Kymera Therapeutics Second Quarter 2025 Results Call | August 11, 2025

Operator:

Good day everyone. My name is Olivia and I will be your conference operator today. At this time, I would like to welcome you to the Kymera Therapeutics Second 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 Bruce Jacobs, Chief Financial Officer.

Bruce Jacobs:

Good morning. I am Bruce Jacobs, and I am kicking this off in place of Justine Koenigsberg, our Head of IR, who is out today.

Joining me this morning are Nello Mainolfi, Founder, President and CEO, and Jared Gollob, our chief medical officer.

Following our prepared remarks, we will open the call to questions from our publishing analysts.

If you would like to ask a question, please use the raise hand icon, which can be found at the bottom of your meeting window. And to help us move efficiently through the Q&A session, we ask that you are ready to unmute your line when called on. In addition, we ask that you please limit your question to one and a relevant follow-on to be sure we have enough time to address everyone's questions this morning.

Before we begin, I'd like to remind you that today's discussion 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, I'll turn the call over to Nello.

Nello Mainolfi:

Thanks, Bruce and thank you for joining us this morning.

As I mentioned at the beginning of the year, we set ourselves up for a very productive and exciting 2025 and we're delivering on that promise. The updates we've shared in the first half of the year represent a powerful validation of Kymera's innovative and disciplined approach to drug development within the biopharma industry, while paving the way for our future progress across our high-impact immunology pipeline. We're committed to leveraging the unique capabilities we have developed to unlock disease biology and deliver groundbreaking oral degrader medicines for areas not served well by existing technologies.

Today's immunology treatment landscape still leaves millions of patients without adequate options, forcing difficult trade-offs between efficacy, safety, cost, and convenience. Millions of patients with life altering immune-inflammatory diseases don't have access to advanced systemic therapies, mostly injectable biologics. This is true if we look across countries with extremely diverse systems on how they prescribe, reimburse and deliver these highly effective medicines. The issue is clearly more fundamental than the inefficiencies of the healthcare ecosystems around the world. Simply put, well-tolerated, oral drugs that can be as effective as these difficult to access injectable biologics have the potential to transform the treatment landscape and in doing so impact lives of millions of patients.

This is what we are set to do at Kymera.

It's an exciting time for the company and I want to take a moment to briefly recap some of the key accomplishments of the first half of 2025.

Starting with our first-in-class STAT6 program.

We completed the first KT-621 trial in healthy volunteers and reported positive results that exceeded even our highest expectations, surpassing our target product profile. Importantly, the data further derisks our path forward and highlights the possibility of KT-621's dupilumab-in-a-pill profile. As potential first-in-class treatment, we believe KT-621 has the ability to be a broadly accessible oral option for many dermatologic and respiratory diseases like AD and asthma. In addition, for Japanese regulatory purposes, we recently completed a second, small healthy volunteer study in Japanese subjects with results that were consistent with the US study. You can expect that we'll present these findings at a future medical meeting.

We also wanted to share a few updates regarding the KT-621 Phase 1b BroADen study in moderate to severe AD patients.

As noted in the release, the patient data we plan to share will include data from two different dose groups. While we initially set out to explore a single dose, the speed at which the trial

enrolled allowed us to evaluate the translation from healthy volunteers into patients more broadly, which we believe gives us an even richer data set to inform our Phase 2b dose choices, which was an important goal of this study. The Phase 1b was designed with a flexible protocol that contemplated this scenario, allowing us to make this choice without impacting timelines, and as a result we are well-positioned to report results in the fourth quarter, as planned.

I am also happy to share that we have selected and finalized the three doses that will be included in the two Phase 2b studies as well as completed long-term toxicity studies. These were really the final important pieces for our planning to start the studies beginning later this year.

Given we are moving into the data collection and analysis mode soon, we are going to limit our comments around the study to what we have said previously until we are able to share the full results in the fourth quarter. But we can certainly say that we are pleased with the speed at which this trial has enrolled, very excited about the trajectory of the program, and we look forward to sharing the full data set when it's available.

The additional piece of news to share is that we have selected a follow-on STAT6 degrader to KT-621, with a strong potency, selectivity, and safety profile, and have advanced it through all required IND-enabling studies. The degrader is IND-ready should we decide to further advance it into the clinic in the future.

More broadly, we're building what we believe is the best in industry oral immunology pipeline, and beyond STAT6 we're also very excited about what's next. Earlier this year, we've unveiled our oral IRF5 program, which is moving through IND-enabling studies. The compelling preclinical data we have generated showcases that targeting IRF5 can lead to correcting immune dysregulation across multiple disease pathologies while generally sparing normal cells. And it remains our goal to progress our early discovery pipeline of novel immunology programs, unveiling one new program per year, to expand access to oral systemic advanced therapies for broad patient populations in the space. We hope to share more about this next year.

Additionally, we announced two important partnership updates in June.

First, we were very excited to announce our first oral molecular glue degrader program, targeting CDK2, will be developed under our collaboration agreement with Gilead. We have a highly innovative research engine and the CDK2 program is a great example of this given the challenges of existing technologies to address this high value target. With our focus in immunology, this program was an ideal candidate for partnering. We and Gilead believe that a highly specific, safe and effective CDK2 degrader has exciting potential to meaningfully improve treatment for patients living with breast cancer and other solid tumors that are inadequately treated today.

