Kymera Therapeutics Fourth Quarter 2025 Results Call | February 26, 2026

Operator:

Good day everyone. My name is Kahealani, and I will be your conference operator today. At this time, I would like to welcome you to the Kymera Therapeutics Fourth Quarter 2025 Results Call. All lines have been placed on mute to prevent any background noise. After the speaker's remarks, there will be a question-and-answer session. If you would like to ask a question during this time and if you have joined via the webinar, please use the raise hand icon, which can be found at the bottom of your webinar application. If you have joined by phone, please dial star nine on your keypad to raise your hand. At this time, I would like to turn the call over to Justine Koenigsberg, Vice President of Investor Relations.

Justine Koenigsberg:

Good morning, and welcome to Kymera Therapeutics' quarterly update conference call.

Joining me today are Nello Mainolfi, our Founder, President and Chief Executive Officer; Jared Gollob, our Chief Medical Officer; and Bruce Jacobs, our Chief Financial Officer.

Following our prepared remarks, we will open the call for questions from our publishing analysts. Please use the raise hand icon to indicate you'd like to ask a question, and we ask that you limit your question to one and a brief follow up so we can accommodate everyone.

Before we begin, I'd like to remind you that today's discussion will include forward-looking statements subject to risks and uncertainties described in our most recent Form 10-K filed with the SEC. Please note that any forward-looking statements speak only as of today's date. With that, I'll now turn the call over to Nello.

Nello Mainolfi:

Thank you, Justine, and thank you everybody for joining us this morning.

As this is our year end 2025 call, I wanted to spend a few minutes recapping what was an incredible year for Kymera. Those of you that know us well appreciate the fact that we are always forward-looking, highly focused on what's in front of us. And the bulk of the call will feature just that. But given how important our 2025 accomplishments were, I am hoping that a quick reflection on the year will provide some context for the foundation we have set for 2026 and beyond.

Before we start, I would like to mention that this year we will celebrate our 10th year anniversary since Kymera's founding in May of 2016. Over the past decade, we have executed on our strategy and have built the capabilities, the platform, and the team to deliver on our goal to develop the next generation

of breakthrough immunology medicines. We have accomplished so much in our short history but arguably 2025 was truly a breakout year.

I'll start with the significant progress in our first- and best-in-class STAT6 degrader program. We shared outstanding results from both our Phase 1 healthy volunteer study and our Phase 1b study in AD patients. In the healthy volunteer study, KT-621 demonstrated robust STAT6 degradation with excellent safety and tolerability. That was followed by highly encouraging impact on efficacy endpoints in Phase 1b that supports our view that KT-621 has the potential to deliver robust efficacy, in line with pathway biologics, with the convenience of oral, daily dosing.

On the strength of those two studies, we launched our first Phase 2b study in atopic dermatitis patients last Fall and started the asthma Phase 2b early this year. Jared will talk more about our KT-621 clinical development plans, but both studies are benefiting from the awareness of, and appreciation for, the data we have recently shared, as well as from clear enthusiasm from clinicians and patients around promising oral options.

We were busy advancing the rest of our pipeline as well. In May, we unveiled our first-in-class IRF5 program, supported by a compelling preclinical profile, and validating human genetics. Last year we completed IND-enabling studies, and we're excited to announce this morning that, after IND clearance from the FDA, we recently initiated dosing in the Phase 1 Healthy Volunteer study with KT-579.

Finally, we are building on the success of our internal pipeline by advancing our existing collaboration with Sanofi around IRAK4, and by signing a new partnership last year with Gilead, around our first-in-class CDK2 molecular glue program. Bruce will provide an update later in the call on the potential upcoming collaboration milestones which would be incremental to our financial position.

Speaking of finances, in 2025 we raised almost $1 billion, bringing our year end cash balance to $1.6 billion. We believe that this amount of capital, which extends our runway into 2029, will enable us to execute on our broad development plans that are designed to realize the full potential of our wholly owned programs, while maintaining the productivity of our discovery engine which we expect will expand our innovative pipeline.

Now, with 2025 behind us, our focus is squarely on 2026 and beyond and the multiple milestones we plan to achieve.

For KT-621, we expect to complete enrollment in the AD study this year and share data by mid-2027. The first patient was dosed in the asthma trial last month and we expect to share that data in late 2027. In the meanwhile, we are planning to report scientific publications and presentations to continue to build awareness of this exciting program.

This is an important year for KT-579, our lead IRF5 degrader. We expect to complete the recently started Phase 1 Healthy Volunteer study and share the data later this year. And the next step will be to advance the program into a patient proof of concept study, which we expect to be in lupus, soon after that.

Our partner Sanofi is expected to start the healthy volunteer Phase 1 trial with KT-485 this year and we also hope to be able to advance our CDK2 program in partnership with Gilead into further development.

Finally, our goal continues to be to announce at least one new program annually, and we are targeting the second half of this year to share our new development candidate program.

We clearly have a busy 2026 planned, which makes me particularly happy to announce the most recent addition to Kymera's leadership team, Neil Graham, who joined us as Kymera's Chief Development Officer. Neil is a seasoned life sciences executive with more than 30 years' experience in global drug development in both early and late-stage clinical trials across a wide therapeutic spectrum including dermatology, allergy, rheumatology, virology and pulmonology. Neil has led several groundbreaking programs including the development of dupilumab at Regeneron. We're thrilled to have him join our team as we enter the next phase of our growth and look forward to his contributions as we continue our efforts to build a fully integrated commercial company.

Now, before I turn the call over to Jared, I wanted to spend the remainder of my remarks speaking in more details of the unprecedented market opportunity of our STAT6 program.

I can't overstate the opportunity we have to significantly increase the number of patients who are treated effectively. We hear overwhelmingly from both physicians and patients that current advanced therapies, including biologics, just aren't sufficient. There is palpable excitement for the potential of a simple and convenient oral therapy for Type 2 diseases that doesn't compromise on safety or efficacy.

