Novartis enters into agreement to acquire The Medicines Company " >

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Slide 1 – Operator

Good morning and good evening, and welcome to Novartis Investor Call and Webcast on Agreement to Acquire The Medicines Company. (Operator Instructions) The conference is being recorded. A recording of the conference call including the Q&A session would be available on our website shortly after the call ends. With that, I would like to hand over to Mr. Samir Shah, Global Head of Investor Relations. Please go ahead, sir.

Slide 2 – Samir Shah, Global Head Investor Relations

Thank you very much, and thank you to everybody who are participating in the investor call today. We realize that we only gave you the information late last night, and we really appreciate you taking the time to join us.

Before we start, I'll just read you the safe harbor statement. The information presented today contains forward-looking statements that involve known and unknown risks, uncertainties and other factors. These may cause the actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. Please refer to our company's Form 20-F on file with the US Securities and Exchange Commission for a description of some of these factors.

And some important information about the planned tender offer. The planned tender offer discussed today has not yet commenced, and our communication is not an offer or solicitation of an offer to purchase any securities of The Medicines Company. On the commencement date of the tender offer, Novartis will file with the US SEC a tender offer statement on schedule TO together with other materials, and The Medicines Company will file a recommendation statement and Schedule 14D-9. We urge you to read these materials that contain important information when they become available. And with that, I'll hand across to Vas.

Slide 3 – Vasant Narasimhan, CEO of Novartis

Thank you, Samir, and thanks, everyone, for joining today's call. We're very excited about our proposed acquisition of The Medicines Company, and we'd like to walk you through the strategic considerations, the asset and why we believe this will be an excellent fit with Novartis for the short, medium and long term.

Now moving to Slide 3, we wanted to start by providing some broad context. The proposed acquisition of The Medicines Company would really add to our portfolio a transformational cholesterol-lowering therapy. We believe there's 5 key points for investors to consider.

First, this is a unique opportunity to address what really is the #1 cause of mortality globally. The asset is de-

risked. It's highly efficacious and safe. It's given twice yearly subcutaneous with room temperature administration. It's a physician-administered injection. And it gives us the opportunity to use value-based pricing to provide an excellent package to health care systems around the world.

It fits with Novartis' global cardiovascular footprint. We've been in cardiovascular disease for over 50 years. We have operations in over 50 countries with reach to 150 countries. And we'll have strong potential synergies around the world, leveraging Novartis' deep cardiovascular expertise both in clinical development and in commercialization.

This is a soon-to-launch potentially first-in-class differentiated asset. And we believe, given the potential of the product, that it could become one of the largest products by sales in Novartis portfolio.

We expect the asset to support our medium- and long-term growth with significant sales and core operating income contribution in the medium to long term. And there's also significant upside potential with the asset, and I'll be walking through some of those opportunities later on the call.

Slide 4

So moving to Slide 4, 3 elements of what we'll be presenting today: the strategic rationale; a more deep dive onto inclisiran; and finally, some closing comments, where Harry will also go through some of the transaction details.

Slide 5

Moving to Slide 5. This deal is in line with our strategy to continue to transform Novartis into a focused medicines company. Over the last 2 years, we have conducted a number of transactions which have really transformed Novartis, of course, the divestment of Consumer Health and the spin of Alcon, and now a fifth acquisition that – a significant acquisition that bolsters our Innovative Medicines capabilities and Innovative Medicines portfolio.

Slide 6

Moving to Slide 6. When you think about this deal from the context of our capital allocation approach, it fits very well with our third priority of going after value-creating bolt-ons when they arise. This is an asset that strengthens our key therapeutic area of cardiovascular disease. It is a first-in-class asset with what we believe is a truly differentiated portfolio. It has an attractive mid- and long-term growth profile, and I'll go through that in a bit more detail in a few slides. And importantly, it has an attractive financial return. When we've evaluated this asset both at the asset’s cost of capital and our own cost of capital through very rigorous financial assessment, we believe the return profile is excellent, it fits very well with our strategic goals, and we're confident that we can generate an attractive return for the capital that we've deployed.

Slide 7

Now moving to Slide 7. We also announced today an update to our midterm margin guidance. As you know, we've been progressing towards our goal of the mid-30s margin in the medium term. And now given the momentum we see in the business, we are upgrading our guidance such that we now are guiding to mid-30s core operating income margin for Innovative Medicines in the near term and mid- to high-30s in the medium term. This is driven primarily by the sales momentum of our key growth drivers as well as strong operational

excellence on recent launches, our productivity programs as well as excellent resource allocation. And we believe this will allow us to offset generic erosion and any launch investments we need to make into key assets.

Slide 8

Slide 9

Now moving to Slide 9. I'd like to walk you through our thinking on inclisiran. First, there's a significant unmet need in atherosclerotic cardiovascular disease despite the availability of PCSK9 monoclonal antibodies. When you think about the significant unmet need, 40% of adults that have high LDL – have high LDL-C, and this is a leading cause of death worldwide. We estimate there are 50 million patients across key markets that fit the profile of this asset with cardiovascular – prior cardiovascular event on current standard of care and not at goal for their LDL cholesterol. Also of note, 7% of all patients who require statins are intolerant of statins. And only 60% of patients treated with statins or ezetimibe meet their goal of LDL level.