Secondly, Sanofi announced that they officially opted in into the IRAK4 program and will assume full responsibility for development activities of KT-485, our second generation oral IRAK4 degrader, which we expect to advance into Phase 1 testing next year. Based on our preclinical results, KT-485 has greater potency, broader distribution, and a generally improved overall profile than KT-474, our first-generation degrader. As a result, Sanofi made the decision not to advance '474 in further development as KT-485 has the greatest potential benefit for patients.

Both these collaborations have the potential to realize significant milestones for Kymera, which Bruce will cover later in the call, and we're very happy to collaborate with two industry leaders on these novel programs.

Finally, to support all we have ahead of us, we've extended our cash runway into the second half of 2028. We raised approximately $288 million in a follow-on offering that we launched at the end of June, and received the upfront payment from Gilead, increasing our cash position to $1 billion as of the end of July. Our well-capitalized balance sheet should allow us not only to take KT-621 through the planned Phase 2b studies in AD and asthma but also to prepare for and initiate several Phase 3 studies across multiple indications, while also progressing our earlier stage pipeline.

As you have heard me say before, our strategy centers on combining the unique power of targeted protein degradation with carefully selected targets and pathways to create a transformative new class of medicines. By focusing on immunology, we're not only addressing large patient populations, but also meeting a significant unmet need to create effective, safe, oral therapies. We believe our approach has the potential to deliver, for the first time in our industry, biologics-like efficacy with the ease and convenience of an oral pill.

Again, I couldn't be more excited about the foundation we built and where we are going. I am looking forward to the Q&A discussion but let me pause here for Jared to discuss KT-621 and our pipeline. Jared?

Jared Gollob:

Thanks, Nello.

Looking back on the last quarter, we were excited to share the first KT-621 clinical data, which we believe greatly derisks the next stage of development. We identified clear goals for the Phase 1 healthy volunteer study and the data not only hit the mark, but in many instances exceeded our expectations with compelling translation from preclinical studies to humans.

The primary objective in the healthy volunteer study was to show that 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.

As shown here, the results exceeded our expectations across every measure.

We showed more than 95% degradation in both skin and blood at very low doses.

The safety profile was undifferentiated from placebo.

And we are encouraged by the biomarker profile which we believe is at least comparable to what dupilumab showed in healthy volunteers or patients and in some cases is superior.

That said, I'd like to take a few minutes this morning to recap the results and next steps with KT-621, which we believe has the potential to profoundly alter how Th2 diseases are treated by delivering an oral drug with a biologics-like profile. For the full data set, please reference the slides presented in early June, which are available on our website.

As a reminder, we enrolled 118 volunteers in a randomized, double-blind, placebo-controlled study to assess single- and multiple-ascending doses of KT-621 across a range of doses from 6.25 to 800 mg in SAD and from 1.5 to 200 mg in MAD.

In all SAD cohorts, including the lowest dose of 6.25 mg, KT-621 degraded STAT6 by 90% or more, and at doses of 75 mg or greater achieved complete degradation, with >95% mean STAT6 reduction and STAT6 levels below the lower limit of quantification in multiple subjects after just a single dose.

In MAD, where volunteers were dosed daily over 2 weeks, we were able to completely degrade STAT6 in both blood and skin at doses of 50 mg and above. In fact, to establish the lower end of the dose response curve, we had to go back after the initial cohorts and add the 1.5 mg MAD cohort given none of the initially planned doses had less than 90% degradation.

The robust degradation of STAT6 led to functional inhibition of the IL-4/13 pathway as demonstrated by median reductions of up to 37% for TARC and up to 63% for Eotaxin-3 at Day 14, a result that was comparable or superior to what has been observed for dupilumab either in healthy volunteers or in patients with Th2 diseases.

Importantly, whether treated at the lowest or highest dose, or anywhere in between, the safety profile was undifferentiated from placebo. There were no serious adverse events, very few treatment-related adverse events that were mild, no treatment-related discontinuations, and no clinically relevant changes in vital signs, laboratory tests or ECGs with daily dosing up to 200 mg, which is 16-fold above the lowest MAD dose with >90% degradation.

As many of you have asked, we are also happy to share that we recently completed our 4-month GLP toxicology study and, consistent with our earlier non-GLP and GLP tox studies, we did not see any adverse events of any type at all of the doses tested. This study completes the

necessary preclinical work to allow us to initiate the Phase 2b trials planned to start later this year and early next.

Prior to reporting the healthy volunteer data, we initiated a 28-day Phase 1b trial, named BroADen, which was designed to enroll approximately 20 moderate to severe atopic dermatitis patients. We've had a high level of engagement from sites on the trial and are pleased to report that we are on track to share data in the fourth quarter.

As a reminder, 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, TARC being the most relevant in AD patients, as well as on the Th2 transcriptome of active AD skin lesions. We will also assess KT-621's effect on clinical endpoints, such as EASI and pruritus NRS.

Beyond the Phase 1b BroADen study which, again, is designed as a streamlined biomarker-focused study, we are planning parallel Phase 2b dose range-finding trials to enable subsequent registrational Phase 3 studies across multiple indications. As Nello mentioned, we have selected the three doses for the studies, and our STAT6 team has done a remarkable job keeping this program moving at a rapid pace, including all the necessary work to initiate two global Phase 2b trials. The AD Phase 2b trial will begin in the fourth quarter this year and the asthma study is expected to initiate in the first quarter of 2026.

And quickly on the IRF5 program.

