Kymera Therapeutics Immunology Innovation Day | May 9, 2025

Justine Koenigsberg:

Good morning and welcome to Kymera's Immunology Innovation Day, our virtual event to introduce our next immunology program, IRF5. I'm Justine Koenigsberg, Kymera's head of investor relations. Please note that we are hosting today's event in lieu of our regularly scheduled quarterly update call. However, we have reported our results and filed our TENQ this morning. For additional details on our Q1 results, please reference our press release issued this morning, which is available in the IR section of our website. During today's presentation, you'll hear from our team about our strategy, our pipeline advancements, and our next high value immunology program. Joining me this morning are Nello Mainolfi, our founder, president and CEO, Jared Gallob, our chief medical officer, and Veronica Campbell, our senior director of immunology and project team leader of our newly introduced program, IRF5.

Here's a snapshot of today's agenda. Nello will begin with an overview of our strategy and the opportunity with small molecule degraders. Then Jared will provide a high-level overview of our STAT6 program, and we'll conclude with our prepared remarks with a discussion of our newly introduced IRF5 program before we open the call to questions. If you'd like to ask a question, please use the raise hand icon, which can be found at the bottom of your meeting window. To help us move efficiently through the Q&A discussion, we ask that you are ready to unmute your line and turn your camera on when called upon. A replay of today's event, including a copy of our corresponding presentation will be available soon after the call concludes in the investor section of our website.

But before we begin, I would like to remind you that today's presentation will include forward-looking statements about our future expectations, plans and prospects. These statements are subject to risks and uncertainties that may cause actual results to differ materially from those projected. A description of these risks can be found in our most recent 10-Q filed with the SEC. Any forward-looking statements speak only as of today's date, and we assume no obligation to update any forward-looking statements made on today's call. With that, let's begin. Nello?

Nello Mainolfi:

Thanks Justine. Very exciting to be here today to share not only a pipeline update, but also our new program IRF5, which Veronica will do in a few minutes. I thought I'll take a few minutes here to just give you an update on our strategy, where we're going, some important decisions we're making and upcoming milestones. So, just to remind you, Kymera was founded, actually just very recently, nine years ago, with the goal of building an industry-leading pipeline of medicines using a novel modality called targeted protein degradation. We believe with this modality, we can give rise to a series of new

programs and medicines that can overcome the challenges that the industry has faced for the past 20 years. In order to do so, we've built some unique capabilities.

I will start with the fact that we have become a key leader in the space of targeted protein degradation. In doing so, we built some really unique capabilities of hit finding and optimization of oral degraders. We've always had and continue to refine a unique target selection strategy based on pursuing traditionally undrugged targets in highly qualified and validated pathways. And that has allowed us to build a portfolio that is poised to really disrupt treatment paradigms. We have made a conscious choice a few years ago to focus in immunology, and the main reason has been, as I'll explain in a few slides, in that particular space, in this place and time, we've been able to combine really the right target with the disruptive potential of targeted protein degradation, delivering for the first time in industry oral drugs with biologics-like efficacy. And this is really a unique opportunities for Kymera and for patients.

Kymera is founded and continues to thrive on three key pillars. One, is a clear vision. So, we have always believed that with a new technology, not only you have an opportunity, but you have a responsibility, to building a fully integrated company. So, we are now building deep development capabilities to advance our programs into Phase 2 and Phase 3 studies with an eye on becoming a commercial stage company. We've been fortunate to always be well capitalized. We now have, as of the end of Q1, $775 million with now an extended runway into the first half of '28. We have brought five new molecules in the clinic since 2020, and we are on path to being able to deliver 10 molecules in the clinic by 2026. We have doses, at this point, way more than 300 between healthy volunteer and patients across our pipeline. And one thing that we're very proud of is our ability to continue to demonstrate impeccable translation from our preclinical studies into the clinic, achieving in all of our programs more than 90% degradation with the desired efficacy and safety profile.

So, just a quick summary about targeted protein degradation. The main feature of the technology is the ability to use small molecules to remove protein. So, you have almost a genetic like knockdown or knockout effect with the flexibility and the convenience of oral small molecules. So, we are able to go after proteins that have not been drugged or drugged fully for the past decades with a simple oral drug that we're able to design, synthesize, and develop here at Kymera.

So, why immunology? Why is this such a unique opportunity for us, and I would say for patients? The team did work in the past year or so looking at the 10 most common immune inflammatory diseases, and those are asthma, AD, COPD, as you can see from the slide HS, multiple sclerosis. And if you look at the seven major markets, that's about 160 million patients that are impacted by these diseases. And if you look at the number of patients that right now are accessing advanced systemic therapies, it's really around 5 million. We basically have a 3% penetration of advanced systemic therapy into this wide variety of immune inflammatory diseases, again in the seven major markets. I don't think we have a problem of innovation in immunology, there is plenty of great drugs in many disease areas. We have a problem of allowing patients to accessing these highly effective drugs.

In fact, of these 5 million patients, two thirds of these patients access biologics, so only one third access oral drugs. And these oral drugs often are not able to deliver the type of efficacy that biologics can. So, we have an opportunity to expand access and expand the reach of highly innovative drugs with oral degraders that have the efficacy of these advanced systemic therapies. And so when you try to put a number on the market, obviously it's really hard to do. If you look at 3% of 5 million, it's a hundred billion market, or more than a hundred billion market. So, we're talking about 90% plus of patients that we believe could be poised to receive our novel oral systemic therapies. And that's a very large number that obviously it's even hard for us to quantify. But our job here at Kymera is to develop, again, as I said, oral drugs that can not only displace biologics because they ideally and hopefully will have a similar efficacy, safety profile and the convenience of oral drugs, but more importantly, we can now offer a

convenient, highly effective, advanced therapy to the 90% of patients that right now are not treated, whether it's for access, whether it's for pricing, whether it's for convenience.

And here in this slide it's really highlighting what are the challenges and the opportunities. So, biologics, as we all know, have transformed treatment paradigms. They have transformed many diseases and how doctors treat diseases. But the challenge that come with them is obviously, they can be very expensive, they can be complex and expensive to manufacture as well as to prescribe and reimburse. They have often, not always, immunogenicity issue, they have cold storage issues. So, if you're taking a biologics with you on vacation, you have to think about cold storage. And obviously, they bring the inconvenience route of administration, often painful, and again, inconvenient. In an industry survey that was done, I think as recently as I believe a year and a half, a few hundred patients were asked, "If you had an option to switch from a biologics to an oral drug with the same profile, would you make the switch?" And 75% of patients said yes. So, there's clearly not only an opportunity, but there is a clear unmet need for patients to access oral therapies that will have a biologic-like profile.

So, the question would be why wouldn't traditional small molecule oral drugs capture that need? And the answer that we try to depict here is in the bottom of the slide. Traditional oral small molecules follow a traditional PK/PD profile. So, the efficacy is driven by the ability of the drug to block that pathway 24/7. And because the PK and the PD of a small molecule drug is really connected, you see a sigmoidal curve mostly that depicts that correlation. So, you're not able to block the pathway constantly 24/7, but you have a peak-to-trough PD effect. And this is very evident when you look at targets, for example, like TYK2 where while you're blocking the IL-23 pathway in principle well, you're not able to deliver the type of activity seen with an injectable IL-23 antibody. And that's really because of small molecules' inability to block the pathway fully. With a degrader that we've shown extensively both preclinically and clinically, we can block the pathway fully a steady state maintaining that degradation consistent. And that, as we've shown, can mimic biologics like pathway blockade.

So, in the next couple of slides, I just wanted to share with you two key features of Kymera that I believe has made us a leader in developing unique programs, especially now in immunology. One, is really around the capabilities that we've built. I believe we're the best company today at finding small molecule ligands to undrugged or difficult to drug protein. We're some of the best structural biology capabilities. And we've published on these extensively in peer-reviewed journals on understanding ternary complex interactions of our drugs with the proteins and E3 ligases, and we've shown consistently our ability to translate in the clinic a deep understanding of PK/PD in different tissues in preclinical species, and then in humans, which really de-risks the translation into patients and hopefully into a disease outcome. And all of these capabilities have resulted in some really important accomplishments in the past few years. We've delivered, at this point, I believe more than nine development candidates against undrugged transcription factors. We've shown now extensively that our degraders are very potent, very specific, orally bioavailable with a great and even distribution across tissues. And we've shown over and over again, as I mentioned, our ability to translate these profiles effectively into the clinic.