Now I know many of you are comparing this in the frame of the current PCSK9 monoclonal antibody treatments. But as I think has been well described, there are some important hurdles for these treatments that have been shown over the recent years: first, their prices were at above cost-effectiveness benchmarks, and I think this provided – proved to be challenging for our health care systems and payers; there were significant reimbursement hurdles leading to an estimated 80% of PCSK9 claims being initially rejected; affordability hurdles leading to a 50% abandonment rate as patients had significant out of pockets that they had to take on to stay on the therapy; and up to 26 injections per year with a cold chain requirement. So really an inconvenience for patients in terms of having to maintain this therapy.

Slide 10

So in the context of this significant unmet need, if you move to Slide 10, we also have more rigorous guidelines being put in place for LDL cholesterol. When you look at the US guidelines, they now recommend LDL below 70 milligram – that above 70 milligrams warrants additional therapy, with primary prevention patients now also being indicated for non-statin therapies. And experts who we've talked to at AHA believe there will be an updated guidance in 2022 more in line with what we see in the EU. In the EU now, we already have a reduced target of 55 milligrams per dL in these patients, so we know there is a high interest now getting better therapies to get LDL lower in these patients. In a sense, the medical community has recognized we need to get LDL as low as possible to minimize subsequent events in this patient population.

Slide 11

Now moving to Slide 11. We believe inclisiran is a new first-in-class [siRNA] asset that's well differentiated from current lipid-lowering agents. When you think about the mechanism of action, it's critical to note that inclisiran degrades PCSK9 mRNA inside the cells, so really preventing the production as opposed to the monoclonal antibodies which are trying to bind from a circulating standpoint. With lower levels of PCSK9, as been well described, you see many benefits both in terms of LDL lowering as well as other effects that improve the cardiovascular profile of these patients. We believe this asset is significantly differentiated because of a number of reasons, as you can see on the right-hand side of the slide. It inhibits synthesis by RNA interference, again, getting to the source of RNA production. It is potent, durable with a consistent reduction of over 50% in LDL levels, as I'll describe in the clinical trial section. The safety profile is similar to placebo, with

no liver, muscle, renal or platelet signals, in the entire clinical program, which is over 10 clinical studies. Excellent convenience with durable efficacy with only 2 subcutaneous physician-administered injections per year, which we believe will lead to less patient abandonment. We believe this medicine can have better adherence because of the – and importantly, payers would have confidence knowing that physician administration would ensure better patient compliance and then allow the systems to get the benefit of lower LDL and lower subsequent events. We have the opportunity for value-based pricing and a flexible access strategy in the US across the medical benefit and the pharmacy benefit. There's a potential for better long-term outcomes, and I'll go through some of our modeling around that. Room temperature storage, which enables physicians to stock the medicine easily with competitive small molecule like COGS. And importantly, patent x-ray, the compound patent for this medicine goes out to 2035 in the US and 2036 in the EU, including anticipated extensions. And there's also the possibility of additional patent protection with secondary patents that are currently pending. This is an important element for your models to consider the longer-term potential of the medicine.

Slide 12

Now if you go to Slide 12. When you look at the clinical development program, this is an expansive clinical development program beginning about 7 or 8 years ago. You can see here the Phase III LDL-C lowering programs ORION-9, 10 and 11 are complete. The Medicines Company anticipates filings imminently, and we'll talk about that in more detail in a later slide. And the Phase III CV outcomes study ORION-4 is now enrolling. It has approximately 6,000 patients enrolled. Full enrollment is expected by the end of next year and completion of the study in 2024.

Slide 13

Now moving to Slide 13. When you look at the data, the data was extremely compelling, as shown in recent medical congresses. Over 3,600 target patients were put into – through the protocols with a standard of 18 months of treatment on top of maximally tolerated statins with ezetimibe allowed. This is an important element as well to consider. These patients were already under maximal control. And in that setting, you saw at day 500 – 510, a 58% lowering in the ORION-10 study and a 54% of lowering of LDL in the ORION-11 study, so very compelling LDL reduction. It was greater than 50% in all populations looked at, the reductions were observed at day 90 and were stable over the time period. So when you look at the pharmacodynamics of the drug, very good over the entire dosing period. And the studies met all key secondary endpoints with highly compelling p-values across the full range.

Slide 14

Now moving to Slide 14. Now when you look at the pooled analysis of ORION-10 and 11, you continue to see that this medicine gets patients to or below recommended goals. You can see on the left-hand side of the chart, when you look at the placebo versus inclisiran, you can see a 56% difference on the primary endpoint in the pooled analysis with a highly significant p-value. And when you look at it, greater than 90% achieved the threshold of less than 70 milligrams, as stated in the guidelines, so really showing that the medicine can deliver versus the cardiovascular guidelines. And greater than 50% LDL lowering in 87% of patients, so again, very, very compelling.

