Horizon Therapeutics plc
VIRTUAL R&D DAY
September 29, 2021

Tina Ventura
Senior Vice President, Investor Relations

Good morning, everyone. Thank you for joining us. Welcome to the Horizon Therapeutics Virtual R&D Day. I'm Tina Ventura, senior vice president of Investor Relations at Horizon.

We are holding our live event this morning at our U.S. headquarters in Deerfield, Illinois, and are very pleased to have several of our Horizon R&D colleagues join us here in Deerfield from our other R&D locations in San Francisco and the Gaithersburg, Maryland area. In addition, we have three key opinion leaders joining us virtually this morning.

Before we begin, as noted here, we will be making certain forward-looking statements today that are subject to various risks described in our SEC filings, available on our investor website. In addition, Doctors Khanna, Kolb and Korn, who are joining us today, have consulting agreements with Horizon.

We have a full program lined up for you this morning with the objective that you come away from today with a better understanding of our pipeline.

Our Chairman, President and CEO **Tim Walbert** will begin with an overview of Horizon's vision and company strategy. **Liz Thompson**, our Executive Vice President of R&D, and **Srini Ramanathan**, our Senior Vice President of Research and Development Sciences, will review our R&D strategy. We will then move to our key pipeline programs, interspersed with three Q&A sessions. Each of the Q&A sessions will be a moderated Q&A where we will be taking your questions via the Q&A submission box on the webcast platform for this event. You can submit questions at any time.

In addition to Tim, Liz and Srini, we have several members of our R&D leadership team joining us today:

- **Theresa Podrebarac**, our senior vice president of Clinical Development;
- **Bill Rees**, our vice president of Translational Sciences; and
- **Kristina Patterson**, our medical director of Neuroimmunology, focusing on UPLIZNA.

We are also very pleased to have three key opinion leaders participating as well – again, all virtually:

- **Dr. Dinesh Khanna**, professor at the Institute of Healthcare and Innovation at the University of Michigan and an expert on scleroderma, who will discuss HZN-825;
- **Dr. Martin Kolb**, director of the division of respirology in the Department of Medicine at McMaster University and an expert on interstitial lung disease, will join us for that Q&A session on HZN-825 as well.
- **Dr. Bobby Korn** is joining us to discuss TEPEZZA in chronic Thyroid Eye Disease, or TED. He is the professor of ophthalmology and plastic surgery at the University of California, San Diego and a leading expert in TED.

We expect to conclude today's meeting between 12:15 and 12:30 Eastern Time. In addition, a replay will be available on our website later this afternoon.

With that I will now turn the podium over to Tim.

INTRODUCTION: VISION AND STRATEGY

Tim Walbert
Chairman, President and Chief Executive Officer

Thank you, Tina. Welcome, everyone, and thank you for joining us. We have a great program ahead of us today.

Let's begin with the focus of today's meeting. First of all, our mission is to deliver breakthrough medicines for rare, autoimmune and severe inflammatory diseases. Our passion comes from a simple philosophy to make a meaningful difference for patients and communities in need. We've consistently delivered on that promise and we are even better positioned today to continue to do so. With our strong foundation and significant cash flow generation, our strategy now includes building out our pipeline. We expect you to leave today's meeting with confidence that Horizon's pipeline is truly "one to watch."

With the completion of the acquisition of Viela in March, our team conducted a thorough review of our new medicines with the results being the following: today we announced five new programs. We expect ten data readouts from 2021 to 2023 with 10 potential new medicine or new indication approvals in the second half of the decade. We're also establishing an emerging research function with stronger capabilities in place following the Viela acquisition.

Our pipeline now has critical mass and will drive significant long-term growth – with our current growth drivers TEPEZZA, KRYSTEXXA and UPLIZNA and now, with our pipeline candidates. Collectively, we see peak annual net sales potential of approximately $10 billion.

Before we move into our pipeline and our science, let me give you an overview of the company's evolution, our strong foundation and the significant near-term growth ahead of us that allows us to further invest in finding solutions for many diseases that today have no treatment options.

In 2014, we had one rare disease medicine in our portfolio. Today we have eight. And we've significantly expanded our net sales with our 2021 estimates representing a 10-fold increase since 2014.

Our three-year compound annual growth rate for both net sales and adjusted EBITDA has been strong at 37 percent and 42 percent, respectively – while significantly increasing our investment in R&D. This has led to considerable value generation for shareholders. Our five-year total shareholder return through September 24 was nearly 500 percent, significantly exceeding that of our peers and the NBI. This has driven an eight-fold increase in our market cap to approximately $25 billion today.

Looking ahead, we remain focused on driving strong growth through our ability to execute, and we have four goals to support that growth:

- first, maximizing our on-market medicines;
- investing aggressively in our current pipeline medicines;
- continuing to expand the pipeline through focused internal innovation and business development; and
- building out our global presence.

These goals translate into key financial goals for the Company over the next three years:

- generating strong double-digit net sales and adjusted EBITDA growth;
- generating meaningful adjusted EBITDA margin expansion, where we expect adjusted EBITDA leverage to more than offset our investment in R&D.
- maintaining our R&D investment at double-digits as a percent of net sales while expanding our margins; and
- we expect to continue to generate top-tier returns for shareholders.

Our strategic and financial goals support our near-term vision for Horizon to be a top-tier biotech, focused on research, development and commercialization of medicines for rare, autoimmune and severe inflammatory diseases.

Three areas set us apart that drive our performance:

- commercial execution;
- our proven and disciplined business development; and
- strong R&D capabilities.

Each of these areas of strength on their own contribute to our outperformance, and it's the combination of these that sets us apart.

To highlight our commercial execution, let's start with KRYSTEXXA. It is our biologic medicine for uncontrolled gout that had net sales of $60 million the year prior to our acquisition in early 2016. Driven by our investment, expertise and deep knowledge of the rheumatology space, we executed on the right commercial strategy for KRYSTEXXA to jump start its growth trajectory.

Key to our success was our investment in a clinical development strategy adding immunomodulation to KRYSTEXXA to offset its immune response, with the goal to improve the response rate for KRYSTEXXA. That has proved to work very well, with response rates of 70 to 100 percent seen across five investigator-initiated studies and case series. As a reminder, this is in comparison to the 42 percent response rate in our Phase 3 program.

Together, our commercial execution and R&D investment has increased the annual net sales by over eight times, and we are well on our way toward our projected peak annual net sales of more than $1 billion. And the runway for KRYSTEXXA growth is still significant. In the U.S., there are 9.5 million gout patients, and this population grows at a low-single-digit rate, meaning that each year thousands of these patients become uncontrolled on their current medicines and become candidates for KRYSTEXXA. In 2020, less than five percent of the more than 100,000 uncontrolled gout patients were treated with KRYSTEXXA, and with increased adoption of KRYSTEXXA plus immunomodulation, we expect to continue to see increased penetration.

TEPEZZA is our biologic medicine to threat thyroid eye disease, or TED, and is another example of our strong commercial execution. We delivered one of the most successful rare disease medicine launches ever, despite launching during the pandemic last year. Three factors are driving the strong growth of TEPEZZA as we progress towards our goal to exceed $3.5 billion in peak annual global net sales:

- first, the dramatic efficacy of TEPEZZA;
- second, because TED is a painful, vision-threatening disease with debilitating and disfiguring symptoms, patients are highly motivated to seek therapy; and
- third, we are significantly investing to drive awareness of TED and TEPEZZA among physicians, patients and advocacy groups – including our highly effective direct-to-consumer television campaigns.

Just as with KRYSTEXXA, the growth opportunity for TEPEZZA is significant. Our primary focus has been patients with moderate-to severe acute TED, given that this phase lasts on average for two years post-diagnosis. There are approximately 15,000 to 20,000 new patients that enter the market each year and can be treated with TEPEZZA. If left untreated, acute TED transitions into the chronic phase. These patients typically experience less inflammatory conditions characteristic of acute TED, but have other painful symptoms that can persist, including proptosis, or eye-bulging, and diplopia, or double vision.

We estimate that the prevalence of this population, which is those patients who have had the chronic disease for three to eight years, to be approximately 70,000 patients. Less than one percent of the chronic patient population has been treated with TEPEZZA today, which leaves considerable room for additional growth.