So we've talked about capabilities. Another key feature of Kymera's strategy is how we think about target selection. And we have these key four pillars that have been the same since day one. We go after targets that have not been drugged or drugged well before where there is strong human genetics for the target. And importantly, where the pathway's been validated with other agents, usually upstream of our targets. We usually, if not always have a clear path to show clinical differentiation early in our development strategy, as well as now, we're very, very keen on programs that have access to large clinical and commercial opportunities. If you look at our targets today that we're actively pursuing STAT6 and IRF5, two undrugged transcription factors where Kymera has delivered the first development candidate, or for STAT6 actually, the first clinical entry and soon the first clinical data. These targets have

been pursued for decades and really the technology has been missing. And here we have first-in-class drug with targets with strong genetic validation. IRAK4, the target has been drugged, but not well with traditional small molecules.

The beauty about our strategy is also that we're going after these pathways that have complementarity. So, not only these are standalone important programs after IL-4/13, Type I Interferon cytokines, B-cells or antibodies, IL-IR/TLR pathways. But also, you can imagine that eventually these pathways can be synergistic in how we think about further development in combination, et cetera. And this is probably even more appreciable. If you look at slide 13 here, we're looking at where we're developing these assets, in not only disease area, but also in which indications. So, you see, for example, for STAT6 we have a big effort in atopic diseases, which are more often in dermatology and respiratory. And here you see seven or eight different diseases. For IRF5, which I would say it's more traditional immunology, rheumatology, you see more in GI and rheumatology, RA, lupus, et cetera, while IRAK4 has places in each of these disease areas. So, not only we can actually capture almost the totality of potential immune inflammatory indications, but then you can imagine when there is overlap, a potential strategy down the road could be combination of these assets.

This is a slide that captures the concept that was made before about the unmet need in the space. And this actually puts number to the concept. We can use STAT6 and the concept can be applied to the other programs. Again, if you look at the seven major market, we have more than a hundred million patients that are diagnosed with TH2 diseases. And you can see the most prevalent there, AD, asthma, COPD, chronic rhinositis, et cetera. The number of patients that have access to advanced systemic therapy, right now dominated by dupilumab, is really around a million patients. So, we have almost a hundred million patients, if not more, that we strongly believe would benefit from an oral drug that has the efficacy and the safety of injectable biologics. So, an oral drug that can change how doctors prescribe medicines for patients with these diseases. And so that's really what we're trying to do, not only for STAT6 but also for IRF5 in diseases that are, as we've said, complementary to the STAT6 diseases. This is really around SLE, RA, Crohn's disease, UC, et cetera, and both Veronica and Jared will share more. And then IRAK4 with again, the more traditional 1 TLR-driven diseases. So, hopefully, this slide give you a sense of the opportunities we have in front of us with oral drugs. They are really best in pathway, that combined, the convenience of oral drug and the efficacy of a biologic.

So, in this slide, we will actually go through the upcoming milestones soon. And so I don't want to spend too much time going through the details of this slide. I just want to say the next 18 months would be the rich of milestones. We have STAT6 upcoming data in June, which we're very excited to finally get there. We have Phase 1b data at the end of the year. We have two Phase 2b studies to start. Veronica will tell you about IRF5. So, maybe I'll give you an update on a couple of programs that will not be the subject of the later presentation. So, first, on IRAK4, as you know, Sanofi is progressing KT-474 in two parallel Phase 2b studies in both HS and AD. We continue to expect these studies to be completed in first half, mid 2026 with data shortly thereafter.

As you know, IRAK4 was our first immunology target. And early success in that program has allowed us and has actually given us the impetus to invest even more in immunology and allowed us to build what we believe to be one of the best, if not the best oral immunology pipeline in this industry. And so while Sanofi has been advancing 474, we've had additional ongoing effort at Kymera under the collaboration. We've said that in the past, as a result of these efforts, we're pleased to announce today that we have recently achieved a preclinical milestone resulting in $20 million payment that we expect to receive in the second quarter. So, validation of both the strategy and the work that both teams have been doing in the past few years.

Secondly, I'd like to touch on the disclosure that we released this morning in the press release around our decision around TYK2. So first, I'll say that it's, I think, widely accepted that we're in a very volatile market period, not only biotechnology, but I would say the broader market. And with that, we believe that Kymera is exceptionally well positioned to navigate this uncertain environment. We have what we believe, as I just said, probably the best oral immunology pipeline in industry. We have multiple upcoming catalysts that we'll go through later in the presentation. We have an incredible research team that continues to deliver novel programs. You've seen IRF5, you'll see more in the near future. And we have a strong balance sheet of $775 million as of the end of Q1.

But obviously, we can't just sit and be complacent. We continue to look for opportunities to ensure that our human as well as our capital resources are always prioritized towards the highest return activities. And in fact, with this philosophy that we've continued to optimize our resource allocation strategy, you've seen changes that we made in the past around our oncology investments. And so it's really with this spirit of prioritizing and funding the highest return activities that we are announcing today, our strategic decision not to advance our TYK2 degrader, KT-295 into clinical development.

Now, I just want to take moment to explain that well. First, I would like to say that we have completed IND-enabling studies with this drug and we have seen no adverse events in any of our studies, in any of our doses. So, this was as a successful IND-enabling campaign as you wish. And I continue to be a strong believer in the differentiated case for a degrader in this highly validated pathway. At the same time, in this current environment, resource allocation is very important, and we believe resource allocation and particularly our people, two programs with the highest probability of success is paramount. So, at this point, we've decided to pause on our TYK2 efforts and redirect those resources. So, this decision will allow us to address two important points. One, we're able now to dedicate more human capital as well as our finances to what I believe it to be potentially one of the largest programs in industry, our STAT6 program and 621. I would say the STAT6 franchise and 621. That is really at the cusp of key inflection points. We also can use some of these both human and financial capital to fund IRF5 and other efforts that we have in other areas.

And then secondly, what this decision has allowed us to do is to extend a cash runway from mid-2027 to the first half of 2028. So, this is very important because now our cash runway is well beyond important inflection points, especially I would say well beyond the Phase 2b readouts for 621. So, I mean, you all know it's never easy when we make this resource allocation decision, but I hope I was able to convey our strategic thinking around this decision and then happy for myself and the team to take questions in the Q&A at the end. So, thought I'll pause here now and pass it on to Jared for him to go through our STAT6 program.

Jared Gollob:

Thanks, Nello. This is a very exciting time for Kymera from a development perspective. We are well positioned to achieve multiple clinical data readouts that we believe will further validate our approach and strategy. Before we formally introduce our IRF5 program, I'd like to give you a brief update on our ongoing and planned clinical trials for KT-621, our first in class oral STAT6 degrader program, and the first STAT6 targeted medicine to enter clinical development. The IL-4/IL-13 pathway drives Th2 inflammation and is highly validated by dupilumab, an injectable biologic targeting IL-4 receptor alpha that inhibits IL-4 and IL-13 signaling and is approved for the treatment of multiple different Th2 allergic diseases, including atopic dermatitis and asthma. STAT6 is the obligate and specific transcription factor in the IL-4/13 pathway and is therefore the critical signaling node controlling Th2 inflammation. For this reason, blocking the function of STAT6 is expected to phenocopy IL-4/IL-13 targeting.

There is also compelling genetic validation for the criticality of STAT6 in driving Th2 allergic diseases and the safety of reducing its expression, including the following. First, the pathogenic role of STAT6 is supported by human genetics showing that gain-of-function mutations of STAT6 cause severe early-onset allergic disease in humans. Second, a recent publication found that human heterozygous STAT6 loss-of-function mutations protected against severe Th2 asthma, showing for the first time how decreased STAT6 protein levels can be protective against Th2 diseases. Additionally, STAT6 knockout in mice is protective in multiple allergic disease models and STAT6 knockout mice develop normally, are viable and are fertile. So, the human and mouse genetics tell us that STAT6 is a compelling target for treating IL-4/IL-13 driven allergic diseases and suggest it can be safely knocked down.

Only the unique pharmacology of STAT6 degradation has the potential to fully block IL-4/13 signaling with an oral daily drug and thereby phenocopy the activity and safety of an upstream biologic like dupilumab. Historically, the development challenge has been to design oral small molecules that can fully block STAT6 around the clock and thereby inhibit the IL-4/13 pathway to the same extent as biologics. We believe the only modality that can do this are degraders. Furthermore, if an oral STAT6 degrader can truly block the IL-4/13 pathway to the same extent as say dupilumab, this has the potential to transform the treatment paradigm for all of the different Th2 allergic indications that have already been de-risked by dupilumab.