Slide 15

So when you go to Slide 15. When you look at the safety of this medicine, we were very compelled by the outstanding safety profile consistently shown across the range of studies even going back to Phase I and Phase II. When you look at the general safety across the study, it's comparable to placebo across all of the relevant MedDra groups, and so I think this was already quite positive. And then when you looked at the prespecified exploratory CV endpoint, there's been some focus in the investor community on this point. We would like to highlight when you look at the prespecified exploratory endpoint across composite CV events, you can see that in ORION-10, there were 58 events versus 79 events in placebo, so you can see a compelling reduction there already even though this was only for safety and not an endpoint that was really to be looked at from an efficacy standpoint. And you can see a similar result in ORION-11. And when you look at the composites in cardiovascular death or fatal, non-fatal MI and stroke, you see a very favorable profile overall. Again, important to note the studies were not designed to look at efficacy, but I think you can already start to see a compelling effect on cardiovascular CVRR in these 2 studies.

Slide 16

Now if you move to Slide 16. One of the elements of this class historically has been a focus on liver signals, and I wanted to just spend a moment to explain the history of that and why we believe this has been addressed by the design of this molecule. Historically, the view and some of the issues with the class related to RNA interference, interfering with non-target RNAs in the liver, so off-target RNA effects. And then the other element of the story was that given the dose given in the patient, the RNA splicing enzyme complex was overwhelmed by the medicine. And this led to other RNAs that needed to be spliced or shut down not to be appropriately regulated.

What the inclisiran now brings to the table is a very uniquely designed molecule. The RNA sequence is highly specific and very designed not to trigger any off-target events. And also the dose, given the GalNAc conjugation, has allowed for a much lower dose of the medicine to be given, which then allows the normal functioning of the RNA splicing mechanisms within the cell. So a very compelling mechanistic rationale for why, as you can see in the clinical data, we don't see any liver signals versus placebo. And this is the case for patients now followed out beyond 3 years who received multiple doses over time. Mechanistically, there is no reason to believe that additional exposure would increase risk to the liver given the overall PK of the medicine. So we feel very good about the liver, [kidney], muscle and platelet profile of the medicine.

Slide 17

Now moving to Slide 17. Now of course, the ORION-4 outcome study will be critical to the longer-term outlook of the medicine. And we feel very confident in how The Medicines Company has designed this critical CV MACE and CV mortality study. Now just in terms of the protocol, it involves patients over 55 years of age with prior MI, stroke or PAD. These are high-risk patients with LDL over 100 milligrams on standard of care so not well managed under the current treatment. The sample size is 15,000 patients and, as I said, 6,000 patients enrolled, plan for full enrollment at the end of next year; standard composite MACE endpoint powered for a 25% reduction with relevant secondary endpoints in cardiovascular death, MI or CV death.

Now the way The Medicines Company has designed the study was informed by the Cholesterol Treatment Trialists Collaboration look at prior trials in this space. And one of the most interesting trends you see is as you follow patients longer with these kinds of therapies, you see effect sizes on the primary endpoint improve. So as you can see on the x-axis here, you see reductions in LDL-cholesterol millimol per liter. The inclisiran assay would be around 1.3. And a follow-up, it is planned of median of 5 years, which is not even on the chart. But as you can see, as you follow longer, you get to higher and higher reductions in CVRR. This gives us confidence

that we can reach the target we hope of above 20% but the potential upside of reaching 20 – above 25% and potentially as high as 30%.

Slide 18

That's been modeled, if you look at Slide 18, in more detail by The Medicines Company. We believe this is a relevant upside. When you use the Phase II and III data and you model it out, you can see that based on the LDL-lowering effects seen both in ORION-10 and 11 of 56%, a time average reduction of 54%. The computed 5-year relative risk reduction would get you to a 30 – 31% to 32% relative risk reduction. When you extend that modeling out to ORION-4, you would get to an estimate of 5 years of a potential 30% reduction in CVRR. We've modeled the base case of reaching 20%, but we believe that with the design of the study, the potential exists to get to as high as 30%, which would provide a compelling case to payers around the world for the use of this medicine.

Slide 19

So moving to Slide 19. The regulatory submissions are based on a very robust and comprehensive development program. You can see extensive Phase III and Phase IIIb studies, Phase II studies, Phase I studies. These studies are complete. In the case of ORION-4, the outcome study I just described, these studies are ongoing. But we want to, of course, indicate that the medicine has been well studied in a large population with well-randomized studies in a consistent way at a high quality. Our teams have gone through this in detail, and we believe these studies have been very well conducted.

Slide 20

Moving to Slide 20. The regulatory discussions are now underway with a clear pathway to approval. The Medicines Company expects a submission in the US for Q4 2019. For modeling purposes, we would recommend assuming a launch in 2021. The Medicines Company expects submission in Europe in Q1 2020. Based on regulatory discussions that have already happened in Japan and China, in Japan, there would be a single-study bridging program to enable bridging to the Japanese population for local approval. And in China, we would need to conduct additional studies using the traditional local development program. However, this has been aligned with the CFDA. So overall, I think good discussions with regulators. And having reviewed this correspondence, we feel very good about where The Medicines Company stands.

