Divya - Interview

The first set of questions relates to new study sites. If working with new sites, how were new sites identified and what percentage sites participating are new study sites? So at the time of deploying this, all of the sites were new to us because this is a brand new study and we already identified the strategy. So this is a 220 site study, or I think almost 240 sites were planned for, and we've got about 220, and I think most of those are new to us. Did you examine a demographic summary of excluded populations? Did you encourage the use of sites with high enrollment of underserved groups? I think this is probably more of a question for Mindy. I know that she and our CRO partner PPD were trying to look at at least areas in the US where the demography was such that we should have more underrepresented populations available. So I think they try to focus on areas such as South Carolina, for example, and trying to map COPD prevalence to those areas as well. But I think she'd be able to give you a better answer on sort of specific sites from within those areas and how they looked at that. Where were new sites found? US or ex us? They're both, I think quite a large proportion of our sites. I think at least 25% to 30%, I think are us. But we have a lot of ex US sites. Did you go to countries that typically were not considered? This is a potentially registrational study, so I think our strategy was to try and get evidence in countries where we intend to market the product as well. There are countries relatively new to us. We're in 25 different countries, so we have countries including South America, we have countries from Asia Pacific. We would have liked to include even more countries from Asia Pacific in particular. We did not end up with as many countries as we would have liked there. That was down to the site feasibility responses that we got when we went to places such as Taiwan, and I think we're trying to explore Thailand as well. We did consider, outside of the study, forming some collaborations to sort of improve our understanding of countries such as China and India, but those plans are currently on similar because we're planning for phase three actually, so those countries are not included in the current study. But that was because we also didn't fully understand what kind of patients and whether the biology might be different because of other sort of cause de factors of COPD,

so that there might have been, other than cigarette smoke, a lot more environmental pollution contributing to disease. So we were trying to understand whether that's something to factor in for patient selection in those countries. Yeah, you bring up a good point though. I mean, we really kind of target our scope and catchment area based on registrational opportunities in those countries. Like we're not necessarily going to go somewhere that we would not be able to register. But yeah, that's just a good call out. Were there any issues with study startup? And if yes, what were the issues related to IRB site staff, study contact or budget? Again, I think it's probably better to ask Mindy some of these questions. But the main challenge that we as a study team faced, we were starting this study up last year. It's not really coming out of the pandemic, but covert was actually the biggest factor in how sites are resourced, as well as protocols for the respiratory study, where we're asking patients to do things such as spirometry and potentially speed them. In some cases, those were actually the bigger barriers and I think Mendy would be able to comment more specifically on things such as patient reimbursement, but that's something that we have proactively planned for, which was how do we get patients reimbursed, how do we try and make it as easy for them as possible. Did the sites need any additional support or training? If yes, how did the study team provide this training? Is this with regards to inclusion and diversity or just ~~generally?~~ I think yeah, both for inclusion, but also just like new sites that are maybe not experienced in clinical trials or maybe not experienced with clinical trials within Rose Genentech. Again, for the brand new site, I don't think that we have provided additional support for. I don't think we've got sites that are so brand new to research that they've required additional support. So even if they're new to us, I don't think they're necessarily brand new sites to clinical research. I only remember one or two sort of new PiS being introduced into the mix, someone sort of taking on a new role. We were trying to ensure that they would actually have a mentor on site and that we provide extra monitoring support rather than extra training. In terms of training at our investigative meetings, we have had a call out for the inclusive research. So we pointed specifically to our goals and asked the sites to contact us. So I think again, Mindy would have better view of how sites are contacting for support there. But that's been a specific call

out. We've had four investigative meetings and then in each of those we have our sites to let us know, can we help with any advertising or any recruitment issues, that if they are facing those, we're still getting up and running. 105 out of those, 220 sites are activated. We started recruiting, but we're still figuring some of this out. That's great though, that's a large number of sites. So getting being halfway there is quite an accomplishment. That's great news. Yeah. Was the site staff adequate for successfully executing the trial or did problems arise too early to know? That right, because as I mentioned, we're sort of halfway through site activation. We are finding, and this is mainly because of coghid. I think we are finding challenges. So we have had some sites drop out because their site staff have gone away because of isolation reasons. They haven't been able to have enough staff also for specific measures, certainly we've had challenges, so a lot of sites they've been interested in speeding collection have said no, we can't do this. Similar resource and constraints on CT scan. So for some sort of study specific things, we've been encountering some challenges, but it's not universal and it's not even sort of a country specific pattern. It's really down to some individual sites overall. For new study sites, what were the successes and what were the pain points or watch outs? I think Mindy would be the better person to ask. I also think it's probably a little bit early on for us to answer this question because we've just started enrolling into a year long study. Right. The next set of questions relates to protocol measures. What specific protocol measures did you implement to increase and ensure diversity in your study? For example, simplifying schedule of assessments or eligibility criteria? Relaxation? I think we definitely consider the schedule of events very carefully. Even though our study requires two weekly visits, we've tried to enable mobile nursing where we can so that patients can be visited at home. So that applies in whichever countries at the Ops team have been able to get that in place and we'll see if we can expand that. We looked at the schedule of activities for that reason so that those home visits can be enabled. So a lot of our two weekly visits for those reasons are very scaled back. And then in terms of the buyer market collection, we've scaled back so that for the main study actually as many people as possible can participate. And then we've tried to pull some of the more involved sampling into a substudy so that doesn't preclude

