Kymera Therapeutics Fourth Quarter and Full Year 2024 Results Call | February 27, 2025

Megan:

Good day everyone. My name is Megan and I will be your conference operator today. At this time, I would like to welcome you to the Kymera Therapeutics Fourth Quarter 2024 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's Quarterly update. As you will notice, we have moved to video format, which we hope you will enjoy. Joining me this morning are Nello Mainolfi, our founder, president and CEO, Jared Gallob, our chief medical officer, and Bruce Jacobs, our chief financial officer. Following our prepared remarks, we will open the call to questions where we will take questions from our publishing analysts on video. To be sure we have enough time to address everyone's questions. We ask that you please limit your questions to one and a relevant follow-up.

Before we begin, I would 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 10K 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 will now turn the call over to Nello.

Nello Mainolfi:

Thank you, Justine. Welcome everybody. We're excited to have you with us today as we transition our quarterly financial updates to a video format. I believe this reflects our continued commitment to transparency, open communication, and deeper connections with our stakeholders. We will have lots of data updates this year, so it'll be productive to have videos and slides. We'll use today's call to briefly reflect on our achievements of 2024, which positions us for what I anticipate will be a very exciting 2025.

Stepping back, we started 2024 with our R&D day where we shared our expanded focus on immunology with the goal of developing therapies that have the potential to deliver biologics-like efficacy with the convenience of an oral daily pill. There we introduced STAT6 and TYK2, which exemplify programs we believe have the potential to disrupt conventional treatment paradigms and expand access to millions of patients around the world.

As we mentioned at the time, the strategic effort was years in the making, but it has materialized rapidly with our recent clinical progress. Our team executed exceptionally over the past year and successfully

delivered on all of our key priorities. Here's a quick recap of what we did last year. For STAT6, we completed IND-enabling studies for KT-621, filed an IND and initiated the Phase 1 healthy volunteer study. Now we're completing the final MAD cohorts. This is the first STAT6 targeted agent to enter clinical development.

While the attractiveness of STAT6 is a target and the strong validation of preclinical work has attracted many others to the space, we believe we are the unquestioned leader, a position in which we intend to build. With TYK2, progress continued as well. Since the first introduction in January again of last year, we named an advanced and novel development candidate KT-295 and are now completing IND-enabling studies. Regarding IRAK4, we continue to support our partner Sanofi in their efforts to progress the two ongoing Phase 2b studies in HS and AD. Importantly, following an interim analysis in the middle of last year, Sanofi expanded the studies to accelerate the overall development timelines on path to pivotal trials. Finally, while less visible to investors, we progressed our early pipeline of novel immunology programs to the point where we're poised to soon share our new exciting immunology target.

So, with all the progress that I just discussed, which reflect really a year of truly outstanding accomplishments, we're positioned to an even more productive 2025 where we'll have several clinical advancements across our immunology pipeline.

To summarize, here is what you can expect this year. Starting with STAT6, we're on track to report KT-621 Phase 1 data this year for both the healthy volunteer trial, which will happen in June, and the Phase 1b trial in AD, which will happen in the fourth quarter of ‘25. And we'll also initiate two Phase 2b studies. AD will start in the later part of ‘25 and asthma will start in early ‘26.

For TYK2, we're on track to advance KT-295 into the clinic next quarter with Phase 1 healthy volunteer data before year-end. Stay tuned in May as we plan to unveil our next program, a previously undrugged transcription factor that has the potential to be first-in-class agent for multiple rheumatic as well as other autoimmune diseases. Importantly, we will not stop here. Our goal remains to deliver at least one new IND per year, so you should expect more exciting new developments to be disclosed at a consistent pace.

I want to finish my comments here where we started this call, which is with our drug development principles and strategy. Kymera is deeply committed to developing an industry-leading immunology pipeline featuring innovative oral small molecule therapies. We're determined to ensure that patients won't have to choose or make trade-off between efficacy, safety, convenience, and cost. We believe that if we achieve this, we will expand the choices available to patients and transform how patients are treated in immunology and potentially beyond.

Traditional small molecules have always offered convenience benefits by delivering powerful pharmacology compared with biologics as being elusive. We believe our oral medicines can provide a differentiated and potentially better solution, oral drugs with biologics-like efficacy, and we're dedicated to making this a reality. Our work to deliver on the promise continues. We look forward to delivering on and sharing multiple data readouts in the next 12 to 18 months that we believe will validate our strategy and put us that much closer to addressing many important markets with next-generation oral drugs.

Before handing the call over to Jared, I'd like to take a moment to thank Leigh Morgan who has been a director at Kymera for the last three years. As you may have seen in the filing today, she has decided not to stand for reelection at our upcoming annual shareholder meeting in June. I would love to personally thank her for all the contributions she's made at Kymera over the last several years, which have been much appreciated. With that, let me pause here so Jared can give you more details on our clinical strategy plans and data.

Jared Gallob:

Thanks, Nello. This is an exciting time for Kymera from a development perspective. We are well positioned to achieve multiple clinical data readouts that will further validate our approach and strategy. So, let's go ahead and jump in. Last month, we laid out our accelerated development strategy for the STAT6 program, which starts with Phase 1, Phase 1b, and parallel Phase 2b trials that enable subsequent registrational Phase 3 studies across multiple indications. Each of these trials serves a distinct and unique purpose in our clinical development strategy for KT-621.