We have cited these numbers in the past. We believe that there are about 140 million diagnosed Type 2 patients in the U.S., five major EU countries and Japan. Of this total, about 50 million patients are estimated to be in the moderate-to-severe category. Yet despite this significant need, only an estimated 2 million patients are treated with advanced systemic therapies, mostly biologics and overwhelmingly with dupilumab.

So, the question is why are so many patients not treated with advanced systemic therapies?

That gap is clearly not due to lack of need, but it reflects barriers built into the current treatment paradigm.

There are many patients who rely on local therapies, most often topicals or inhalers, depending on the diseases. However, most of these treatments do not address the underlying drivers of Type 2 diseases and, as a result, do not deliver adequate treatment for many moderate-to-severe patients.

There are existing oral systemic therapies, in both asthma and AD, for example but those can be limited by efficacy and, certainly, for example, in the case of JAKs, safety concerns including box warnings and the requirement for blood monitoring at initiation and/or during treatment.

Finally, injectable biologics have delivered important advances and now account for the majority of systemic therapy use – actually more than 75%. However, they are associated with significant treatment burden: injection-site pain, needle fatigue, burdensome loading regimens - often four to five injections in the first month — cold-chain storage requirements, and ultimately with high drop-off rates over time.

So, when we ask why so many moderate-to-severe patients remain untreated with advanced therapies, the answer lies in the limitations in efficacy for some, safety concerns for others, and very real convenience and access hurdles built into the system. The consequence is that millions of patients who

would benefit from more effective therapy remain undertreated, cycling through suboptimal options and living with inadequately controlled disease. This is the unmet need, and this is the opportunity in front of us.

Going from patients' numbers and unmet needs to market opportunity, the gap is even larger.

As previously mentioned, about 2 million patients are currently receiving advanced systemic therapies for Type 2 diseases. This segment represents an annual market value of about $20 billion, with dupilumab serving as the predominant drug. Although this is already a significant figure, the broader market opportunity is much larger given that there are tens of millions of patients that are not reached by current approved drugs. In fact, I would characterize the current Type 2 market as very early in its development.

Historically, the introduction of new products and mechanisms has expanded immunology markets by enabling access to additional patient populations. In addition, an oral therapy that overcomes many limitations associated with existing treatments, while maintaining safety and efficacy, could, for the first time, provide a viable alternative for millions of patients across all age groups.

It's reasonable to assume, in my opinion, that the current market for Type 2 diseases is positioned for substantial expansion well beyond the current $20 Billion.

In fact, a comparable example can be found in the psoriasis market, which has experienced a five-fold growth over the past decade mostly thanks to new drugs and oral therapies.

I think this all comes well together when we consider the limitations of existing therapies and what KT-621 has to offer.

A drug that has the potential to deliver biologics-like efficacy and safety, without requiring patients to compromise efficacy and safety for convenience, a drug that has the potential to change the way patients are treated around the world.

How will it do so?

In two important ways: One. Expand the existing treated patient population, which for us is the number one goal. Second. Provide an easy and convenient alternative to patients currently on injectable biologics, many of whom, based on our market analysis and industry survey data, are eagerly waiting to switch to an oral therapy.

So, then, how might this paradigm shift look and what would it mean for patients with Type 2 diseases? Our goal, and the cornerstone of our development plan, is to position KT-621 as the product of choice, for this large, underserved or inadequately served patient population. In many inflammatory diseases, advanced systemic treatments are typically reserved for patients who fail conventional therapies, which in turn are typically biologics. We believe having an effective, safe, oral medicine we can fundamentally change the treatment paradigm, making it practical to intervene earlier in the disease course rather than waiting for significant progression or treatment failure.

If successful, we believe KT-621 has the potential to shift advanced therapy from being a last resort for a small subset of patients to a mainstream option for millions. and improve standard of care.

I hope that context around the market opportunity makes it clear why we believe that KT-621 has the potential to be one of the biggest programs in the biotechnology and pharma industry.

With that context, let's turn the call over to Jared and discuss clinical progress with KT-621 and KT-579, our IRF5 degrader.

Jared?

Jared Gollob:

Thanks, Nello.

As you've heard, we're building significant momentum across our pipeline driven by the strong scientific, clinical and operational foundation that we've established.

This morning, I'll discuss our ongoing KT-621 Phase 2b trials in atopic dermatitis and asthma. I'll then provide additional context on our clinical development strategy for KT-579, our oral IRF5 degrader.

I'll begin with KT-621, our oral STAT6 degrader.

In December, as many of you are aware, we released the BROADEN Phase 1b results, providing the first look at KT-621's impact on patients with atopic dermatitis. The data demonstrated a dupilumab-like profile that strongly supports continued development of KT-621 in both AD and asthma.

Across all of the study's objectives, we exceeded expectations. We demonstrated strong fidelity of translation from healthy volunteers to patients with deep STAT6 degradation in blood and skin. We observed a significant reduction in Type 2 biomarkers across blood and skin lesions, including TARC and Eotaxin-3, and importantly also in lungs as measured using fractional exhaled nitric oxide, or FeNO, testing. The greatest impact on FeNO was observed in AD patients with comorbid asthma who had the highest baseline FeNO levels.

We also achieved robust improvements across all key AD clinical endpoints, including EASI, pruritus NRS, IGA, SCORAD and patient-reported outcomes, or PROs, addressing disease severity and quality of life. For all of these endpoints, KT-621 data were in line with or numerically exceeded published data for dupilumab at 4 weeks, further highlighting the exciting potential patient impact. In addition to these effects on AD, KT-621 had a clinically meaningful impact on patient reported outcomes measuring disease control in patients with comorbid asthma as well as on symptoms and quality of life in patients with comorbid allergic rhinitis. And importantly, KT-621 was well tolerated with a favorable safety profile. I should also note that we recently completed the six to nine-month GLP toxicology studies in rat and NHP and, consistent with earlier KT-621 tox studies, we did not observe any adverse findings of any type across all doses and concentrations tested.

We now have two parallel Phase 2b dose-ranging, placebo-controlled trials underway in AD and asthma supported by the positive biomarker and clinical endpoint results in both AD and comorbid asthma from BROADEN.