Dupilumab has transformed the lives of patients with dermatologic, respiratory, and gastrointestinal Th2 diseases and has become one of the largest drugs in this industry. We think we can change the treatment paradigm and reach an even broader patient population with an oral drug targeting STAT6 across all the indications de-risked by dupilumab and perhaps open up new opportunities in additional allergic indications beyond these.

We have a robust preclinical data set to support this program, and I'll walk you through this at a high level. Preclinically, KT-621 was shown to be exquisitely selective for STAT6 and shows no functional inhibition of other STATs. It degrades STAT6 at low picomolar concentrations across all disease-relevant human primary cell types evaluated, including lymphocytes, myeloid cells, epithelial cells, and smooth muscle cells among others.

We've shown preclinically that KT-621 is more potent than dupilumab at blocking IL-4 and IL-13 pathway functions relevant to Th2 disease manifestations in cell systems and is equal or superior to dupilumab at blocking Th2 inflammation in preclinical disease models. This was demonstrated in the mouse house-dust-mite asthma model at doses achieving 90% or greater STAT6 degradation. Overall, the preclinical data generated highlight the best in pathway potential of KT-621, given its dupilumab-like activity and the convenience of an oral pill.

In higher species, including dogs and monkeys, we have shown with oral daily dosing that we can fully degrade STAT6 at steady state in all relevant tissue types, and we did not observe any adverse safety findings in four-week GLP talk studies in non-human primates and rodents.

In light of the enormous potential for KT-621 to transform the treatment paradigm for patients with Th2 allergic diseases, we have adopted an accelerated development strategy that begins with Phase 1 studies in healthy volunteers and AD patients to quickly enable demonstration of clinical proof of concept and inform dose selection for Phase 2b dose range finding studies.

Our plan is to run two sentinel Phase 2b trials in AD and asthma starting in Q4 2025 and Q1 2026, respectively. That will enable dose selection for subsequent Phase 3 registrational studies, not just in AD and asthma but also across multiple other dermatologic, respiratory, and gastrointestinal indications de-risked by dupilumab.

The Phase 1a healthy volunteer SAD/MAD study has been completed, and we're on track to report data next month. The primary objective is to show we can robustly degrade STAT6 in blood and skin, which we define as a reduction of 90% or more at doses that are safe and well-tolerated. Given the extensive clinical pathway validation by dupilumab, all the human STAT6 genetics data, and the preclinical data we generated showing dupilumab-like activity with 90% STAT6 degradation in disease models of asthma and AD, we believe that if we can achieve this study objective, it will largely de-risk the program and meaningfully increase the probability of success as we move into patient studies.

We're also looking at how KT-621 impacts several circulating Th2 biomarkers including TARC and IgE. Our expectation entering the trial was that the effect would likely be comparable to what has been reported in healthy volunteers for dupilumab. Though, as we have said, we believe the best opportunity to show a significant effect on Th2 biomarkers will come in patient studies where baseline levels are greatly elevated due to IL-4/13 pathway activation.

Importantly, while completing the Phase 1 healthy volunteer study, we were able to initiate the first KT-621 trial in AD patients well ahead of what we had initially planned. The ongoing Phase 1b trial, named BroADen, is a single-arm open-label trial that will enroll about 20 moderate to severe atopic dermatitis patients. Patients will be administered KT-621 once daily for four weeks. The key study aim is to show that robust STAT6 degradation in blood and skin lesions by KT-621 has a dupilumab-like effect on multiple Th2 biomarkers in the blood and on the transcriptome of active AD skin lesions.

The study will also assess KT-621's effect on clinical endpoints, such as EASI and Pruritus NRS. We expect to report the Phase 1b data in the fourth quarter.

In summary, we believe that targeting STAT6 for degradation with KT-621 is the only oral small-molecule approach with the potential to achieve a dupilumab-like profile with once-daily dosing and are approaching KT-621 development with a strong sense of urgency and focus on execution.

This program has enormous potential to dramatically change the way we can treat patients with inflammatory diseases and expand their access to transformative drugs.

We're excited by the progress we've made in completing our Phase 1a healthy volunteer trial and initiating our Phase 1b trial in AD patients and look forward to sharing data next month for healthy volunteers and later this year for AD patients and gearing up for the start of Phase 2b trials in AD and asthma.

I'd like to pause here and introduce Veronica Campbell, the research lead on the IRF5 program. With her team, she's done a terrific job advancing this exciting program to development candidate and into IND-enabling studies, and we are excited to share the details with you now.

Veronica Campbell:

Thanks, Jared. I'm Veronica Campbell, Senior Director of Immunology at Kymera. I've worked at Kymera for eight years, and I'm proud to be part of this pioneering team working to develop transformative treatments for chronic immunological diseases. As a project team lead, I'm very excited to share with you the story of our first-in-class IRF5 degrader, KT-579, and why we believe it has the potential to be the first IRF5 targeted oral therapy to deliver transformative activity in several rheumatic and autoimmune diseases, superior to standard-of- care drugs including several biologics.

Today, I will cover first how Kymera's TPD approach has a unique opportunity to provide a novel oral therapy against what has been historically undrugged transcription factor. From there, I will describe the well-established biological function of IRF5 and the genetic and clinical pathway validation. Next, the clinical development and commercial opportunities IRF5 presents. Then I'll describe the exciting

preclinical data package for our development candidate, KT-579, and finally the expected timelines and next steps for the program.

I'd like to start by introducing our latest first-in-class oral development candidate, KT-579. KT-579 is a highly potent selective oral degrader of IRF5, which is an essential signaling node in genetically and clinically validated immune pathways driving inflammation in multiple autoimmune diseases with significant unmet patient need. I'll share details in the coming slides on the robust activity of KT-579 in primary cell systems, including patient donor cells and preclinical efficacy models of RA and lupus. In addition, KT-579 has a highly encouraging safety profile in preclinical tox studies where it was well tolerated at up to 200-fold above the predicted human efficacious dose. Our compelling preclinical characterization of KT-579 is consistent with the innovative science we've shared across our immunology pipeline and positions this program well on the path to development. The program is currently in IND-enabling studies, and we're on track to initiate Phase 1testing in early 2026.

Consistent with Nello and Jared's discussion of our rigorous approach to target selection, IRF5 meets all our criteria of what we think makes a compelling target for oral TPD approach. IRF5 is an undrugged target with strong human genetic validation and supporting biological functional data within pathways that have been clinically validated.

As seen in the pathway image on the right, IRF5 is a central node activated downstream of pattern recognition receptors that can recognize foreign or self antigens and is critical for mounting a pro-inflammatory response. For example, downstream of endosomal TLR7, TLR8, and TLR9 activation, IRF5 regulates Type 1 Interferon responses, pro-inflammatory cytokines, such as IL-12, TNF, and IL-6 and antibody production. Its expression is cell and activation specific making IRF5 an attractive target with potential to block immune dysregulation while sparing normal cell function.

IRF5 is a highly validated target through human genetics and clinically pathway validation. IRF5 functional risk variants that have been identified associated with increased susceptibility to lupus, Sjögren's, RA, IBD, and systemic sclerosis. For clinical validation, the IRF5 regulated pathways have been validated by multiple cytokine biologics and B cell targeting agents highlighting the importance of pro-inflammatory mediators like Type I Interferons, TNF alpha, IL-12, interferons, and IL-23 and autoimmune disease pathogenesis. I'll expand on these two points in subsequent slides.

IRF5 has been challenging to drug to date likely due to its multiple complex activation steps splicing isoforms in high degree of IRF family member homology. As previously reported, TPD is well suited to deplete undrugged transcription factor targets like IRF5 where a single and specific binding event drives molecule activity and can disrupt all IRF5 signal.

Let's discuss IRF5 more in disease context and as a master regulator of innate and adaptive response. IRF5 is selectively expressed in dendritic cells, monocytes, macrophages, and B cells. Pathway specific IRF5 dysregulation is cell and stimulant dependent. In autoimmunity, it is activated by pattern recognition receptors that can recognize nuclear self antigens in the body to initiate and amplify both innate and adaptive immune responses. By increasing pro-inflammatory cytokines like TNF alpha IL-6, IL-12, IL-23, Type I Interferons and pathogenic autoantibodies, this can lead to immune complex formation and propagate subsequent inflammation in autoimmune diseases such as lupus, systemic sclerosis, and dermatomyositis among others. Therefore, targeting IRF5 offers the opportunity for a transformative and multipronged approach to treat these complex and heterogeneous diseases.

Now, let's look further into the genetics associated with IRF5. Literature shows the pathogenic rule of IRF5 is supported by human genetics where multiple genome-wide association studies identify IRF5 as an autoimmune susceptibility gene.