Historically an undrugged transcription factor and genetically validated target, IRF5 is a master regulator of innate and adaptive immune response pathways involving pro-inflammatory cytokines, B cell activation and autoantibody production, and Type I Interferons. We believe IRF5 degradation has the potential to be the first broad anti-inflammatory mechanism that effectively addresses immune dysregulation while sparing normal cell function. KT-579, our potent, selective and oral degrader, has the potential to be the first IRF5-targeted therapy to deliver a completely novel and potentially transformative treatment option, in many cases superior to pathway biologics, in a range of autoimmune and rheumatic indications such as lupus, RA, Sjögren's and others.

This program is progressing in IND-enabling studies, and we expect to advance KT-579 into Phase 1 testing in early 2026 with what we believe will be the first oral IRF5 degrader to enter the clinic.

Across our portfolio, we see strong potential to advance multiple first-in-class oral degraders that address major market opportunities in immunology. Our STAT6 and IRF5 programs represent significant advancements, not only for our pipeline, but for the industry and patients, as we look to deliver the first oral therapies with biologics-like profiles in immunology. We're

excited about their continued progress and remain focused on our goal of expanding access to transformative treatments for millions of patients.

So let me pause here and Bruce will review our second quarter financial results and provide a collaboration overview. Bruce?

Bruce Jacobs:

Thanks, Jared.

I will quickly run through our results for the quarter. Also, because this past quarter has been busy with collaboration and financing activity, I wanted to provide a brief summary of our recent news as well.

As I walk through the second quarter results, please reference the tables found in today's press release and 10-Q, which was filed this morning.

Revenue in the second quarter of 2025 was $11.5 million dollars, all of which was attributable to the Sanofi collaboration.

With respect to operating expenses, R&D for the quarter was $78.4 million. Of that, approximately $8.0 million represented noncash stock-based compensation. The adjusted cash R&D spend of $70.4 million, which excludes that stock-based comp, reflects a 3% decrease from the comparable amount in the first quarter of 2025.

On the G&A side, our spending for the quarter was $17.6 million dollars, of which $7.4 million was noncash stock-based comp. The adjusted cash G&A spend of $10.2 million, again, excluding that stock-based compensation, reflects a 6% increase from the comparable amount in the prior quarter.

Overall, adjusted operating expenses were down slightly from the prior sequential quarter.

We ended June with a cash balance of $963 million. Our quarter-end cash balance included the base proceeds from our $250 million follow-on offering that closed at the end of June. The June total does not include either the additional proceeds from the underwriters' overallotment option, which was fully exercised in July, or the first payment that we received from Gilead as part of our recently signed CDK2 partnership, both of which were received in July. As a result, we ended the month of July with a cash balance of approximately $1 billion dollars, providing a cash runway into the second half of 2028.

Just a quick reminder that our runway calculations exclude any unearned milestones. And with that in mind, I'd like to take you briefly through the key financial terms of our two collaboration agreements.

Starting with Gilead: under our collaboration, we are eligible to receive up to $750 million in total payments, in addition to tiered royalties on net product sales that range from the high single digits to the mid-teens. This $750 million includes $85 million related to the upfront payment, which was received in July, and you can see on our balance sheet shown as deferred revenue, and the potential option exercise. If Gilead chooses to exercise its option for an exclusive license, they will assume global rights to develop, manufacture, and commercialize all products arising from the collaboration.

Turning to Sanofi and the development of KT-485: Under the existing collaboration, we could earn up to $975 million in clinical, regulatory, and commercial milestones for KT-485. We retain the right to opt into a 50/50 cost and profit share in the U.S. prior to the first Phase 3 trial, in addition to international royalties. If we decide not to opt-in, we would instead be entitled to worldwide royalties ranging from the low double digits up to the high teens.

To conclude, as you've heard today, there's a great deal of momentum across our programs. And, importantly, we have the resources in place to continue executing on our development strategy and the progression of our earlier stage pipeline. With that, we'll pause here so we can convene in our main conference room, at which point we will open the call for questions.

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 have joined 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 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. First question is from Michael Schmidt from Guggenheim. Please unmute yourself and begin with your question.

Paul Jeng:

Hey guys, it's Paul on for Michael. Thanks for taking our question. I had one on the dose levels that you're exploring for 621. Maybe first, could you provide some color on that decision to add the second dose in the Phase 1b study? I think it's probably safe to assume that both the doses fall within the broad range that achieve complete STAT6 degradation, but just wondering how you're thinking about exploring both the high and a low dose versus perhaps two doses in the higher range?

Nello Mainolfi:

Yeah, thanks Michael. Want to make sure you can hear us? As we said today, so the doses, both doses are within the range that we explored in the Phase 1 healthy volunteer study, and as we also said, as you're aware, we had initially decided to explore one dose thinking that roughly 20 patients will be enough to give us the data to speak to what is the profile of that one dose.

Then, obviously, as we were moving along with the enrollment and given how quickly it was going and given that we were able to assess the performance at one dose, we decided to explore an additional dose so that we'll get even robust translation from healthy volunteer to patients of STAT6 degradation. I think it's important to keep in mind that in the healthy volunteer data we had multiple doses. I would say almost all doses besides one, that met our target product profile, and so we wanted to confirm that the really, really robust profile could be translated into patients with the same level of fidelity. I think we're happy that we did that. Obviously, I'm not going to speak to high, low, medium, et cetera. Rest assured that the main goal was really to refine the Phase 2b dose selections. All that happened so quickly that now between the healthy volunteer data and whatever data we have access from this study, we're able to firm up and select the Phase 2b doses even in the absence of completing the Phase 1b study.