The BROADEN2 trial in approximately 200 adult and adolescent patients with moderate to severe atopic dermatitis has a primary endpoint of percent change from baseline in EASI at 16 weeks. The study continues to progress as planned with completion of enrollment expected by the end of 2026 and announcement of top-line results by mid-2027. We will update you all on enrollment later in the year, but we can say now that we are confident in achieving this timeline based on the strong interest from patients and clinicians in a safe and effective oral therapy, and given the high level of awareness of, and appreciation for, the KT-621 data we have generated.

Moving on to asthma, just last month we announced that we had dosed the first patient in our Phase 2b BREADTH trial in approximately 264 adult patients with moderate-to-severe eosinophilic asthma. The trial's primary endpoint is change from baseline in pre-bronchodilator FEV1 at 12 weeks. Using pre-bronchodilator FEV1 will allow us to separate effects across dose levels in a smaller, faster study and will inform dose selection and probability of success for subsequent Phase 3 trials. Data from this trial are expected in late 2027.

Taken together, we expect to generate data in close to 500 patients next year from both KT-621 Phase 2b studies while also continuing to build our safety database with long-term treatment in AD patients rolling onto the 52-week open label extension portion of BROADEN2. Importantly, these trials are designed to support parallel Phase 3 development beyond atopic dermatitis and asthma in other Type 2 dermatologic, respiratory and gastrointestinal diseases as part of the overarching regulatory strategy for KT-621.

Turning now to our novel IRF5 degrader program. We view IRF5 as an exciting new opportunity to address complex autoimmune diseases. We continue to receive positive feedback from KOLs and investigators on the potential of KT-579 to offer an effective oral treatment for diseases such as lupus, IBD and RA. This past fall we presented additional compelling KT-579 data in lupus and RA preclinical models at the American College of Rheumatology meeting in Chicago.

Chronic, heterogeneous inflammatory conditions like lupus, RA, IBD and others are driven by broad immune dysregulation across multiple inflammatory pathways, including Type I interferons, proinflammatory cytokines and B cell-derived autoantibodies. While biologics have clinically validated each of these pathways individually, the current treatment paradigm has been constrained by the reliance on injectable therapies optimized for narrow segments of disease biology and therefore incapable of addressing the full complexity of the inflammation underlying the various disease manifestations. As a result, many patients experience incomplete responses or loss of efficacy over time. An oral medicine capable of modulating multiple disease-defining immune pathways simultaneously could enable more effective and durable disease control and potentially expand access to treatment across broader patient populations.

IRF5 is a genetically validated transcription factor that functions as a central amplifier of immune responses. In autoimmune diseases where there is strong genetic association with IRF5, persistent IRF5-mediated immune activation drives skewed inflammatory signaling across Type I IFN, proinflammatory cytokine and autoantibody pathways. KT-579 is designed to selectively degrade IRF5, enabling modulation of these interconnected inflammatory pathways through targeting of a single master regulator with the goal of rebalancing the immune system while avoiding the infectious adverse events

caused by broad immunosuppression. We are encouraged by the strong genetic rationale, our compelling preclinical efficacy and safety data, and the potential to deliver a novel oral therapy across multiple serious autoimmune diseases with significant unmet medical need.

With that said, we are now focused on advancing KT-579 in our ongoing Phase 1 healthy volunteer trial and reporting the first in human data in the second half of 2026.

In terms of the Phase 1 specifics, the study is designed to evaluate both single- and multiple-ascending doses of KT-579 administered orally once daily compared with placebo. The primary aim of this SAD/MAD study is to demonstrate robust degradation of IRF5 in blood, which we define as a reduction of approximately 90% or greater, at dose levels that are safe and well tolerated.

Because the IRF5 pathway is not activated in healthy volunteers, we plan to use whole blood *ex vivo* stimulation assays to assess the functional impact of IRF5 degradation on the induction of Type I interferons, proinflammatory cytokines and inflammatory pathway gene transcripts by TLR 7, 8 and 9 agonists. It's our expectation that we should see a 50-80% reduction in these biomarkers across the three TLR pathways assessed if we're engaging IRF5 effectively, which would increase the probability of IRF5 degradation translating into clinical activity in subsequent patient studies with KT-579.

As we did with our STAT6 program, we also expect to conduct a Phase 1b patient study and intend to share more details on the design and patient population later. We have said, however, that we would expect to focus this study on lupus patients, which we believe is the right patient population for our first proof-of-concept study given the strong genetic association of IRF5 with lupus and the robust activity of KT-579 across multiple mouse models of lupus.

I'll now turn the call over to Bruce for a review of the fourth quarter results. Bruce?

Bruce Jacobs:

Thanks, Jared.

As I walk through the fourth quarter results, please reference the tables found in today's press release, which was filed this morning.

Collaboration revenue in the fourth quarter of 2025 of $2.9 million is attributable to our Gilead partnership.

More broadly with respect to Gilead, we received an upfront payment of $40 million upon signing the licensing and option agreement last year. Under this agreement, we are eligible for up to $750 million in total milestone payments, including a $45 million payment payable, if and when, Gilead exercises its option on the CDK2 program at the declaration of a mutually agreed-upon development candidate.

In addition, Sanofi is advancing KT-485, our oral IRAK4 degrader, with plans to initiate Phase 1 testing this year. We expect to share additional updates on this program in the coming months, including the receipt of a milestone upon dosing of the first healthy volunteer. As a reminder, under the structure of the Sanofi agreement, we have the potential to realize nearly $1 billion in total milestones.

While these potential milestones are not reflected in our current cash guidance and are not expected to materially impact our runway, they remain important validation points and support the continued advancement of these partnered programs and the downstream value we can realize. We look forward to sharing further progress as these programs move forward.

With respect to operating expenses, R&D for the quarter was $83.8 million. Of that, approximately $7.6 million represented noncash stock-based compensation. The adjusted cash R&D spend of $76.2 million, which excludes that stock-based comp, reflects a 16% increase from the comparable amount in the third quarter of 2025.