The addressable incidence and prevalence rates for TED are comparable in many countries outside the U.S., including Japan, one of several countries where we are targeting global expansion for TEPEZZA. Outside of the U.S. and Europe, we see a peak annual net sales opportunity of greater than $500 million.

And finally, UPLIZNA, our third key growth driver. It is approved for neuromyelitis optica spectrum disorder, or NMOSD, which is a rare disease affecting approximately 10,000 people in the United States. As UPLIZNA was launched by Viela during the height of the pandemic with relatively minimal resources, we are relaunching it over the next few weeks, applying many of the successful strategies we have used with KRYSTEXXA and TEPEZZA. We have completed the expansion of the commercial team to support the complex UPLIZNA patient journey. Internationally, we are building the infrastructure and capabilities necessary to support the potential launch of UPLIZNA in Europe in 2022 as well as in other key global markets. Finally, we are developing UPLIZNA for myasthenia gravis and IgG4-related disease, which Kristina and Theresa will discuss in more detail shortly.

Business development will continue to play a critical role in building our pipeline. Our criteria for future deals include:

- maintaining our strong focus on rare diseases with unmet needs;
- expanding beyond rare disease opportunities in autoimmune and severe inflammatory diseases;
- balancing the pipeline across the development life cycle, with early- to late-stage programs to drive continued growth over the long-term; and
- increasing research-based partnerships and collaborations, particularly for preclinical programs, as Srini will discuss further.

Supporting our business development efforts is our strong financial position, including low leverage and significant cash generation. This gives us flexibility to continue to pursue future opportunities. Our priority is licensing and acquisition opportunities with risk-based milestones as successful outcomes are achieved. However, for the right strategic fit, we will consider larger transactions, as we did with the acquisition of Viela.

The returns that we have generated to date tell the story of our successful business development efforts. For KRYSTEXXA and TEPEZZA, the total net sales generated from our acquisition to our expected 2021 net sales exceed the upfront acquisition cost by three and 16 times, respectively.

Our acquisition of Viela in March of this year was a significant acceleration point for our R&D strategy. Leveraging the combined strengths of both companies makes Horizon even stronger today and in the years ahead. With Viela:

- We expanded our pipeline with four candidates, which are now in 13 development programs in rare diseases and key therapeutic areas;
- We have a stronger innovation platform with Viela's legacy early-stage research and translational capabilities; and
- We enhanced our R&D team, adding R&D talent with broad expertise and a deep scientific knowledge of autoimmune and severe inflammatory diseases.

Let me give you a snapshot of our pipeline. In 2019, we had one development candidate, TEPEZZA; three pre-clinical programs in gout and two Phase 4 programs for KRYSTEXXA. Fast forward to our pipeline in March of this year following the Viela acquisition. Our legacy Horizon pipeline, in purple, increased by six programs since 2019. The nine Viela programs, in blue, added significant breadth and depth to our pipeline, with four candidates in programs across all stages of clinical development. Not only are these promising candidates in areas of autoimmune and severe inflammatory diseases, but importantly, they filled out our mid-stage pipeline.

But what we saw in the Viela pipeline was also its future potential. And that's what you see layered here in pink. Today we announced four additional indications for HZN-7734, or daxdilimab, and one additional indication for HZN-4920, or dazodalibep. The sixth program in pink is our ARO-XDH preclinical program in gout, which we licensed from Arrowhead in June.

We see tremendous opportunity to drive future growth with seven potential blockbuster medicines, including our key growth drivers and pipeline medicines. In total, this represents combined peak net sales potential of approximately $10 billion – more than three times our total net sales today. This tremendous potential is driving our excitement in our growth prospects for the future, and we are pleased today to be able to share with you more detail about these candidates.

Next, Liz and Srini will discuss our R&D strategy in more detail. Liz Thompson, our head of R&D, joined Horizon in 2018 and in her prior role, led the development, expedited filing and the successful approval of TEPEZZA. Liz?

R&D STRATEGY

Elizabeth Thompson, Ph.D.
Executive Vice President, Research and Development

Thank you, Tim. It is such a pleasure to be here this morning and have the opportunity to talk with you about our R&D strategy, as well as introducing several of my very talented colleagues who are going to talk in greater depth about those new programs Tim just mentioned.

I joined Horizon a little over three years ago and, as Tim noted, our pipeline and our R&D capabilities have come a long way in that time. Our original R&D focus was on maximizing our marketed medicines. A prime example of that is our ongoing evaluation of immunomodulation with KRYSTEXXA, but you can also look to examples like our trials evaluating the potential to improve the patient experience with faster or less frequent infusions. And this is the kind of innovation we will always practice – seeking to understand how we can make our existing medicines more impactful for patients.

But as we look to the future, a key part of our success will also be based on also maximizing our *pipeline* molecules – through understanding and planning for the patient experience – but also through evaluating the full range of potential diseases that we could impact.

As far as business development is concerned, historically, our activities have been largely focused on marketed or late-stage molecules, and TEPEZZA, as Tim just referenced, is a shining example of how we've made that model successful, combining disciplined business development with regulatory and clinical execution, to deliver a medicine that is now making a real difference in patients' lives. We are expanding our BD focus – as Srini will discuss in more detail – to also enable us to meaningfully harness earlier-stage innovation, which will be necessary to build a deep and diversified pipeline.

To do all this, we've invested in the people who make up our R&D organization, adding top scientific and technical talent, as well as rounding out our development capabilities. This will now expand to include building out our research capabilities to be able to generate early-stage candidates ourselves; and expanding our therapeutic areas of focus – taking our areas of strength and expanding into other areas we want to grow into. Overall, we've established and are building on a strong R&D foundation – one that is going to allow us to drive future growth for Horizon.

Over the next several minutes we'll highlight these areas of opportunity and go into more detail on our core foundational elements, and I'd like to start with our R&D leadership team. Our focus for the R&D organization over the past several years has been on augmenting our capabilities to encompass all the critical R&D functions. The Viela acquisition further advanced those efforts, enhancing our early-stage research and translational capabilities as well as deep therapeutic knowledge in autoimmune and severe inflammatory diseases.

The leadership team, shown here, illustrates the significant breadth of talent and expertise of Horizon's R&D organization today. Since 2018, we've roughly quadrupled the size of our R&D organization, bringing on scientists and technical experts at all levels to enable us to execute on the ambitious plans we're laying out. To do this and ensure the strongest talent base, it has been important to have a presence in some key geographic locations where we can maximize our ability to attract and retain the best talent.

We've seen growth across our locations and look forward to the recruiting power of our new key R&D hub on the east coast, added to Dublin, Deerfield, and our hub in the Bay Area.

As I mentioned at the outset – a key part of our focus will always be the continual innovation to improve our marketed medicines. To that end, we currently have five ongoing trials that are evaluating ways to optimize the usefulness of KRYSTEXXA, focused on potential ways to improve the response rate, evaluate the benefit in broader populations, or improve the patient experience.

KRYSTEXXA can be a strikingly efficacious medicine for patients with uncontrolled gout, but that utility has historically been limited by a few things. One is the rate of anti-drug antibodies that are formed, which can lead to significant reactions and a loss of efficacy. Our ongoing MIRROR trial explores the impact on response rate of using methotrexate with KRYSTEXXA, and we look forward to sharing the top-line results of this trial in the fourth quarter of the year.

As we explore the potential benefits of immunomodulation, one of the critical questions is whether it will aid in the ability to retreat patients who previously weren't able to get a complete response. These uncontrolled gout patients have few or no other options for their gout management, and this trial will help us answer a really critical question: whether or not immunomodulation will aid in the ability to retreat patients. Finally, the duration and frequency of infusions can impact the patient experience, so we have separate studies looking to understand the potential for shorter or less frequent infusions.

With TEPEZZA, our approach is similar to that of KRYSTEXXA. We are working to demonstrate the benefit of TEPEZZA in a broader population and improve the patient experience.

Our chronic TED trial aims to generate additional data on the use of TEPEZZA in this population. While TEPEZZA does have a broad indication for all TED patients, and physicians can – and do – prescribe TEPEZZA for chronic patients today, we want to generate clinical data to better inform payers and physicians about the performance of TEPEZZA in patients who have been in the chronic phase for three to five years. Dr. Bobby Korn, one of the physician experts speaking today, will discuss this in more detail toward the end of our program.