Paul Jeng:

Great, and if I have quick follow up on that point and mostly on just what back into the dose selection for the Phase 2 studies, was it predominantly the healthy volunteer data you presented? Was there anything emerging from the Japanese studies or GLP tox? Can you say if there's a different range of doses being explored between the AD and the asthma studies? Thank you.

Nello Mainolfi:

Yeah, no, so a great question actually. As you saw, it was a very, very busy Q2. I don't think we've had a busier Q2 in the history of the company given everything that we've accomplished. I will say that if you look back at the healthy volunteer data, there was a dose selection based on this data. Everything else that we've done confirmed was able to confirm our initial instinct. We didn't learn, to be honest, anything new that made this change the initial instinct, let's say, on dose selection, but it was highly encouraging that everything that we'd seen in healthy volunteers was supported by obviously, the four-month tox, which we said was completely clean. The Japanese study, which was very much in line with the US study and the early, let's call it, early data for the Phase 1b.

Paul Jeng:

Great, thanks very much.

Operator:

The next question is from Derek Achila at Wells Fargo. Please unmute yourself and begin with your question.

Derek Achila:

Hey, good morning and thanks for taking the question. Congrats on the progress here. Just one in a follow up. Basically, just want to understand maybe following up on this line of questioning just in terms of what you would expect to see at these additional doses that you're looking at in the Phase 2b. Ultimately, we saw very good degradation and pretty quick. I guess how do you think some of the doses will differentiate? Then just a follow up to that, what do you actually expect to see with the follow-on STAT6 that you're developing? What sort of optionality are you really looking for with that molecule? Thanks.

Nello Mainolfi:

Great question, Derek. The first one I just want to confirm we're talking about the dose for the Phase 2b. I think the important thing for a drug obviously is to find a dose that has the best risk-reward profile. I think what we want to ask in a, let's say for AD, a 16-week study is what is the maximal or we believe close to maximal at that point level of clinical activity that we will see and what is the safety profile at different levels of degradation? Obviously, we will explore maximal degradation, which we call complete, which again, is where really we see in most subjects STAT6 level be below the lower limit of quantification. We want to ask that question, what is the clinical profile of maximal degradation? Then obviously, we want to ask the question at a couple of lower doses just to, again, at the end of the study being sure that we're taking into Phase 3 the profile that we believe has the best risk-reward.

It is obviously a necessary step that we need to take as a company to fulfill regulatory requirements to do dose ranging studies before selecting a Phase 3 dose. I think we have bets in the company what that Phase 3 dose will be already, but we've got to run the studies and make sure that we do all the right steps to de-risk the program.

With regards to the follow-on molecule, that's something many of you that has followed us for years know that every program, we always have a next-generation molecule. As you saw for IIRAK4, Sanofi decided to focus the efforts on the follow-on, we call it the next-generation molecule, KT-485. For STAT6, to be honest, we didn't really have a particular goal with the next-generation compound given how well KT-621 has performed, and this is the reason why we've advanced a very good molecule that in many ways looks at least in terms of profile, very much

like KT-621. It's potent, extremely well-tolerated, very active in vivo, and the principle is to support the franchise for one is for the eventual unlikely scenario that we need another molecule or for a strategic choice of eventually advancing another molecule should we choose to do for different severities or different indications.

I think given how well KT-621 is doing, we have decided for now to keep this follow-on molecule IND ready, meaning that we have everything we need to file an IND, but we're not planning to file an IND in the short term. I think another important point in this highly competitive space that STAT6 is becoming, having a molecule IND ready probably ahead of any other, let's call it competitor that is behind us. We have two molecules ahead of every other competitor. I think he also sends a message how committed the company is to this franchise and to the potential of this franchise.

Derek Achila:

Excellent. Thanks, Nello.

Nello Mainolfi:

Thanks, Derek.

Operator:

Question is from Andrea Newkirk at Goldman. Please unmute yourself and begin with your question.

Andrea Newkirk:

Hi guys. Good morning. Thanks so much for taking the question. Two for me as well. Maybe the first recognizing the primary objective of the Phase 1b data is to show a dupi-like profile here on biomarkers, but I was hoping you might be willing to frame your expectations on what you'd like to see on the clinical efficacy measures, particularly EASI 75 as well as NRS. Then secondly, just noting the completion of the GLP tox studies that you mentioned, and obviously your Phase 1 healthy volunteer also looked really clean, but if you could just speak to the potential safety risks of degrading STAT6 completely, what type of signals are you most looking for in the Phase 1b to really feel comfortable here with the safety profile as you move forward? Thanks so much.

Nello Mainolfi:

Well, thanks. Great question. Jared, I thought maybe you could take at least the first one, if not both.

Jared Gollob:

Yeah. In terms of on the clinical expectations, I think we've emphasized always that the primary objective here is to show robust STAT6 degradation in the blood and in active AD skin lesions, and to show that results in a dupi-like biomarker effect, both in blood and in skin, where in skin, we're looking at the TH2 transcriptome and the wanting to see a dupi-like effect there. We sort of have set of expectations around biomarkers. I think TARC is the most important blood biomarker, probably in AD. Where dupi studies have shown even at 28 days about a 70 plus percent reduction in dupilumab. That's a general ballpark that we would expect to see in patients who, like in those dupi AD studies had greatly elevated TARC levels at baseline. We'll be looking at other biomarkers in the blood as well as these various transcriptional biomarkers in the skin. In terms of clinical endpoints, again, we've always emphasized that in the absence of a placebo control, these are more exploratory. However, we think we do have an opportunity to look at endpoints like EASI and pruritus, NRS and IGA because we know from dupi that you can see impact on those biomarkers as early as 28 days, and we're not really giving specific numbers where that bar would be set. I think the published data are out there with duip and one can look at those published data at 28 days and get a sense for what we mean by sort of being in the ballpark with regard to those clinical endpoints.