On the G&A side, our spending for the quarter was $16.9 million dollars, of which $6.9 million was noncash stock-based comp. The adjusted cash G&A spend of $10 million, again, excluding that stock-based comp, reflects a 1% increase from the comparable amount in the third quarter of 2025.

And finally, we are well capitalized to execute on our goals. As Nello mentioned previously, we ended December with a cash balance of $1.6 billion, providing a runway into 2029. This allows us to complete both KT-621 Phase 2b trials in AD and asthma, and to fund a large part of the first Phase 3 trial for KT-621. The runway also will allow us to advance KT-579 through initial POC testing, and to progress our research pipeline as we scale and grow Kymera.

With that, we'll pause while we regroup in our conference room and assemble the queue for your questions. Thank you.

Moderator:

Thank you. At this time, if you'd 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 join by phone, please dial star-nine on your keypad to raise your hand. When it is your turn, you'll receive a message on your screen inviting you to join as a panelist. Please accept and wait until you're 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'll now pause a moment to assemble the queue.

Your first question comes from the line of Marc from TD Cowen. Please unmute your line to ask your question.

Marc Frahm:

Hi guys, thanks for taking my question, and congrats on all the progress. Maybe a high-level one for Nello. Since your Phase 1 data came out with the STAT6, a handful of other early mid-stage programs in AD have also read out data and there were some data even ahead of yours, so over the past year, there's just a lot going on in AD. What's your vision for what the treatment of AD looks like and how these therapies all fit together when you roll the clock forward a few years? And then maybe if I can sneak a little bit in for Jared, also just for IRF5, can you just remind us what really can be learned in the healthy volunteer portion of that trial beyond target engagement and safety? Or do we really to learn more, have to wait for that lupus cohort to enroll?

Nello:

Thanks, Marc. Great question. So, I'll start with the first one. So just to remind you, as we share today, hopefully even more clearly than before, the AD, I would say the type 2 diseases market is still very early. Again, there is, if you look at moderate-to-severe patients, there is about 40 to 50 million patients in the seven major market, and only about two have been those with advanced systemic therapy. So clearly there is a need of more therapies, and as we mentioned and others have done, so we mentioned if you parallel AD to psoriasis, psoriasis market in the past 10 years has grown fivefold. Maybe AD somewhere around where psoriasis was five, 10 years ago. So, we expect this market to increase dramatically, and you can only do that by bringing new therapies to the market.

First, I want to start by saying that this is obviously not a non-zero sum game, right? I think there is a need of new therapies and new therapies would benefit patients first, but also, actually, companies that develop all the other therapies. I mean for two simple reasons. We need, especially from our viewpoint, patients need convenient oral options that can increase the probability of patients with moderate to severe disease to access effective therapies. And so, I think that that will transform how these diseases are treated.

With our mechanism, with STAT6, I think the main difference that I could point to without going company by company, which will take us half a day, is that we're targeting an intracellular target of the most validated pathway in Th2 inflammation, which is IL-4 and 13. So we're going after well-validated efficacy and safety, we're going after well-defined patient population, and so I think we have a level of de-risking that I would point to being, I think, superior to many other agents that are still interesting and exciting that are out there.

So, I think we need more therapy, I think it's great that there are more drugs, and obviously we need to move into late- stage development to really assess for our drug and many others what is the risk benefit that we can bring to patients.

Jared, do you want to take the IRF5?

Jared:

Sure. Yeah, Marc, regarding IRF5, as you mentioned, the primary clinical objective is safety and then our primary translational objective is to show 90% or greater IRF5 knockdown in blood. And showing that knockdown is going to be important, we think, from a de-risking standpoint for the subsequent patient studies because of the strong genetic association between IRF5 and lupus and the strong preclinical activity in multiple lupus models that we've seen with that degree of IRF5 knockdown.

Now, with that being said, yes, it's true that unlike STAT6, where we have circulating biomarkers like TARC and eotaxin-3 that were useful for us to assess that sort of translation in healthies with regard to IL-4, IL-13 pathway, here, for IRF5, while we don't have those circulating biomarkers, as we mentioned, we have these ex vivo stimulation assays, which I think will provide very important functional information around IRF5 degradation. You know, these assays are looking at stimulation of toll-like receptor 7, 8, and 9, which are the three toll-like receptors driving type-I interferon, pro-inflammatory

cytokine, and B-cell autoantibody production. And to be able to show an impact across those three pathways with ex vivo stim would, we believe, significantly de-risk our probability of success in subsequent patient studies, including the lupus studies.

Nello:

Maybe just to add a quick thing on top of Jared's, like if I think a bit more from my point of view, maybe higher, more simple level, which hopefully is still scientifically sound, we know that the strength of this program is the genetic association, right? There is very few programs in the history of drug development that have the strength and the depth of genetics that we have with IRF5, and that's why it's one of the most interesting programs in immunology, I think, in the next five to 10 years. But when you have genetic association, you try to figure out, "Okay, biologically what does that mean?" So, we've shown preclinically, actually, IRF5 activation leads to, as Jared said, activation of this pro-inflammatory cytokine, type-I interferon, and B-cell activation, autoantibody activation. So even in active volunteers, we can prove, even ex vivo, that we can block these three axes of inflammation, I think it's going to tell us that you combine that with the genetics, that it should work into patients.

Moderator:

Your next question comes from the line of Geoff Meacham with Citi. Geoff, you'll need to unmute to ask a question.

Geoff Meacham:

All right. Hey, guys. Can you hear me?

Nello:

Yeah.

Geoff Meacham:

Okay, awesome. So just had a couple. Thanks for the question, first of all. So on 621, the BROADEN2 and BREADTH studies are probably matured next year. We're used to seeing you guys have Phase 1 biomarker data and maybe a lot of data points along the way. For these Phase 2bs, is it going to be, let's just wait until the full and final or are you guys planning on having any kind of biomarker or interim analysis or anything like that for these two studies?

And then for the IRF5, interesting program for sure. The indications you guys have talked about include some that are very much unmet need, lupus, Sjogren's in particular, and definitely not as crowded. I'm curious how that informs your priorities when you think about development for this program. Thank you.