Specifically, if you look at the bottom-left chart, meta analysis of GWAS studies have shown IRF5 to be a strong risk locus in lupus with risk haplotypes and functional variants identified in patients that associate with high-serum interferon alpha levels, anti-double-stranded DNA autoantibodies, or anti-RNA-1 binding protein antibodies. Beyond lupus, genetic associations and functional variants have also been identified in RA, IBD, systemic sclerosis, and multiple sclerosis.

Looking at mouse knockout studies, IRF5 knockout mice are viable and fertile with normal B cell development. In the bottom chart showing a mouse model of lupus, IRF5 plays an essential role in lupus development in pathogenesis that is interestingly independent of Type I Interferon pathways. As shown in the survival curves below where Riches, et al knocked out IRF5 and showed increased protection versus a knockout of interferon A receptor that results in modest protection against lupus.

Additionally, knockout studies demonstrated attenuated disease in other mouse models of lupus, RA, and IBD showing biological functionality in supporting the therapeutic potential of IRF5 degradation.

As previously mentioned, IRF5 is only expressed in a limited number of cell types and only activated by specific stimuli. This indicates that IRF5 degradation has the potential to selectively block inflammation to restore immune regulation. Dendritic cells, monocytes, and macrophages, when activated by members of the TLR family or other pattern-recognition receptors like Dectin mediate a pathogenic immune response via many pro-inflammatory cytokines including TNF alpha, IL-6, and Type 1 Interferons.

In addition, IRF5 is activated by endosomal toll-like receptors and B cells resulting in pathogenic autoantibody production. There are many agents which are approved in targeting some of these pro-inflammatory mediators like anti-TNF alpha, anti-IL-12/23, anti-interferon-alpha, and some which target B cells directly further validating the target.

The multifaceted functions of IRF5 which occur in specific cell contexts and upon specific stimuli point to superior efficacy and tolerability profiles compared to current agents for autoimmune disease with the potential to be best in class to treat complex diseases like lupus, Sjögren's and RA, IBD, and others.

The development opportunity for targeting IRF5 is vast, and there are numerous potential indications across multiple immunological therapeutic areas with a total potential patient impact of more than 10 million patients. KT-579, our oral IRF5 degrader, is designed to block the source of multiple pro-inflammatory mechanisms and improve on effectiveness, durability, and tolerability over currently approved agents and diseases such as RA, lupus, Sjögren's, systemic sclerosis, IBD, among others listed on this slide. Our IRF5 degrader has the potential to be a transformative oral therapy superior to oral and biologics standard of care across all indications on this slide as a result of its broad but cell-specific mechanism.

Now, let's look at the exciting profile of KT-579 and its impact across the biological mechanisms and pathways just discussed. We have an incredible opportunity with KT-579 given its potential to have an enormous impact on the treatment of autoimmune and rheumatic diseases. As we've walked through the preclinical characterization, we hope you will share enthusiasm for what we believe is another high-value target to emerge in our pipeline. I will show you the potent selective activity of KT-579 in normal human primary cells, donor cells from lupus patients, and in vivo disease models of lupus and RA.

I'll start with KT-579's effects in human primary cells from healthy donors.

KT-579 is an exquisitely selective degrader. As you have seen from our programs over and over, we look at concentrations well above that achieving maximal degradation of our intended target. IRF5 is the only protein degraded out of the 10, 000 or so proteins that were detected by mass spec. No other IRF family proteins were degraded to any extent. Looking at specific cell-based assay degradation of IRF3 and IRF7,

which are IRF5's closest family members, again, we see no degradation even at concentrations as high as 10 micromole.

Additionally, as seen on the right, KT-579 is a very potent degrader of IRF5. KT-579 demonstrated picomolar to nanomolar potencies across functionally relevant human cell types evaluated, including B cells, dendritic cells, macrophages, and monocytes, all key players in the pathogenesis of inflammation associated with IRF5. As seen with our other degrader programs, it is critical for us to understand degradation across all relevant human cell types and preclinical settings to build the right translational package to predict our human efficacious doses.

Next, we wanted to demonstrate selectivity not only through proteomics but also through downstream pathway-activated biology and IRF5 cellular mobilization. KT-579 selectively depletes IRF5 over other key transcription factors within the same pathway axes and downstream of TLR7 and TLR8 activation. This is an important aspect of KT-579 given the high- sequence homology between IRF5, IRF3, and IRF7. As seen in the staining on the slide, depleting IRF5 with low nanomole concentration of KT-579 leaves these other critical transcription factors completely intact. These data provide additional evidence that the functional inhibition we've observed in subsequent slides is driven through IRF5 depletion only and highlights how selective the compound is. In addition, we show we can degrade IRF5 both in the cytoplasm and the nucleus as shown in the bottom panel.

Here, we see that KT-579 demonstrated potent inhibition of key pro-inflammatory cytokines and Type I Interferon production downstream of TLR4, TLR7, and TLR8 and TLR9 activation in primary cellular assays shown in the table and graphs. For example, we show KT-579 can block IL-12 interferon beta production and monocytes and block the production of TNF alpha in IL-23 in PBMCs. These data highlight KT-579's broad and potent activity that is both cell and stimuli dependent.

Additionally, transcriptomics analysis demonstrates that KT-579 dampens Type I Interferon response and select interferon-stimulated genes that are reported to be elevated in systemic autoimmune diseases such as lupus and Sjögren's. Type I Interferon responses can be induced by endosomal TLR7 and TLR8 activation via single-stranded RNA nuclear self antigens. On the left, differential gene analysis demonstrates that KT-579 can block the Type I Interferon at least as effectively as an anti-TLR7/8 inhibitor, Afimetoran, at concentrations predicted to be clinically active.

On the right, we see that KT-579 can achieve comparable inhibition to Afimetoran of select ISGs that have been associated with increased disease activity in lupus.

Turning now to KT-579's activity in patient-derived donor cells. We examined KT-579's impact on lupus patient-derived PBMCs. Endosomal TLR7/8 activation can be IRF5 dependent, and KT-579 effectively block TLR7 and eight induced pro-inflammatory cytokines and interferon beta production. These data include some patients with IRF5 common functional variants where we observe similar activity on both IRF5 degradation and downstream functional effects. By inhibiting pro-inflammatory cytokines in Type I Interferon, we hope to reduce inflammation, suppress the development of autoantibodies, and ultimately mitigate the progression of autoimmune diseases like lupus independent of IRF5 genotype. We plan to share more of these data in subsequent presentations.

Continuing with the lupus patient samples, on this slide, you can see how KT-579 significantly inhibits IgG production in B cells, cultured with CpG-B with or without KT-579 for seven days. In lupus, double-stranded DNA nuclear self-antigens or anti-double-stranded DNA immune complexes can activate endosomal TLR9 in B cells leading to B-cell activation, differentiation, and pathogenic autoantibody production. This data really shows the promise of an IRF5-directed treatment to reduce the B-cell mediated inflammatory cascade in lupus patients.

And finally, let's turn to the in vivo preclinical data.

In the first model shown here, we evaluated KT-579's activity in mouse-acute TLR models that elicit a potent inflammatory cytokine response. In these studies, KT-579 dosed orally once a day for four days achieved deep degradation of IRF5 here measured in the spleen. Importantly, as we discussed with other programs in our pipeline, degraders require higher doses in mouse models compared to other species due to higher plasma protein binding and lower affinity. While in higher species, like NHP, which is more translatable to humans, we can achieve full degradation at much lower doses.

Then on the fourth day, TLR7 or TLR9 stimulants were administered systemically, and KT-579 activity was compared to a TLR7/8 inhibitor, M5049, as shown on the charts to the right. As expected, only KT-579 led to dose-dependent inhibition of cytokines in both models, blocking both TLR7 and TLR9 induced cytokines including TNF alpha and also IL-6, IL-12, and interferon beta, which are not shown here. This demonstrates KT-579's advantage in blocking both TLR7 and TLR9 activities which should translate to greater efficacy in several autoimmune diseases. This potential advantage is further supported by mouse TLR knockout studies where TLR7 and TLR9 double knockout led to greater impact on disease onset and severity in mouse models of lupus, for example. In addition, these acute studies allowed us to select active doses for use in chronic mouse models of lupus NRA.

In the next few slides, we will go over our preclinical efficacy studies and show you how our IRF5 degrader, KT-579, compares to existing agents in lupus NRA models phenocopying IRF5 knockout studies.