Slide 21

Now moving to Slide 21. When you think about the patient population that inclisiran could treat, it is a large potential population. When first you look at the prevalence of secondary prevention for atherosclerotic cardiovascular disease in patients who have experienced a prior event and are at high risk given other factors, you can see the numbers of patients here are significant: 36 million in the US; an estimated 30 million in China; 30 million in the EU; 13 million in Japan. When you look at those that are not at goal despite available lipid-lowering treatment, again, you see significant numbers, and you can see the numbers here amounting to nearly 50 million patients. And then even when you take a tougher look and say who are the patients that are at highest risk that still, despite optimal therapy, are at high – even higher levels of cholesterol based on local guidelines, you can again see a very large population across all 4 main geographies. So when you think about your models, you can see a very significant patient population. And even with relatively low share in penetration rates, there's significant opportunity for such a medicine.

Slide 22

When you move to Slide 22. We believe in the US, the ability to have a physician-administered product twice a year will enable us to launch through both the medical benefit under a potential buy-and-bill model as well as the pharmacy benefit. We believe under the medical benefit for primary care physicians who focus on cardiovascular patients, lipidologists as well as cardiologists, this is an attractive profile. It allows physicians most importantly to get their patients to goal. The physicians know that patients are not getting to goal.

And I think one thing that's very clear in physicians' minds now is they need to get LDL under control for these patients, so there's better LDL control, a lower administrative burden relative to the current situation in these offices, a lower cost to the practice because of the cost recovery mechanisms in place within Part B and, of course, lower prior authorization burden particularly for patients – clinics that choose to use Part B as well.

We believe that the medical benefit will be particularly attractive for large clinics. We believe in our models, 50% of relevant patients are in larger systems or larger IDNs with another 30% in medium-size clinics and IDNs, all of which would benefit from having the ability to use the medical benefit.

We also believe this will be attractive for patients. It's more convenient than the regular injections at home. It seamlessly integrates to the regular visits these patients have with health care providers given their risk profile. And overall, we hope we can achieve better compliance given the physician administration route.

Slide 23

Moving to Slide 23. We also know that there's significant potential cost synergies given the overlap with the current Entresto® field force in the United States. And we've gone deep to quantify this to really assure ourselves we can leverage our substantial footprint in primary care and cardiology with Entresto® in the US. When you look at the Tiers 1 through 4 of Entresto® HCP prescribers, they cover 80% of statin and PCSK9 prescribers. So when you look at our ability to cover the top tiers by quintile, they cover 80% of the relevant market. We have about an 81% overlap with our existing field force. And so you can see that on the left-hand side, it allows for a significant synergy with the US Entresto® field operations.

We believe with an incremental few hundred reps, we can support the launch of inclisiran, including a specialized force to enable medical Part B utilization with the relevant health centers and providers. And there's a high potential – the high potential primary care prescribers would be covered in the model that we've now put together.

We would leverage Novartis' deep operational expertise in primary care medical education market access. And we can also, over time, leverage the broader Novartis pipeline. As I said, we've been in cardiovascular disease for 50 years. We have an outstanding research organization, NIBR, a clinical development organization; we have TQJ for Lp(a), now in Phase III clinical trials with additional projects now coming forward from our NIBR organization. This will enable us to maintain our long-term presence in cardiovascular disease.

Slide 24

Now moving to Slide 24. We also believe there will be excellent synergies in the ex US market. As we know, there's established dyslipidemia management outside the United States. We think we can get competitive access once we have the mortality benefit with the CV outcomes trial. And importantly, there's the access to the large and growing China market, where we've built a substantial presence to support the launch of

Entresto®. There'll be a number of countries around the world we'd focus on initially in the launch, but we estimate 90% of the inclisiran field force requirements could be managed with the existing Entresto® field force.

Slide 25

Now moving to [Slide 25]. There's also significant upsides we've not included in our own base case but we believe are worth mentioning because there's advanced discussions now ongoing. First is discussions with health systems around the world to provide a population based approach to target high-risk patients. And there will be additional potential in other HTA markets around the world. We've already seen The Medicines Company advancing these discussions. This would enable the potential to take a population-based approach in these markets. Second, as I mentioned, the outcome for major acute coronary events of greater than 25% in the CVRR study for ORION-4. And then lastly, with the potential for the US guidelines to be reduced even further, as I mentioned in an earlier slide.

Not on this slide and as has been discussed by the leading KOLs in cardiology in the United States and many around the world, there would be an additional upside potential for primary prevention using this medicine with the potential for a once-a-year administration. This is something we would look to explore on closing the deal and, of course, would be massively transformational if successful over the longer term.

Slide 26

Now moving to Slide 26. When you look at external worldwide forecast, they indicate a strong global potential. And I think it's very important that all of the analysts listening in the call take a few factors into account. Most brokers currently only look at this asset from a US perspective, modeling a partnership for the ex US, not taking into account sales for the ex US. We, of course, would globalize the asset with our substantial global cardiovascular presence around the world. It's worth noting, of course, we have a long legacy. And with Entresto®, Galvus®, Diovan® and Exforge®, we have a substantial presence in cardiovascular disease globally, so this should be modeled as a global asset.