Nello:

Yeah. Thanks, Geoff. So, on the first one, obviously we'd love to get data along the way and understand what's going on in the Phase 2b studies, but obviously these are important study that are placebo-controlled, and to protect integrity of the study. We're going to wait until the end of the study to unblind and obviously share the data.

For IRF-5. Yes. So, I think I go back to the reasons to believe, and as I say, human genetics, lupus, Sjogren's, myositis, RA, IBD, those are areas that we believe this target is extremely relevant. And so we're letting that, combined with the preclinical data, guide us.

So, the reason why we've talked often about some of those indications is because they match so well both the genetics, the preclinical data, the unmet need. I mean, if you look at the ones you mentioned, lupus, Sjogren's, these are diseases that don't have effective therapies that are approved, or at least some, they don't have. Maybe I should say, at least oral effective therapies that are approved, which will serve a much broader population than what's being evaluated now in clinical development that I believe are really probably going to be positioned for really late-stage patients.

I think another important axis of our development plan will be outside of, let's call it these interferon-related pathways or pathologies, which could be, again, IBD, could potentially be a way down the road. And I think we plan to share more data on IBD, which is increasingly becoming an area of focus for this program, at least preclinically. And we hope for it to be clinically as well in the not-so-distant future.

Geoff Meacham:

Awesome. Thank you.

Nello:

Thank you.

Moderator:

Your next question comes from Charles Ndiaye with Stifel.

Charles Ndiaye:

Sorry, I was on mute. Congrats on the quarter. One question from our side. I guess as you think about starting Phase 2s for 621 outside of asthma or AD, what are some of the gating factors?

Nello:

Yeah. So, as we've outlined in the past, I believe it's still on our corporate deck, there's a new one today on our website, our strategy is to use the ongoing dose-ranging Phase 2b study, the one in AD to support late development in all the other derm indication. The one in asthma is to support late development in the other respiratory indications.

So, we actually do not plan to start any new Phase 2 studies. The new studies that you'll see us starting will be, we believe, all registrational studies.

Now obviously some of these still has to be vetted with the right authorities, but that's our current strategy, and we believe this is the strategy that is being proven to be successful with other drugs in this pathway. So it wouldn't be the first time that this is adopted.

Charles Ndiaye:

Thank you.

Nello:

Thank you.

Moderator:

Your next question comes from Brad Canino. Please unmute to ask your question.

Brad Canino:

Okay. Good morning.

Question from me on the trigger to start the KT-621 Phase 3s. So, to initiate, how far into the Phase 2s do you need to reach, and what needs to be collected from those studies? And will this be one study start or multiple at once? Thanks.

Nello:

Yeah. Thanks, Brad.

So, unlike what we may be getting everybody used to that we start a study while the previous one was still ongoing, as we've done for the healthy and the Phase 1b. For starting a Phase 3 study, we need to complete Phase 2. We need to have an FDA meeting post-Phase 2, and then we can start Phase 3.

I assure you that we will do our best, as we always had, to do that as quickly as possible. But obviously, there are some things that we must do in order to move into Phase 3.

With regards to how many, as you know, at least the paradigm that companies have adopted in the past 10 years for, let's say atopic dermatitis registration, has been three Phase 3 studies. There are two placebo control, mostly placebo control studies, and then one on top of topical corticosteroid.

So, if that will continue to be the paradigm, which is something obviously we will explore given the recent news from FDA, but let's say that continues to be the paradigm, you should expect us to start all studies as much in parallel as possible.

Moderator:

The next question comes from-

Nello:

Right, yeah, once we select.

Moderator:

Great. The next question comes from Ellie Merle with Barclays.

Nello:

Go ahead.

Ellie Merle:

Hey, guys. Congrats on all the progress.

In terms of 621, if you could talk about both the clinical and preclinical data that you've seen, where do you see the most potential room for efficacy improvements over dupilumab?

And can you talk about some of the respiratory preclinical model data and compare that to what's been seen preclinically in atopic dermatitis? Thanks.

Nello:

Yeah. Thanks, Ellie. You often ask the tricky question.

So, we want to make sure we maintain our credibility when we compare a drug that has been so successful in millions of patients with the drug that has been, so far, in about a couple of hundred patients or subject and up to 28 days. So, I'm always thoughtful about how we make comparisons.

What I can say is that in our preclinical models, if you look at the asthma models that we've both published, KT-621 has performed always at least as well, and in many cases better than dupilumab. We don't know whether that is a result of the model or it's actually real biological differences or drug distribution differences. And that's why we're really excited that we're in Phase 2 studies so we can assess the full clinical activity of our drug in a large study with hundreds of patients.

With regards to AD, the preclinical AD models are not very robust. We like to talk about the asthma model because it's a highly translatable model. The AD preclinical models, you have this local activation with a pathway activator that it's not really, in many cases, a type 2 discrete pathway activator so we also show really robust activity. But to be honest, as a scientist myself, I don't like to talk about preclinical AD models that are mostly useless.

But if we look at the clinical data, obviously you've seen the data from last December, we have shown really robust activity. I start from biomarkers. I look at what we've shown even with biomarkers that were either not shown to change much with dupilumab like IL-31 or the ones that we showed comparable, if not superior Eotaxin, even FeNO. And then you look at all the clinical endpoint that we've measured, we've been consistently at least as good as the injectable biologics.

So again, it's hard for me to say will be equal, slightly inferior, slightly better, but I think we delivered that ballpark scenario that we talked about from last year. And so for us to really know how it looks, we

need to wait for the Phase 2 studies. And to be honest, the only other thing to keep in mind is you can never compare drugs unless you run a head-to-head study.

But our goal, again, is to deliver an oral drug with biologics-like activity, with great safety and the convenience of being an oral pill that one can take once a day, stop and start whenever they want. I think that will transform the treatment paradigm for type 2 diseases, well beyond whether the drug is exactly like dupilumab, slightly less or slightly better. I don't think that will matter if we can deliver the type of drug with the profile that we speak about.

Ellie Merle:

Great. Thanks so much.

Nello:

Thank you.

Moderator:

Your next question comes from Anna Li with Truist.

