Hello, good morning and good afternoon. A very warm welcome to everyone here in person as well as everybody out there on the livestream. My name’s Oliver Maier. I’m the head of investor relations at Bayer. It’s a great pleasure to welcome you here at Bayer’s Research and Innovation Centre here in Cambridge. This is a hub that we’ve inaugurated about a year ago. We have so much in store for you today and we are really excited to share that with you, with an update on our key pillars of our R&D strategy, which we think is a step change in innovation, including investments in our leading technology platforms and cell and gene therapies and proteomics. We have significantly expanded our R&D capabilities in our presence in the world’s leading innovation hubs.

I know everybody might have lots of different questions, but still I think we should focus on the R&D and innovation side of things today. This is such a unique opportunity to have all these great minds in one room, and we should make use of that and stay focused.

So let’s have a short look at the agenda today. You see that we will have live presentations from seven speakers as well as several Q&A sessions, two short ones and a longer one at the end, and I think we can cover some of the questions of a commercial nature maybe at the end of today because that’s a longer Q&A. In addition, we are very pleased to tell you that, while our CEO, Bill Anderson, is not being able to join, Bill recorded a video message that he wanted to share with you.

We will start out today with Stefan Oelrich, president of our pharmaceutical division and member of the board of management. Stefan will kick off the first set of presentations with an update of the division’s strategy and how we expect its revised innovation model and late-stage pipeline to continue to generate sustainable growth in the long term. Christian Rommel, then, our global head of R&D, will then illustrate that the division’s R&D strategy is truly reshaping innovation at Bayer to deliver an innovative, differentiated and sustainable pipeline. Christian will also share our plans to make a difference in neurology and rare diseases, where we currently do not have a commercial position yet.

I think this nicely transitions to Vividion’s CEO, Aleksandra Rizo. Aleks will show you how the company’s proteomics platform can remove traditional boundaries of druggability. We will have then the first Q&A session and, after that, in the second session of our presentations today, led by Dominik Rüttinger, our head of research and early development oncology. Dominik will show us how he wants to drive leadership in focus areas of cancer treatment. Following Dominik, we will
have Maria Borentain, head of cardiovascular and renal clinical development, and Maria will give you some insight in how we’d like to reshape new treatment paradigms in cardiovascular diseases before we will do a second round of Q&A.

Very exciting and with special news this morning – Seth Ettenberg, CEO of BlueRock Therapeutics, will give you an update on the company’s leading role in pluripotent stem cell therapies before we end that set of presentations with Jude Samulski. Jude is our chief scientific officer and co-founder of AskBio. Jude will take you on a journey into AAV-based gene therapies and the truly pioneering role AskBio has in that field. We will then end with some concluding remarks from Christian and the last Q&A session, followed by a lunch with the Bayer team.

Before we begin, I would like to bring to your attention, obviously, as always, the forward-looking statements that I always have to mention that are included in the materials today and that you currently see on the screen.

See disclaimer

I think, with that, I’m done with the formalities and the housekeeping items, and I think now let’s start with the video from Bill Anderson, please.

Bill Anderson
Chief Executive Officer, Bayer AG

Well, a very warm welcome also from my side. I’m currently in the midst of a whistlestop tour around the world. I’m meeting with our customers, our employees, visiting our labs, factories, offices. I’m so excited with the level of engagement and passion that I’ve encountered already. We have an incredibly strong and dedicated workforce, and I’m sure they can’t wait to tell you about the work that we’re doing in support of our mission: health for all, hunger for none.

Now, those of you who know me from my previous roles know that I care deeply about innovation. It’s fundamental to our organisation because it’s innovation that drives our success and our growth so I’m really pleased that you’ve decided to join us today to learn more about the innovation we have underway at Bayer. You’ll spend some time with our key business leaders, and you’re going to hear about some of the exciting things we have in development throughout our pipeline.

I’m energised and I’m optimistic about the potential we have at Bayer. The areas where we operate have huge impacts for society. We’re making that impact today, but the opportunity ahead is even greater. So the event is all about pipeline and innovation, and you’re going to get some deep dives on some of our key technologies and projects and learn more about our areas of focus. Hopefully you’ll appreciate how this innovation will help create sustainable growth for Bayer in the future.