I'll walk you through some details on each of these trials today, but I want to first start at a high level. So, starting with the Phase 1 healthy volunteer study, our primary goal there is to demonstrate STAT6 degradation and safety. In addition, we will also take an early look at several Th2 biomarkers. Now, while we will look at biomarkers in the Phase 1a, the Phase 1b study will be a much more relevant and meaningful opportunity to assess the impact of STAT6 degradation on multiple Th2 biomarkers in blood and skin, and that study will also take an early look at any clinical efficacy signals.

After these two Phase 1 studies, the parallel Phase 2b trials in AD and asthma are intended to measure the clinical activity in two key indications and enable dose selection for registrational studies in multiple indications. In terms of the specifics on some of these activities, our Phase 1 healthy volunteer study is ongoing and is evaluating single and multiple ascending doses of KT-621 versus placebo. The primary objective is 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.

Given all the human genetics data, the preclinical data we have generated and the pathway validation, we believe that if we can demonstrate this, it will largely de-risk the program and increase the probability of success once we move into patients. As we've shared in the past, in healthy volunteers, we expect to see some impact on several Th2 biomarkers such as TARC and IgE. Our expectation entering the trial is that the effect would likely be comparable to what has been reported for dupilumab. Though as we have said, we believe the best opportunity to show effect on a variety of Th2 biomarkers will come in patient studies where these are greatly elevated at baseline.

In terms of the trial status, we are recruiting the last remaining cohorts and we're on track to report results in June.

As we approach the start of the Phase 1b trial next quarter, we want to take a moment and provide a few more details about the study. The Phase 1b trial in moderate to severe atopic dermatitis will be a relatively small single-arm open-label trial with dose selection optimized based on Phase 1 healthy volunteer results. Patients will be administered KT-621 once daily for four weeks. The trial is expected to include approximately 20 patients.

The key study aim is to show that robust STAT6 degradation in blood and skin by KT-621 has a dupilumab-like effect on reducing multiple Th2 biomarkers in the blood such as eotaxin, TARC, periostin, IgE, and others, and on the transcriptome of active AD skin lesions. The study will also assess KT-621 effect on AD clinical endpoints such as EASI and pruritus NRS. We decided to make this a streamlined biomarker-focused study to transition quickly into Phase 2b, which is on critical path to Phase 3 initiation and eventually registration. In the fourth quarter, we'll read out the Phase 1b data and also initiate the first Phase 2b placebo-controlled dose range finding trial in moderate to severe atopic dermatitis. In the first quarter of 2026, we will start a second Phase 2b trial in moderate to severe asthma. This initial parallel development strategy is intended to accelerate late-stage development across multiple Th2 dermatological, gastrointestinal, and respiratory indications. So, turning now to TYK2, this is another program where we believe we can mimic the human genetics TYK2 loss-of-function profile and achieve biologics-like activity with an oral drug. We're on track to start the KT-295 Phase 1 healthy volunteer study in the second quarter. The primary goal is to demonstrate safety and full TYK2

degradation in blood and skin, which if achieved, we believe would be the first time an oral small molecule was able to show complete blockade of TYK2 signaling. And we expect data will be shared in the fourth quarter of 2025.

Now to round out our immunology franchise, I'll wrap up with IRAK4. As Nello mentioned last year, Sanofi took steps to accelerate the overall KT-474 development timeline. The decision to expand the Phase 2 program was to structure the hidradenitis suppurativa and atopic dermatitis trials with the necessary regulatory perspective to enable dose selection and advancement directly to pivotal Phase 3 studies ultimately with a meaningfully shorter development timeline.

To support this strategy, the size of the studies increased with additional doses planned for evaluation in both trials. There are no changes to the Phase 2 study endpoints. With the planned expansion of the trials, the primary completion dates were adjusted to the first half of 2026 and mid 2026 for HS and AD, respectively.

The progress made by our team in 2024 sets us up to execute in 2025. Importantly, within our immunology franchise, we believe KT-621, our first and we believe best-in-class oral STAT6 degrader has the ability to transform the treatment of Th2 inflammatory diseases and we look forward to sharing Phase 1 data in healthy volunteers next quarter and advancing the program into patient studies while also initiating the TYK2 KT-295 Phase 1 trial next quarter and sharing data by year-end.

And as Nello mentioned, we're excited to introduce our next immunology program, which aligns perfectly with our pipeline portfolio strategy. We're planning to host a company webcast in early May to unveil the new target, and we'll share more information as we get closer. I should point out that the KT-621 Phase 1 healthy volunteer data, which we expect will be reported in June, will be its own separate event. I'll now turn the presentation over to Bruce for a review of the fourth quarter and full-year financials. Bruce?

Bruce Jacobs:

Thanks, Jared. As I review our fourth quarter 2024 financial highlights, please reference the tables found in today's press release. Revenue in the fourth quarter of 2024 was $7.4 million. All of that was attributable to our Sanofi collaboration. With respect to operating expenses, R&D for the quarter was $71.8 million. Of that, approximately 6.8 million represented non-cash stock-based compensation. Adjusted cash R&D spend of $65 million excluding that stock-based comp reflects a 23% sequential increase from the third quarter. G&A for the quarter was $16.3 million. Of that, approximately $7 million was non-cash stock-based comp and adjusted cash G&A spend of $9.3 million. Again, excluding stock-based comp was up 13% sequentially.

