEB, you are protected from liver fat, but you are protected from going on to develop the drivers of the disease, which is the fibrosis and the inflammation, and ultimately, the liver failure.

So this is a very differentiated approach. It's the first that directly addresses what is shown genetically an important pathway that's driving directly this disease as opposed to indirect. And it covers the entire spectrum of the problem here. Starting with liver fat in terms of genetic protection, you're protected against liver fat, but you're also protected against fibrosis, inflammation and you're protected against developing liver disease subsequent to that.

Gary Herman
Senior Vice President of Clinical Development Unit Head & Genetic Medicines

I would also add, beyond the biology, a single subcutaneous dose that can normalize or near normalize liver fat for 6 months that does not have GI intolerability, we see is tremendously differentiating.

George D. Yancopoulos
Co-Founder, President, Chief Scientific Officer & Co-Chairman

I think that, that is huge in a long-term chronic silent disease, probably nothing is more important than something that will better ensure that patients stick to the therapy and stick to the therapy long term. And we all know, if you have to take a daily pill for 10

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to 15 years, most people are not going to be doing that, especially if there's tolerability issues. If you have to take a weekly injection with a lot of tolerability issues, as Josh told you, less than 25% of patients stay on that therapy for more than 2 years. The hope here is CIDEB continues to look like a very well-tolerated therapy and which you may only have to take twice a year treatment, it could really dramatically be game-changing in terms of really driving the sort of compliance that you will need to really make a difference in this public health problem.

Operator

Our next question comes from Dave Risinger with Leerink Partners.

David Reed Risinger
Leerink Partners LLC, Research Division

Yes. Thanks for the very impressive presentation today. So my question is for the planned F4 Phase III, what magnitude of impact on cirrhosis are you hoping to show?

Ryan Crowe
Senior Vice President of Investor Relations & Strategic Analysis

Perhaps we can start with Gary on Phase III expectations.

Gary Herman
Senior Vice President of Clinical Development Unit Head & Genetic Medicines

Yes. So that's a great question. Cirrhosis, as you know, there are no precedents yet, no regulatory precedents, no approved agents. And so we're in the middle of deep discussions to really think about whether it's worth trying to demonstrate histological improvements, namely reversal of fibrosis from the F4 state, so improvement towards F3 or lower or to look at outcomes. And the types of things that happen related to cirrhosis, portal hypertension-related events, et cetera. But this is a complicated area, and we're in the middle of thinking through that.

Operator

Our next question comes from Salveen Richter with Goldman Sachs.

Elizabeth Daniels Webster
Goldman Sachs Group, Inc., Research Division

This is Elizabeth on for Salveen. Wondering about the potential for the wider adoption of the proteomic panel as a noninvasive diagnostic here. And have you discussed the possibility with the FDA to use the panel or another noninvasive diagnostic in lieu of a biopsy? And then kind of what the time frame is that this could potentially be implemented on a wider scale?

George D. Yancopoulos
Co-Founder, President, Chief Scientific Officer & Co-Chairman

That is a great question. And all the questions that you're asking are exactly what we're discussing and trying to figure out right now. We really do think just like this proteomic test looks like, it's a noninvasive approach that can replace a difficult, expensive and actually a procedure that results in risk to patients, similar tests that we've been developing can replace a lot of other tests across many other diseases. And so we think that this approach could really be revolutionary in terms of changing how we manage health care in America today, and you'll be hearing more about this going forward.

Operator

Our next question comes from Brian Abrahams with RBC Capital Markets.

Brian Corey Abrahams
RBC Capital Markets, Research Division

Congrats on the data. Really cool to see the translatability of the genetic data. A question on CIDEB dosing. The highest 600 mg dose that you were looking at looked to maybe a little bit more durable than the other doses, but the baseline PDFF scores were rather different there. So I'm curious how you're interpreting the dose dependence and optimal go-forward dose here? And could you even go higher just given the tolerability?

Ryan Crowe

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Senior Vice President of Investor Relations & Strategic Analysis

Maybe I'll ask Gary to opine on that.

Gary Herman
Senior Vice President of Clinical Development Unit Head & Genetic Medicines

Yes. So astute observation to see that there's higher baseline in the 600-milligram group. We do think there was slightly more liver fat reduction at those higher doses. But there's always a trade-off between high dose and tolerability. And what you can see is that all doses studied gave very similar levels of liver fat reduction and all achieved near normalization.

Operator

Our next question comes from Gregory Renza with Truist Securities.

Gregory James Renza
Truist Securities, Inc., Research Division

Congrats on the data and the presentation. Just on the safety side, as Gary walked through the hyperglycemic event that was not drug related, just curious, what did you learn from that event? Are you seeing anything across the broader glycemic data that perhaps just warrants some consideration or a follow-up here?