Well, obviously, there’s a lot more work for me to do, learning about the organisation, about our customers and our opportunities, and I look forward to doing that in the weeks and months ahead. As a management team and board, we’ll need to reflect on how best we can deliver our value to society, to patients, to our clients, to employees and especially to you, our shareholders. You can be assured that, as we consider our options, we’ll take deep, deep consideration of your views.
I’ve enjoyed already hearing from many of you. I look forward to continuing those discussions. In the meantime, you’ll hear from me during quarterly results and roadshows, but for today the focus won’t be on financial targets or overall strategic directions, which I know many of you are keen to hear about. The time for that will come, but today the focus will squarely be on the innovation efforts and our pipeline.

So I wish you a very productive time at the event, and I hope you come away as excited as I am about our pipeline and the potential it offers. Thank you again for attending. Have a wonderful day.

Oliver Maier

Thank you very much, Bill, and I think we are ready now to start with the first set of presentations, and I would like to ask Stefan to join me on stage. So, Stefan, the floor is yours.

Transforming Bayer Pharma for Sustained Growth

Stefan Oelrich
President of the Pharmaceuticals Division and Member of the Board of Management of Bayer AG

Well, thank you, Oliver, and welcome, everyone, here to our Boston site. Today is, for me, a really exciting day because we’re going to talk about innovation, and I always like to say that not only is innovation the lifeblood of our industry; it’s also the thing that gets all of our employees out of bed in the morning and is what drives me in my current role. What you’re going to hear today is truly how we have transformed our innovation approach here at Bayer over the last few years.

Let me, before we get into innovation – even though you mentioned that we’re going to talk about commercial stuff later – just address very quickly one elephant in the room. You saw some news yesterday on aflibercept 8 mg. So already a lot of people are asking me, ‘How does that affect Bayer?’ What I can tell you is that our currently marketed Eylea business is not at all affected by that, and we have submitted to European and Japanese and other authorities our new drug application for aflibercept 8 mg. We think we have tremendous data and we’re very optimistic that this will follow its planned course, just to get this out of the way.

So today I would like to have you focus on three things because those are the three things that we’ve really tried to not only bring into this day but that we’ve been working on very much over the course of the last four years. It’s our revised innovation model. It’s our moving away from a very Europe-centric approach into a much broader US presence, and, when I say ‘presence’, it’s not just brick and mortar, like those that are here in the room – and thank you for attending – but also for those that are following us on the web. Our presence in terms of quality people – and I’m humbled by the power of science that is just in this room assembled that has joined us over the last few years. We’ve truly expanded our US footprint both scientifically and commercially. And then, last but not least, it’s our late-stage pipeline.
I know that many of you are aware, but let me just remind you, when you look at a company of our size, with about €19 billion in sales, that is facing significant loss of exclusivities with Xarelto and Eylea, and you look at the value of our late-stage pipeline, we have probably in size in late-stage, two launched and two in the waiting in phase III, one of the best ratios in terms of late-stage pipeline compared to existing sales, and we will have certainly one of the lowest LOE exposures post Xarelto going off-patent in the entire industry. So the next few years, while they constitute still a transition, are really exciting years because we’re really changing the trajectory, as we speak, of Bayer Pharma.

So today we’re going to talk about, I think, three things, and the first thing we’re going to talk about is more focus: more focus on value, more focus on differentiation, on effect size, on better data. And, when I’m talking about better data, it’s about the quality of what we do. And you’re going to see, I think, an unprecedented level of science and quality from Bayer. Many people have told me, ‘I don’t recognise your company’, and you’re going to see why today, and this is also why we brought you here to this event.

And then ultimately one of the things that our industry, quite frankly, is struggling with very often is productivity. We have great science, but then can we actually translate that into products that actually hit the needs of patients and that actually find someone who also wants to pay for that? So we’re really shifting not just to quality and focus but also to actually making that translate into real medicines and churning out at a much higher clip than what our company has done traditionally. We’re at a time – and you’re going to hear this from Christian – where science is advancing at unprecedented speeds and also with unprecedented quality, and you’re going to see our focus areas represent exactly that, and our willingness and our ability to bring innovation to the next level is exactly represented by that.