Our cash balance at the end of 2024 was $851 million. Our cash balance is expected to provide a runway into mid-2027, and that will enable us to execute on multiple data readouts you heard today, including several important Phase 2 trials across our programs.

So, this concludes our prepared remarks. If you'd just give us a moment to assemble in our conference room, we'll be happy to address any questions you have there. Thanks very much.

Megan:

We will now move to our question-and-answer session. 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. You may remove yourself from the queue at any time by lowering your hand. When it is your turn, you will receive a message on your screen asking to be promoted to a panelist. Please accept, wait a moment, and once you've been promoted, you will hear your name called and you may unmute your

video and audio to ask your question. As a reminder, we are allowing analysts one question and a relevant follow-up. We will now pause a moment to allow the team to gather and assemble the queue.

Our first question will come from Faisal Khurshid with Leerink Partners. Please unmute your audio and video and ask your question.

Faisal Khurshid:

Hey guys, good to literally see you and congrats on the updates. Just a quick one for us. What supports your view that the 28 day dosing in the atopic derm Phase 1b is enough time to show a robust biomarker activity? And then could you also comment a little bit on how you've kind of thought about the inclusion exclusion criteria for that Phase 1b?

Nello Mainolfi:

Thank you. Good morning. Good to see you as well. Jared, why don't you take this one?

Jared Gollob:

Sure. It's an important question and we know from prior dupilumab trials where there have been 16-week endpoints in AD, in moderate to severe AD, that when you look at the time course of what's happening, they don't just look at six weeks, they also look at earlier time points. And looking at four weeks, it was shown that there was a clear, very clear impact on Th2 biomarkers as well as on clinical endpoints like EASI and Pruritus NRS. So, I think we're very confident that 28 days of treatment using an optimal dose selected from Phase 1a should allow us to see a clear impact on Th2 biomarkers, which is the primary objective of the study. And to also give us an opportunity to see an impact on clinical endpoints.

In terms of eligibility criteria, I think here, it's going to be very important that we have stringent criteria that make sure that we're getting number one patients that definitely have AD. And secondly, patients that have moderate to severe disease. I think that's very important in trying to minimize any sort of placebo effect, is to pay close attention to those particular eligibility criteria. That's going to be a very important part of the study.

Maybe just mentioning a few other things that are important to reduce or minimize placebo effect. One is having a rigorous approach to site selection, making sure we bring on sites that are able to select the right AD patients for the study. And have personnel that can perform the clinical assessments in a rigorous manner. And to also make sure that we're closely monitoring for drug compliance on the study, and also making sure that patients are not taking any other con meds.

Nello Mainolfi:

Maybe if I can just add one thing. Obviously, hopefully it's appreciated that I think we have not only an amazing opportunity with this drug, but I also think we have a unique responsibility to do the right type of drug development. And so also another reason for the 28-day study, besides being long enough to measure... And actually the study's powered enough for 28-day to measure strong biomarker changes, is that what’s on critical path is going into a dose-ranging Phase 2b study, which is on path to go to Phase 3and registration. So, what we don't want to do is spend time unnecessarily in early clinical development in studies that are informative but not critical.

Faisal Khurshid:

And then could I ask you to clarify on the choice to not have a placebo arm in the Phase 1b, especially given what's been seen in other atopic derm studies?

Nello Mainolfi:

Yeah, maybe Jared, maybe I'll start and it kind of goes back to what I just said. So, the goal of the study, as Jared said, is to demonstrate a biomarker profile in blood and skin that we believe will be robust and can be compared to, for example, the dupilumab, four week data. And for that type of study, actually we don't believe we need the placebo. We know that biomarkers do not move substantially in the placebo arm of these studies. And again, if we had to run a placebo-controlled study for four weeks powered to demonstrate a difference on clinical endpoints, this would be a much larger and longer study. And again, this does not fulfill our drive, which is to go into Phase 2b ASAP.

Faisal Khurshid:

Got it. That's super helpful. Thank you guys so much.

Megan:

Our next question is connecting. One moment. Our next question will come from Andy Chen with Wolfe Research. Please unmute your audio and video and ask your question.

Andy Chen:

Hi, nice to see you in person. So, the Phase 1b is designed to be single arm, so we won't be able to see dose response on biomarkers. Do you think the Th2 biomarker data is going to be so clean that we won't need to see dose responses across different doses to be comfortable with the data? Just curious if we're going to have enough data to answer additional questions about efficacy by Q4. Thank you.

Nello Mainolfi:

Yeah, so maybe I'll start, and Jared can add more specific points. So, thanks, Andy. I think this is a great question. So, our goal is to take into this Phase 1b study a dose that has demonstrated in healthy volunteer the type of profile that we're looking for. And as we said, at least 90% degradation in blood and skin. We have shown preclinically that that type of profile leads to extremely robust biomarkers effect in a plethora of readouts. So, our development is based on our understanding of the biology and both in terms of all the preclinical data we've amassed as well as on human genetics.

So, we expect that a dose with that profile will have a dupilumab like effect. And that's really what we want to show. If we were not certain, and if this was really an exploratory Phase 1b study to show an early proof of concept, we would probably design it differently. We're designing this study with expecting a successful outcome based on all the experience that we've built internally and all the data we've generated so far.