In terms of your second question around safety risks, as you noted, we've been very pleased with what we've seen in our GLP tox studies. We've now completed our four-month tox studies as Nello indicated, and we've seen no safety signals whatsoever. That's very in line with our four-week GLP tox and our prior non-GLP tox studies. We were very encouraged by the fact that our safety profile was undifferentiated from placebo in healthy volunteers with two weeks of dosing, so that's very encouraging. Now, we'll be looking at safety with four weeks of dosing, of course, in the Phase 1b.

I think overall this is in line with our expectations based on our mechanism of action and based on the fact that it appears that STAT6 is highly selective for the IL-4, IL-13 pathways. And human genetics have pointed not just to the phenotype of abnormalities in STAT6, but also to the safety of knocking down STAT6 as have mouse knockout studies. And so this is all in line with what we expected for a transcription factor that is very specific for IL-4 and IL- 13. And for a drug like ours that is highly selective just for STAT6.

Nello Mainolfi:

I would only, thank Jared. I wouldn't say anything differently, I will only add one thing just to be clear. Again, as Jared said on the clinical endpoints, it's also difficult to compare placebo control randomized study. Like the industry is full of these arguments over comparing placebo-controlled studies. So, it's even more difficult to compare non-controlled study. But I just want

to say our expectations are that we will have a very active drug. I don't want to hide behind the impossibility to compare. We expect that this mechanism is going to be on par with what dupilumab has been shown. And that's the bar for us without talking about numbers.

Andrea Newkirk:

Okay, understood. Thanks guys.

Operator:

The next question is from Faisal Khurshid at Leerink. Please unmute yourself and begin with your question.

Faisal Khurshid:

Hey, good to see you guys. Thanks for taking the question. Just want to ask on the doses for the Phase 1b and the Phase 2b. Are you able to confirm if the dose that you added to the Phase 1b is higher or lower than the dose that you originally went in with? And could you also confirm if either or both of these doses are part of the three that you selected for Phase 2b?

Nello Mainolfi:

So I don't want to get into the higher or lower because I think whatever I say is going to be viewed one way or the other. What I can say is that both doses have being tested in the healthy volunteer studies. I don't want to talk about what doses are for the 2b because I think we might choose to keep that, as I've said in other venues, to keep that close to the vest for as long as we can, only for competitive reasons. All I can say that we have several doses in the healthy volunteers that performed really well.

And so really the main driver here are these doses going to perform as well in patients? Given that, I actually don't remember the number, Bruce will know better. But we're spending tens if not 100 plus millions of dollars in these two studies. And we're not going to optimize over for these studies on thinking that we selected the right doses. These are consequential decisions. And so given that we had the time to do it, we said let's make sure. So that's really what's behind this. And I think once we'll share the data, we can add a bit more color to what came first.

Faisal Khurshid:

Got it. Makes sense. And then could you confirm if it's still 20 patients for the Phase 1b? And then also between the two doses, would you like to or do you have to see a dose response between those two doses?

Nello Mainolfi:

Great question. So I think what we said that the goal of the 1b was approximately 20 patients, and that's still the case. I don't want to get into the dose response. I think we will talk about it once we share the data.

Faisal Khurshid:

Sounds good. Thanks for taking the questions.

Operator:

The next question is from Alex Thompson at Stifel. Please unmute yourself and begin with your questions.

Alex Thompson:

Hey, good morning. Thanks for taking my question. I guess another question on the next gen STAT6, how different is the scaffold binding to STAT6 than 621? Is that a key part of this decision making? And when might you consider potentially splitting indications here? Is that a near-term decision or are you going to wait quite a while before that comes down? Thanks.

Nello Mainolfi:

Yeah, so what I can say, that's a great question Alex. So we have several scaffolds, let's call it across actually all binding moieties, whether it's E3 ligase or it's STAT6, we have plenty of chemistry. Some patents have published from us. As many have seen, there is plenty that haven't yet. So we have a plethora of chemistry in this program that covers everything that you can imagine. So maybe I'll leave it at that.

On the indication splitting, it is a bit obviously challenging to think about that particular end game given the evolving landscape right now in terms of pricing and reimbursement and global versus US. So I think we want to keep maximal optionality and that's the goal behind everything that we're doing. But it's difficult for us right now to at least disclose what's the latest thinking on that.

But as we get closer to Phase 3, which actually with the recent raise hopefully was clear from our remarks earlier. Now with the money we have in hand, we can actually initiate multiple Phase 3 studies. So I think we get closer to those, we'll be able to disclose more about what our indication sequence and strategy will be.

Alex Thompson:

Great, thank you.

Operator:

The next question is from Tazeen Ahmad at Bank of America. Please unmute yourself and begin with your question.

Tazeen Ahmad:

Hi guys. Good morning. Thanks for taking my question. Going back to the data that you're going to have by year-end, I just wanted to ask, you've talked about your expectations for what data you're going to show. Should we assume that you're also going to be able to show some level of itch data? I ask because some doctors have indicated that in addition to let's say EASI scores, that is something that they feel is important when they're going to make a decision in a real world setting about what potential options they might choose. Thanks.

Nello Mainolfi:

Yeah, Tazeen yeah, it's a great question. And as Jared said, yes, we will show EASI, pruritus, NRS, so itch is going to be an important factor. As you know, itch probably has the biggest impact on quality of life of these patients. And so it's something that we're watching very closely. So we will share that data as well.