For that, we will, going forward, focus into four areas that you see here on the screen and that will be represented in our presentations. We’re going to be continuing to be strongly present in oncology, with Nubeqa. You’re going to hear about it in a second. We’ve really created a cornerstone of our oncology presence. In cardiovascular, we have an incredible legacy and we continue to be clearly a leading company not just with our marketed products but also with our late-stage and with our early pipeline. In neurology and rare diseases, with our platform companies, we’ve acquired an incredibly strong position. You’ve seen this morning we published or we showed first data on our Parkinson’s treatment phase I data. Here, of course, we’re going to show you the real thing not in the press release. And then, last but not least, in immunology, we think there is an incredible wealth of opportunity, and our platform with Vividion is a testament to our ability to unlock some of these targets that have been sought after for so long and that we can now address with our chemoproteomics platform.

When you think about Bayer traditionally, there was this internal innovation thing that was very much focused around cardiovascular research and women’s healthcare with a little bit of oncology on the side, if I may, and a little bit of this and a little bit of that, but we’ve really changed that. We’ve expanded our capabilities and our pipeline through a number of acquisitions. Just over the last four years we’ve signed more than 100 deals in total. I was saying this last night at our reception. I looked into a face that was, ‘Really? More than 100 deals – are you kidding me?’

So we’ve really transformed our business from the ground up. We’ve established a really cutting-edge cell and gene therapy platform with the acquisitions of BlueRock and AskBio, and you’re going to hear from Jude Samulski, one of the world’s top scientists when it comes to gene therapy, a man who has, together with this team, revolutionised the field of AAV therapy, and, with recent approvals, this is a platform that people talk more and more about. With Vividion and our science foundation coming out of the Scripps Research Institute in San Diego, we are creating a
chemoproteomics platform that addresses targets that were undruggable so far. And then we continue to collaborate with others in all of these fields and with LEAPS we have an incredibly powerful engine in our venture funding area.

So all of this has created these, let’s say, three circles that you see here that give us a completely different look and feel on the innovation side.

I talked about the US footprint, and we’re talking about here our Boston offices. Those that are here, even though it’s a little rainy today, will not only enjoy the views here but I think are getting a sense of what our innovation approach is really about. But it’s not just that. Four years ago we did have just one site in the US where we were doing some level of research. Today we’re present in North Carolina; we’re present in California in two areas; we’re present here; we’re in the New Jersey area. So we have a much broader presence geographically, but most importantly talent-wise because we have added so many very strong science talents to our organisation.

And on the commercial side we’re really shifting away from a very Europe-centric approach to a much broader footprint in the US. We’ve established a cardiovascular salesforce for Kerendia that I’ll talk to in a second, but we’ve also made significant inroads in oncology, as witnessed by our strong large performance with Nubeqa. So US is becoming more and more key to a company that was completely underrepresented here in the most attractive pharmaceutical market in the world.

Talking about the late-stage pipeline, Nubeqa is this product that at first, when we introduced it, many people were thinking, ‘Well, this is a me-too’ and, ‘Yeah, nice to have, but who needs this?’ Well, we’re redefining the standard of care in prostate cancer patients with our two indications both in non-metastatic and metastatic hormone-sensitive prostate cancer. We have not only had a very successful launch; we’ve secured by now the number-one position in non-metastatic cancer and only a few weeks after launch we’ve already secured the number-two position in metastatic.

There is a data gap in the middle that we’re addressing currently, but we’re well underway with continued increases in new prescriptions week after week to our promised goal of more than 3 billion in sales – so a true cornerstone that constitutes a very strong presence in oncology that we can continue to build on through our innovation.

Kerendia is a product in the cardiovascular field, and you know launches don’t come easy in cardiovascular, but we’re tracking exactly at the same clip as one of the most successful cardiovascular launches in recent history here in the US, and we’re doing so having launched in the middle of the pandemic, and you know that in the middle of the pandemic there were very few good launches getting underway, but we did that. We did that with a brand new footprint in the US, and why did we do this? Because our data is strong. We’re addressing an incredible amount of patients with renal disease, diabetics with renal disease, and we’re hoping in the following years to also broaden our indication spectrum to patients with heart failure with preserved ejection fraction.