participation in the main study and allows some dedicated people, if they really want to come in for added for the speed of measures, et cetera. But that's just unlimited sites. I'm interested to have any. I know that you're still early on in site activation and enrollment, but have you got an adoption of mobile nursing services from any of the sites or are you hearing anything back from the investigators about any hesitancy to use that? I would ask Mindy. I know that some investigators in countries where we've not included have expressed interest in that interesting. I don't think at least to the medical monitor level, I haven't heard people say that they don't want to use it. I know from the mobile nursing themselves, they've been a little bit of concern about to what degree they carry the sort of safety equipment do they carry epen, do they carry more things? And with the fe pen there's the concern it would have to be prescribed by the Pi to the patient and make sure that the patient has it at home and kept up to date. So there are a few concerns raised by them, but I haven't heard of Pi's raising concerns so far with that. In fact, at least from the KL interactions that we had prior to that, they welcomed that idea and I think there has been adoption. So I think it's mainly us. And I know that the Upstream, we were exploring a couple of other countries, but I think we need to tell you about the uptake there. Great, thank you. Yeah, I think that's really key that your team took a look at the assessments and the schedule of assessments and really had that kind of forethought and that mindset to think about, okay, how would we enable this for these safety collection safety visits? That wouldn't necessarily require an in clinic visit, but of course, by providing that choice to the patient, that's huge. Rather than just kind of expecting everybody to come in every two weeks with far travel or difficult work schedules. Yes, we recognize that that's a barrier. And then even in terms of the total number of visits, I know that our PK team, for example, really wanted some extra visits for PK and that's where the team had a lot of discussions so that we really try to limit those extra visits even if it was for a substudy, but trying to limit that burden on patients. And I think the other thing that the Ops team has done is they've engaged with GreenFire as a vendor to enable payments to patients so more seamless reimbursement for travel and so on. You also mentioned inclusion criteria. I wish there was more that we could have done here. I think we've tried to make it as simple

as possible and I think we've had feedback to that effect from PiS and MSLs. That's actually quite a broadly inclusive study, not just for DNI, but this is more just for disease. We've tried not to exclude, say, former smokers, current smokers. In terms of the safety criteria, one debate that we did have was two main things. So I think TB screening and HIV, two key areas. And it would have been nice to have been able to get away from the HIV screening. I think the molecule was at a point that perhaps we could have done that, but I think we'll try and push more for the phase three if we can, because we don't have any suppressive effect as far as we can see. So I think that would be nice to be able to have more permissions there. But for TP, yeah, we tried to we haven't done it as a universal screen only in where regulators have specifically asked for it. So in South Africa and Czechoslovakia they asked for it, the Czech Republic, they asked for it because of the higher prevalence. And so we've enabled the local sites to implement that at screening, but haven't required that for all sites in the study. Was the protocol review for feedback by patient partners or community partners? Sadly not. I don't support excuse. It's just we were under immense time pressure for competitive reasons. We got from governance approval to the critical approval, I think it was about four or five weeks. So there really wasn't a lot of time. That being said, I worked with the COPD Foundation for a long time and certainly know COPD patients quite well. And we are engaging with the foundation separately, at least the foundation, although they did not have patience at the time of reviewing this, but the foundation did review our intended protocol. Sorry, I shouldn't say the full protocol. They at least reviewed our study design overall for protocol measures, what worked and what was not successful and why. I think it's a little bit too early still, right? But I think so far we've had good enrollments ahead of schedule. If anything, we have not had an amendment. The only amendment we had was after our FDA introduction. But since the study has been up and running, we've not had an amendment. We have had some country specific amendments, but not a global one. So by those measures it's working. But I think it's too early to know, especially in terms of are we really recruiting the underrepresented populations? It's too early because we only have about 70 of the 900 patients enrolled. But I think we'll be looking at that as we get sort of over the 100 mark, what does that