Tazeen Ahmad:

And will that be for all the patients that you're going to show or it'll be a subset?

Nello Mainolfi:

Well, if we have collected the data, so we will share it. So yes, it should be all patients.

Tazeen Ahmad:

Okay, thank you.

Nello Mainolfi:

Yep.

Operator:

The next question is from Kelly Shi at Jefferies. Please unmute yourself and begin with your question.

Kelly Shi:

Congrats on the quarter. So one question on STAT6. Conjunctivitis is believed to be an on-target AE of Dupixent. So do you expect to see similar level of conjunctivitis in KT-621's Phase 1b trial, like in one or two patients? And also could a daily oral drug differentiator in safety profile versus injectables due to a potentially more flat PK curve? Thanks.

Nello Mainolfi:

Maybe I'll start and then I'll pass it to Jared that can speak more to the medical part. Our view at Kymera is that STAT6, and hopefully it's not just here at Kymera, STAT6 is the selective transcription factor of IL-4 and 13. And we've shown preclinically, early clinically, and hopefully we'll show in Q4 that if you bought STAT6 you can phenocopy dupilumab.

So if conjunctivitis, which is actually mostly, if not only seen in atopic dermatitis patients, so it's really a feature of the disease and these IL-4 and 13 biologics. So again, if conjunctivitis is a on-mechanism adverse event for IL-4 and 13 biology, then we expect to see if. It's to do with the receptor or the cytokines, then we wouldn't see it. So it's hard for us to know. Maybe Jared you can speak to... also, is this seen after only four weeks? I don't know.

Jared Gollob:

Yeah, I mean mechanistically, it's not really known why some patients, especially AD patients do develop conjunctivitis. If you look at the dupilumab studies, when you do see conjunctivitis, oftentimes you'll see it within the first say four to eight weeks or so of treatment. And then over time it actually tends to diminish. It is an adverse event that one does see with dupi, it's not a dose-limiting adverse event. And most of the cases with dupi are in the mild to moderate range.

I think importantly we haven't seen it preclinically, in our talk studies we haven't seen in healthy volunteers and we really wouldn't expect to see it there in healthy volunteers since this appears to be something unique to AD patients. But as Nello said, we don't have any reason to believe that we'd see either less or more in AD patients compared to what dupilumab has seen.

Nello Mainolfi:

Yeah, we're watching it because it's an interesting... obviously the feature of many of these drugs, it's not only dupilumab, the other IL-13 drugs have it. So, we're watching that very closely and see if we see it in our four-week studies, and we'll obviously we'll share all the data in 4Q.

And then you talked about the safety difference between once oral daily and a biologics. From what we have both understood and what we've empirically derived in our preclinical studies, dupilumab has a very, very robust pathway blockade. I would compare dupilumab pathway

blockade pretty much in-line with the level of pathway blockade we see from our 50, 100 mg dose, 200, the complete degradation type of pathway blockade. I would put it on that level of pathway blockade. So, if that's the case, then I don't see why pathway blockade coming from STAT6 degradation should look different from pathway blockade from an IL-4 receptor alpha blockade.

So anyway, I think that's another feature and another part of the analysis that we will do. Again, I'll repeat in our preclinical study now we're adding the four-month talks. KT-621 has been exceptionally well tolerated. And so we'll continue to, again, watch everything that happens in the clinic.

Kelly Shi:

Super helpful, thanks.

Operator:

Question is from Judah Frommer at Morgan Stanley. Please unmute yourself and begin with your question.

Judah Frommer:

Yeah, hi guys, thanks for taking the question. Just one for us. I guess can you comment a little bit further on enrollment progress and the success you're having there? Maybe what feedback is from investigators? Is the oral administration of the drug resonating? And curious if you think you'd have similar success if there were a placebo arm in a trial? Thanks.

Nello Mainolfi:

Yeah, it's a great question. So the challenge of a 28-day study, remember, is that patients are not going to be on the drug beyond day 28. We don't have an extension arm to the study. So I would say before we started the study, we were nervous because there aren't a huge amount of incentives for patients to come onto the study, besides knowing there'll be on an active drug. And that's part of the reason why we decided not to have placebo. We thought it would've had an impact on our enrollment rate.

As we expect, part of us, our expectation was the patients do want an oral drug. And so I think we are seeing that in our study. And this has allowed us to meet our enrollment goal. I would say even exceed our enrollment goal for sure. And maybe that's where I'm going to leave it. I think once we start seeing more differentiation, it's probably going to be in the Phase 2b study where now you're offering 16-week potentially OLE. And so that would be interesting to see our

enrollment versus biologics and whether it's telling us also something about what patients are also looking for in the market.

Judah Frommer:

Great, thanks.

Operator:

The next question is from Kripa Devarakonda at Truist. Please unmute yourself and begin with your question.

Kripa Devarakonda:

Hey guys, thank you so much for taking my question and congrats on the progress through the quarter. I'll ask one non-STAT6 question. So congrats on your CDK partnership with Gilead. I know this diversifies your pipeline into oncology where you've been focused a little bit more on I&I in the recent past. But given the data we've seen so far with CDK2 inhibitors, can you talk a little bit about how you think the degrader could be differentiated based on the data that you have? And what the strategy of development is? And then I have a follow-up.