So here you can see truly what our strength in cardiovascular translates to when we really bring it to a broader geographic footprint, and you know that we have no marketing and sales rights, or very limited, to Xarelto in the US, and we’re now really seeing how transformative it can be for our organisation to have the strong US presence. But let’s not forget it’s not just going to be about the US. We just got China NRDL listing and we expect Kerendia, given the unmet need, also to be a very important cornerstone of our future China business, where we have an unbelievable legacy as one of the leading companies overall and certainly leading company in cardiovascular there.
Then our next one is maybe one of the most unsung heroes in our late-stage portfolio. With elinzanetant, we expect not only to get data by the end of this year; we expect to have a very differentiated product with the dual non-hormonal mechanism of action, which we feel will not just be differentiated by its mechanism of action, but that will translate into efficacy. We’ve seen strong signals for efficacy in phase II. We’ve seen strong belief that this is a product with a really good side effect profile, and now we’re waiting for the OASIS trial program to read out in the second half of this year with a potential launch in 2025.

I don’t need to tell you how big the unmet need and the potential market for this is. 80% of women will present vasomotor symptoms and 60% of all women are currently untreated. So there’s a vast potential here for this product, and we believe that it has all the makings, potentially, depending on read-out of data, of course, to be, again, a class-leading product here.

And last but not least, when we talk about our late-stage pipeline, let’s not forget asundexian. Asundexian has the potential to redefine anticoagulation. It has the potential to redefine anticoagulation because, if our plan works out as we’ve put it into our clinical trial program, we will separate the bleeding risk from efficacy in these patients, and we currently have in patients that are eligible for anticoagulation about a third roughly that are either not treated or definitely undertreated in their anticoagulation regimen. That means there is a vast potential of unmet need here beyond factor Xa innovation and other anticoagulation mechanisms that are out there.

And who is better than us as a pioneer, with Xarelto, to actually be credible in this space? The amount of patients that need us – and I’m sure that each and every one of you has examples amongst your friends or amongst family, with patients that have suffered from a stroke where the doctor says, ‘Actually, I am not going to give you an anticoagulant because I’m afraid of bleeding, for example, in the brain area’. If we can pass this barrier, that constitutes already an incredible accomplishment. If, on top of all of that, we will be able – and the studies are powered for that – to prove that we have efficacy advantages over standard of care, then I think there is a potential that is going to be difficult to measure – so extremely exciting stuff.

All combined, these four assets have given more than €12 billion in peak sales. Again, €12 billion in peak sales, late-stage pipeline, against total sales currently of €19 billion, with Xarelto going off patent, makes me very glad because, when I started this job four years ago, the only question that I was getting from you investors was, ‘What are you going to do past Xarelto?’ and I’m very happy and proud to say I no longer get that question. So that means we’ve really created a new Bayer on the innovation side.

In the next two hours, three hours, you’re going to hear about this revised innovation model and you will be hopefully leaving this session just like I feel about this: that this is truly a different look and feel to what Bayer Pharma has traditionally been. You’re going to see how well placed we are in the US just by the sheer talent that you’re going to be witness to today.

And ultimately – you’ve heard me say it – the late-stage pipeline potential is probably better than what we’ve ever had in the history of our company. Bayer has typically worked with one or two blockbusters in their pharma portfolio. If our two products that are currently in phase III work out – and we’ve had quite some success with our phase III pipeline in general – we will be, for the first time, having four new blockbusters in launch phase, and let’s not forget that with Eylea 8 mg we’re going to extend the life of Eylea also outside the US. So that will give us five strong reasons to really bet on this company.

And I hope you’re with me with that bet because there is definitely upside potential when I look at our share price, but today we’re not so much into that. Instead, I would like to hand over now to
Christian Rommel, and, before I do so, just for you, Christian has joined us about a little over two years ago now, and I’m super-glad that I could actually convince him to come over to Berlin.