We are exploring additional administration options for TEPEZZA with our subcutaneous administration program. And, as we are doing all across our pipeline, we are interested in understanding the potential in additional indications, so we'll shortly be initiating a Phase 1 exploratory trial to evaluate TEPEZZA in diffuse cutaneous systemic sclerosis.

We are also building for our future by evaluating additional indications to expand the potential of the candidates in our pipeline and bring new treatments to patients. Following the acquisition of Viela in March, this was our team's top priority. We completed an in-depth assessment of the Viela molecules.

In determining new indications to pursue, we consider four major criteria: scientific rationale, unmet need, the competitive landscape and feasibility. We first evaluate each individually and then in aggregate to identify the most impactful disease states that we could pursue.

First and foremost, of course, we consider the scientific rationale. Where do existing data suggest the greatest potential impact on disease biology? For daxdilimab, for example, we dug through existing literature and our own molecule understanding to identify the diseases where plasmacytoid dendritic cells and type 1 interferon were thought to play an important role.

We then assess the targeted indication from the perspective of the patient experience and whether the medicine could address unmet needs. In many cases, there are few if any existing treatments and so the area of need is vast.

It is important to understand the overall competitive landscape and the potential commercial viability of a new medicine. That said, the sheer number of candidates in a particular disease is not necessarily enough to deter us if we believe we have a molecule that could effectively address an important unmet need or provide a potential differentiated benefit compared to other molecules in development in the same area.

We also consider factors like logistics and feasibility and ask questions like: can we identify and enroll the patient population? What do we understand about the disease, its progression and how its impact may best be measured? What aspects do we think will be most important to regulatory bodies? How much information will they require, and do we expect different regulatory agencies to view a disease differently?

We then assess all the criteria together to determine the overall potential for success and whether it makes sense for us to commit to clinical development for the disease state under consideration. Our intent is to always be both thorough and highly disciplined.

And our updated pipeline overview shows our results to date: a pipeline with 27 programs distributed across the development life cycle from preclinical to post-marketing. Five of these programs we announced this morning, and we expect them to start next year: four additional indications for daxdilimab, and with these additional programs, we'll be evaluating the potential for broad impact in lupus and expanding upon the impact we've seen in skin with two other dermatologic indications. We're evaluating one additional indication for dazodalibep, in the nephrology space, exploring the potential for the molecule in focal segmental glomerulosclerosis, or FSGS – it's also a disease with significant unmet need.

We expect 10 data readouts over the next two years, with 10 potential approvals in the second half of the decade. And we are continuing to explore additional opportunities. We are currently evaluating potential new indications for UPLIZNA and anticipate sharing the results of our assessment in the coming months.

This has been a year of tremendous progress for the expansion of our pipeline.

Today, we are focusing in on some of our most exciting programs, as noted on this slide. With the addition of Viela and the additional indications we are pursuing, we're also expanding our therapeutic areas of focus.

For the last several years, our core therapeutic areas of focus have been rheumatology, nephrology, ophthalmology and endocrinology – and each of these was firmly rooted in at least one of our on-market medicines. As we looked to the future, we are expanding into additional therapeutic areas where we have not only scientific and commercial expertise, but also strong relationships within the medical community. Our expanded portfolio has given us that opportunity. For example, we're expanding in neuroimmunology from our foundation in NMOSD. We're able to leverage our relationships with leading neuroimmunology key opinion leaders in the designs of our two MG and IgG4-related disease trials.

Dermatology is a growing therapeutic area with high unmet need and a core of passionate medical dermatologists excited about the possibility of developing new therapies to address these needs. We see significant opportunities for daxdilimab in alopecia areata and other dermatologic diseases, and this gives us a strong foundation for further growth in new diseases and with new molecules.

Our trials in HZN-825 for idiopathic pulmonary fibrosis and diffuse cutaneous systemic sclerosis provide us with an entry into the respiratory therapeutic area, also one of significant unmet need.

Moving into these additional therapeutic areas expands the opportunities for our current molecules in development and also gives us a broader foundation for our future.

As we look to the future, building our research capabilities to build a sustainable and scalable pipeline is of critical importance. Our approach here is designed to most effectively leverage our expertise and allocate our resources effectively – a balanced approach between internal research and external collaboration. Our goal is to identify and make the most of opportunities – and tap into the capabilities necessary to advance our earlier-stage innovation.

I will turn the podium over to Srini Ramanathan next to spend a few minutes discussing our research strategy in more detail. Srini joined Horizon in 2018 and leads discovery research, translational sciences and biometrics. Srini and I have worked together in different capacities over many years, and it's such a pleasure working together again here at Horizon. Srini?

Srini Ramanathan, Ph.D.
Senior Vice President, Research & Development Sciences

Good morning, everyone.

The Viela acquisition earlier this year has substantially strengthened our scientific talent and research capabilities, as well as expanded our therapeutic areas of focus. In the months since the acquisition, we have further refined our

research strategy to build a robust, innovation-focused organization that will drive our discovery engine.

Our strategy is designed to generate a steady pipeline of programs moving to the clinic to benefit patients and support Horizon's continued growth.

Our research programs broadly fall into two categories. First, there are programs where we have unique capabilities and insights, based on our deep expertise and knowledge of diseases, pathways and targets – and we are best equipped to drive these programs ourselves. Second are programs where we will collaborate with external partners, of which there are two types. The first type includes programs where we have a clear scientific vision of what we need, and we partner in a very specific manner with companies with the technical expertise to implement our plan. Our partnership with HemoShear is an example. The second type of external collaboration entails specific opportunities with the potential for a transformational value proposition, through a combination of novel modalities, disease strategy and probability of technical success. Our work with Arrowhead to identify and develop a siRNA-based therapeutic for gout, falls in this category.

Overall, our approach represents a balance between internal and external innovation while staying aligned with our core focus areas. We will consider which modalities are the right fit for specific opportunities based on the scientific value proposition that can best address the patient need. Our goal for this dual approach is for a discovery pipeline that will generate high-quality novel-product candidates over the next several years with the potential for profound therapeutic impact.

I'll now illustrate how our internal research team works closely with business development, to identify high value external opportunities.

Horizon is a leader in gout. Despite the significant inroads we've made, including our KRYSTEXXA immunomodulation strategy, there remains an unmet need of more than 500,000 patients who don't respond to the current standard of conventional care and are not good candidates for KRYSTEXXA. Accordingly, we sought out external partnerships, to find novel therapeutics to address this unmet need.

Our collaboration with HemoShear is centered around new-target discovery – using HemoShear's proprietary technology that combines biological and computational disease models, our teams have identified two new targets to lower serum uric acid. This approach is an example of continuous innovation using a foundational knowledge of mechanistic pathways, and we're excited about the potential for the novel small molecules we expect to come out of this collaboration.

With Arrowhead, we're working on a novel approach to a clinically validated target – xanthine dehydrogenase or XDH. Here, we are using RNAi technology that Arrowhead specializes in to target and silence XDH, the gene responsible for uric acid production in the liver, which is the largest producer of uric acid in the body. This approach offers the potential for an effective treatment using a novel modality, as well as a patient-friendly, infrequent dosing regimen that could be self-administered subcutaneously.

Both HemoShear and Arrowhead are examples of how our internal research group works closely with the commercial and clinical organizations to identify critical unmet needs and then develop customized approaches to building a pipeline that will serve those needs. Given our leadership in gout, we are uniquely positioned to successfully commercialize the candidates that result from these programs.

As we continue to execute our research strategy, we will take this approach in the context of one therapeutic area – rheumatology in this case – and apply it broadly across other therapeutic areas of focus.

Turning the focus now broadly to immunology, with our internal research, we are interested in developing therapeutics that address various critical elements of the pathophysiology that drive autoimmune diseases.

The three candidates that we are evaluating each focus on one of the premier pathways of immunology – going from left to right, targeting co-stimulatory aspects of adaptive immunity, autoantibody production, and innate immunity.

Dazodalibep specifically targets the interaction between CD40 ligand and its receptor and its consequent impact on autoantibody and cytokine production. As a CD40 ligand antagonist, dazodalibep interrupts the important handshake between B cells and T cells, thereby disrupting the overactivation of the CD40 / CD40-ligand co-stimulatory pathway.

UPLIZNA, a B-cell depleter, is a CD19 antagonist with the potential to impact autoantibody levels and B-cell interactions with other types of cells – thus addressing inflammation and disease progression via multiple mechanisms.