Second, the compound patent goes out to 2035; and in EU, 2036, including anticipated extensions. We've noted some brokers only go out to 2025. Others only go out to 2030. It'd be important to consider the full life cycle of this potentially transformative medicine. We would note there will be a slower initial ramp as we get the access model set up in the US and also await the ORION-4 outcome study. But then we expect an acceleration in the mid-2020s for a significant peak sales and, as we noted in the press release, the potential for a mega blockbuster and something that would be amongst the largest medicines in the Novartis portfolio.

Slide 27

Now moving to Slide 27, I will now hand it over to Harry for comments on the deal.

Slide 28 - Harry Kirsch, CFO of Novartis

Yes. Thank you, Vas. Good evening and good morning to everybody. Thanks for calling in at such an hour.

It is an important transaction for us. And just want to maybe, as the first point, clarify what is the fully diluted equity value of this asset as there, I think, have been a few difficulties to figure that out. But as you can see in our first bullet point, if you take last Friday's closing price the fully diluted equity value of The Medicines

Company is USD 7.7 billion. And it's important to include not only the 80 million of outstanding shares but roughly 27 million from convertible notes and 7 million from options, so we get basically close to 114 million shares. If you take that with the USD 68.55, you arrive at the USD 7.7 billion roughly. It's also detailed in footnote #2. Now our offer would be USD 85 a share, cash per share. And there would be roughly a 41% premium if you take the 30-day volume weighted average of USD 60. And that would value the company approximately at USD 9.7 billion on a fully diluted equity basis. And maybe 2 details on that: there is about [USD 0.2 billion] (corrected by company after the call) of cash; and in our NPV calculations, we also have roughly USD 0.5 billion of a tax benefit from losses carry forward, so basically, the returns have to be returned on USD 9 billion. It's a significant amount of money, but I'm very excited that we will have very strong financial returns on that investment.

Now what are the expected financial benefits? As Vas alluded, we expect the medicine to contribute to Group sales from 2021. We expect it to be a significant pillar of further growth in our cardiovascular franchise and potentially one of our largest products in our portfolio. Also very important, very long exclusivity is expected in the US, 2035; EU, 2036, including anticipated extensions. Now it has a portfolio of a cardiovascular mega blockbuster, and we expect to have modest dilution of core EPS during the first few years due to expected investments. Of course, we have significant synergies, but we still believe also some investments are needed to turn it into a mega blockbuster, and Vas alluded to some of the key actions that we expect to take. Now we expect also significantly – significant accretion to Group core operating income and core EPS medium term as of medium – mid-20s driven by the sales growth and the operational synergies leveraging the cardiovascular worldwide footprint. In terms of financial returns, given the significant sales growth, the synergies and the contribution we expect here, we really see a return well in excess of cost of capital of the target as well as the Novartis cost of capital, resulting in significant value creation for our shareholders.

Now the transaction has been approved by both Board of Directors, and we plan to fund the acquisition through available cash and mainly long-term borrowings. Probably roughly 1/3 would be cash, 2/3 would be long-term borrowings.

Just want to highlight also before we go – Vas goes into closing that this product fits very well into our overall financial plan. It's, of course, not a reason to make such an acquisition, that's on stand-alone financial returns and strategic fit for the asset itself, but the fit into our overall financial plan is also great. And that's why Vas also mentioned in the earlier slide, that we do expect the core margin of Innovative Medicines in the near term, including the investments in this asset to be in the mid-30s margin and mid to long term in the mid- to high-30s margin. With this, I hand back to Vas.

Slide 29 – Vasant Narasimhan, CEO of Novartis

Great. Thank you, Harry. So moving to Slide 29, just recapping the key points: a potentially transformational cholesterol-lowering therapy: a unique opportunity with a unique profile; fits with our global footprint with very strong synergies; soon to launch, well differentiated, with substantial sales potential, could be one of the largest products in Novartis portfolio; it supports our long – mid- to long-term growth profile, which is, of course, high in our minds to ensure that we continue to grow the company; and significant upside potential both from the trial readouts and population health agreements.

So with that, we thank you for listening. And here in the room with me, I have, of course, Harry; Marie-France Tschudin, our President of Novartis Pharmaceuticals; John Tsai, our Head of Global Drug Development and Chief Medical Officer; and also David Soergel, our Head of Drug Development for Cardiovascular Diseases. So I'll hand it to Samir for – I'll hand it to the operator for questions.

Slide 30 - Q&A

- Operator

A. (Operator Instructions) And your first question comes from the line of Andrew Baum from Citi.

- Andrew Simon Baum - Citigroup Inc, Research Division

Q. It's Andrew Baum from Citi here. A couple of questions. Firstly, it seems that a substantial part of your argument rests on the ability to secure reimbursements under buy and bill. Could you just talk us through the mechanics of that in order to obviate the risk of white bagging? And PBM is basically doing it through a pharmacy benefit and, thus, all the formulary management issues which have besieged your competitors.

And then second, perhaps you could comment on pricing relative to the existing marketed agents and, in the same context, how that may relate to your OUS opportunity. What should we read about the fears of the [IPI] baskets given the ability of Europe to bear premium prices and the impact that could have on OUS price assuming you do get Part B or buy-and-bill reimbursements for Medicare patients?