Jared Gollob:

And maybe just to add, the opportunity for being able to see an impact on both Th2biomarkers and clinical endpoints to see a dose response there will come from Phase 2b where that will be a true dose range finding study. And that will give us a strong opportunity to do that. And as Nello said earlier, the key really is for us to use Phase 1a information to select the doses for the dose range finding Phase 2b study, and to get to Phase 2b as quickly as possible. And then Phase 2b becomes a great platform for us to show perhaps differences in impact on Th2 biomarkers and clinical endpoints depending on the doses

that we select for Phase 2b. And that will ultimately allow us to pick the optimal dose for the Phase 3 registrational studies.

Andy Chen:

Thank you, Nello. Thank you, Jared.

Megan:

Our next question will come from Michael Schmidt with Guggenheim. One moment as they connect. Michael Schmidt with Guggenheim, please unmute your audio and video and ask your question.

Paul:

Hey guys, thanks for taking our question. This is Paul on for Michael Schmidt. Just on the STAT6 program, what do we know currently about the potential bioavailability of KT-621 in tissues of interest? For example, skin versus lung tissue or others that might be disease relevant down the line. How predictive are the preclinical models there? Is there any opportunity to look into that in the early Phase 1 or 1b? Thank you.

Nello Mainolfi:

Yeah, so obviously I can't speak to the Phase 1 healthy volunteer data, but I can speak to the preclinical data that we generated. And we generated extensive data across all species that you can imagine, mouse, rat, dog, non-human primates, and others where we've been able to demonstrate that KT-621 not only is orally bioavailable, but is actually highly active at low oral doses and distributes evenly across all tissues of interest. We've shown in non-human primates equal both distribution and degradation in blood, skin, spleen, lungs. And so, our expectation is that the preclinical profile will translate equally in human. And the way to measure that, obviously we can take lung and spleen, but obviously we can take blood and skin, as we've done for other programs. And so we believe that those are great surrogate tissues to show not only hopefully that the desired degradation that we expect to have, but also a consistent degradation across multiple tissues.

I would just go back to what we've been saying for the past years, I would say. That we've been fortunate that all of our programs have translated impeccably, I would say, between preclinical and clinical. So, we hope and expect that ‘621 will follow suit on that particular front.

Paul:

Great. And if I could just add a quick follow-up on the plan design for the Phase 2 AD study. Is the sort of ongoing IRAK4 study a reasonable comp, three different doses plus placebo, any meaningful differences in the type or severity of AD patients you might recruit there?

Nello Mainolfi:

I'm going to save Jared on this one. I think at this point, we're not going to comment. Hopefully you guys appreciate that we're sharing the relevant information when it's the right time, as we're doing today for the Phase 1b. We promise you that when it's the right time, we will share that kind of information as well.

Paul:

Great. Thanks very much.

Nello Mainolfi:

Thanks, Paul.

Megan:

Our next question will come from Ron Feiner with JP Morgan. Please unmute your line, your video, and ask your question.

Nello Mainolfi:

... I was just going to say-that you guys don't have to show the video in case you don't want to, right? I think it's okay just to ask the question. But anyway, go ahead.

Ron Feiner:

Thanks. This is Ron on for Eric. I just wanted to ask again on the dose selection, maybe you will be evaluating only one dose in this Phase 1b for AD. And how does the SAD, MAD data so far from the healthy volunteers trial kind of give you information on the effective range, at least from a PD perspective?

Nello Mainolfi:

Yeah, I mean unfortunately, we can't go into the answer. But what I think I can say, Jared has already said it, but I'll say it again. The beauty of protein degradation, unlike any other technology out there that you can measure target engagement both in a dose-responsive manner as well as in a time-responsive manner. So, you know what is the level of degradation of your target at different doses, at different time points. And so, we have designed a really comprehensive Phase 1 healthy volunteer study that is looking at a range of doses that will allow us to understand as well as we can, the relationship between those PK and degradation in blood and skin. With that set of data, as we said in clinical trial.gov, we expect up to 120 subjects on the study. So, we'll have a really large dataset. We will be able to have enough to confidently select the, let's say, three doses for the Phase 2b studies.

And we don't believe... And we've already shown with IRAK4 that there is a really strong translation of degradation between healthy and diseased patients in terms of degradation profile. And so, we believe that everything that we've designed going from a very comprehensive Phase 1 healthy, going into 1B to really demonstrate that one of the doses that likely will be taken into Phase 2 is given the type of profile that we expect in patients, it's a, let's say, confirmatory study. And then go into a Phase 2b ASAP. We feel very confident about our plan right now. And so again, we look forward to sharing the data along the way and then get to the end of the year with those big studies.

Ron Feiner:

Thanks. And then just maybe if I can try, on the new program, are you guys geared more towards staying in the Th2 space? Or anything additive or orthogonal to the current programs, or is it going to be completely new?

Nello Mainolfi:

Well, I think what we've tried to do, if you look at our pipeline, so in immunology, I think we're shaping up to have the best oral immunology pipeline in industry. I know my team doesn't like me to say it, but I keep saying it. If you look at IRAK4], this is a classical Th1, Th17 program with IL-1TLR activity. If you look at TYK2 it's IL-23, type one interferon. If you look at STAT6, it's a classical, maybe the best Th2 target, I

would say. And so, these are all complimentary pathway that actually one can imagine could be synergistic in a combination one day. And so, you should expect this other target to be a complimentary pathway to the ones that we've shared so far.