With the innate immunity pathway, we are looking at targets such as plasmacytoid dendritic cells, or pDCs, through daxdilimab. Daxdilimab targets ILT7, which in turn depletes pDCs and therefore prevents the formation of many pro-inflammatory cytokines, predominately type-1 interferon alpha, but also IL-6 and TNF-alpha. This blocks downstream pathogenic events such as inflammation and tissue damage – and as you'll hear momentarily from Bill Rees, pDC depletion has a sustained effect following a single dose.

To summarize, we have selected these targets for our internal development programs in a highly curated manner. Our goal for research is to continuously bring novel therapeutics to patients using a range of autoimmune targets, through a deep understanding of disease biology in immunology and fibrosis.

I will now turn it to Bill Rees to begin our discussion on daxdilimab. Bill leads the Translational Sciences group for Horizon, which helps us generate robust early evidence of biological and clinical activity as we pursue new indications with our pipeline assets and also supports clinical development all the way through approval and post-marketing efforts. Bill joined us from Viela, and we are so pleased to have really talented and experienced colleagues like Bill to expand our team and broaden and deepen our expertise in research, as well as development. Bill?

DAXDILIMAB (HZN-7734)

First and Only pDC Depleter in Clinical Development; Now Pursuing Five Indications

Bill Rees, Ph.D.
Vice President, Translational Sciences

Thank you, Srini, and good morning everyone. I am super happy to be here this morning to discuss daxdilimab, or HZN-7734 and its role in reducing type-1 interferon and other cytokines and chemokines that drive autoimmune diseases.

The story we are going to share with you this morning is about pioneering science. Going back 10 years now, when the early research and development of daxdilimab was happening at MedImmune, I was following this story closely. In fact, I came to MedImmune to specifically work on this exciting molecule because I could see that the team there – many of which have since moved to Viela and now Horizon – was thinking differently about the science. The team was thinking bigger and freer, and I wanted to be a part of that.

While the industry was focused on inhibiting the myriad interferons or receptors or downstream consequences of type-1 interferon, our team took a different approach and searched upstream for the predominant source of type-1 interferon in autoimmune disease. Now, if such a thing exists, and if we could identify it, we knew that we could solve the problem.

By asking the right question, we explored the role of a rarely talked about blood cell called a plasmacytoid dendritic cell, or pDC. They are small in number but play a large role in producing an incredible amount of interferon and other cytokines and chemokines, which result in chronic inflammation and multiple autoimmune diseases.

So yes, I have a long history with this mechanism, but I have never been as excited about it as I am today. Because today, we are talking about the best part of a scientific journey – when you're studying a medicine in patients, patients with diseases you are trying to attenuate.

Today, Theresa and I will provide an overview of pDCs and why they are a critical driver of inflammation in a variety of autoimmune and inflammatory diseases. Daxdilimab is the first and only pDC-specific depleter in clinical development. We will walk you through the preclinical and clinical data generated to date that provide, as you will see, strong evidence that daxdilimab could be a viable therapy in multiple diseases including systemic lupus erythematosus, which is the first indication in development. We are also announcing four new indications that we will be studying, bringing the total indications we are exploring to five.

So, what do pDCs do? Why are they important? In healthy individuals, pDCs are present in very low numbers in the blood and available there to be recruited to tissue to help fight viral infections. They are like a special ops team – a small team that comes in before the rest of the immune system is mobilized, in this case to drive an appropriate immune response to fight the infection.

In individuals with certain autoimmune diseases, these pDCs are found in large amounts and chronically activated in the tissue, which can result in substantial inflammation and tissue damage, and serve as a hallmark of autoimmune disease. This is where daxdilimab comes in. It was designed to be an efficient pDC-specific depleter, binding to the ILT7 protein and targeting this key upstream driver of inflammation – and importantly, not impacting the body's myriad other antiviral response mechanisms. To help you visualize this, take a look at this video:

> *Plasmacytoid dendritic cells (pDCs) are immune cells that help the body fight off infection. pDCs may also contribute to autoimmune diseases, where the immune system mistakenly attacks the body.*
>
> *Normally, pDCs circulate in the blood. In response to external invaders like viruses, they become activated and produce many molecules that help coordinate an immune response. In particular, pDCs produce Type 1 Interferons.*
>
> *In chronic autoimmune diseases, pDCs are continuously activated and relocate to specific tissues. Therefore, levels of type-1 Interferons are increased in many autoimmune diseases such as lupus.*

For example, in cutaneous lupus erythematosus, pDCs are thought to move from the blood and accumulate in the skin where they produce type-I Interferon, as well as IL-6 and TNFα, suggesting they may play a direct role in continued disease propagation and progression in the skin.

Daxdilimab (HZN-7734) is a potentially first-in-class, fully human monoclonal antibody that binds to the ILT7 protein on the surface of pDCs. Once bound, daxdilimab is designed to recruit effector cells, such as a natural killer, or NK cell, that helps to kill pDCs.

Though pDCs are the main producers of type-1 interferons, other cells can also make these molecules, so daxdilimab may target a specific autoimmune disease driver without impairing the general antiviral response.

Daxdilimab reduced levels of both pDCs and type-1 interferons versus a control in preclinical studies. These early data support the potential of pDC depletion in disrupting the ongoing chronic inflammation in autoimmune diseases driven by pDCs and type-I interferons.

So, in the video you just saw, daxdilimab was shown to effectively and efficiently deplete pDCs, which is exactly what we observed in our preclinical studies as noted on this slide. The graph on the left shows pDCs in blood, where the magenta line shows the pDC count in blood after dosing with daxdilimab. As you can see, the level of pDCs in the blood dropped quickly and significantly, and this reduction persisted for a considerable amount of time after dosing ended.

What's important as well, in the graph on the right, when we measured the level of type-1 interferon produced by blood cells after stimulation with a pDC activator, we saw a very similar pattern, where the levels of type-1 interferon dropped off soon after the time of dosing, coinciding with the deep and durable depletion of the pDCs in the blood. This durable pDC depletion was still evident three months after the dosing was completed, a very promising finding, providing for the potential of less frequent, patient-friendly dosing. You will hear more from Theresa about this.

And the findings from the preclinical studies have also been reflected in humans. In our multiple ascending dose study in patients with autoimmune disease, we also demonstrated this deep and durable depletion of pDCs in the blood, where daxdilimab was also safe and well-tolerated. This Phase 1 study set the foundation to now study daxdilimab's ability to deplete pDCs in human disease.

Theresa will now share with you our clinical experience to date in cutaneous lupus and outline the five indications that we are excited about studying. Theresa Podrebarac joined Horizon early this year and has been working in clinical development for 20 years. Theresa is a rheumatologist and a practicing immunologist and has witnessed the evolution of several life-changing therapies to address serious diseases including rheumatoid arthritis, lupus and inflammatory bowel diseases. Theresa?

Theresa Podrebarac, M.D., M.Sc.
Senior Vice President, Clinical Development

Thanks, Bill, and good morning everyone.

As Bill just shared with you, preclinical data and early stage clinical trials demonstrate daxdilimab's potent ability to deplete pDCs. We believe that pDC depletion can be applied to a number of autoimmune conditions such as systemic lupus erythematosus, or SLE, where we see elevated type-1 interferonlevels and involvement of other proinflammatory cytokines.

With daxdilimab, we started by investigating the skin in cutaneous lupus. Skin can respond quickly to an effective treatment and can be easily biopsied.

The images on the left are immunohistology slides of the skin from a patient with active disease. On the top row it shows pDCs staining in dark pink and MXA protein staining in dark brown which indicates functional interferon signaling at baseline. The bottom row shows both pDCs and interferon levels 85 days after the first dose of daxdilimab. The observable difference is striking. On the bottom row, you can no longer see the individual pDCs or the dark brown staining. We were able to remove the pDCs and the cytokines that they produce to drive an improvement in the skin.

On the graph to the right, what we observed was robust depletion, with 98 percent of pDCs removed from the tissue. These data are also from our Phase 1b trial in cutaneous lupus patients.

Starting on the left-most graph, we see the time course of the disease activity in the skin, as measured by CLASI. As we saw earlier, daxdilimab depleted the majority of pDCs in blood by Day 8 in the trial; what we see here is that this quickly begins to translate to a clinical impact, with separation from placebo becoming evident in the first month. In this trial, the last dose was given on Day 57 and the improvement was observed in the 150 mg dose group out to Day 141.