When he first met me in my office, it was in the middle of the pandemic. He came by train because he wouldn’t want to take a flight, and he asked me, ‘Why would I join a company like Bayer?’ and I said to him, ‘Because we’re going to reinvent the science coming out of Germany. We’re going to make this company as great as it has been historically, and you’re going to be Germany’s number-one scientist and you’re going to make a true difference in this company, but, most importantly, in the lives of so many patients’. With that, I introduce you to Christian Rommel. I hope I didn’t overpromise.

**Reshaping Innovation at Bayer Pharma**

**Christian Rommel**

Ph.D., Global Head of Research and Development, Pharmaceuticals, Bayer AG

Thank you, Stefan. I feel challenged already to top your level of energy and the kind words. So meeting with you today marks a very important milestone event for us because we have an opportunity to share indeed with you our new story, and that has been the focus for the team and I over the last two or three years, and let me tell you already upfront, what do we mean by ‘new’? By ‘new’ do we mean a new R&D strategy? You will see new faces, new leadership. We will even share in this meeting with you new data that some of us haven’t seen. You will also see new assets in our pipeline, new ways of working. So there will be a lot of new, and I hope you will be as excited, inspired and build shared confidence that we want to bring forward to you.

Now, we are very well aware of the challenges in the pharmaceutical industry, and this is on the left-hand side, but for the rest of the day we will actually focus on our solutions to address those challenges, and it’s very clear to us that, as Stefan already mentioned, we’re living in an unprecedented time of scientific innovation, in particular the scale and speed that happens.

Now, we also agree that the only way to address those challenges is through innovation. However, it can’t be any longer incremental innovation. It requires breakthrough innovation, and today we have an opportunity to share with you our commitment and the progress we’ve been making in some of those breakthrough innovations. We’re placing strategic bets in certain areas. I would also invite you that this requires vision and courage, and I know that the team will also present that to you.

Now, we have significantly, over the past two years, reshaped our approach and refocused on value differentiation and being competitive in the areas we want to play. We know where we can make a difference and we also have access now to technologies that enable this scientific breakthrough innovation. We did some key strategic acquisitions with bringing on board BlueRock, AskBio and Vividion, and you will learn so much today about their progress, their vision and how it all comes together.

What may not be as visible to you today is that we also significantly reshaped our portfolio and over the last two years we took out about 40% of the projects that are in the clinical stage, I would
say, from phase 0 to phase III, and this was guided by our commitment to how we can create more value, more focus, again in the areas that you will learn more about and in which technologies, and with this I think we will create value in the pipeline.

Our people are the most important asset, and today you will see new leaders, but we didn’t only stand still at the level of leadership team. We have about 70%, over the last three years, renewed the leadership at Bayer Pharma R&D. In addition to this, as Stefan mentioned, we have shifted today about 30% of our R&D resources and efforts into the US, and we have presence not only here in Boston but also in other innovation hubs in the US, but also in Japan, in China. So I think that is in effect a testament to the significant transformation in R&D Bayer Pharmaceuticals.

With the opportunity to begin to work together with the platform companies, AskBio, BlueRock and Vividion, we challenged ourselves. We asked about, ‘How can we create an environment that attracts the best talent? How can we create in Bayer an operating system that really accelerates the efforts in innovation?’ and we agreed to move away from the traditional way of working in large pharma companies, which is normally very much top-down command and control. It’s a hierarchy system, and this requires lots of processes, and we all know it results in slow processes and often not good decision-making.

So we thought we need to experiment and do something different, and what I’m telling you is the way we work now, with the opportunity to work with the teams in AskBio, BlueRock and Vividion, we have agreed on a new operating system that is value-based and that we give each other’s space, but, while we’re working together, we see opportunities to collaborate and to embrace synergies.

So you see the elements, how they come together. There is the R&D team at Bayer. Then we have AskBio, BlueRock and Vividion. We work together, I hope you will confirm, in a very empowered, autonomous and independent way, but it doesn’t mean we will not embrace the opportunity to support each other and to embrace synergies.

In addition to this, as you see, we have done a number of strategic partnerships that either strengthens the pipeline, accelerates the pipeline and also accesses new technologies. So it is a really, I think, unique ecosystem that focuses not on structures and governance; it focuses on value creation and innovation and learning from each other.

And you may not be as aware of it as we experience and value it, but, with the acquisition of these biotech companies, we also have been introduced to different ways of working, and we first of all give space to maintain this, and second, we learn from this and change the way we work all together at Bayer.