Ryan Crowe
Senior Vice President of Investor Relations & Strategic Analysis

I'll ask Gary to start and perhaps Tom and David can also opine.

Gary Herman
Senior Vice President of Clinical Development Unit Head & Genetic Medicines

Yes. I will just say that it's been very well tolerated. We have not seen any clear treatment-related effects on glucose or hemoglobin A1c. With respect to this specific SAE, I'm going to call on Tom Norton to elaborate.

Thomas D. Norton

Sure. Happy to. Thanks, Gary. So this was an event that occurred in the patient that received the CIDEB siRNA. And it was someone that had pre-existing diabetes, and it was assessed as not related to study drug by the investigator, but rather due to poor control or natural progression of their pre-existing diabetes. And the patient was subsequently diagnosed by an endocrinologist with the diagnosis of latent autoimmune diabetes in adults. This is a form of Type 1 diabetes that is often misdiagnosed as Type 2 diabetes, which was the case in this patient.

Ryan Crowe
Senior Vice President of Investor Relations & Strategic Analysis

Okay. Thank you. Let's move -- I think we have time for 2 more questions. Let's move to the next one, please, Kevin.

Operator

Our next question comes from Mohit Bansal with Wells Fargo.

Mohit Bansal
Wells Fargo Securities, LLC, Research Division

Congrats on all the data. My question is rather commercial in the landscape where you probably have retatrutide on the market as well. So George, on one end, I agree with you that the tolerability and the discontinuation risk is definitely higher with retatrutide. But at the same time, there's an inherent compliance relative to the weight loss. When you see weight loss, you probably stick to the drugs more often. So wondering like how do you think about the CIDEB's role in that market? And do you think the low-hanging fruit is patients who are low BMI, but they still have MASH?

George D. Yancopoulos
Co-Founder, President, Chief Scientific Officer & Co-Chairman

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I think as we said, there is clearly, as recognized by many that the GLPs are not able to be used by a large proportion of the unmet need population for tolerability reasons and for other reasons. And despite the fact they do cause prominent weight loss, the numbers indicate less than half the people stay on them for a year, less than 25% stay on them for longer than 2 years. So it's hard to imagine, hard to imagine that you can be treating the many patients who are suffering from MASH with a drug that has these profiles in terms of lack of long-term usage.

On the other hand, having a drug that you could take just twice a year instead of weekly injections, hopefully, continue to see this very favorable tolerability profile without nausea and vomiting is something that a lot of people will be able to stick to and we'll be able to have a long-term impact on these patients. But there may be no one size fits all. There's such unmet need here that even if substantial numbers might be treated with one, there's going to be enough room where a lot of other people are going to need something else. And we think we have a very favorable profile in terms of convenience, in terms of tolerability and also in terms of the potential efficacy that we're seeing from these early trials. So a profile that could really, really be very useful for many of the unmet need patients here.

Ryan Crowe
Senior Vice President of Investor Relations & Strategic Analysis

Let's move to the final question, please, Kevin.

Operator

Our last question comes from Ellie Merle with Barclays.

Eliana Rachel Merle
Barclays Bank PLC, Research Division

Congrats on the data, a really exciting CIDEB data there and completely agree on your liver fat commentary. Just a question on the registrational pathway. You mentioned the Phase IIb has registrational intent. This would be the first time a Phase IIb would be accepted for filing in MASH. Can you maybe elaborate on what's informed the thinking and how you're potentially thinking about starting another potential Phase III study? Would you feel comfortable starting a Phase III based on the data that you've seen to date?

And then just another question in how you're thinking about the confirmatory study plans with histology at least historically being used for accelerated approval. Would you plan to do an outcome study in F4 or in F2, F3 or both to serve as a confirmatory study, I guess, based on your review of the genetics and the biology here around this target?

George D. Yancopoulos
Co-Founder, President, Chief Scientific Officer & Co-Chairman

These are really great questions, and we're not going to reveal all the details of our registrational strategy right now. Great questions, though. You're thinking all the right things.

Ryan Crowe
Senior Vice President of Investor Relations & Strategic Analysis

And we have some upcoming discussions with regulators that should better define that path. But that will conclude today's call. Unfortunately, we have no more time. There's a few folks left in the queue that we will talk to afterwards. Thanks for everyone on the line and your interest in Regeneron and in the RGC and in our MASH development programs. Have a great day, and we may now disconnect.

Operator
Thank you, ladies and gentlemen. This does conclude today's presentation. You have a wonderful day. You may now disconnect.

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