In the middle graph, we are showing the proportion of patients who experienced at least a 50 percent reduction in disease activity. And here, the higher-dose group in magenta had the highest levels of response.

Looking at the data in a different way, in the far-right graph, we show that the highest dose group experienced the best improvement, with more than 80 percent of patients achieving a seven-point reduction in disease activity, as measured by CLASI.

So I'm very pleased to tell you about our ongoing Phase 2 SLE program, which we initiated in June. SLE is the prototypic autoimmune disease in which the immune system attacks its own tissues affecting multiple organs. It affects younger women about 10:1 compared to men. Patients are selected who have moderate to severe disease activity, as measured by the SLEDAI and BILAG. We're evaluating two dosing regimens in this study, which will have its primary endpoint at 48 weeks.

Again, what is important in the study design here is not only are we looking to suppress disease activity in these patients, but we also want to demonstrate a clinically meaningful reduction of corticosteroid use. For those of us who have been treating these patients for a number of years, we know that steroids carry a significant risk of side effects even at low doses, some of which can cause serious health problems including osteoporosis, diabetes, cataracts and increased susceptibility to infection. The goal is to not only decrease the steroid dose, but to virtually wean patients off of corticosteroids entirely. In addition to lupus activity measures, we'll also examine the skin, because we know that's an early indicator of the effectiveness of daxdilimab, along with other measures of safety and tolerability.

Because this mechanism is so compelling – it essentially eliminates these little production factories of interferon and cytokines that drive diseases in several areas – we probed to see where else this mechanism can benefit patients.

As Liz mentioned in her presentation, once we understand that the medicine works, we evaluate the scientific rationale – in this instance, what other diseases are caused by high levels of interferon; we look at unmet need and the competitive landscape; and we also look at clinical logistics and feasibility. This slide provides a snapshot of that evaluation.

Once we did a thorough review of all the indications that we could pursue, we honed in on four additional indications: alopecia areata; discoid lupus erythematosus; lupus nephritis; and dermatomyositis.

Now let me talk through this in some more detail on the next slide to give you a better understanding of the diseases we are talking about. I already mentioned the importance of these cells in the skin, so we are going to be kicking off two new programs in skin disease.

The first is alopecia areata, where patients experience baldness to varying degrees and there are no approved therapies to date. Here is a photo of someone who has had significant hair loss. It can involve the entire scalp or even the entire body. Just imagine for a moment how challenging this must be from a self-esteem perspective and having this appear at such a young age. What we do know is that this disease is autoimmune-mediated due to the immune effects on the follicular stem cells that produce hair growth. These follicles are damaged by an immune attack, and that's what causes the progressive hair loss. What we also know is that pDCs are present, and type-1 interferon signature is elevated in alopecia areata lesions. So this is an opportunity for us to get into the skin and show the difference. We expect to initiate a Phase 2 trial in the first half of 2022.

Thinking about our overall lupus strategy, we are focusing on one of the most difficult to treat skin manifestations – discoid lupus. One of the misnomers is that discoid lupus only affects lupus patients. About 20 percent of discoid patients can develop concomitant lupus while 80 percent of discoid patients are classified as primary discoid lupus, and do not have systemic symptoms. This is a scarifying disease. When it scars, it can be quite disfiguring, as you can see in the image here and it also can leave you with hair loss. We know in cutaneous lupus that the interferon signal is strong. We also know that pDCs are present in DLE skin lesions, and type-1 interferon activity is significantly elevated in DLE compared to healthy tissue. So we are going to launch a dedicated program to study discoid lupus in the first half of 2022.

One of the most important manifestations in lupus is involvement of the kidney. We know that pDCs can promote kidney damage and are also associated with more advanced disease with interferon activity detected in kidney tissue. I feel much more confident today than I did even 10 years ago working in lupus nephritis because now there's a path forward with two approved products. We believe this mechanism could be an important driver in lupus kidney disease. And we've also learned from prior trials of how to make these studies successful. This Phase 2 trial will also start in the second half of 2022.

In total, we have a comprehensive approach to address critical needs in lupus patients.

And finally, we will be studying dermatomyositis, which shares the high interferon phenotype. activity is high in patients with dermatomyositis and correlates with disease activity. DM is a rare condition that manifests as skin rash and disabling muscle weakness. It also can affect children in a very severe way, so once we know that the mechanism is safe and efficacious in adults, we'd like to then study children, because this condition can be so heartbreaking in this population. This Phase 2 trial in dermatomyositis is also expected to begin in the second half of 2022.

So in summary, I hope Bill and I have convinced you that pDCs are an important driver of inflammation and autoimmunity. This mechanism has potential across multiple autoimmune and inflammatory disorders.

Daxdilimab is the first and only pDC depleter in clinical trials, with a very differentiated mechanism of action. We have clear preclinical and clinical evidence to show that pDCs are important, and by depleting them, we can reduce interferon and inflammation.

SLE is the first indication in our development plan; however, we are rounding that out with four additional indications for a total of five indications. We have a lot of work ahead of us, but we are so excited to potentially bring this medicine to thousands of patients who could truly benefit from daxdilimab, and we could have a true pipeline in a product.

And now Bill will take you through our next pipeline product, dazodalibep. Bill?

DAZODALIBEP (HZN-4920)

CD40L Antagonist Designed to Block a Central Pathway Involved in Many Autoimmune and Inflammatory Diseases

Bill Rees, Ph.D.
Vice President, Translational Sciences

Thanks Theresa.

Dazodalibep, or HZN-4920, is another example of how we think differently about our science. Many of you are probably aware of the CD40 pathway and first-generation antibodies targeting the CD40 ligand. They demonstrated promising efficacy in autoimmune disease but had safety concerns and were halted because of adverse thromboembolic events. These events were related to platelet aggregation caused by cross-linking of CD40-ligand-targeting antibodies on platelets – specifically, the co-binding of these antibodies to CD40 ligand on the platelets and Fc receptors on adjacent platelets.

Our team has successfully addressed this issue by designing a novel fusion protein that can entirely circumvent these safety concerns while effectively blocking the pathway for potential therapeutic benefit. And from what we have seen to date, we are very excited about its potential. We believe this internally designed next-generation CD40-ligand antagonist has the potential to help patients with many autoimmune diseases.

We will follow a similar framework as we did for our daxdilimab discussion. I'll provide an overview of the mechanism of action for dazodalibep and the role of this key pathway in autoimmune and inflammatory diseases. I'll discuss how dazodalibep was designed to address immune overactivation attributed to this key pathway. And then Theresa and I will guide you through our clinical work, which demonstrates how dazodalibep can suppress immune responses and autoimmune disease activity in a dose-dependent manner and even more important, how it demonstrates sustained, long-term benefits. Theresa will also share with you our important clinical efforts in both Sjögren's syndrome and our new indication in focal segmental glomerulosclerosis, or FSGS, which is a rare and most grievous kidney disease.

The CD40/CD40 ligand pathway is a key co-stimulatory pathway that plays a crucial role in driving adaptive immune responses, including T-cell-dependent activation of B cells and B-cell activation of T cells, resulting in inflammation. CD40 ligand is believed to be central to the production of pathogenic autoantibodies – driving inflammation through its interaction primarily with its cognate receptor CD40.

CD40 is expressed in a variety of tissues including the salivary glands, spleen, kidney, joint, gut and skin, and has been implicated in many autoimmune diseases, such as Sjögren's syndrome, rheumatoid arthritis, a variety of immune mediated kidney diseases and in transplants.

As I referenced previously, first generation antibodies demonstrated promising efficacy but had complications. As we thought about different ways to solve this problem, we thought differently about the science. Instead of engineering and re-engineering the antibody, our research team designed and generated a CD40 ligand-specific fusion protein, freed entirely of the antibody scaffold.

Dazodalibep, a CD40-ligand antagonist that binds to CD40 ligand, blocks and prevents interaction with the CD40 receptor. What we saw in our pre-clinical studies is that dazodalibep basically shrinks the production factory for B cells and T cells, or germinal centers, thereby disrupting overactivation of this pathway and reducing autoantibody production. To further test this mechanism, we designed a Phase 1 study in healthy volunteers to understand the ability of dazodalibep to suppress an immune response.