Ron Feiner:

Thanks.

Megan:

Our next question will come from Jeff Jones with Oppenheimer. Please unmute your audio, video, and ask your question.

Jeff Jones:

Good morning, guys, and thanks for taking the question. I think we've asked a lot on STAT6. Curious to get your view on the TYK2 program from a similar perspective, as we think about biomarkers and tissue penetration. How we should think about looking at the healthy volunteer data, which is obviously some way out. So, can you share how you're going to be looking at not only safety but efficacy signals there from a perspective of TYK2 and biomarkers?

Nello Mainolfi:

Jared, do you want to take this one?

Jared Gollob:

Sure. Yeah. I think for the TYK2 program, I think we have a unique opportunity to show pharmacology that is differentiated from what's out there for typical TYK2 small molecules. And that's why we believe this program can eventually attain biologics like activity hopefully, which has not really been attained by the small molecules. And to do that its important, we believe that for the pharmacology to show that we can fully degrade TYK2 with 95 plus percent and keep that degradation level 24/7, sort of round the clock, in order to give us that full pathway blockade, that would be the equivalent of what you can get with an injectable upstream biologic. So, I think when we look at the Phase 1 study, just as we've done in STAT6, we're going to have very detailed looks at the impact on TYK2 levels in blood and in skin in healthy volunteers, and looking over time, looking at different dose levels in SAD as well as in MAD. And that's going to really give us a very good idea as to whether our pharmacology can really achieve what we've seen preclinically in animals, where we can achieve that sort of profile of very deep chronic degradation of TYK2 at doses that are safe and well tolerated. So, that's going to be, I think, critical for us in terms of the biomarkers that will be looked at in that TYK2 study. There will be other opportunities potentially to look at additional biomarkers that reflect impact on IL-12, IL-23, Type 1 interferon pathways and sparing IL-10. But I think the primary focus will be on achieving that sort of pharmacology that I just mentioned in terms of the impact on TYK2.

And if we're able to see that sort of impact, I think that will be very encouraging for us. And our plan then is the next step after Phase 1 is to then do a Phase 2 proof of concept study, probably a placebo-controlled study that might be in a disease like psoriasis, where there we want to be able to bring optimal dose or doses from that Phase 1a study into Phase 2, and really demonstrate there that we have biologics-like activity, for example, that we have Skyrizi-like effect on PASI-90 in psoriasis. And that would be the key inflection point for us to then say, okay, here we have a compound that is clearly differentiated from small molecule inhibitors. It has biologics-like activity, and then we would want to

move it forward potentially across multiple potential different indications that are both interferonopathies such as lupus, IBD, in addition to psoriasis.

Jeff Jones:

Great, appreciate that. And just one quick follow up, as you mentioned the possibilities in Phase 2, how do you think about, in terms of patient selection, patients who have prior exposure to say deucra or one of the biologics impacting the IL-23 pathway?

Nello Mainolfi:

Maybe it's a bit too early, Jeff, to discuss it. Obviously, let's say we end up going in psoriasis, there is lots of patients that are available to us to ask the question in a way that is not influenced by failures on, let's say, pathway agents. So, we'll obviously be very thoughtful by the patient selection, but we'll share more of that as we getting closer to the study.

Jeff Jones:

Thank you.

Nello Mainolfi:

Thanks.

Megan:

Our next question comes from Kelly Shi with Jefferies. Please unmute your audio video and ask your question.

Yi Fan:

Hi, thank you for taking my question. This is Yi Fan on behalf of Kelly from Jefferies. Another question on STAT6. So, for the biomarker analysis in the MAD portion, how long is the follow-up going to be? Can we expect data from IgE and TARC at multiple time points across the dosing period and after 14 days of dosing? Or we may only expect one or two time point? And also wondering how would this biomarker data in health volunteer guide your decision on dose levels in Phase 1b and the Phase 2 trials in patients? Thank you.

Nello Mainolfi:

Maybe I'll start. This is a great question, actually. So, the first part, it's obviously it's easy. Yes, we will have several time points, both during doses and post-dosing period. The second question is, actually it's a great question because it allows us to touch on a very important point, which is if you look at the dupilumab healthy volunteer studies where we now have it in our deck sometimes to show it to investors, what does their data look like? Instead of just talking about numbers, actually looking at the totality of the dupilumab data, you will actually see that in most cases, if not in all cases, there is actually a lack of dose response between the different doses.

So, if you actually chose the healthy volunteer biomarker data for dose selection for dupilumab, let's talk about dupilumab, you would probably pick the wrong dose to go into Phase 2 or Phase 3. But obviously, how we're going to select these doses by looking at the totality of the data, right? For us, the key information is can we degrade STAT6 robustly? And by that, we mean 90% or more in blood and skin. Is

that safe and well tolerated? And that's really what we're going to use to make a dose selection. But we will also look at the totality of the data and obviously share with you at the right time.

Yi Fan:

Thank you.

Megan:

Our next question will be coming from Brad Canino with Stifel. One moment as he connects.

Brad Canino, please unmute your audio video and ask your question.