Nello Mainolfi:

Yeah. Yes, thank you. So just to be clear, our discovery engine has been also very focused on immunology. We have programs that we were working on from the earlier days and one of our program was on CDK2. And so with our strategy shift to focus on developing immunology drug, we decided that it was best to place a very exciting CDK2 program from a development standpoint in the hand of a partner that was committed to that space. So that's a bit to the strategy.

The reason why we have that program is because we firmly believe that small molecule inhibitors of CDK2 are really not able to selectively target CDK2. They all inhibit to a large extent CDK1 at pharmacologically active doses to different degrees, and that it leads to clinical doses that are probably not optimally blocking CDK2, again, for the risk of hitting CDK1.

Another important aspect for us to develop this drug was to have a brain penetrant asset so that we would also address potential brain secondary tumor or metastasis from breast cancer. And so our degraded program, molecular-glue degraded program is highly specific CDK2 also reaches the CNS. And we believe it has the potential to be best-in-class. If I look at the small molecules out there, it's by far superior. Obviously, I'm not aware of other programs that are in early discovery, early development, so I can't say obviously for sure, but with regards to the

development, that's a question you have to ask Gilead. We can't speak for them on that particular front.

Kripa Devarakonda:

Okay, thank you so much. Just following up on Tazeen's question about itch relief, and this is something that we've heard from KOLs too, that it's really important to see rapid itch relief, will we get a sense of that when we see the data, the rapidity of response?

Jared Gollob:

Yeah, we will. As Nello already mentioned, looking at itch or pruritus NRS is a key part of the suite of clinical endpoints, and we'll be looking at it fairly regularly as we'll be looking at EASI, so we'll have a good sense of the kinetics of impact on itch as well as on EASI, and that will be certainly part of the profile that we share once we have those data in Q4.

Nello Mainolfi:

Yeah. I think you'll see, hopefully that will be the case, but it will be like... We'll show day 7, day 14, then 21, day 28, so you'll be able to see the kinetics of all of these parameters.

Kripa Devarakonda:

Okay, great. Thank you so much.

Operator:

To note, each questioner can ask one question now, no follow-up questions. The next question is from Mayank Mamtani at B. Riley. Please, unmute yourself and begin with your question.

Mayank Mamtani:

Yes, good morning. Thanks for taking our questions and congrats on the progress, team. Any color you're able to provide on the baseline EASI scores of the patients you're enrolling or have enrolled? I wonder always about the screen failure rate for the atopic derm trial sites. Maybe just remind us how you're measuring degradation in skin tissue, there's obviously a couple of ways to do that. Lastly, anything you've learned on the degradation from the four months GLP tox studies you completed?

Nello Mainolfi:

You asked four questions in there, so that's a way to-

Mayank Mamtani:

I will not ask a follow-up, I promise. No follow-up.

Nello Mainolfi:

You asked four, so let's see if I remember. The first one was the EASI... Yeah, we're not going to comment on the baseline EASI, but I will refer you to entry, so the baseline criteria for entering the study EASI above 16, 16 or above. There is obviously itch as well, there is BSA more than 10%. We have strict criteria that really overlap with what has been done with the dupilumab. Again, on the failure rate, again, I don't know if we'll speak when we release the data. All I can say is that our team is watching the study very closely and we've worked very, very hard to make sure that patients that enter our study actually have atopic dermatitis, which would be shocked that that could be possible if you don't watch the study closely, that their disease is active and, obviously, that their lab work is in line with making sure we're not taking sick patients on our study. I think when you take all of that, that results into, obviously, screen failures that, again, I'm not able to comment on today.

On the degradation in the skin, as we've done in many of our studies, we are fortunate enough to have patients on our study be willing to take biopsies, which as you know, it does add an additional layer. That's why we're so impressed on how we were able to enroll patients again quickly, because we asked patients to undergo biopsy of baseline on day 28 to measure STAT6 with the mass spec. That's how we're going to measure it.

Mayank Mamtani:

Anything you learned from the GLP tox study on degradation?

Nello Mainolfi:

All we learned in these studies is that we... obviously, at these doses, there is no STAT6 anywhere to be found that we degrade it completely. That's maybe all I can say. Yeah, if the question is, "Does the STAT6 degradation wane off after some time?" Obviously, the answer is no, we see STAT6 degradation all throughout the study.

Mayank Mamtani:

It's great to hear, thank you.

Operator:

The next question is from Jeet Mukherjee at BTIG. Please, unmute yourself and begin with the question.

Jeet Mukherjee:

Great, thanks for taking my question. I know we're a long ways out, but can you speak to payor willingness to cover therapies in the dermatology space that, given alternative administration format, like an oral option with Dupixent-like efficacy for KT-621, or is there bar truly superior efficacy versus standard of care options? Thank you.

Nello Mainolfi:

Well, no, it's a great question. We believe that when you make the case for an oral option, first, you will hear from prescribers that, actually, you don't even need to have dupilumab-like activity for expecting a substantial adoption in the market. It just speaks to the fact that there is a need of flexible, easy-to-prescribe, reimburse, and take medicines. The reason why we say dupi like in a pill is because all the data we've seen so far speaks to that. That's why our bar has always been there and hopefully will continue to be there. Again, I think when you make the case for having a therapy, even with the same activity, you're telling actually insurance companies and prescribers and patients that this drug has a much bigger impact on their quality of life and asking for a lot less. In terms of visit to the doctors, testing, needing or lack thereof of cold storage of the drug, needles, injection site reactions.