As noted on the bottom left side of the graph, these healthy volunteers were introduced to a foreign antigen, which induced an immune response. The colored lines on the graph show the impact of several different doses of dazodalibep. The closer the line is to the bottom of the graph, the better it worked. This shows that dazodalibep drove a dose-dependent response – with the dark pink line showing the best response at the highest dose, suggesting a near-complete suppression of the immune response.

These data show intended biologic activity, demonstrating its potent ability to suppress B-cell activation and plasma cell differentiation. These data, combined with the previous successes of inhibiting the CD40 pathway, gave us confidence to start exploring the impact of dazodalibep in human disease.

And now Theresa will take you through these data, beginning with our experience in rheumatoid arthritis, or RA.

Theresa Podrebarac, M.D., M.Sc.
Senior Vice President, Clinical Development

Thank you, Bill.

As Bill shared with you, with dazodalibep we found a way to address a central pathway in immunology which we believe has utility in multiple indications. This slide shows the results from our Phase 1b multiple ascending dose study in patients with moderately active rheumatoid arthritis.

As you can see from the chart on the left, there is a substantial reduction in disease activity for the two highest dose groups – as shown in the magenta and purple bars. Seventy-five percent of patients from the highest dose achieved low disease activity, or remission compared to 13 percent of placebo-treated patients.

Another intriguing feature of the results is the potential for prolonged response, shown in the graph on the right. In this trial, the last dose of drug was given at Day 85. For those patients with follow-up data out to Day 169, disease activity remained low. Dazodalibep was also safe and well-tolerated.

Based on the success we saw in the Phase 1b RA study, we moved into Phase 2 clinical development in three indications: rheumatoid arthritis, kidney transplant rejection and Sjögren's syndrome. And just as we did with daxdilimab, we probed to see where else dazodalibep could provide a benefit for patients. Following that work, we decided to pursue an additional indication for dazodalibep – in focal segmental glomerulosclerosis, or FSGS.

I will use the rest of this presentation to highlight our work in Sjögren's and FSGS.

Sjögren's syndrome is a chronic, systemic autoimmune disease where the CD40-ligand pathway is thought to be central in the disease pathogenesis. We know that both CD40 receptor and CD40 ligand are overexpressed in the circulation, but especially in inflamed tissues such as the salivary glands in patients with Sjögren's syndrome. As shown here, patients experience dry mouth, dry eyes, salivary gland enlargement and can experience arthritis, fatigue, kidney or lung dysfunction. These patients are particularly at risk for lymphoma because of the chronic B-cell stimulation.

There are approximately 50,000 Sjögren's patients in the U.S. who we believe would be appropriate for a novel medicine such as dazodalibep. Currently, there are no FDA-approved disease modifying therapies.

Here is our Phase 2b program in Sjögren's where we will evaluate approximately 175 patients across two different patient populations. Population One consists of patients with moderate-to-high systemic disease activity. These are patients that experience a score of at least five on the ESSDAI Index, which is the standard in measuring systemic disease activity in Sjögren's patients. The primary endpoint for this is the change from baseline in the ESSDAI score at Day 169. Population Two includes patients with moderate-to-severe symptoms. These are patients that score at least a five on the ESSPRI Index, which is a patient-reported index for symptoms of Sjögren's, such as dry mouth, fatigue and pain. The primary endpoint for this patient population is the change from baseline in the ESSPRI score at Day 169. We are continuing to enroll patients in this trial and anticipate having data from both patient populations in 2023.

Turning now to focal segmental glomerulosclerosis or FSGS, the new indication we will be pursuing. FSGS is a progressive kidney disease characterized by the biopsy findings of scarring, or sclerosis, of glomeruli and podocyte damage. Glomeruli are the filtering function of the kidney and as a result, FSGS leads to nephrotic syndrome or excess protein loss in the kidney in both children and adults. Kidney failure is common.

Similar to Sjögren's, overactivity of the CD40 pathway is a likely driver of pathogenesis. We know that CD40 is not normally expressed in healthy kidneys, but biopsies from FSGS patients show upregulation of CD40 by cells in the glomerulus and can be further induced by CD40 ligand. In addition, animal models demonstrate that blockade of this pathway protects against renal injury. With no FDA-approved treatments available, we are very excited to be pursuing this new indication to potentially help the 50,000 patients that could benefit from a novel therapy such as dazodalibep.

In fact, our head of patient advocacy was impacted by this disease directly. His brother has FSGS, and back when he had his first of three kidney transplants, there was nothing in development that offered any hope. Unfortunately, his disease recurred after his first two transplants. He is doing well now, and stories like these truly motivate us to do all that we can to find effective treatments.

We expect to start this trial in the second half of 2022. One of our strengths at Horizon is that we are agile and creative in clinical trial design and we are also looking for ways here to quickly determine an early signal in FSGS.

So, I hope you are as excited as we are for the potential of dazodalibep. We designed this molecule to target the CD40/CD40-ligand pathway, which is a well-validated target that is central in many autoimmune and inflammatory diseases. The clinical evidence to date shows that it delivers powerful efficacy with benefits that persist long after you dose, providing for the potential of a less frequent, patient-friendly dosing regimen. In addition to Sjögren's and our other Phase 2 trials, we are looking forward to starting a development program in another autoimmune disease where the CD40/CD40-ligand pathway is central – such as FSGS.

HZN-825

$LPAR_1$ Antagonist with Early Signals of Benefit in Fibrotic Diseases, Areas with High Unmet Need

Srini Ramanathan, Ph.D.
Senior Vice President, Research & Development Sciences

Up next is our presentation on HZN-825, our $LPAR_1$ antagonist that has shown signs of benefit in fibrotic diseases – areas with huge unmet need.

Joining me to discuss HZN-825 will be Dr. Dinesh Khanna, who is joining us virtually from Michigan, where he is a professor at the University of Michigan Health, and serves as the director of the Michigan Medicine Scleroderma Program and is board certified in rheumatology. His program sees between 1,400 to 1,600 scleroderma patients a year and Dr. Khanna is the Coordinating Investigator of our upcoming Phase 2b trial for HZN-825 in diffuse cutaneous systemic sclerosis and completed some of the early-stage work on the mechanism.

As you've heard from the prior presentations, Horizon is very discerning about the way we build our pipeline. In particular, we target mechanisms that are core drivers of disease. And that's why we are so excited about HZN-825, which is a small molecule targeting $LPAR_1$, and the potential it has for people with fibrotic diseases such as diffuse cutaneous systemic sclerosis and idiopathic pulmonary fibrosis, or IPF.

Today, Dr. Khanna and I will discuss with you why we believe that selectively inhibiting $LPAR_1$ with HZN-825 is so compelling. There is a large body of pre-clinical and clinical evidence that supports the development of HZN-825 in multiple diseases – and we look forward to building on this through our two Phase 2b clinical programs in diffuse cutaneous systemic sclerosis and IPF.

Let me first dive deeper into the role of lysophosphatidic acid, or LPA, in the body. In healthy people, LPA enables beneficial cellular events to take place, such as cell growth, migration and survival. These help during important events, like wound healing, for example. And it does this by signaling through one of six LPA receptors, termed LPARs 1 through 6. In people with fibrotic diseases, as shown on the right, LPA signaling is dysregulated and causes damaging events at the cellular level.

Specifically, the LPA_1 receptor, or $LPAR_1$ – which is the receptor that HZN-825 selectively targets – has been implicated in inflammation and fibrosis. Essentially, it is involved in three key activities in disease, which are: blood vessel leakage to access target tissues; damage of the protective epithelial cells that line the tissues; and increased activity of fibroblasts, which results in excessive collagen deposition, resulting in the impairment of various organs.

So, how does HZN-825 stop this dysregulation and fibrosis? As an oral $LPAR_1$ antagonist, HZN-825 binds to this receptor and blocks proinflammatory and profibrotic signaling. As I noted on the prior slide, $LPAR_1$ is considered the main LPA receptor that drives the major activities that cause inflammation and fibrosis. LPA, the ligand that binds to LPARs 1 through 6, performs many important, diverse functions, so shutting down all LPA signaling may affect its normal activities. That's why we are selectively targeting $LPAR_1$ with HZN-825, to inhibit fibrosis, without impacting other LPA actions.