Anna Li:

Hi. This is Anna on for Kripa.

One quick question on 621. I was just wondering if you could give us kind of an overview on how you're thinking about compliance or seeing it in the Phase 2b trials right now and how the durability of 621 kind of ties into that. Thank you so much.

Nello:

Cool. So that's a great question.

So, when compliance, you mean patient taking the drug? That's what you mean or... Yeah.

So, I think that's obviously, it's a very important point, because when you're on a clinical trial or on injectable biologics, you can actually ensure 100% adherence, right? Because patients often, in most cases, actually go on site to receive the injection.

The beauty of oral drugs, actually you give patients freedom, right? That's the beauty of oral drugs, and that obviously plays a role into clinical studies. So, we have measures that probably go even beyond what has been done generally to make sure that we understand a patient's adherence well. So, we are confident that the adherence of patients will be the one that will allow us to have a great integrity of our study.

I will also add that the beauty about protein degraders, unlike small molecule inhibitors, if you miss a small molecule inhibitor dose, you actually lose all your activity. If you miss one dose of KT-621, this is not an advertisement to not take the dose every day, but I will say if you miss a dose of KT-621, if you

miss one dose, you will not lose any of pathway degradation. So, we have that additional layer of, let's call it protection, against any challenges that might come with humans forgetting one dose during a study or during normal life.

Anna Li:

Thank you so much.

Moderator:

Your next question comes from Judah Frommer with Morgan Stanley.

Judah Frommer:

Hey, guys. Thanks for taking the question. Congrats on the progress.

Just on IRF5, I think we're clear on how you think about that's it's degradation versus inhibition. Same question for IRF5. I think we'll get a little bit of preclinical data from an inhibitor next month.

And then just on the targeted nature of your degrader, any risk of kind of pan-IRF inhibition? I think IRF8 has been a question in degrading IRF5 previously. Thanks.

Nello:

Yeah, maybe I'll start with that. I'll pass it to Jared to speak, even maybe it's an opportunity to talk about how we think about the safety of IRF5. But maybe I'll talk more about the chemistry of it, given that I'm technically still a chemist.

So, the beauty about this target and the challenges with this target is that it's extremely hard to find a molecule that binds to IRF5 only without binding to all the other IRF. You mentioned a few, I think there is 11 or 12, but sometimes I lose count, but there is more than 10 IRFs. So, we need to bind only to IRF5, and there are different, I like to call them splicing variants, people call them differently. There are different IRF5 splicing variants. They all need to be targeted. So, you need to be consistent across the IRF5 family, but do not bind to any other IRF. So, we've been able to do that. Our selectivity is pristine because we've been able to find this molecule that is actually not function so it does not inhibit anything. It only binds to IRF5, all the IRF5s splicing variants, but not other IRFs, and this allows us to give the utmost selectivity. So, we're not worried about any of those things.

But Jared, do you want to speak about why we think 5 only is potentially really interesting?

Jared:

Yeah, think IRF5 because it is one of multiple different IRFs, there is a certain redundancy there when it comes to the role of IRFs in innate immunity. So even getting rid of IRF5 really does not impact overall innate or adaptive immunity.

It's also true that IRF5, its expression is very restricted, essentially to certain immune cell subtypes, like B cells and dendritic cells and monocytes and macrophages. So, it's not ubiquitously expressed, which is another reason why one can knock it down and do so safely.

And its activation is also very context-specific. So here in the context of pathologic inflammation, and that's where you're going to see activation, but you're going to see activation in restricted cell types. And that's the reason why you can really degrade IRF5 strongly and chronically and not get broad immunosuppression and not have infectious adverse events.

And, in fact, if you look at mouse knockouts for IRF5, you don't see any susceptibility to infections or any phenotype. And in our preclinical animal tox studies, including our four-week GLP tox studies and non-human primates as well as in rats, we don't see any adverse events, adverse findings, and we don't see any susceptibility to infection.

So, for all those reasons, we believe that this is a safe target for us to degrade deeply and chronically.

Nello:

Thank you, Juddah

Moderator:

Your next question comes from Joe Cantanzaro with Mizuho.

Joe Catanzaro:

Great. Thanks for taking my questions. Hopefully you guys can hear me okay.

Maybe one on 579, and something kind of maybe related to something you just said, Jared.

But I was looking at another healthy volunteer study for another anti-inflammatory drug, and they actually utilize a skin immune challenge model where they injected volunteers with actually a TLR agonist and then looked at cytokines. I'm wondering if you guys are aware of that model, whether you consider this. And if you did consider it, why you didn't decide to use it?

And then I guess related, what informs the 50 to 80% target reductions in biomarkers? Is that all preclinical, or is there some genetic basis for that, for that target reduction? Thanks.

Nello:

So maybe I'll take the first one, and Jared takes the second one.

So yes, we're obviously well aware of there are many type of skin challenge models, sometimes even systemic models, systemic challenge model. People have done LPS, inhaled LPS, local LPS. So there are many models that one could run preclinically for healthy volunteer studies.

We, philosophically, feel like the right context to ask these pathway questions are in patients. And what you do by activating the skin is you artificially activate a pathway, and then you look at downstream

regulation. You can do that just the same way by taking the blood and ex vivo activating the pathway. So yes, you could do those things. We just don't believe that the complexity of it de-risks us any more or less what we would do with an ex vivo blood stimulation.

If you have questions about does your drug reach particular tissues, and especially with small molecule inhibitors where you actually cannot measure target engagement, that is a way to do it. But we can measure target engagement directly, so we don't need a surrogate downstream biomarker to make sure our drug gets to the tissue. So that's at least our view.

Jared, do you want to speak to the...