Now, in terms of a little bit going deeper in our way of working together with the platform companies. I also want to make sure that we reduce eventually, when we refer to platform companies, to technical terms. However, with AskBio, BlueRock and Vividion, we acquired so much more. We acquired pipeline assets that you already see in our pipeline, and you will learn more about it. All of the companies – and, I think, Aleks, you were at the doorsteps to become a clinical-stage company – are clinical-stage companies.

In addition, as I said, we have now the opportunity to have a diversity of leadership, diversity of culture and approaches in innovation and in R&D, and I also want to remind us that those companies at the time, when we acquired them, they didn’t fall out of the blue. There was like decades of innovation in academic prior work by one of the very finest and one of the most awarded scientists in their field, and Stefan, rightly so, you already mentioned that with Jude we
have someone close in the family. So this is a tremendous opportunity to lead innovation with cutting-edge science and how to work together.

I also want to share a few examples with you where I do see the opportunity or the power comes when we create the best of the world, when we really have an opportunity between pharma and biotech inside Bayer to create ‘1+1=3’, and what comes to mind is that, for instance, at AskBio, where we primarily focus on AAV-based gene therapy, we see opportunities to move beyond, and here’s where I experienced how the teams can work and create value together, such as non-viral vector delivery. Eventually, we will be able to have gene expression control of gene therapy approaches, vectorised antibodies and integrating genome editing.

Similarly, when I think of BlueRock and how pharma and biotech can create value together, it’s adding strengths to the process because it’s not only an opportunity; it’s necessary to give space and operate differently in the areas of cell and gene therapy because the process of developing the product is so much integrated earlier in the R&D process. Today, we are already producing cell therapies in commercial-grade facilities that Bayer added to the strengths of BlueRock.

Finally, with Vividion, the opportunity to take radical innovation, the vision of doing drug discovery in the area of small molecules and combine this with the legacy strings – we have a track record of literally 160 years of delivering and making a difference by small molecules therapy. Now we’re combining this with unprecedented innovation as Vividion. So while we operate in an autonomous, independent manner and support our colleagues at the platform companies, we have begun to really embrace the synergies in adding value and intelligence to each other.

So I will not go through this in much detail. I just want to make sure that you’re aware that those elements have to play together. First and foremost, we have to start – and you will learn more about it – with the unmet medical need. In which areas do we think we can innovate and achieve value for patients and growth for Bayer? And with the access to new technologies – in order to make this difference, you need access to new technologies. You will learn about our choice of unlocking the potential of precision medicine in the core therapeutic areas and, again, how we can do this and accelerate our efforts by, I think, a very unique way of working at Bayer in the R&D ecosystem.

So for us to achieve our ambitions and to make the difference and deliver, create value and growth, we needed to identify the therapeutic areas, disease areas, where we believe we can innovate best, enabled by our technologies at Bayer, and then contribute to growth, and we’ve been through this analysis, and I would think, perhaps not surprisingly for you, as you can see in blue, the focus areas are oncology, cardiovascular, immunology and also areas in neurology and rare diseases have become a priority or the priority for us.

At the same time, in order to succeed with this commitment, we needed to take some difficult and challenging decisions, and we did. So we decided to move from – I think it felt like 20; I think it was 12 therapeutic areas. We are now down to four, and we took a very difficult decision to stop investing in research and early development in women’s health, in pulmonology and also in chronic pain, and it also shows you the consistency of the strategy because our commitment is to develop drugs that fall in pursuit of disease-modifying mechanism to go to the route cause of diseases and not modifying symptoms.

So in essence it is important for us to provide this clarity for you on the therapeutic areas that we will be focusing going forward. And here, once again, you’ve heard this from Stefan. I bring it up again because this clarity is a big change, a big step forward for us. We will contribute more, we will grow and become a more important leader in oncology, and you will learn from Dominik, who
joined us two years ago from Roche. I mentioned to you there is new leadership and this is an opportunity to introduce Dominik, and you will learn more about oncology.