- Vasant Narasimhan, CEO of Novartis

A. Great. Thank you, Andrew. First, on buy and bill, we've modeled this in a way that we've assumed that there would be a flexible access model. So of course, some physicians might still choose to use the pharmacy benefit. Some could white bag. But we believe that large IDNs and larger health care organizations, larger clinics and medium-sized clinics would find it compelling to go with "buy and bill" or "brown bagging." Both from a practice economic standpoint, also in terms of the overall ease of administration, we think there's a compelling case to be made here. There's, of course, very relevant analogs in areas like ophthalmology, neuroscience and others. And we think because of the opportunity to better manage these patients in terms of the cholesterol lowering, this could be a highly attractive opportunity. Now we all have to do work, so our US organization would build out an organization to focus solely on enabling practices to utilize this option and therefore reduce the administrative hurdle of providing this therapy to patients.

In terms of pricing, we would aim to price this medicine within the approximate cost-effective range that's been put out in the past. And we, of course, want to ensure that we are pricing appropriately to create value for society, and we think we can do that. We, of course, can't comment on specifics, but it's high in our mind to use a compelling offering and knowing that we want to ensure that also health care systems can create value. And we have done extensive work in preparation to look at that. Overall, we would also plan to use an approach where we think we can manage price corridors around the world. Should an IPI-type approach happen, we believe in a medicine like this one, where there's compelling health economics, high interest that we've already seen from HTA authorities outside the United States, we could manage the window not to have the issue that perhaps other medicines might have in the pricing. Thank you, Andrew.

- Operator

A. And your next question comes from the line of Keyur Parekh from Goldman Sachs.

- Keyur Parekh - Goldman Sachs Group Inc., Research Division

Q. Two questions, please. Can you confirm when you expect to earn returns on this kind of beyond your cost of capital? So I know you said attractive IRR, but just from a timing perspective, when do you expect to cross that hurdle? And secondly, Vas, you said kind of the EU launch, we should think of – for the EU opportunity, to think of as beyond once we get the CV outcomes data. So I want to clarify if we should think of this as an opportunity in ex US kind of post 2025. And then lastly, just kind of a follow-up to Andrew's question.

Obviously, a key premise of your transaction here is that you're going to get access better than – and reimbursement better than everybody else has been able to. Just help us think about the specific due diligence you've been able to do on that end that gives you the confidence to conclude completion.

- Vasant Narasimhan, CEO of Novartis

A. Thank you, Keyur. So first, on returns, Harry?

- Harry Kirsch, CFO of Novartis

A. Yes. So of course, returns are done over the whole life cycle of such a product. But as I mentioned a few years of some low dilution on a stand-alone basis or versus a no-deal scenario, then we expect, basically, as of mid of next decade, significant contributions; and starting in the second half of next decade, also ahead of IM margins or very accretive to the IM margin already. Of course, it has to be taken with the expected sales uptake, but that's how I see this profile. It's very consistent with cardiovascular mega blockbuster financial profiles.

- Vasant Narasimhan, CEO of Novartis

A. Thanks, Harry. And then on the EU launch, Marie-France, do you want to take this?

- Marie-France Tschudin - President, Novartis Pharmaceuticals

A. Yes, so good morning, everyone. So we will be looking at a submission in Europe in the first quarter of 2020. And we – as Vas mentioned, we will be looking at the additional studies needed for Japan and China to support the registration in these countries. Clearly, in the first years, the focus will be on the US. So the outcomes-based study for Europe will be essential. However, we will be working with the [competent] authorities to make sure that we get access as much as possible across the world. We're looking at this from a global perspective. We do have the global footprint when it comes to our cardiovascular and Entresto® field force. And there is a huge potential across the globe, so this is definitely going to be a global asset for us.

- Vasant Narasimhan, CEO of Novartis

A. Yes. And just to add to that, we would recommend probably a modest uptake in Europe initially until we get the outcomes trial. But I would note we are having conversations – or The Medicines Company, I should say, is having conversations on potential population-based agreements. And if those agreements were to come into force, we would, of course, let you all know.

And then lastly, on the due diligence, and this has been probably the topic we've spent the most time on, we've gone extremely deep with payers, with providers, doing our own independent market research, reviewing The Medicines Company's market research to give ourselves confidence that we can overcome the access barriers. The medical need is very clear. These patients are at a high risk for a second cardiovascular event. It is the leading cause of morbidity and mortality in the United States. There's high motivation amongst physicians to actually get patients to goal. And so we believe with a responsible pricing and working with physicians to put in place a buy-and-bill model, also to enable if they would like to white bag on Part B and, if needed, to also use Part D, we can provide the flexible access with low administrative burden that would enable a broader use of the drug. Importantly, we are not endeavoring to switch patients who are on current PCSK9 mAbs. Our aspiration is to tackle the very, very large number of patients who need to get their cholesterol lowered. And we believe, based on everything that we've seen in the due diligence and our own independent research, there's high willingness to do this, and we can get this access program in place and then enable broad access to this medicine. Thank you, Keyur.

- Operator

A. And your next question comes from the line of Graham Parry of Bank of America.

- Graham Glyn Charles Parry - BofA Merrill Lynch, Research Division

Q. So firstly, how set are the primary care physicians to buy and bill and administer the products? And is there an analog you can point as to where primary care physicians have done this in the past and in significant amounts? And what proportion of your scripts would you expect to come from primary care?