I think that's the value case that a drug like this will have, especially if you compare it to... For example, the only drug that right now is approved in AD, it's a drug with a black box, and that drug actually is doing quite well. It's a drug that requires testing before you start that therapy, so it speaks to the hunger that this market has for an oral drug. I think you've seen in all markets, oral drugs and multiple effective therapies are needed to expand access and penetration. Especially the atopic dermatitis market is really dominated by single player, I would say mostly with dupilumab, but it still has less than 15% penetration. I would say, if you look at all moderate to severe, it's less than 10%. I think we need this option to expand access dramatically in the US and all over the world.

Jeet Mukherjee:

Appreciate it. Thanks, guys.

Operator:

The next question is from Jeff Jones at OpCo. Please, unmute yourself and begin with the question.

Jeff Jones:

Good morning, guys, and thanks for taking the question. One question from us on IRAK4. Can you provide any additional detail behind what drove the exchange of 474 for the 485 candidate? Given the specificity differences, was there something that was being seen with 474 that was concerning?

Nello Mainolfi:

Great question, Jeff. Thanks for asking about this. Just to remind everybody, the decision was made by Sanofi to focus all the resources of the IRAK4 collaboration on KT-485. Based on preclinical data, KT-485 seems to be superior to 474 on both potency and distribution, and we demonstrated also complete lack of the subclinical QT finding that we had seen with 474 in our clinical studies. I will also reiterate that that particular finding was self-resolving with continued dosing, meaning that it will go away as you continue to dose, and we didn't learn anything, even in the ongoing Phase 2 studies, that spoke negatively with regards to the safety of the drug beyond what we'd already shared. I think it was really focused on the fact that 485 overall seemed to have a better profile and we believe both clinically and maybe commercially more competitive.

Since you asked me about actually IRAK4, I thought it's also interesting to see how the landscape is evolving. I don't know if you guys have seen AstraZeneca about to start a big phase two study in COPD after they've run a small earlier study, which we haven't seen data for, but they've shared that they're going to share that data for their IRAK4 inhibitor in COPD. That's another indication that we, at Kymera, thought IRAK4 could be well-positioned for... It's exciting that big companies, I think it's 400 patients... No, it's more than that. 1,000-patient studies. Anyway, just the field continues to learn and evolve, and we're excited to have a great asset out there that hopefully could also go towards that direction, but that's something that we need to obviously discuss with Sanofi.

Operator:

The next question is from Andy Chen at Wolfe Research. Please, unmute yourself and begin with your question.

Andy Chen:

Hey, thank you for taking the question. On IRF5, is there a reason for degradation and cytokine reduction and all that would not translate into humans? It looks like your STAT6 degrader has more than translated. Wouldn't all of that read through to IRF5 or is there still something special about that molecule that makes you think that you're still maybe semi-concerned and

maybe the de-risking steps are still ahead of you? Also, what are the top two, three safety signals that you'll be watching for in humans? Thank you.

Nello Mainolfi:

Yeah, great question. IRF5, we're at this stage... To be honest, we've been here for a while, where all of our programs have translated really well. You can argue whether you like the target and the biology that translate, but all of our programs have translated really well in the clinic. We expect IRF5 to translate just as well as KT-621. Also, for IRF5 KT-579 in non-GLP tox, we've seen no adverse event of any type when we went up to 200 fold above the expected 90% degradation human exposure. We are in the midst of IND enabling studies. I'm confident we'll continue to see an exceptionally well-tolerated drug. We're excited about that drug, we're working already really hard not only to prepare for the healthy volunteer study that will start early next year, but the team has been spending the past few months working on and planning our patient study that will start soon after the healthy volunteer study. We're prioritizing indications, we're talking to KOLs, and refining protocols. Yeah, we are working under the assumption that the translation will be happening just as well as it did for 621.

Andy Chen:

Thank you.

Bruce Jacobs:

We're just about up against time, operator. We'll try to just move really quickly through these last few.

Operator:

One moment whilst we wait for questions. The next question is from Ellie Merle at UBS. Please, unmute yourself and begin with your question.

Ellie Merle:

Hey, guys, thanks so much for taking the question. Just another one on IRAK4. Can you elaborate a little bit on what was seen clinically with the first generation IRAK4, and what gives you the confidence in the efficacy of this target in AD and HS? I heard your comments on AstraZeneca, any difference now in terms of how you might be thinking about the opportunity set across indications now for IRAK4? Then also just a follow-up on CDK2, can you elaborate on some of the learnings on working with molecular glues versus heterobifunctional degraders and your confidence in the selectivity for CDK2 with these programs? Thanks.

Nello Mainolfi:

Yeah. On IRAK4, quickly, we can't speak to what we've seen or not seen in these studies. Unfortunately, that is Sanofi's guidance on that. On indications, again, this is again another question for Sanofi, but asthma and COPD have always been on the high priority list for that biology. Obviously, we're talking about non-eosinophilic COPD, which is a huge patient population.

With CDK2, again, we've historically said that these two, the heterobifunctional degrader and molecular glue are two complementary technology and they're not one the next generation of the other, although many companies seem to go in that direction. We use molecular glues where we believe that binding site and ability to bind to the target is either not feasible or not with the selectivity. If you use specific binding to CDK2, it's really difficult to find selectivity against CDK1, and that's why we built our CDK2 degrader, which does not have any cross-binding with CDK1. That's why we went in that direction.

Ellie Merle:

Great, thanks.

Operator:

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

Nello Mainolfi:

Well, thanks, everybody. Sorry we went a bit too long today. Another exciting quarter, we're here for any follow-up questions, you know where to find us. Thanks again for joining, have a great day.