In cardiovascular, as you know, we have received leadership and we have a vertically integrated business from lab to clinic to market and, as you’ve heard from Stefan, important products also in late-stage development. Maria, who joined us about a year ago from BMS, will provide more insights in this. Yet upfront in cardiovascular we will focus on cardiology, nephrology as well as certain acute care indications.

What is now new – and I’ll share more about this – is the area of neurology and rare diseases, where we think that our cutting-edge technologies in the area of cell and gene therapy will enable us to make the difference and ultimately put a vision to reality of introducing restorative therapies for so much need in the area of neurodegenerative diseases.

An area that we are now beginning to invest in and will have greater presence is immunology, but I’ll have an opportunity to go back to neurology and rare diseases and immunology because these are new areas, and I’ll tell you in a moment a little bit more.

Now, across all therapeutic areas, we will focus on precision medicine because we think this is a great opportunity to unlock more value for patients and for the business, and we consider three different value pools in rare diseases, as well as still to recognise – and, make no mistake, if we see opportunities with new technology, with innovation, to disrupt large indications, we will pursue them. However, our primary focus will be applying precision medicine approaches across all therapeutic areas, and precision medicine often means different things to different people. It’s also in the context of the therapeutic areas.

I just reach out to you and say it’s well established, of course, when you can follow molecular insights in genetics and in oncology, similar to, of course, in rare diseases with monogenetic diseases. It’s the prime example of precision medicine. Yet there, we have to raise the bar. Can we make a big difference? Can we actually access the patients for the clinical trial where you already learn and get insights whether there will be later enough access to be commercially successful? So, while we’ve seen opportunity and we have the technologies available, being sure we’re raising the bar before we enter the space of rare diseases.

In the middle of larger indications – we think of precision medicine in relatively simple terms. There are different subtypes of diseases where we have now access to much better understanding of the underlying disease biology by molecular profiling. So basically in the next decade we will see step-change progress of aligning genotype with phenotype, and you can, as Stefan mentioned, achieve a larger effect size of therapies if you align the target, the mechanism, the proper modality in the right subpopulation. Then you have refractory situations; you have resistance; you have subtypes; and even I think we need to commit more to understand gender differences, ages and stages of diseases.

And all of this comes together, but I think we have to be smarter and better in how to position our therapeutic approaches in the right patient populations, and this also will enable productivity and decision-making in the earlier phase of clinical development, where I think that is where you have to be best in R&D in the industry. Can you find a signal? And, when you find a signal, can you have enough data evidence to have confidence that you can scale and accelerate the signal to take it to approval? And we believe that precision medicine is the right thing going forward.
Now, our ambitions across all these therapeutic areas is to deliver and bring forward this diverse and innovative medicine that will be enabled by our modality toolkit, which – again, I’m confident to say that this is unique in the industry.

Let me start with small molecules. I mentioned that we have a very strong track record and are often seen as amongst the very best in the industry, but now, combining this with what you will learn from Aleksandra in a moment, the CEO of Vividion, there is a situation where we can create and unleash even more value.

You also see in our pipeline a stronger footprint of protein therapeutics. It is a testament – we always ask ourselves, ‘What is the right modality for the right mechanism to create the best therapeutic outcome?’

In radiotherapeutics, which is limited and a focus for Dominik and his team in oncology, we are building on the experience of the infrastructure and logistics of radiotherapeutics with Xofigo. We have all the capabilities and the know-how to succeed in our ambition to try for innovation with targeted radiotherapeutics. So be prepared. You will see a robust pipeline, and I’m sure Dominik will speak to that in a moment.

I mentioned chemoproteomics, and you will learn it much more authentically from Aleksandra. She will inspire everyone, and then in cell and gene therapy we really believe we have the leading technologies where we can make the impact for neurodegenerative diseases, and in genetic medicine you see we have the AAV platform, but we didn’t stand still, and we did some smart bolt-on business development deals to move into the next phase of innovation, accessing genome editing technologies as well as non-viral delivery, which will consolidate our leadership in this space.

Now, in addition to this, how can we accelerate? How can we do what you expect us to do and what we expect from ourselves, to do drug discovery and development better? And ‘better’ often means also ‘faster’, and one of the first decisions I took when I joined Bayer was to install an awareness and leadership in data sciences, in machine learning, and let me walk you quickly through where we see the opportunity in what we’re currently pursuing by applying data science technologies and machine learning across the value chain of R&D.