Jared Gallob:

Great. Good morning. So, look, I think you've done a really good job previewing the STAT6 healthy volunteer data, and I can see how the target profile will allow you to move into patients with conviction. You can marry that to the pre-clinical outcomes. Just the outstanding question, you started to touch on this in some of the prior responses is how you see the Phase 1b building on that conviction. A 20-patient study, short four-week treatment, how do you really see that being a useful tool to shape the view of the profile potential, even though it's not designed to be a definitive assessment of the drug in patients?

Nello Mainolfi:

Yeah. So, look, Brad, our view is that this is going to be, I don't know what we want to call it, the drug of the decade or the drug of the century. So, we have to be really thoughtful about the study designs along the way, and we have to really ask the right question in each study, otherwise we end up creating confusion instead of clarity. So, the questions for our studies are very well-thought-out and I think we're going to get the right question in the right study. So, for healthy volunteer, the question is, I'm going to keep saying it, can we degrade the target well? Robustly, I should use the same word. And is that safe or well tolerated? To me, to us, this is a huge de-risking step. This is the first time the STAT6 have been drugged. So, this is paramount type of information. We will collect the biomarkers. I expect they will look like dupilumab in health, I was talking about. And then, the study is really designed for us to move into Phase 2b ASAP. Now, why are we running the Phase 1bB study? First of all, the main goal is really to generate data, especially around biomarkers, that will allow us to, I think close the circle on, is a STAT6 degrader a dupi-like agent? We really cannot do it in healthy volunteers for all the reason we discussed. These biomarkers don't move enough, there is a lot of noise. In many cases, you don't even see a dose response. It's more of a yes or no do they move. Can we change them? I expect, right? But in patients, we have a plethora of chemokines, cytokines in blood and skin, and in four weeks, we can actually see a big window that we should be able to reduce robustly with our drug.

And to me, that's really what we're trying to show in that study. That study is telling potential investigators and patients on our Phase b studies, look, this is a drug that is safe and well tolerated, degrades the target well, and actually also shows has a dupi-like effect in biomarkers. And I'm confident that that will translate into a beneficial clinical effect in these patients so that we can power up the studies and recruit fast our Phase 2b studies. That's really what we're trying to do. I think the Phase 1b, it's in a luxury, it's not a critical part study, but we believe it's a powerful study to really demonstrate everything that we've been saying for the past year and a half on the STAT6 to be a dupi in a pill. I think that data will clearly demonstrate that without the need of other doses or placebo because biomarkers don't lie.

Brad Canino:

Thank you.

Megan:

Our next question comes from Marc Frahm with TD Cowen. Please unmute your audio video and ask your question.

Marc Frahm:

Hey guys, thanks for taking my questions. Just start off, one clarifying question on some of the enrollment criteria you guys mentioned earlier for the Phase 1b, just take the obviously no concomitant meds, but will you be requiring people to be biologic and JAK therapy naive, or could there be a patient or two that end up in this trial that have at some point seen some of these more modern agents? And then, I'll have a follow-up after?

Jared Gollob:

Yeah, that's a good question, Marc. No, I mean, we will allow patients who have had prior systemic therapy or biologics that could include dupi or could include a JAK inhibitor as long as they responded to it. So, there will be those patients enrolled onto the study as well as patients who are biologics naive.

Marc Frahm:

Okay, thanks. And then, just on the Phase 2bs that you're planning in AD and asthma. Dupixent has a kind of a range of, a handful of different kind of dosing paradigms depending upon the indication. Do you think those trials give you, well, ultimately give you enough information about dosing to go to Phase 3 for kind of across the board of the IL-4 STAT6 pathway? Or are you expecting that you'll ultimately need more Phase 2bs and some of these other indications as well to help select dose for the different indications? And if so, should we see, expect to see those trials done in parallel to AD and asthma, or you were going to really wait for AD asthma data until you would open up anymore?

Nello Mainolfi:

So, as we said in the last discussion around our healthcare conference early in the year, our development plan is based on previous experience of other pathway agents in this space, in TH2, where eventually they were able to select a dose from, let's say AD to go a Phase 3 dose, in AD to go into other skin indications, and a Phase 3 dose from asthma to go into other respiratory indications. And so, we have a high degree of confidence that these would be the only Phase 2b studies that we will run that will allow us to go into seven, eight or more Phase 3 programs. But obviously, just to be absolutely clear, that will have to be demonstrated also along the way. Obviously, we think that can happen, but we'll have to go through the studies to make sure that will happen.

Marc Frahm:

Okay. And then lastly, as you get that more robust efficacy readout from these Phase 2bs, obviously the goal is to every bit match Dupixent, it may be even potentially exceeded a little bit. But if that isn't the case and you end up being a bit lower on efficacy, is that acceptable, and how close do you think you need to be to justify kind of the expense of late stage trials?

Nello Mainolfi:

Yeah. So first, I like to say, I'd like to clarify our expectations. I hear yours, Marc. So, our expectation is that based on the biology and what we've seen preclinically, that we should have an effect in TH2 diseases that is similar to dupilumab. Again, we've shown some numerical superiority preclinically, but I think for us, our expectation is that it will look dupi-like. We, to be honest, are not expecting that we will have lesser an effect. We have talked to, and others have done calls with KOLs in the space that have made the case, that a less active drug that is oral and safe and well tolerated could be also extremely successful. So, we believe that the bar for success is not dupi-like, but our bar is that we're going to be dupi-like.