To start, MRL-lpr mice have a susceptible genetic background in single-gene mutation and Fas quickly developing lupus-like symptoms and manifestations. Disease biomarkers can be detected as early as eight weeks of age. Treatment began at Week 10 and ended at Week 19 when mice are expected to present with extensive kidney pathology. KT-579 daily oral dosing was well tolerated at both doses of 50 mg/pk and 200 mg/pk for the duration of treatment. KT-579 demonstrated sustained and near-complete reduction of protein urea and 100% survival at both doses, achieving at least 85% degradation with activity superior to approved or clinically active drugs such as Afimetoran, deucravacitinib, cyclophosphamide, and an anti-interferon A receptor mouse surrogate antibody administered at the top dose reported in literature. Additional endpoint readouts are currently ongoing.

Next, we evaluated the impact of IRF5 degradation in the long-term NZBW1 spontaneous lupus model using an earlier potent and selective IRF5 tool degrader. This degrader was used for proof of concept in this model while characterization was ongoing for our development candidate KT-579. NZBW1 mice have a polygenic background and spontaneously develop lupus that present with high levels of circulating anti-double-stranded DNA, anti-ANAs, protein urea, and immune complex mediated glomerulonephritis, similar to human lupus. Treatment was initiated at week 21 during early onset of disease. Daily oral doses of an IRF5 degrader for four months were well tolerated, and doses that achieved greater than 80% IRF5 degradation led to sustained reduction of proteinuria and near-complete reduction of circulating serum, anti-double-stranded DNA autoantibodies generally better than standard of care, cyclophosphamide, approved anti-interferon A receptor one surrogate, and clinical stage testing agents, ephimetarin and deucravacitinib. These are really exciting results that demonstrate the ability of an oral IRF5 degrader to achieve similar activity on IRF5 to genetic depletion. We will be testing KT-579 in this model and we expect it to look very similar to this given the similar potency of the drugs, and we plan to share the results at a subsequent presentation.

Next, in the antigen-induced arthritis mouse model of RA, daily oral dosing with KT-579 that achieved approximately 90% degradation led to significant reduction in joint swelling comparable to tofacitinib. IRF5 degradation phenocopies IRF5 knockout and leads to reduction in ankle swelling, circulating pro-inflammatory cytokines as shown here with IL-12 and infiltrating inflammatory pathogenic Th-cells

evaluated by flow, which is also shown here on the right. These data exemplify the potential for an oral IRF5 degrader to impact multiple inflammatory biologies in autoimmune diseases.

As part of KT-579's preclinical characterization, we looked at degradation of IRF5 across several preclinical species. As shown on the chart to the right with daily dosing for seven days, we observed KT-579 can robustly deplete IRF5 at steady state with low oral doses in non-human primate. Importantly, the degradation was measured 24 hours after the last dose. KT-579 was also very well tolerated with no adverse effects or relevant findings up to 200-fold the predicted human efficacious exposure in our non-GLP toxicology studies in both non-human primate and rodents, de-risking our path to human translation and proof of concept.

In summary, I've shown you that first, IRF5 has the potential to be the first broad anti-inflammatory that effectively addresses immune dysregulation while sparing normal cell function in both human and mouse genetics, along with preclinical validation indicating best-in-class profile for IRF5 in treating lupus, Sjögren's, RA and other diseases. Next, KT-579 stands out as a highly selective potent oral IRF5 degrader. Also, our in vivo studies show that IRF5 degradation leads to robust cytokine inhibition and demonstrates superior or comparable efficacy in lupus and RA models compared to approved drugs in the space. In addition, KT-579 achieves complete degradation across multiple preclinical safety species and relevant tissues, maintaining a favorable safety profile.

At last, we're very happy that this program is progressing in IND-enabling studies and we expect to advance KT-579 into the clinic in early 2026 as we believe the first oral IRF5 degrader. With that, I'd like to now turn the call back to Nello for his closing remarks.

Nello Mainolfi:

Thank you, Veronica. It's always exciting to hear these stories even if I've heard that multiple times internally. I think when we do this public disclosure, it is just an exciting time to put all our data out there and show how productive the team can be and more importantly, the level of sophistication that the team goes when we build these preclinical packages. Very excited to take this program in the clinic. Why don't I maybe complete this presentation today by going through our pipeline and spending a bit more time on the upcoming milestones and then we'll look forward to take questions from the audience and the analysts.

First, as we've repeated now multiple times, obviously KT- 621 is moving very rapidly, as we've said, likely much more rapidly than we anticipated, which is a great problem to have. We've been able to complete our healthy volunteer study in really dosing in March. We are collecting the last small data points and then we're really excited to being able to share our Phase 1 healthy volunteer data in June. That's an important date on your calendar.

As you also know, we have started our Phase 1b AD study in April. And again, kudos to the team, the 621 team for being able to do that, as I said, very rapidly. We're now recruiting patients and we expect to be able to share data from this study in the fourth quarter of the year. The team is already gearing up to initiate these two large Phase 2b studies. We'll start the AD study in fourth quarter of '25 and the asthma study in the first part of '26. Very busy with all these activities. Important two data readouts, healthy volunteer in June and then AD patient data in the fourth quarter of the year. And then we'll embark in these large studies that will obviously take longer than the Phase 1b study and we'll share more details about expectations around timing and data readouts as we get closer to them.

For IRF5 KT-579, as Veronica said, the preclinical package both on safety and efficacy looks extremely impressive and so we're expecting to file an IND towards year-end starting at Phase 1 early next year with Phase 1data already next year. And then as we mentioned with IRF4, we expect to have data in '26 for both HS and AD.

Thank you everybody for taking the time. I know it was during the morning on a Friday, but hopefully you'll appreciate the level of details that we shared today and we're happy to reconvene and take questions once we get together in a couple of minutes.

Operator:

Thank you. At this time, if you would like to ask a question, please click on the raise hand button, which can be found on the black bar at the bottom of your screen. If you've joined by phone, please dial star nine on your keypad to raise your hand. When it is your turn, you will receive a message on your screen inviting you to join as panelist. Please accept and wait until you are promoted to panelist. Please unmute your audio, turn on your camera and ask your question. As a reminder, we are allowing analysts one question and one related follow-up today. We will now pause a moment to assemble the queue. Thank you. Your first question will come from Derek Archila with Wells Fargo. Please unmute and ask your question.

Bruce Jacobs

Hey, Derek, we can't hear you. Can you unmute if you haven't?

Yvonne:

Hi, can you hear me?

Bruce Jacobs

Oh yes.

Yvonne:

This is Yvonne for Derek. Thanks for taking our questions. Just a quick one from us. Can you talk a bit about your confidence on targeting STAT6 in AD and of showing an effect in the four-week study? Should we be expecting a relatively noisy dataset given it's such a short study? Thanks.

Nello Mainolfi:

Yeah, thanks for the question. Obviously, the underpinning of this program is that IL-4 and 13 mass signal through STAT6 to propagate the signal and to impact downstream TH2 cytokines. The de-risking and the expectation that we're set on this program are purely driven by the data that's been shown in AD already by the vast IL-4 and 13 agent, which is the dupilumab, which is actually the only drug that blocks both IL-4 and 13. We know with that drug, even in four weeks, you can actually generate quite compelling differentiated dataset. The first one is that even in four weeks, you can impact both circulating and skin biomarkers of Th2 inflammation very robustly. And actually if you look at the dupilumab data 4 weeks in terms of EASI scores and others clinical endpoints, while they do not reach maximal effect, they are quite robust. Given all the preclinical data that we've generated on our program with KT-621 and the fact that all the models and assays that we run this compound through, we've shown a dupi-like effect, in some cases, even a dupi-better effect, we expect that we'll be able to see really robust data, first in biomarkers because that's really what the style has been powered on, but also on clinical endpoints.

Yvonne:

Got it. Thanks.

Operator:

Your next question comes from the line of Jeet Mukherjee with BTIG. Please unmute and ask your question.

Jeet Mukherjee:

Hey, good morning. Can you hear me?

Nello Mainolfi:

Yeah, we can see you even, Jeet.

Jeet Mukherjee:

Great, thanks for taking the question. Maybe just one question around the decision not to advance the TYK2 program. You obviously talked about the decision in the context of being capital conscious and the macro backdrop, but it appears you've swapped TYK2 for perhaps IRF5. Was there anything there in terms of the molecule's profile or just the evolving competitive landscape that influenced your decision? Thanks.

Nello Mainolfi:

Yeah, no, great question. I think it's important to maybe spend even a bit more time as you're suggesting. We remain, and I can say even personally, I remain confident in the TYK2 opportunity with a degrader. I think that the decision is really around today where we are with both resources, both human and capital, we feel like being able to power up even more so our 621 program, given that it's really accelerated in terms of pace, and obviously I can't speak to the data, but obviously we have a lot of confidence going into these larger studies. Given the risk reward in that program, we feel like that's the place where we want to go and put a lot of resources in. I think the IRF5 program is actually quite different from TYK2. TYK2, it is true to reflect that the TYK2 space is obviously there is a lot of competitive intensity. We look at not just TYK2, but I always look at all the other IL-23 drugs out there, including the quite impressive J&J peptide. Obviously the barrier in that space has been raised.