Jared:

Yeah. I mean, we know in terms of the amount of knockdown that we think we need or the amount of functional inhibition that we would need for those pathways, one has to keep in mind that here we're talking about not just one pathway that's controlled by IRF5, but multiple pathways. Here we're looking at three different TLR pathways, for example, 7, 8, and 9. And so whereas if you're talking about one pathway and all your activity is dependent on one pathway. You may have a threshold that could be 80, 90% or more to really have clinical impact. Here we know that if you're impacting multiple different pathways in parallel at the same time, you don't need necessarily 90 plus percent inhibition. 50 to 80% inhibition from our preclinical data across multiple different pathways can have a synergy that can give you significant activity in preclinical models. So, that's the reason why we say that that's sort of a range, which is really just a range. If you're seeing it across multiple different TLR pathways with these ex vivo stim models would be very encouraging, and we would expect to translate into activity in subsequent patient studies in diseases like lupus.

Joe Catanzaro:

Great, thanks. Super helpful on both points. Thanks again.

Nello:

Thank you.

Moderator:

The next question is from David Archila... sorry, excuse me, Derek Archila with Wells Fargo.

Hao Shen:

Good morning. Thank you for the question. This is Hao. I'm calling you for Derek. So, I guess our question is about the potential oral autoantibody degrader program, just kind of the timing and what data, what events maybe we can hear more from this asset?

Nello:

Sorry, say that... I didn't quite get the question. Say that again.

Hao Shen:

The internal potentially oral autoantibody.

Nello:

Oh, so do you mean the next oral immunology program that we are going to disclose? Yeah, so as we said, I believe it's in the press release and in our remarks earlier, we plan to disclose at least a novel program, most likely an immunology program this year, and likely will be in the second half of the year.

Hao Shen:

Awesome. Thank you.

Nello:

Thank you.

Moderator:

The next question comes from Brian Cheng with JP Morgan.

Brian Cheng:

Hey, guys, thanks for taking our question this morning. Just on IRF5, as you mentioned, 50 to 80% reduction across the TLR 7, 8, 9 pathways. Just thinking about IRF5 regulates many of the levers in the pathways, are there any specific downstream cytokines that you can point to today that will be the most impacted, most reliable, and perhaps the easiest to monitor from an ex vivo stimulation test setting to best assess the PD of the drug? Thank you.

Nello:

Yeah, that's a great question. Jared, do you want to take that one?

Jared:

Yeah. Through the autostimulation of these pathways, there are key cytokines that we can look at. So, for example, type one interferons like interferon beta. We can look at interferon beta protein production in these ex vivo stim assays. We can also look at gene transcripts that are part of the type one interferon pathways. So, looking beyond just the interferon itself, you can look at various genes that are part of the type one interferon pathways. We can also look for pro-inflammatory cytokines like IL-12 and tumor necrosis factor, and even IL-6, which are stimulated by macrophages and dendritic cells. So, these were a number of different pro-inflammatory cytokines that are coming off of these TLR pathways

that can all be measured either at the protein level or the gene transcript level. That will be very helpful biomarkers for us.

Nello:

Thank you.

Brian Cheng:

Thank you.

Moderator:

Your next question is from Brian Abrahams with RBC. Brian, please unmute to ask your question.

Kevin Meli:

Hi, guys, can you hear me?

Nello:

Yep.

Kevin Meli:

Yep. Hi, thanks so much for taking our questions. This is Kevin on for Brian. Maybe just on IRF5, how are you guys thinking about degradation in, I know you mentioned whole blood, but just in PBMCs and maybe potentially skin as well? I think that's something you're looking at in the MAD portion, and I know you talked about IRF5 not being as activated in healthy volunteers, so just maybe curious what our expectations should be there for degradation in those tissues. And just how much do we really know about sort of IRF5 expression in healthy volunteers and how that impacts your expectations for the study?

Nello:

Yeah, in blood we know that we can measure IRF5 well. And in fact, when we say blood, we obviously then practically mean PBMCs because we isolate PBMC as we measure it using mass spec. The expression of IRF5 in healthy volunteers in the skin is extremely low, and so for that reason we believe it would be really hard to measure IRF5 in healthy volunteers. This is something that as we go into patients and especially if we go into lupus with cutaneous manifestation or even SLE, eventually, that's, maybe it's a context where we can look at IRF5 expression. I think a healthy expectation is to be extremely low, lowest than any other program that we've looked at, even preclinically.

Kevin Meli:

Thank you.

Nello:

So hard to measure. Yeah, thanks.

Moderator:

From now on, we'll be moving to only one question due to time. Your next question comes from Sudan Loganathan at Stephens.

Sudan Loganathan:

Good morning, everyone. I wanted to ask my question around 621's opportunity in asthma. Looking at the current FDA approved treatment options for AD, not all of them have really panned out that well in asthma as maybe people have expected. STAT6 degradation is a new approach, so curious to hear what theoretical and preclinical data you may have that gives you some conviction here that it also has an opportunity in asthma. Thanks.

Nello:

Yeah, I think IL-4 and 13, and just I remind everybody that there is only one drug that blocks IL 4 and 13, which is dupilumab, and so that is shown to have really, really robust activity in eosinophilic asthma and actually eosinophilic COPD, chronic rhinosinusitis with nasal polyps. So, it's well established to really have huge impact on patients with type 2 inflammation in respiratory tract. So, STAT6 biology, again, we've shown it extensively preclinically and also in the early clinical development that we can mimic the same IL-4 and 13 blockade. And, again, I refer you to the asthma studies that we've published, preclinical study that we've published showing the robust activity we see both on biomarkers and efficacy endpoint, the FeNO reduction that we've seen in patients is actually even more robust than biologics in asthma patients. So, we have all the ingredients to have reasons to believe that this drug actually has the potential to be extremely effective in asthma.

Sudan Loganathan:

Thanks.

Moderator:

The next question is from Jeet Mukherjee with BTIG.

Jeet Mukherjee:

Great. Thanks for taking the question. As we just look ahead to the evolving competitive landscape in atopic dermatitis, and specifically on the next-gen oral agents that might be coming around the corner, just your thoughts on ITK as a target and some of the recent data we've seen there, and how that might compare and contrast to STAT6? Thank you.