Marc Frahm:

Okay. Super helpful. Thank you.

Megan:

Our next question will come from Ellie Merle with UBS Securities. Please unmute your audio/video and ask your question.

Ellie Merle:

Hey guys, congrats on all the progress. Just in terms of dose selection, how are you thinking about how the doses you plan to study in Phase 2b will compare between atopic derm and asthma? I guess, do you expect to study the same doses in each indication? And then, kind of a broader question about STAT6 as it relates to dose selection, is how does STAT6 expression potentially differ across indications or maybe between patients? Thanks.

Nello Mainolfi:

So, I let Jared answer the question. I just want to add one thing to address the later part of your question. So, we have seen, and I can only speak about preclinical data that expression level of STAT6 have no effect on our degradation kinetics. So, which means that our expectation is no matter the expression levels, we'll be able to degrade it to the level that we need to or we want to, which pre-clinically has be 90% plus. But Jared, do you want to speak to the Phase 2 dose?

Jared Gollob:

Yeah, Ellie, in our preclinical models and we have I think good preclinical models for both asthma and atopic dermatitis, we've shown in both those models that doses of ’621 that give us at least 90% degradation lead to sort of optimal activity or dupi-like effect. So, I think our expectation therefore is that the doses that we choose for Phase 2b coming out of Phase 1a will be similar doses for both the Phase 2b asthma study and the phase 2b AD study.

Nello Mainolfi:

Then the question could be, is the Phase 3 dose going to be different? I think it's unlikely, but that's the point of the Phase 2b studies. I asked the follow-up already, Ellie, so...

Ellie Merle:

Okay. Great. Thanks guys.

Megan:

Our next question comes from Parth Patel with Morgan Stanley. Please unmute your line and ask your question.

Parth Patel:

Hi, guys. Can you hear me?

Nello Mainolfi:

Yep.

Parth Patel

Sorry, my video's not working. This is Parth on for Vikram. So just a question on ‘621. So, following the Phase 2 studies in AD and asthma, how expansive of a Phase 3 development program would you expect to initiate for KT-621? And how would you prioritize indications given the broad potential you've laid out for the molecule?

Nello Mainolfi:

Okay, I'm going to take this and we're going to move quickly because here we have many questions at a limited time. So, what we've said is that we want to develop this drug with two key goals in mind that are actually not mutually exclusive. One is pace and path to registration and breadth of opportunities.

And so, we're going to run these important Phase 2b studies to inform Phase 3 selection for potentially eight different indications. And we're going to run parallel Phase 3 campaigns for several of those indications.

I think it's too early for us to say which and how many, but you can expect that if you look at dupi market where now asthma and AD account for more than 80% of the revenues, I would add that once COPD picks up, it'd probably be another important pillar of the revenues for that drug. I would expect that we will definitely prioritize those three. And then we have to, between now and Phase 3 campaign start, decide whether we want to add additional campaigns in parallel versus slightly staggered.

Parth Patel:

Okay, thank you.

Nello Mainolfi:

Yeah, thanks.

Megan:

At this time, we will only be taking one question and no follow-up. Our next question comes from Kripa Devarakonda with Truist Securities. Please unmute your audio video and ask your question.

Kripa Devarakonda:

Hey, guys, thank you so much for taking the question. This is a really interesting format. So, you have mentioned this before, but in terms of degradation levels, do you expect to see, similar to what you've seen in the preclinical studies, degradation levels similar in different tissues, skin and plasma? I know you're measuring it in healthy volunteers. And, do you expect that to follow through into patients as

well? Like, what you've seen in healthy volunteers would you expect similar degradation levels in patients, as well?

Nello Mainolfi:

Yeah, so again, preclinically, we've seen robust degradation. If you look at our studies, we were able to show more than 90% degradation in all species. We've also seen, as I mentioned, we have non-human primate, we also have other species that we haven't shared data for, but where we've seen consistent degradation across tissues.

So, we do expect to see robust degradation, again 90% or above in healthy volunteers. And, yes, based on both STAT6 preclinical data where we've done, let's say, healthy animals versus disease models where we haven't seen changes of degradation profile. But I would probably speak more about, for example, IRAK4 where we haven't seen any difference of degradation between healthy and AD, which is relevant, obviously, for STAT6 in a way.

So, yes, we expect all of that. Obviously, we'll have to show it, and that's the point of some of these studies that are ongoing or will be ongoing.

Megan:

Our next question comes from Derek Archila with Wells Fargo. Please unmute your video and audio and ask your question.

Yvonne:

Hey, guys, this is Yvonne for Derek. Thanks for taking our question. A quick one from us. So, you mentioned on biomarkers for the STAT6, that they should be comparable to dupi. So, could you provide a little bit more color on what this means in terms of the TH2 biomarkers? And just remind us what did we see for dupi here? Thanks.

Nello Mainolfi:

Well, yeah, thank you. So, if you're talking about healthy volunteer studies. So, if you look at data from a publication from Regeneron, they showed, for example, that dupilumab in a dose response manner, both IV and sub q with multiple doses, were able to show within the first two weeks, we need to compare the first two weeks of effect, a maximal effect in TARC around, I believe, 35%. Actually, peaked early and then started to be less already by week two. Again, it was not really dose responsive, so it seemed a bit stochastic in nature, but there was a clear reduction for one of the doses.