We think IRF5 is a totally different program. I think that's going to be a best in class drug for a wide variety of diseases and that's a program we want to go all in would be first. The competitive intensities right now in that program in those pathways is close to zero and we have an opportunity to have a highly differentiated profile. Again, there is obviously competitive intensity and risk reward conversations that have happened within the company on how programs have been prioritized. I think we are alluding to is fair. But at the same time I would say the main driver is we have the largest program in industry in our hands, probably, maybe if you remove the GLP-1 drugs and we got our resources at the maximum that we can do in this point in time.

Jeet Mukherjee:

Thanks for taking the question.

Operator:

Our next question will come from Marc Frahm with TD Cowen. Please unmute your line and ask your question.

Marc Frahm:

Thanks for taking my question. Beyond the IRF5 program that you disclosed today, just as you get into the clinic, what does that minimal target profile in terms of degradation look like? And as we get to clinical data, as you highlighted with your intro, Nello, the bar in some of these other diseases where you've started going after orals, things like psoriasis is extremely high. There really isn't much room even there or to some extent AD to push efficacy higher. But some of these diseases you're talking about for IRF5, there's certainly much more room for clinical improvement for efficacy. How important is that to ultimately show versus just matching available therapies but offering oral convenience?

Nello Mainolfi:

Yeah. I think it's a great question. Maybe I can start and others can follow. First, I think that's an insightful question. I would start with just looking at our preclinical data as you could appreciate, I know we've only just gone through it and you didn't have a lot of time to digest. At least so far it looks like at least 80% degradation and above is able to deliver some really best-in-class profile. We're actually doing more work to understand is even less than 80% degradation sufficient to drive the activity that we've seen. I guess to answer your question, there's even more work that we're doing. I think if you look at, and just in both lupus and RA, but I would start maybe with the lupus model, clearly targeting IRF5 in these quite translational models of lupus seems to have by far the best effect, which I think if you look at approved therapies in lupus, that right now they don't really work very well.

There is clearly an unmet need on the efficacy. Being able to deliver both efficacy and convenience that is superior to existing and even clinically active drug I think is really what we're trying to deliver there. Maybe even one step over some of the conversations we've been having in the past few months and then the team with Veronica's leadership has come up with an extremely well-behaved molecule that we believe will be highly differentiated in the clinic. But Jared or Veronica, if you guys want to add,

Jared Gollob:

I mean I think I'll only add that importantly we know that number one, we can achieve greater than 90% knockdown of IRF5 across multiple different species including higher species like non-human primates. And that in our 14-day studies that can be achieved with very favorable safety. I think that's very important. It's also very interesting to note in terms of your question around, well, how much knockdown do we really need, even if 90% or greater is safe, it's very interesting that these heterozygous IRF5 knockout mice are actually fairly well protected from diseases like lupus. It's possible we might not need that much knockdown for efficacy, but we know we can achieve that high degree of knockdown and that would be safe. That's going to be very important for us.

Veronica Campbell:

Yeah. And I think our expectation is, again, that we would see superior efficacy and that's because of the multiple biologies that we can hit with IRF5, right? As we talked about during the presentation, being able to impact auto antibody-producing cells, Type I Interferon and then also pro-inflammatory cytokines, that will be very important when you go after complex and heterogeneous diseases like lupus. I think even compared to let's say anifrolumab, we would expect to have a lot more efficacy.

Marc Frahm:

Good, thank you.

Operator:

Our next question will come from the line of Ellie Merle with UBS Securities. Please unmute and ask your question.

Ellie Merle:

Hey, guys. Just on IRF5, just a quick search, there's obviously a lot of literature showing that this plays a critical role in a lot of diseases, but curious how you're thinking about balancing the safety here. It looks like there's some data showing that IRF5 can act as a tumor suppressor. I mean obviously we're new to this target and it seems like it's involved in a lot of diseases, but just can you explain why you're comfortable with the safety here? And I know in the last question you mentioned you can even get disease protection or modification perhaps with the 50% degradation just from a clinical development perspective. Even if early on 90% degradation is safe, would you also explore moving forward with say 50% degradation, 90% with multiple dose levels and thinking about the long-term safety profile? Thanks.

Nello Mainolfi:

Yeah, so I'll let actually Veronica address the first part of your question. I just want to touch on high level. The beauty about IRF5, which will require a few days of work from everybody to get up to speed, is that what Veronica said multiple times, that is cell-specific. It's really only expressed in a subset of cells, and it's also really only activated in the presence of diseases. There are multiple other IRFs that are contributing to let's say immune surveillance from a safety perspective, from an infection perspective. It's really one of those great targets and that's why it's been pursued without much knowledge because with a lot of failures by the whole industry in the past 10 years, at least that we know of, because it actually combines this broad anti-inflammatory effect, IL-12, 23, IL-6, TNF, IgG, Type I Interferon, but in a context-specific manner. And that's really why even in these preclinical studies, we can remove the target completely. We've gone 200-fold above that dose and have not seen any activity. Veronica, do you want to take that? I know you have the answer to that question better than I do.

Veronica Campbell:

Yeah, no, thank you for the question. That was part of our due diligence in the beginning. We evaluated the target, some of the studies that you mentioned and we looked across TCGA aggregate studies. There's actually very little evidence that loss of IRF5 associates with cancer. And in fact when you look, it seems like gain of function is associated with cancer. And the one report that pops up is from one lab. There has been no follow-up work and with a target that's more highly expressed in heme cells, it's hard to believe that loss in a breast cancer epithelial cell will lead to cancer. There has been really no follow-up there. And again, with our broader analysis, we don't really see a risk in that area.

Nello Mainolfi:

Thank you. Thanks, Veronica.

Ellie Merle:

Great, thanks.

Operator:

Your next question comes from the line of Sudan Loganathan with Stevens. Please unmute and ask your question.

Sudan Loganathan.:

Hi, good morning. And thank you this morning again for this detailed presentation and for taking my questions. My first one is on the IRF5 program. In your preclinical work or any of the literature out there, did the degradation of IRF5 trigger any feedback mechanisms that may have activated IRAK4, MYD88, IL 2 or any other IRFs that could be a means of causing an untargetable relapse in a disease state whenever treated in humans going forward?

Nello Mainolfi:

Yeah, no, that's a great question. This is something we pay a lot of attention to across our programs, right? Do we see either an evolving potential resistant mechanism or other pathways coming into play? We haven't seen any of that in our studies. I mean, as Veronica showed, some of these are probably some of the longest studies that we've run preclinically. You see the lupus model, it's a four-month study. I think mice were dosed 106 days in a row, if I remember correctly. And with that, we haven't seen during the study, and obviously the mice are taken down at the end, but even when it's happened that in the other studies we've dosed and then stopped dosing, we have not seen any flares or rebound of these inflammatory pathways. The beauty about these inflammatory pathways is that these are not overexpressed or activated in inflammatory processes, or sorry, they're not overexpressed, they just signal through. There is just a signal that moves into a particular pathway in this case, let's say through IRF5. And so the reason to an increase of protein expression that you're slowing down or removing, which will make the cell react with producing some other protein. Anyway, the short answer is we haven't seen it. We don't expect to see it. We haven't seen it for any program so far.

Sudan Logonathan.:

Great. I appreciate that. And just if I can squeeze in a follow-up just in regards to the STAT6 program and the degradation. I think you've mentioned before obviously also achieving a pretty high level of STAT6degradation hopefully in human population as well in your trial. Between the different indications they're going after with STAT6 degradation, does the level of that degradation need to be exceeding 90% for all the indications or is it different between each one to get a clinical benefit specific to each type? For instance, with AD in the skin and blood, are there targets between the two different tissue types there when it comes to looking at the STAT6 degradation to form a clinical benefit?

Nello Mainolfi:

Yeah, it's a great question. I mean, I think that there is two answers. One, our goal of our Phase 1 study was to hopefully being able to achieve 90% plus in blood and skin. The reason for that is there are two, right? One, preclinically, we've shown in mice that if we get to 90% plus we have a dupi-like effect. The second reason is why do we want to have also the same target in skin is because we don't want to be left with the question of, well, what if we had more than 90% degradation in skin, what would the activity look like? That's why we would like to target a profile that has similar degradation in both blood and skin so that we maximize our probability of success. Second part of your question, which actually was Ellie's question that I don't think I answered, is what is the level of degradation needed for particular diseases for both STAT6six and we'll throw in IRF5 as well. I think that's why we're so keen on running at least for STAT6 for now imminently this Phase 2b dose ranging studies.