Dr. Khanna will share the disease burden and the challenges experienced by the patients he sees every day. But mechanistically, what is happening when a patient has a fibrotic disease is that the fibroblast recruitment is creating layer upon layer of collagen – making the patient's skin much too thick. And in an organ like the lungs, this collagen deposition doesn't allow the lungs to expand or contract freely, which impairs gas exchange and ultimately restricts the ability to breathe. That's why so many patients with scleroderma also have interstitial lung disease, or ILD – it's impacting the skin and many other organs, such as the lungs. Therefore, it is critically important that the mechanisms we study target different organ systems, and that is the case with HZN-825.

HZN-825 has been able to demonstrate improvement in multiple organ systems in various models of animal disease. Both $LPAR_1$ deletion and $LPAR_1$ antagonism have been shown to reduce inflammation and improve fibrotic activity in the skin (as shown on the left), lungs (as shown in the middle panel), and kidney and heart (as shown on the right). In some

cases, $LPAR_1$ targeting can even reverse fibrosis. As you can see, this multi-organ system impact is important, because you want to be able to treat fibrosis wherever it appears in a patient. Dr. Khanna will talk more about this.

Additionally, HZN-825 was safe and well tolerated in more than 160 healthy volunteers across several Phase 1 studies. Based on these data, as well as additional Phase 2a clinical data that Dr. Khanna will discuss shortly, we are investing in a clinical program to evaluate HZN-825 in patients with diffuse cutaneous systemic sclerosis and idiopathic pulmonary fibrosis. I'll now turn it over to Dr. Khanna to talk more about these diseases and our clinical programs.

Dinesh Khanna, M.D., M. Sc.
Professor, Institute for Healthcare and Innovation, University of Michigan

Srini Ramanathan, Ph.D.
Senior Vice President, Research & Development Sciences

So, as you've heard, HZN-825 is an oral, small molecule with a really exciting mechanism to target fibrotic diseases because of its breadth and diversity of impact across various different disease-driving activities going on in these patients. This clinical development program truly highlights what we do well: collaborate with key experts in the field, like Dr. Khanna and Dr. Kolb, and leverage their disease knowledge to complement our strong in-house scientific and regulatory organizations to drive agile and impactful programs in the clinic, with the potential for meaningful benefit for patients. We look forward to sharing more with you about HZN-825, as we enroll our clinical programs and share the clinical data in the years ahead.

I will now turn the podium over to Dr. Kristina Patterson, Horizon's medical director of Neuroimmunology. Kristina is an M.D., Ph.D., and she recently joined us from the University of Pennsylvania, where she was a practicing neurologist and NIH-funded investigator. Her expertise is in neuromyelitis optica spectrum disorder, or NMOSD, multiple sclerosis, autoimmune encephalitis and IgG4-mediated neurological diseases. Kristina?

UPLIZNA

Next-Generation B-Cell Depleter with a Novel, Targeted Approach

Kristina Patterson, M.D., Ph.D.
Medical Director, Neuroimmunology

Thank you, Srini. It is a pleasure to be here.

Our presentation this morning is focused on UPLIZNA, a next-generation B-cell depleter that is approved for neuromyelitis optica spectrum disorder, or NMOSD, a severe, rare, relapsing, neuroinflammatory autoimmune disease that attacks the optic nerve, spinal cord and the brain stem. As Srini mentioned, I'm a neurologist with a specialty in immunology. Before I came to Horizon, I took care of patients with NMOSD as part of my practice.

Prior to the advent of FDA-approved medicines, this was a disease where I had limited treatment options for my patients and often hoped for the best. Specifically, I hoped that they didn't have an attack, because they are devastating and can cause blindness, weakness and paralysis – sometimes permanently. Now that there are FDA-approved medicines like UPLIZNA, I can tell you my practice changed dramatically – there was finally optimism. It feels wonderful to work at a company that brought forward a medicine for NMOSD and to continue to serve patients in this community with significant unmet need.

So, today, Theresa and I look forward to sharing with you more about UPLIZNA. It is an anti-CD19 therapy and a humanized monoclonal antibody with exciting potential in NMOSD and many other autoimmune diseases. By targeting the CD19 molecule, UPLIZNA depletes a broad array of B cells, including plasmablasts and many plasma cells. These are cells that are not targeted by anti-CD20 therapies like rituximab.

B-cell dysregulation plays an important role in the pathogenesis of several severe autoimmune diseases: NMOSD, where UPLIZNA already has an indication; myasthenia gravis (MG); and IgG4-related disease – and we have trials underway in both of these diseases, which Theresa will discuss in more detail.

Let's start by talking about how B cells contribute to the damaging pathology of multiple autoimmune and inflammatory diseases. B cells are a type of white blood cell and an integral component of the adaptive immune system. One of the ways in which they fulfill their function is by making antibodies. In a normal state, antibodies attack foreign pathogens such as bacteria and viruses. And if you think about it, there are millions of pathogens that our immune system has to recognize and protect us from. In an autoimmune disorder, sometimes the immune system makes a mistake. It makes an antibody that attacks the body's own tissues, thus leading to disease.

Now, B cells play other roles in the immune system in addition to making antibodies. In a healthy inflammatory response, B cells help with the production of cytokines and chemokines. But when these cytokines and chemokines are produced chronically and in excess, it can lead to prolonged activation of other immune cells, such as T cells, and lead to tissue destruction.

Moving to UPLIZNA … It is engineered for a differentiated mechanism of action and clinical profile. Let me explain why – starting on the left-hand side. UPLIZNA selectively binds to CD19 with a high affinity and targets a broad array of B cells for depletion – including plasmablasts and many plasma cells. The CD19 expression on these cells persists after CD20 expression has been lost. This could have positive mechanistic implications for autoimmune diseases where dysregulated B cells play a prominent role in the immune pathophysiology. UPLIZNA is designed to offer broader and potentially deeper, longer-lasting depletion of B cells than CD20 depleters such as rituximab. Because UPLIZNA is humanized, it is designed to decrease anti-drug antibody formation and improve tolerability. And finally, looking at the bottom of the graphic, the afucosylated Fc portion design allows for enhanced therapeutic efficiency at lower doses.

As you can see here with the pink bar, CD19 is expressed in a broader array of B cells, all the way from the pro-B cell in the bone marrow, thus targeting more precursor B cells, but also targeting plasmablasts and many plasma cells, which make pathogenic antibodies in diseases like myasthenia gravis and NMOSD. You can see that UPLIZNA provides a broad, deep and durable depletion of B cells.

And with that, let's briefly review NMOSD. NMOSD is a devastating disease of the central nervous system; most commonly, the optic nerve, the spinal cord, and sometimes the brain, are attacked by the body's own immune system with pathogenic autoantibodies against a water channel called aquaporin-4. UPLIZNA is indicated to treat patients who have these autoantibodies to aquaporin-4. Aquaporin-4 autoantibodies lead to widespread inflammation that could result in blindness, paralysis, in addition to other forms of disabilities, and the damage is often permanent. So, in NMOSD, it is of the utmost imperative to prevent future attacks.

UPLIZNA is a well-studied and well-understood medicine that prevents attacks, as you see here. The chart on the left shows data from the UPLIZNA pivotal Phase 3 NMOSD trial, where 87.6 percent of UPLIZNA patients were relapse-free at the end of six months compared to just 56.6 percent for placebo, and we saw these effects well into our open-label period, with four years of data showing the durability of effect. The graph on the right shows data from the open-label period.

The pink bar on the left shows the patients who started out on UPLIZNA in the Phase 3 trial and then continued on UPLIZNA during the open-label period: 87.7 percent of these patients were relapse-free during the open-label period. The gray bar on the right shows the patients who started out on placebo during the Phase 3 trial and then were put on UPLIZNA during the open-label period: 83.4 percent of these patients were also relapse-free. Furthermore, UPLIZNA was generally well tolerated in both the Phase 3 trial and the open-label period.

We have a few more data points from the Phase 3 pivotal trial supporting the efficacy and safety of UPLIZNA in NMOSD. The chart on the left shows the favorable disability outcomes seen in patients on UPLIZNA. Across all subgroups, there was a trend towards decreased disability for patients on UPLIZNA. The middle panel highlights patients who switched from rituximab to UPLIZNA, with significant reduction in NMOSD attacks. Seven patients entered the study as rituximab "failures," defined as having an NMOSD attack while on, or within six months, of the last dose of rituximab. None of the seven failures had an adjudicated attack after receiving UPLIZNA, with a mean follow-up period of two-and-a-half years.