And secondly, the monoclonal antibodies is poorly – given the lack of outcomes data initially, is there a risk here that payers just push inclusion around the high monoclonal antibodies if you don't have outcomes data at launch?

And then thirdly, just from a financial perspective, what year would you expect this to become accretive to EPS? Could you help us just understand the margin impact in the very near term 2020, '21 versus the mid-term and the impact this has had on your guidance?

- Vasant Narasimhan, CEO of Novartis

A. Yes. Thanks, Graham. So the way we look at this is health care providers, really what we tried to look at is statin and PCSK9 writers. And so I think there is a, it seems to be, desire to kind of put people in a bucket of primary care versus cardiologists. But what we looked at was health care providers who write PCSK9 and statins. So about 30% of these physicians currently are already doing buy and bill in some form already. So we have 30% already there. We also know that 50% of these patients are in large systems, are in large clinics that – in our target and our model. So we believe there's compelling practice economics with those 50% of clinics to get them rapidly onboard and then another 30% are in medium-sized clinics. The bigger challenge will be the last 20%. This is kind of the classic smaller clinics that, of course, we would have to then do some heavy lifting. But given that 30% already have it, 50% to 80% have very compelling case to put it in place, we feel like we can get this put into place with good confidence. And so I guess we'll have to come back to you with a relevant analog, but I think what we looked at was PCSK9 and statin writers, and that's how we model this, of course, with a strong overlap with the Entresto® field force, as I already noted in the slide.

Now we also would say there's going to be an initially modest ramp to the product both because we need to get this in place. So it will take us time to get this all fully in place and get cardiologists, primary care physicians, lipidologists to take this up. And then second, because the outcome study would come, we believe, based on the diligence that we've done and conversations The Medicines Company has had, that there will be solid payer acceptance in the United States early, perhaps earlier than you might otherwise expect. But still, this will be a slower ramp and then building over time. And of course, as I set out to 2037, we'll have the opportunity to make this into a very significant medicine. In terms of EPS accretion, Harry?

- Harry Kirsch, CFO of Novartis

A. So as I mentioned earlier, we do expect a modest core EPS dilution in the next few years. We see it combine – a combination of the mainly M&S upfront investments as we launch as well as some financing costs. So the next few years, let's say the next 4 years roughly, we would expect a low to mid-single-digit core EPS dilution versus a no-deal scenario. Now as we mentioned, for the total company, we expect margin improvements. We even updated our Innovative Medicines margin guidance that in the near term, we expect already to achieve mid-30s; and then in the midterm, to expect to achieve mid- to high-30s for the IM core margin. And I expect significant contribution already in roughly 2025, let's say middle of next decade, of course, depends on the exact uptake so don't want to get too precise on this, and then supporting significantly

in the second half of next decade and then up until LOE so to the whole company. So a significant mid- to long-term growth driver on top line and also mid- to long-term on the bottom line and cash flows.

- Vasant Narasimhan, CEO of Novartis

A. Thank you, Graham.

- Operator

A. And your next question comes from the line of Jo Walton from Crédit Suisse.

- Matthew Weston - Crédit Suisse AG, Research Division

Q. It's Matthew Weston from Crédit Suisse. A few questions, if I can. I note on Slide 12 there is the – which is the time line slide, there's this bar showing CMC development including scale up, device and supply. So given the potential of this drug to be one of the biggest in the portfolio, can you just explain the constraints in the early years, where we are on CMC development and supply constraints that may impact the early phase of launch?

And then a couple of questions around the financials. Vas, I think you said you're going to price within the previously indicated ICER range. But obviously, those ICER ranges are for drugs that have demonstrated a cardiovascular outcomes benefit. So can you just clarify that at the start of launch, you're going to be aiming for that assumption of a CVOT benefit, but we may see slower uptake as a consequence?

And then finally, just looking at that idea of a slow ramp, you were kind enough to give us consensus expectations in the slide. Would you comment as to whether or not you see that expectation looks like on average of about USD 2 billion of revenue in 2024? Do you see that as too challenging given all the concerns we have prior to CV outcomes data?

- Vasant Narasimhan, CEO of Novartis

A. Thank you, Matthew. So first, on the supply scaleup, so we've done due – detailed due diligence on the supply, the relevant supply sites around the world. All site visits were completed. We feel very good about the supply. These are all facilities that have been either used for FDA-approved drugs or are in very good situation. We don't see any supply constraints in our model, and we feel very confident. What we do plan to do over time is to internalize the supply chain into the Novartis supply chain and try to radically reduce the COGS of the product over time. We believe we have the know-how and capability and scale to do that to get the COGS to a very attractive position on variable COGS, of course; then on top, the relevant royalties that need to be paid.

In terms of the CV outcomes study and the ICER range, we would assume CV outcomes benefit. When you look at the compelling cholesterol lowering of this agent and given that we have made the adjustments to the trial – The Medicines Company has made the adjustments to the trial design. And that's been written about extensively. And I think you all can talk to the relevant experts. The study overall is seen by the TIMI Group and the UK relevant experts in the United Kingdom. It is a world-class group of KOLs who are overseeing this program. It is a rigorously done study, and it has the longest follow-up, as you saw in the graph of any relevant study, all of which give us great confidence the CV outcomes benefit will be delivered. So we price assuming the CV outcomes benefit.