It's the ability to correlate a degradation profile with a clinical outcome that will allow us to select the right dose for Phase 3. Right now for STAT6, at least based on our preclinical data, we're going into the clinic with the expectation that 90% plus is the desired profile. But once we run a Phase 2b study where we'll be able to ask the questions of multiple doses, multiple degradation profile, we might learn that

less than 90 is sufficient. I don't know. We expect that more than 90 is needed, but that's why we run the dose ranging studies is really to establish those relationships.

Sudan Loganathan.:

Great. I appreciate the details here and thanks again for this detailed presentation today.

Nello Mainolfi:

Thank you.

Operator:

Your next question comes from the line of Vikram Purahit with Morgan Stanley. Please unmute and ask your question.

Vikram Purahit:

Great. Good morning. Can you hear me?

Nello Mainolfi:

Yeah, Vikram.

Vikram Purahit:

Thanks for taking the questions and for the presentation. We had a follow-up question on IRF5. I mean, you've alluded to how challenging this target has been through your prepared remarks and also through the responses to the last few questions. But we were wondering if you could speak in a bit more detail about prior competitive approaches that may have been attempted for IRF5 and where specifically these approaches may have faltered and how 579 has been engineered specifically to address some of the missteps that others in the space may have faced in the past. And I have a follow-up, but I'll save that for post your response.

Nello Mainolfi:

Okay. I think that's a great question. So the main challenge with IRF5, and actually I would say from a chemistry perspective, this has probably been the hardest program in the company. And the reason is identifying a highly specific IRF5 binder, or for others has been inhibitor is extremely difficult. There is a high sequence homology. Veronica showed you IRF3 and 7 versus 5. And we were, I would say, also lucky to find, thanks to the great team that we had, a molecule that is basically 100% specific to IRF5, does not bind to any IRFs. The other point is IRF brings this kind of complex activation.

And I think you have to really inhibit all type of IRF5s with the right type of biology, and with our drug we bind to basically degrade all types of IRF5s. And so it has been a really difficult target to drug. I think it's probably underappreciated how difficult it has been. And this is a highly... I think this program has a lot of focus on by I think the external immunology community because this will be the first time that we finally hit this target selectively and well.

Vikram Purahit:

Great. And then as a follow-up. On the development program, how broad of an initial development plan do you think you'll end up pursuing for a 579? Is it reasonable to expect something like 621, where you started with the two sentinel indications, excuse me, and then go from there? And relatedly, you

mentioned a mid-2028 runway. How far in development do you think you can get with 579 through to that time point? Thanks.

Nello Mainolfi:

All right. So, I'll answer high level. So first, I think it's a bit early for us to get into the actual development plan, but what I would say is that there is a plethora of opportunities where, I think there was an earlier comment from one your colleagues that was quite apt, which is this drug can actually really, really make a difference for many patients with these, let's call it rheumatological autoimmune inflammatory diseases. And so we believe that this is going to be also a relatively broad development program with more than one indication that will be prioritized. I think the runway, just to be clear, I think we've said first half of '28. You give us mid-28, I'll take it, if you also give us the money. But I think what we said... It's all good. What we said is that we plan to start Phase 1 early next year. We plan to complete Phase 1 within that year. So you can expect that we'll have some meaningful clinical data within this runway.

Vikram Purahit:

Very helpful. Thank you. Appreciate it.

Nello Mainolfi:

I see Eric ready.

Operator:

Your next question will come from the line of Eric Joseph with JP Morgan. Please unmute and ask your question.

Eric Joseph:

Thanks. Thanks for taking the questions. Just on IRF5, can you talk a little bit about the relative infection risk given the broader or more pan pro-inflammatory cytokine suppression profile here? To what extent are you able to model that preclinically, perhaps? And then in what sounds like lupus or SLE being one of the focal indications with this approach have you preclinically looked at the comparative efficacy of 579 versus some of the B-cell depleting or modulating approaches to the extent that this is also feasible to do it in mice models? Thanks.

Nello Mainolfi:

Great question. I'm going to let you guys answer on the infection risk. We have tons of answers. I don't want to give all the answers. Veronica, you want to go first, and then Jared, maybe you can speak to that and some other aspects of it.

Veronica Campbell:

Yeah. No, no, thanks for the question. We don't think that IRF5 will work like a broad immunosuppressant, right. And the reason for that is because it's really selectively expressed in very key immune cells. Those four that I listed is really where it's highly expressed. And not only that, but it's also specifically activated through certain stimuli. So I think that combination when we look into these certain autoimmune diseases will be an advantage, because we won't have this broad immunosuppression against all stimuli, really only the ones that are elevated in those autoimmune diseases that we're going after.

Nello Mainolfi:

And that may be the immune surveillance, you can talk about the other IRFs.

Veronica Campbell:

Right, exactly. So, we will be leaving, like we showed IRF3 and 7 intact, and those are really important for viral infections, right. Those are actually the transcription factors that drive high Type I Interferon response. So, by leaving those intact and blocking IRF5, we don't think we'll have anything as severe as, let's say, Saphnelo, anifrolumab. We probably would expect it to look less, because there you're blocking all Type I Interferon response. So that's just an example.

Jared Gollob:

And then Eric, I think your second question was around comparison to B-cell depleters. The data that Veronica showed so far, the comparisons have not been to the B-cell depleters per se, but we have looked at comparisons in those lupus models to deucra. Sotyktu, inhibition, and TLR7, 8 inhibition with afimetoran, alpha interferon receptor antibodies. We've been at least comparable, probably better actually, in our activity in those models compared to all those standards of care, even cyclophosphamide. And I think probably looking at B-cell depleters will be something that we can do in the future. I think it's important to recognize that IRF5 impacts multiple different components of inflammation. B-cell is one part of that inflammation, but there's also the dendritic cell component, there's also the T-cell component that is stimulated by macrophages and dendritic cells. So we would anticipate that we would have a broader effect and potentially could be even more active than the more selective B-cell depleters.

Nello Mainolfi:

And safer, I think. Yeah, I think also better tolerated.

Veronica Campbell:

And it's actually known that anti-CD20s, as an example, don't perform very well in these lupus models.

Eric Joseph:

Okay.

Nello Mainolfi:

Okay. Anything else Eric?

Eric Joseph:

No, no, no. I appreciate you taking the questions. Thanks for the updates.

Nello Mainolfi

Thank you.

Operator:

Your next question will come from Faisal Khurshid with Leerink. Please unmute and ask your question.

Faisal Khurshid:

Hey guys, good to see you. Thanks for taking the question. So we're still early in our few days of work, I think you said, Nello, to understand the target. But I saw that there is one other disclosed development program for IRF5 that's an allosteric modulator. Could you talk a little bit about how you see the potential benefits of a degrader approach over an allosteric modulator?

Nello Mainolfi:

Yeah. As I mentioned earlier, yeah, there are disclosed programs. We haven't seen any data, so I always don't comment on those because they're just a word on a slide. But I think the main really challenge has been can you do it selectively? And then can you block all the functions of IRF5, including all splicing variants, right veronica?

Veronica Campbell:

Mm-hmm.

Nello Mainolfi:

And I think it's really hard to do. I'm not going to say it's impossible to do. I'm going to say, we believe in our hands it's extremely hard to do with an inhibitor. Then you put on top of it the fact that with an inhibitor, if the need is to block IRF5 at high level continuously, obviously we made the case that degraders allow you to do once a day an oral drug with a low dose with inhibitor, to stay on top of that target 24/7 is going to be really difficult. But I think for this one, it's really the selective context independent inhibition is going to be hard, but we'll see.

Faisal Khurshid:

Got it. Great. Thank you for taking the question.

Nello Mainolfi:

Thanks Faisal.

Operator:

Your next question will come from Geoff Meacham with Citi. Please unmute your audio and ask your question.

Nishant Jadav:

Hey guys. This is Nishant on for Geoff. Thanks for the questions and really helpful presentation. So, first for IRF5. So there has been genetic links between certain IRF5 isoforms and lupus susceptibility. So, are there any concerns that 579 could exacerbate disease in some subset of patients, and whether you have designed this degrader to target specific isoforms to avoid this effect?

Nello Mainolfi:

Veronica, you want to take it? I think the second one was if we get all the isoforms.