The right panel is from our Phase 3 clinical trial. The pink is UPLIZNA; the gray placebo. After just a few weeks of therapy, you see rapid and deep B-cell depletion for patients on UPLIZNA – and the depletion was sustained. This B-cell depletion is what has propelled us to evaluate UPLIZNA for two additional indications – myasthenia gravis and IgG4-related disease.

Theresa is here to talk you through those diseases and our clinical programs. Theresa?

Theresa Podrebarac, M.D., M.Sc.
Senior Vice President, Clinical Development

Thank you, Kristina, for that compelling overview of B-cell biology and the pathogenesis of several of these autoimmune disorders.

As Kristina said, I'll be discussing the areas we are further investigating with UPLIZNA. Up first is MG, which is a debilitating, rare disorder that disproportionately affects younger females and older males. There are two main types of myasthenia gravis: MG in patients who have autoantibodies against the acetylcholine receptor and those who have autoantibodies directed to muscle-specific kinase.

A common symptom of myasthenia gravis is drooping of the eyelids, or ptosis, which is depicted here and is a result of muscle weakness. MG can also lead to difficulty in swallowing, speech and chewing, and during a myasthenic crisis, patients would often require a ventilator to help them breathe. The current standard of care includes steroids, immunosuppressants, intravenous immunoglobulin, plasmapheresis, off-label rituximab and other biologics, such as complement inhibitors.

Let's take a moment here to better understand the role of B-cell dysregulation and how it causes MG and a muscle cell. This basically allows you to move your muscles where you want them to go.

On the top left panel, you see a depiction of the normal neuromuscular junction, along with some of the mediators and receptors needed for effective signaling in the muscle tissue, including the acetylcholine receptor and muscle-specific kinase. On the top right you can see what happens with MG when autoantibodies attack specific targets.

Acetylcholine receptor autoantibodies bind the acetylcholine receptor and interrupt signaling. They can also activate complement. Both can lead to damage and remodeling of the neuromuscular junction. Autoantibodies to muscle-specific kinase also interfere with normal signaling. Importantly, these autoantibodies do not activate complement.

The net result in MG is suppression of synaptic efficiency, which leads to muscle weakness.

So where do these autoantibodies come from? As you can see in the bottom right panel, they originate in the germinal center of the lymph node and then enter the circulation.

From a proof-of-concept perspective, we have seen the benefit of B-cell depletion in treating MG in both populations. Several case series have reported that rituximab, an antibody that depletes CD20-positive B cells, can reduce disease activity. However, not all studies have found that rituximab is beneficial in MG, and it is not approved for MG.

As Kristina discussed in great detail, UPLIZNA is an anti-CD19 antibody, and CD19 can persist on antibody-secreting cells after CD20 expression has been lost, and we believe that this has an important role in treating MG, as well. This is what we are aiming to prove in our Phase 3 trial in MG, given the fact that UPLIZNA is a next-generation B-cell depleter that offers a deeper, longer lasting and potentially broader depletion of B cells.

This is our Phase 3 trial design, where we continue to enroll patients. We will be studying both populations of patients; again, those with autoantibodies against the acetylcholine receptor and those with antibodies directed to the muscle-specific kinase. In fact, Horizon is the first company to design a Phase 3 trial in MG with clearly delineated populations of AChR+ and MuSK+ patients – so we will be better able to understand how UPLIZNA works in each patient population.

In the study design we are using the same regimen as was approved in NMOSD. The main inclusion criteria are patients who have an MG-Activities of Daily Living score equal to or greater than six, with more than 50 percent of this score coming from non-ocular symptoms, along with a Quantitative MG score equal to or greater than 11. The primary endpoint therefore is to show improvement in the MG-Activities of Daily Living score at Week 52 for acetylcholine receptor patients and Week 26 in the muscle-specific kinase patients. The trial continues to enroll patients, and we are tracking for an expected readout in 2023.

Now let's transition to IgG4-related disease. This is one of the newer fibro-inflammatory diseases. IgG4-related disease is rare and more prevalent in men, as is illustrated here. It has been diagnosed in every organ system, and the histology is strikingly similar in the various organs – which helps in the diagnosis. Common organs of involvement include the pancreas, the lacrimal glands where you have tear production, the salivary glands and the kidneys. It's also a disease that's characterized by a waxing and waning course and punctuated by flares. While nothing is FDA-approved to treat IgG4-related disease, high-dose steroids are often used, as is rituximab.

IgG4-related disease became officially recognized as a disease in 2003 and is characterized by a fibroinflammatory process leading to tumor-like enlargement that can affect multiple organs. In IgG4-related disease, it is thought that B cells trigger and perpetuate the disease; and that IgG4 levels can either be elevated or remain within the normal range. There are many ways that B cells cause this disease:

- IgG4 class switching occurs in plasmablasts, which leads to IgG4 tissue infiltration and enlargement;
- Additionally, activated B cells produce cytokines such as IL-1, that further drive tissue inflammation;
- Activated B cells also produce other cytokines such as transforming growth factor beta (TGFβ), that promote fibrosis or scarring; and
- Lastly, B cells can activate T cells, that can further lead to a cycle of cell-mediated tissue destruction.

Here are some images of patients with IgG4-related disease. In the upper panels you can see the tremendous enlargement of the lymph glands under the chin and around the cheeks, which is a common area of involvement. In the lower panel you can see the bulging of the eye due to lacrimal gland enlargement. The CT image on the bottom right shows pancreas enlargement and also changes in the kidney.

We have designed and initiated the very first Phase 3 trial in IgG4-related disease for regulatory approval. Our goal is to determine if UPLIZNA could be used as a first-line therapy for these patients. This is a randomized placebo-controlled trial. We are including those patients that have a clinical diagnosis of IgG4-related disease according to the latest criteria based on the 2019 ACR classification criteria. They must have recently experienced a flare that required a corticosteroid treatment. We also require that they must have greater than two organs or sites involved in this disease. The primary endpoint is time to the first adjudicated flare. This trial continues to enroll patients, and we expect data in 2023. However, because this is an event-driven trial, we will continue to assess the timeline and how events are occurring. As a result, the readout timing may extend beyond 2023.

In summary, we believe UPLIZNA has significant potential as a next-generation B-cell depleting therapy. We know UPLIZNA has a tremendous impact for patients with NMOSD. UPLIZNA has the potential to extend into other neurological diseases such as myasthenia gravis, and to also be important in other rare conditions, such as IgG4-related disease, to provide a clinically meaningful benefit. In addition, as a team, we are continuing to assess if there are other indications beyond these three where we can take UPLIZNA.

We look forward to sharing more information on that progress in the future. With that, I believe we have reached another break in our agenda, so I will turn it back over to Tina.

TEPEZZA

Building the Evidence to Help Treat More Patients with Chronic TED

Tina Ventura
Senior Vice President, Investor Relations

Up next is Dr. Bobby Korn, who will be discussing the growing body of evidence of TEPEZZA helping more patients with chronic Thyroid Eye Disease

Dr. Korn is a professor of Ophthalmology and Plastic Surgery at the University of California, San Diego. He is an active researcher who has been widely published in peer-reviewed articles, and a leading expert in TED. With that I will now turn the presentation over to Dr. Korn.

Bobby Korn, M.D., Ph.D. FACS
Professor of Ophthalmology and Plastic Surgery , University of California, San Diego

CONCLUDING REMARKS

Tim Walbert
Chairman, President and Chief Executive Officer

Thank you for joining us, Dr. Korn. I really appreciate your participation. And thank you to everyone who was able to join us today.

In summary, we have transformed significantly since our IPO 10 years ago. Today, we are a leading, high-growth, profitable biotech with more than $3 billion in net revenue expected this year and a market cap of nearly $25 billion. Driving the uptake of TEPEZZA, KRYSTEXXA and UPLIZNA and now, building our pipeline is our key focus.

Our goal is to develop new medicines for patients to address these critical needs for people impacted by rare, autoimmune and severe inflammatory diseases, much of what you heard today. We have made significant progress in a short period of time – now
with 27 programs and the potential to have 10 new indications or new medicine approvals in the years ahead.

We have a lot of exciting work ahead of us to maximize not only our current pipeline and add more programs through business development but also begin also begin our own internal research. We look forward to sharing our progress with you.

Thank you again for joining us today and have a great rest of the day.