representation look like and do we need to do anything more? I should also add that for COPD, are we including more black people or more Caucasian people? Well, naturally, Caucasian people are usually fairly well represented in trials, but our previous COPD studies had very low minority representation. They also had over representation of male patients and compare them to female patients. When you consider the real world data, realworld data shows about 50 50 disease prevalence. We're definitely trying to get to that sort of gender parity. That's one of our goals. We'll see how that pans out. And then because of the global nature of the study, because we've got 25 countries, I think what we're definitely trying to do is to mirror the US. Disease population where we know what that looks like. But I don't know how that's going to fare for the rest of the world because I'm not sure we have the data for all the countries. It depends how many patients we're getting from those countries as well. So this is a little off script, and I apologize, Dave, but I'm interested to hear about the real world data source that you may be referencing. Hit those targets. Yeah, sure. So we'd reach out to our real world data colleague, Carl. She actually referenced and Haines Publications in this regard, but I know that she's also done I'm forgetting which claims databases she has, but she has a couple of different claims databases where she's looking at COPD exacerbation. So when she looks at that but the gender parity is definitely there and that's over hundreds of thousand patients, basically worth of data. But enhance also pointed to about 50 50% representation and that's why we were driving the minority. The next set of questions relates to communication strategies. Was there a communication strategy for increasing the diversity of patients enrolled in the study? So mainly through the study newsletters and the investigator meetings. So far we do plan on having our investigating meetings have been virtual, so we hope to have an update or sort of a refresh point a little bit later in the year. I think we will plan to include it there as well. And I know that it's also mentioned that SIBs by the CRAs, so is there like a training deck that's been developed and that's being used, or is it just kind of like a discussion topic? It's not a training deck as such. There are a few slides in our investigative meeting deck that speaks to it. So it's more sort of a call to action that we're asking sites to look specifically for patients that may not typically be included. We're also

asking, as I mentioned, that if they're finding that there are barriers to let us know so that we can help them address those. But no, we don't have a specific training deck for how to improve that inclusion. What communication strategies do you use with study sites? For example, personalized communications, video calling option, alternative language options, or extended office hours? I think, again, probably Mindy would be the better person. We haven't got to the point of offering extended office hours yet. We've just actually had a slew of investigative meetings. The Gentech team has definitely tried to be on the early SIVs prior to our investigative meetings being rolled out. There's a conference just next week actually in San Francisco. So we're offering meet and greets for the investigators that are attending. So I think this is something that we need to develop more as the study continues. But right now the focus has been so much more on the start up. I think Wendy could help me with that overall for communication strategies, what worked and what was not successful and why. Okay, I'm probably a little bit early. I think one clear feedback we've had is that the virtual IMS, mostly people have been positive sorry, excuse the noise. Just put this on silent. Yeah, mostly people have been positive about the content and the duration of the virtual ions. But a lot of people have said that they missed the in person interaction and opportunity to discuss. So that's an element that we're missing. I think that's where sites can also learn from each other and where strategies can help each other and invite that discussion. That's one thing that we hope to address by having that sort of mini im or update meeting later in the year. The next set of questions relates to recruitment measures. Were there any specific recruitment measures or targets for inclusive research? So a specific targets are, as I mentioned, to mirror the US population as both for gender and for the ethnic composition of COPD in the US. And the third is that we increase minority participation over previous COPD studies in our disease area. So those are the three targets that we have for the current study. I think you asked another question, sorry, I missed that. Your first question was recruitment strategy. So I think for that purpose we have engaged with the COPD Foundation. So they will be helping with, I think the pre screening both in developing a tool but also sort of getting this study out on their website. So I think that we haven't worked out before content for that

because we were waiting for the US sites to be all up and running before deploying that. But that's where we can also include language for patients to consider participating in the study. So that's direct targeting of patients. What specific recruitment measures did you implement to increase or ensure diversity in your study? For example, specific sites, specific advocacy, specific vendors, specific educational materials. Sure. So I think COPD Foundation is probably what you want to call it, the advocacy or vendor that would be helping with that. And it's not specific sites but more the geography of where we've been picking the site. As I mentioned, trying to go for areas where we know there are more COPD patients with underrepresented communities. I think that's what we've been trying to do. Are there like, I don't know, like pamphlets or literature that the COPD Foundation could provide to sites to kind of help, I don't know, educate newer sites or patients that are not very well versed in the disease area or clinical trials in general? That's a good question. They have a lot of information on their website generally for participation in research. But whether we could customize that for the study, that's something we can ask there. That's not part of what they mentioned initially. But yeah, we have meetings with them in the next week too, so we can certainly waste that overall for recruitment measures, what worked and what was not successful and why? Again, too early to answer that question. Right? Because we're still ramping up so we don't know how successful our measures have been. We'll be able to answer that question a little bit better by the end of the year, I'd hope. Did you support community outreach, for example, outreach to community leaders, groups and providers? I don't think we've been asked for that. I'm sure we'd be happy to support it, but I don't think we've been asked for that. I can confirm with Mindy, but that's not been a request so far. Were there retention challenges related to diverse patient populations enrolled in the study again too early. We've only had three discontinuations so far. It's just way too early to know. Sure. Did you leverage existing internal toolkits resources or other teams experience in setting up your inclusive research strategy at the time? So, a couple of things like, as you know, we were under a lot of time pressure, but also this was the time setting this study up. The protocol was finalized in April last year. There were not a lot of other teams with an inclusive