And then lastly, I won't comment on specific sales in 2024, of course, but we do see a few years of slow ramp, and then we see a significant uptake. And not just relevant as the CV outcomes trial, also is just are fully getting on board the buy and bill. But you've seen our Entresto® ramp took a few years. We hope to do better

than that, but I think that's where we stand at the moment. And we'll be able to provide, I think, more detailed guidance as we – once we get the medicine approved after closing. So thank you, Matthew.

- Operator

A. And your next question comes from the line of Peter Welford from Jefferies.

- Peter James Welford - Jefferies LLC, Research Division

Q. I've got 3 questions, please. Firstly, just with regards to the ORION-4, I wonder if you can confirm is this still an interim analysis or is there an interim analysis planned in that trial. And would Novartis still go ahead with that given your commentary you made on the importance potentially of seeing the 5-year benefit to get the sort of magnitude of risk reduction that you're looking for?

And secondly then, I wonder if you could just comment on the change in MACE that we saw recently presented for the ORION-10. I appreciate this is under the definition, as you said, of adverse events rather than necessarily as an event-driven primary endpoint. But nevertheless, there does seem to be a shift, I guess, in the wrong direction in the ORION-10 study.

And then just finally, a point of clarity on the royalties. Are they owed right until the IP expiry on inclisiran? Or do the relevant patents related to the royalty mean that, that will change over time?

- Vasant Narasimhan, CEO of Novartis

A. So I'll have David Soergel – David Soergel is our Head of Cardiovascular Drug Development Overseas, Entresto®, TQJ and relevant programs. So David, on ORION-4 interim?

- David Soergel - Head of the Cardiovascular, Renal & Metabolic Development Unit

A. Yes, thanks for the question. Indeed, there is an interim analysis planned in the ORION-4 study. Of course, we'll be looking at some design features in the trial once we bring the asset into the portfolio and seek to optimize it to deliver the best results that we can to ensure access, so I think to be determined in the future.

- Vasant Narasimhan, CEO of Novartis

A. And David, also on the ORION-10 and the data that we've shown with ORION-10?

- David Soergel - Head of the Cardiovascular, Renal & Metabolic Development Unit

A. Right. So if you look at ORION-10 and you pool it with ORION-11, I think given the small numbers of events in both of those trials, it's best to pool these 2 data sets. You'll see that there's a consistent reduction in the – in MACE events overall, about 20%, 25% reduction. And while, again as Vas mentioned, this is an exploratory analysis and was done as more of a safety endpoint, it's consistent with what we would expect and consistent with the powering assumptions that went into ORION-4.

- Vasant Narasimhan, CEO of Novartis

A. And the – I think it's also about the depth and balance also if you pool it, maybe you could...

- David Soergel - Head of the Cardiovascular, Renal & Metabolic Development Unit

A. Exactly. So then there's the – once you pool the 2 trials, you really don't see a difference in the outcomes.

- Vasant Narasimhan, CEO of Novartis

A. Thank you, David. And then I think on the inclisiran LOE, how the royalties evolve, I don't know, I don't have the answer to that. I don't know if you have it, Harry.

- Harry Kirsch, CFO of Novartis

A. Yes. No, we have it. So I think it's very public knowledge anyway that tiers – royalties are tiered to an item, now starting at double – low double digits, and then as of roughly 1 billion going close to being to roughly 20%. So you can – for modeling, given the size, we expect to assume the 20% as a simplified assumption, and this is until the LOE.

- Vasant Narasimhan, CEO of Novartis

A. Great. Thank you, Harry.

- Operator

A. Your next question comes from the line of Simon Baker from Redburn.

- Simon P. Baker - Redburn (Europe) Limited, Research Division

Q. Just one question left. Going back to the issue of pricing and cost effectiveness, the challenge that cost effectiveness analysis come up to against increasingly these days is on basic affordability, so I was wondering if you had looked into the potential for outcomes-based pricing models in any of the key markets here.

- Vasant Narasimhan, CEO of Novartis

A. Yes. So as I mentioned and tried to allude to throughout the presentation, The Medicines Company has, I think, been very forward-looking in their thinking around engaging relevant health authorities around the world and actually payers in the United States on population-based outcomes agreements. And those payers have been particularly interested in the medicine because as a twice-a-year medicine with physician administration fitting with the standards of these patients, they can ensure high compliance, and then yet the benefit of lower cardiovascular events in the population that they cover if it's in the US or insure – covering ex US or insure in the US. In some cases, these discussions are quite advanced. And so we had, of course, on closing continue these discussions with the goal of trying to find population-based agreements wherever we can because we believe the medicine’s effect is compelling and can significantly improve the cost of health care systems in covering cardiovascular patients.

So with that, that concludes today's call. We really appreciate you calling in so early or staying up very late. We hope this provided some important context. We're very excited about the opportunity. It fits with Novartis' strategy. It fits with our long-term growth profile. And we look forward to speaking you all – with all of you at R&D Day next week. Thank you.