Veronica Campbell:

Can we selectively target certain isoforms that are expressed in these variant patients? Yeah. That's really difficult to do because the isoforms are really cell specific expression, right? So that would be really hard to do. What we do know is that 579 can degrade all the different isoforms that are expressed, whether it's those that are caused by the variants or not, which might actually be important in these autoimmune diseases because there are also other mechanisms besides the variants that can turn IRF5 on. So we believe that really the best is to try and block all of the different isoforms for IRF5, but we have not seen any.

Nello Mainolfi:

Yeah. We want to get all isoforms because we want to get the broader population and also in our hands, already we know that there is biology that is disease relevant that has nothing to do with the splicing isoforms activation, right?

Veronica Campbell:

Right. Right.

Nello Mainolfi:

But it's a pathway activation. Next one. I'm trying to catch up.

Operator:

Your next question will come from Michael Schmidt with Guggenheim. Please unmute and ask your question.

Michael Schmidt:

Hey guys, good morning. I just wanted to come back to KT-621 and STAT6, especially heading to the June update coming up here very soon. How important will be interpretation of some of the PD marker analysis in this Phase 1 healthy volunteer study? Especially given that, as you mentioned earlier, the biomarkers in health is really very low at baseline. And also asking because there was a lot of variability, especially with TARC in some of the dupi studies. So how meaningful is interpretation of these biomarkers in the June dataset? And perhaps then following up on your upcoming Phase 1b study in patients. What are some of the things that you're trying to address in this study ahead of starting your randomized Phase 2 trial later this year? Are there any particular outcomes here or questions you're trying to answer in patients before starting a Phase 2? Thanks.

Nello Mainolfi:

Yeah. I was thinking about a rapid way to give you an answer on all the questions, which is we made the case from the beginning for this program that a STAT6 degrader should perform like the dupilumab. And so I would say the expectation across the studies is to perform like dupilumab. In the healthy volunteer study, obviously dupilumab didn't look at STAT6 degradation, but whatever they saw in biomarkers, you should expect from us.

In the 1b study, they did a nice 28-day study of both biomarkers and clinical endpoint. I would say we expect to see a dupi-like effect. That's probably the quickest way to answer this question. In addition to dupilumab, the beauty about working in protein degradation that if you're good, you can actually understand what's going on. You just don't look at some biomarkers after you dose a drug. But you can see, okay, what is the level of pathway blockade that I can achieve in blood and skin? And so we're going

to be able to look at degradation of STAT6 in blood and skin. Obviously safety is going to be paramount for this drug in this environment, in this landscape. But in terms of biomarkers, I would just say that we expect to have dupi-like because that's what we've seen all along in our preclinical study and we've been seeing for a while.

Michael Schmidt:

And maybe just a quick follow up. Can I ask a follow up? So, on dosing in particular, Dupixent is typically given at a high initial loading dose and then there's a lower maintenance dose. How do you think about that in context of the KT-621 dynamics? Is that something that you're evaluating too for the Phase 2 perhaps?

Nello Mainolfi:

Well, obviously I can't speak to the data. I just would go to preclinical data. With KT-621, we're able to achieve in preclinical models the full extent of the desired degradation in hours. And so based on the data, we've never built a loading dose model preclinically. We hope that will be the case in the clinic too.

Michael Schmidt:

Helpful, thank you.

Operator:

Your next question will come from the line of Yifan Zhu with Jefferies. Please unmute and ask your question.

Yifan Zhu:

Hi. This is Yifan from Jefferies for Kelly. Thank you for taking my question. Maybe another question on the STAT6 program. Could you please provide some additional color on the dose level used in the Phase 1b trial? Because this is a single arm trial, how does it compare to the highest dose tested in the healthy volunteer studies and how might it relate to the potential dose that you are going to use in the upcoming Phase 2b trials? Thank you.

Nello Mainolfi:

Yeah. Thank you, it's a great question. We can't really comment on the dose. I think what we've said is, we had a target in terms of degradation. And we believe that is an important target, which as we said, 90% plus in blood and skin. And that is the target that we'll like to explore in patients. But I'm not going to speak to the dose and the profile. I think once we share our healthy volunteer data, we can talk a bit about the profile, but then as we share the data from 1b, we'll talk about the dose as well likely.

Yifan Zhu:

Okay, thank you.

Operator:

Your next question will come from Andy Chen with Wolfe Research. Please unmute and ask your question.

Andy Chen:

Hey, thank you for taking the question. On IRF5, do you see this as a conceptual equivalent to a combo therapy including belimumab and anifrolumab, and perhaps also Humira? Is this a dual biologic or maybe triple biologic? So, in terms of the studies that you have done in vivo, do we have reasons to believe that it would act like a dual drug or even a triple drug? So, I noticed that in the mouse model you tested, you tested deucravacitinib and IFNAR separately, but can you combine them in mice and would you see better efficacy that way? Thank you.

Nello Mainolfi:

So, I'll take a quick and then maybe Jared and Veronica, you guys can add. So, I think that as we've said, the beauty about IRF5 is that you can actually, yes, you can imagine having a multi-asset combo in a single drug in a context specific manner, right. If you think about anti-TNF, or anti-23, or anti-interferon, these are antibodies that block those cytokines independently of what's going on in your body. This is why they work well, but they also have in some cases, they have some side effects because you probably don't want to remove all of your Type I Interferon consistently all the time. So, the beauty about IRF5, why it's a broad anti-inflammatory agent, but also well tolerated is because we only do it in those cell types in those disease contexts. Maybe Jared, do you want to comment about it from a medical clinical perspective, what would that mean?

Jared Gollob:

Yeah. No, I think the fact that we can have this broad effect that's context specific and then hopefully therefore have a safety profile that would be very favorable, should allow us even as a single agent to potentially have activities that are equivalent to combining multiple different drugs. I think with that being said, I think Nello earlier in his presentation, talked about how these various pathways that are in our pipeline are complementary, right? Whether it's TYK2, IRF5, now IRF5, IRAK4 and STAT6, one could think about combining these across certain diseases if there are potential synergies that could be obtained, especially if a drug like IRF5 ends up being safe and well tolerated, that really opens up the optionality, especially as an oral drug for combining several different oral drugs from within our pipeline, or combining our oral drug with other standard of care agents that are out there. But again, I think our expectation based on the data that Veronica showed in the preclinical models, is that we should have substantial activity even as a single agent. So, it's not as though we're obligated to combine it, but we certainly have that optionality.

Nello Mainolfi:

Great. I think we've-

Bruce Jacobs:

Operator, we're a smidge over time. Maybe one last question and then we'll wrap up. Thanks Andy.

Nello Mainolfi:

Thanks Andy.

Operator:

Your last question will come from Kalpit Patel with B. Riley. Please unmute and ask your question.

Kalpit Patel:

Yeah. Hey, good morning and thanks for squeezing me in here. Nello, I just had one question on the degradation kinetics that you may show here with the STAT6 degrader in patients by the year-end. For the IRAK4 program previously in that paper that was published, there was a rebound of the protein between day 14 to day 28, which you attributed to the variability and the method used, the testing method used and the storage conditions. So, I guess going forward, what steps are you taking to ensure that the kinetics will more accurately reflect the true target knockdown rather than any measurement or sampling high and low issues?

Nello Mainolfi:

Yeah, thanks for the question. Just to make sure we're all on the same page. So, with IRAK4, what we've shown is, and the healthy volunteer studies, we were able to show robust degradation using mass spec technology that would follow from obviously day one to day 14. When you go into this broader study, in the patient study, it's really hard to use mass spec because the isolation procedure, it's difficult to use in multiple sites that you're using. So, we ended up using flow. And in flow what happens is, unfortunately that in some cases the sample can deteriorate, and so it makes it more difficult to measure the effect of the degrader with time. And so what we have planned for obviously the existing study of 621 and the Phase 1b studies, that we'll have several opportunities to ensure that we can measure protein levels well. And I think I can't speak because I will speak about the data as well, but I think once we share the healthy volunteer data, it might be easier for me to comment more on your question.

Kalpit Patel:

Okay. Thanks very much for taking our question.

Operator:

There are no more questions at this time. I'd now like to turn the call over to Nello Mainolfi for closing remarks.

Nello Mainolfi:

Thank you. First, I wanted to thank everybody for attending our call. I want to thank the team at Kymera for putting together a great story today. Obviously, we have a lot more opportunities ahead of us to engage further on some exciting milestones that we're reaching soon. In the meanwhile, if you have further questions, you know where to find us. We want to make sure that the richness of the data we shared today can be appreciated to its fullest. So again, thank you everybody for attending. The slides are on our website so you can review it in your own time. And we'll see you actually soon.