Nello:

Yeah, Jeet, great question. As I said earlier, I think more mechanisms are great for patients first. I think obviously these are very different mechanisms. STAT6 is an IL-4 and 13 drug, as I said, the most validated pathway in the space, both in terms of safety and efficacy. We have shown preclinically that we can mimic biologics, both in terms of efficacy, and I would actually argue that in safety. We just shared today that we completed chronic tox, so six to nine month tox in rodents and nonhuman primates, again, without any adverse event. Other targets, ITK is a target that we've looked extensively at Kymera.

We decided not to work on it because the human genetics show that because of challenges with clearing EBV, I think all patients end up developing some form of lymphoma. So, this is a reason why we decided not to work on that target. That doesn't mean that could not be a great target. It's just something that we don't believe will fill the risk benefit profile of Kymera and how our target selection strategy has been evolved over the years. But, again, I think more mechanisms, especially with complementary pathways, whether it's ITK or others, I think are going to be great for patients that expand this market that we need to do, so that more patients get access to more therapies.

Jeet Mukherjee:

Thanks for taking the question.

Nello:

Thank you.

Moderator:

Next question is from Faisal Khurshid with Jefferies. Faisal?

Faisal Khurshid:

Hey, guys. Thanks for taking the question. Wanted to ask, as you guys get the sites up and running in the Phase 2b studies, do you expect to provide any kind of color or context around how enrollment is going in those studies?

Nello:

No, I think what we, obviously if we feel we're not on track, obviously we will share, but as long as we remain on track with the expectation, we don't plan to be providing ongoing updates of enrollment. I don't think it's necessary, but obviously, again, if we deviate from expectation, we will make sure to do so.

Faisal Khurshid:

Sounds good. Thank you.

Moderator:

Next question is from Biren Amin with Piper Sandler.

Biren Amin:

Yeah. Hi, guys. Thanks for taking my questions. And congrats on the quarter and all the progress. For the Phase 2b AD trial, what measures are you taking in the trial to mitigate against placebo response? For example, will you be requiring photographic evidence of AD at baseline to provide evidence of moderate to severe disease on screening? So, I guess that's first question. Second question on 579, I know you're enrolling healthy volunteers, however, there are healthy volunteers that may have positive antinuclear antibodies, but do not have autoimmune disease. Would you potentially screen for these types of healthy volunteers, that may potentially provide read through into your Phase 1b lupus trial? Thanks.

Nello:

Great question, Biren. I'll take the second one quickly. Jared, do you mind taking the first one? Yeah, so great idea. Sometimes simple is better than complicated, so we're going to actually enroll healthy volunteers that are healthy more quickly through it, so that the dose and go into patients. That doesn't mean your idea is not a good one, it's just not what we're planning to do. Jared, do you want to take the first?

Jared:

Yeah, I think with the Phase 2b, your question about avoiding high placebo raises an important one, and while I can't get into all the details at a high level, I can tell you that we're paying a lot of attention to this, both with regards to our eligibility criteria, how we're providing oversight with every patient that comes on and is screened in terms of looking to make sure that patients are truly meeting eligibility criteria, not just in terms of actually having AD, but also having moderate to severe disease. And we've carefully trained the investigators and selected investigators who are Board-certified dermatologists to make sure they're fully capable of doing all of the clinical endpoint measurements across the study and that they're doing it consistently from baseline all the way through to the end of the study. And we also have global site selection.

So, we're not just in the US, we're also ex-US. And in fact, the majority of our sites are ex-US, whether that be in Europe or in Asia and Australia. And I think that's also important because access to drugs like Dupilumab are diminished ex-US, and so those are patients who are more apt to come in, maybe more on the severe end of the spectrum of disease. And that can also be very helpful in helping to mitigate placebo effect, which you tend to see in milder patients compared to more severe patients. So, I think all of those steps are being taken, and we're really very actively staying on top of all of that to try to mitigate a high placebo rate on the study.

Nello:

We're doing, I'm sorry we're way out of time, but we're doing lots of things, probably more things that anybody has done before, to ensure that we do that. Obviously, we can't guarantee the lowest placebo rate, but we're trying our best.

Biren Amin:

Perfect. Thank you.

Nello:

Excellent. Thanks, Biren.

Moderator:

Your final question comes from Paurav Desai with B. Riley.

Paurav Desai:

Hello. I am on for Mayank. Thank you for taking our question. On asthma trial, if you could kindly confirm the dose levels are the same as BroADen 2? And how might you be enriching for FeNO in your target patient population? And is there a chance your 12-week FEV1 endpoint data could come around the same time as your 16-week BroADen Phase 2 study? And also would be helpful to learn competitive trial enrollment dynamics in atopic dermatitis versus asthma. Thank you.

Nello:

Yeah, thank you. These are four questions in one, but let's see if... You guys have to help me remembering. So, the first one, the dose levels, yeah, they're the same across AD and asthma. So, the inclusion criteria for the asthma studies, high eos, more than 300, high FeNO, more than 25. So, that's how we're going to select that patient population. In terms of timing, we said that we expect Phase 2b AD study data by middle of next year, while the asthma data by the end of next year. So, I guess that answers the questions. Things can always change one way or the other. And as I said earlier, if they change materially, we will share.

And then competitive dynamics, all I can say that we have seen a ton of enthusiasm for our study in both, actually I would say AD and asthma. And that's for two main, actually I would say three reasons. One, sites and hopefully also patients appreciate the really, really interesting and innovative science of our program. They appreciated this. While this is a novel target, it's within well-established biology and clinical experimentation. It's an oral drug and has some compelling early data. When you put all of that together, we have seen a ton of enthusiasm. So, we believe and hope that this enthusiasm will translate into good enrollment. And that's what we're seeing so far, but we're still a long way to the finish line.

Paurav Desai:

Thank you.

Nello:

Thank you.

Moderator:

There are no more questions at this time. Yes, there are no more questions at this time. And now, let's turn the call over to Nello Mainolfi for closing remarks.

Nello:

Yeah, so, first let me apologize. This call has taken longest that we've ever done. I'm not really sure why, but I want to thank everybody for attending the call, all great questions. So, I don't blame our analysts. And you know where to find us. We're very excited about where we are. This is a pivotal time for the company, and so we're excited to engage beyond the call if there are questions. And enjoy the rest of the day.