research strategy for us to leverage, at least in Gren. Yes. I think that would hopefully be different now, but just in the context of when we were starting out the study, there wasn't as much available for the team. What did you think was helpful to help you build and implement your inclusive research strategy and what do you think was missing? I think it was helpful that at least as an organization, we had one COPD study before, so we had at least something to go on in terms of what that representation looks like, at least in our existing studies. There's a lot of literature for disease prevalence, so that also helped us. I'm sure it'll be different in diseases. I think it's challenging when you have this many countries to consider. And I think covert was definitely a complicating factor because that impacted Usability quite a bit. So we had to consider these two things in parallel. What I wish that we could have more of is knowing which sites to approach, if there are newer sites, and perhaps this is something Wendy could speak to more because it's working with PPD, so it's not just our own site network, it's what the CRO is also recommending. But in terms of which sites are sort of being raised to us, like whether that includes sites that are naive to research. I don't know if we've missed some sites I'm sure we have. But whether there's an opportunity for us to go to more sites that are nice to research and more underrepresented communities. I know that one of the clinical scientists was suggesting reaching out to I forget the name, that there are certain hospitals in the US serving basically patients who are really socioeconomically disadvantaged. Now, that presents a challenge in terms of the standard of care that's required for entering the study. And again, we've tried to keep that as we needed to be scientifically rigorous, but trying to keep it as minimal as possible. I think that in future studies, that would be the other area that how can we enable more treatment so that standard of care treatment in those populations? I know that Ashley, I think one or two pi's have reached out around that for their patients, and we've provided reimbursement for those patients to have a standard of care alongside. So that's another barrier in reaching these populations. And it would be good to have an upfront strategy. I think this has been on a case by case basis for investigators reaching out to us. It'd be nice to be able to spell that out up front, that the support is available. The last set of questions is related to clinical planning

disease areas where there is biological plausibility for population specific differences. How are you or how have you considered incorporation of meaningful clinical questions into trial design in the pivotal setting? So far, I'm not sure we have that biological plausibility, but we also have not had enough patient numbers, especially in African Caribbean populations. So I think I should also add that in those populations, at least from the epidemiological data, it's not the majority COPD, that the majority of patients, at least according to epidemiology, are Caucasian. So I don't think we've got enough data to suspect differences, but it's something that we will definitely look at as we get that data in the data to date, I think we have for this molecule, for COPD, it's only an 80 patient study, but in that, it was a UK single center study, and I think there was one nonwhite patient in that study. So, yeah, I don't think we have that on the ship, but we can definitely do sensitivity analysis and self analysis, subgroup analysis to look at whether there are differences. Is there an overall evidence generation strategy for inclusive research beyond dedicated trials or Creasing enrollment that might be implemented across our global affiliates? Good question. Not that I know yet. I think this will be part of the base re planning that's about to kick off, hopefully next month. It sounds like your study will inform a lot of that strategy going forward, just for the large number of sites and the broad geographic areas that you'll be standing. So that'll be really interesting. Is there anything else that you'd like to share? Or leah, do you have any additional follow up questions? No. Yes, I think we have a good sense, at least from the clinical perspective, of kind of your thought process and your ideation of inclusive research strategies into the study design and inclusion exclusion criteria. So that's really helpful, and it's always very inspiring and encouraging to hear that study teams such as yours have been really thoughtful about that. And I think that, as I said, really looking forward to hearing how a lot of the strategies might kind of come to the forefront as you progress on with site activations and enrollment. Glad to hear that. Your retention so far has been very good, so hope that stays. Thanks so much for sharing your time and sharing all of these insights with us. It's so helpful for us to kind of get a better understanding of what's going on within our roast genetic ecosystem. So thank you. Thank you, Mayor.