And then for IgE, for the first two weeks, we really don't see much. I think if you draw a line, it's probably five, six, 7%. I haven't actually done the calculation myself, yet. So, for the first two weeks, IgE is pretty minor. And it does take, I think, people that understand TH2 biology, it's understood that it does take longer to impact IgE.

So, now that I've shared some numbers and a bit of context around, it's not surprising that we're trying to guide to, we'll probably look like that without getting too hung up on the actual number because those are, again, noisy, for example, for IgE, pretty close to baseline.

Yvonne:

Okay, thanks.

Nello Mainolfi:

Excellent.

Megan:

Our next question will come from Eric Wong with Goldman Sachs. Please unmute your audio and ask your question.

Eric Wong

Hi, this is Eric Wong on for Chris Shibutani. Thank you for taking the question. Just a quick one for me.

So just thinking beyond the Sanofi collaboration, how are you thinking about strategic partnerships to accelerate development or de-risking programs, I guess particularly in oncology? Can you elaborate on the criteria you'll be using to select partners and how you intend to maximize the value of those assets and potential deals?

Nello Mainolfi:

Yeah, so I will start, maybe, with mostly a general answer. So, I think that the biopharma industry can thrive by creating win-win partnerships. And it has done so for decades. So, we are part of this ecosystem and we will continue to think about where are the win-win opportunities.

As we've said, clearly, for our immunology pipeline, we don't believe that partnering in this point will add any value or accelerate our programs. So, for those reasons, we are continuing to advance our immunology pipeline independently and we're building the team. Jared is building a great team of immunology development that, I believe, is and will be even more so best in class at doing what we're doing.

So, with regards to the oncology, again in immunology, at some point that might happen, right, as we get closer to Phase 3 and registration. And if we're amazingly successful across the whole pipeline, it is possible, if not likely, that there could be some partnership for a program or another.

For oncology, as we said clearly last year now, that we had decided to continue those programs through the end of Phase 1 and then advance it beyond only in partnerships. And so, in order for us to partner a program, it will have to be a win-win for both parties, the company that takes the program on and us. And the criteria are simple.

I don't know that I need to go through the details, but obviously, a company that is driven, interested, and has the capability to do justice to those programs. Next question?

Megan:

Our next question will come from Jeet Mukherjee [with BTIG]. Will you please unmute your audio and your video and ask your question.

Jeet Mukherjee:

Great. Thanks for taking the question. So, just given the novel nature of STAT6 as a target, thoughts on its potential in the post-Dupixent setting, and if this is an area you plan to evaluate in a more fulsome manner, considering the Phase 1b will enroll some biologic experienced patients, as you just mentioned? Thanks.

Nello Mainolfi:

Yeah, I just want to clarify. So, the biologically experienced would be enrolled only if they didn't fail for lack of response. Right? So, it might be that they discontinued for other reasons, tolerability, or they just got tired of injecting themselves, for example, which we know happens.

So, I would say, look, the potential for STAT6 is to be the Th2 drug and to be the first option for every patient that has TH2 inflammation, whether it's asthma, AD, COPD, or EOE, etc. So, yes, is there an opportunity for post-dupi? Sure. But I don't think that's really the problem we're solving. I think the problem we're solving is getting these millions of patients that are not on dupi, that either can get it, can get reimbursed, they don't like the needles, to actually have an effective drug.

And I'm sure we will recruit enough patients as we continue development to also look at what that will look like. But I would say, honestly, it's not really where I think this drug will be positioned for. That's not the problem we're trying to solve. The problem is patient access to an amazing drug that solves a lot of problems. Thank you.

Megan:

Our last question comes from Sudan Loganathan with Stephens. Please unmute your audio and ask your question.

Sudan Loganathan:

Yes. Thank you for taking the questions and being on video today. So, mine is going to be just on the R&D and the spend. Just kind of curious on, as you're ramping up 2025 in those two trials for ‘295 and ‘621, how do you expect that to be the R&D expenses to be allocated between the two programs?

And then, could we anticipate any expense profile changes as depending on the progress of those two trials over the next one or two years?

Bruce Jacobs:

Thanks, Sudan. I thought I was going to escape talking on this call, but I guess not. Or at least on the Q &A part.

So, just, obviously, we have $850 million. That runway takes us into the middle part of 2027. If you just do the math over that 10 quarters, obviously, our cash burn will increase.

I'd say that the trajectory gets a little steeper into 2026 when the bulk of some of the clinical trial activity really kicks into higher gear and then maybe rises at a slower rate into 2027. So, hopefully, that gives you a little perspective. But, obviously, the important point is that we are well capitalized to get us through many of these important readouts that we discussed on the call today.

Nello Mainolfi:

Maybe the only thing I'd add is you should expect the STAT6 portion of it to be dramatically superior to the TYK2 portion of expenses, especially as we continue, at least in the next two to three years. Is that fair?

Bruce Jacobs:

Yeah.

Sudan Loganathan:

Thank you. Appreciate it.

Megan:

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

Nello Mainolfi:

Well, great. I want to thank everybody for joining us today. I also, hopefully, the new video format is appreciated. I assure you the background is real. It's not fake.

And as you all know, we're available for any follow up. We'll be at the Cowen conference in Boston, finally a conference in Boston, next week. And happy to, again, take any questions offline. Thanks again and see you again.