And, first and foremost, let’s start with clinical development, where we have a partnership with Google Cloud, which enables us to have speed and scale of data management in large studies. For instance, a clinical decentralised trials with asundexian or, from a regulatory perspective, to submit data from a cloud basis. This will ensure quality and speed. In the discovery space, I have to give credit to the scientists at Bayer that we are one of the first to bring in the technology excellence from Schrodinger to do virtual screening so we can save, again, time and can go to a space you cannot go with conventional methods. And, indeed, I can assure you that we have discovered molecules just by such technologies, and with Recursion we go into approaches of machine learning to unmask new targets and new mechanisms in disease biology so that the innovation can also start with the selection of new targets.

So, in essence, in the R&D process we see several opportunities to increase our productivity and meet our ambitions. I mentioned to you the opportunity of its precision medicine to develop drugs in a better way and to increase our probability of success. Let me move to the opportunity to reduce costs by digitalising our R&D processes as well as cycle times. So, with this end, I do think that we have strengths in our capabilities to meet our ambition to increase the outcome of R&D.
Now, that is a very meaningful slide. This is a slide – you’ve seen it in the case of Stefan also already. Normally, the energy goes up because this is the mirror image of all the efforts, and the pipeline represents at core our new strategy, and I will walk you very briefly through all of this because you will learn way more from all the other team members today in our program.

I think of asundayxian as an example of seeing an opportunity with a new approach to disrupt large indications and to establish a superior standard of care, and this is born out of our own expertise. Similarly, I mentioned to you that we see opportunities in acute care with very novel approaches that you will see and increasing also the presence of protein therapeutics.

I mentioned to you that in our innovation ecosystem we have strategic partnerships. You may ask, ‘Does it really make an impact? Do they deliver?’ and, yes, here in Boston, at this institute, across the hallway, we have the Broad Institute, and we’ve been working with this institution for several years, and in fact, the program targeting mutant EGF receptor in HER2 is a result of our partnership, and you will learn more about it in a moment from Dominik.

We see a new target in cancer immunotherapy that came out of a partnership with the German Cancer Research Center. The opportunity to work with Vividion already contributes to assets in our pipeline, for instance, NRF2, and I should also mention to you, to be consistent, that you will see more of targeted radiotherapeutics in oncology. The efforts, of course, at AskBio and BlueRock have diversified and strengthened or pipeline in a new area, and elinzanetant is an example of business development, an asset that we acquired that was just about to go into phase III, and Stefan mentioned we expect data readout by the end of the year.

So across the board, out of the 45 programmes that we have, after the reshaping of the portfolio and the pipeline, we’ll show you sort of a snapshot that represents our new R&D innovation strategy, and also I hope you recognise that, as an example, for the entire pipeline the majority are opportunities in first-in-class or highly differentiated best-in-class assets.

So in essence, as I said, it is an incredibly important milestone today to come out and share our renewed story. We have clarity on the therapeutic areas where we want to play. We have clarity of what is required to create value and how will we enable our ambition by access to a range of modalities. We have narrowed our therapeutic area scope, but we have widened access to therapeutic modalities and, in our value-based ecosystem, how we work in R&D, the important role that the platform companies play, AskBio, BlueRock and Vividion.

I also want to make sure, and make no mistake, that we are clear on our priorities in the near term, and that is to succeed in late-stage development with elinzanetant and asundayxian. We also acknowledge that our pipeline needs further work, and we are committed and have a lot of activities going on to strengthen our pipeline by, I would say, clever bold-on selected business development deals and how we can accelerate the winners of our pipeline – and some of them I think we showed you today already – to accelerate them going into the next phase of development.

I also emphasised a lot that you can expect us – and you don’t deserve anything less, and especially the patients we serve don’t deserve anything less – to increase our outcome, our productivity, and you’ve seen the strategy, the focus and investment of technologies. You’ve seen the new way of working that enables speed of decision-making that will increase our level of productivity significantly over the next few years to come.
Making a Difference in Neurology & Rare Diseases  
Leveraging a Unique Platform to Build a Presence in Immunology  

Christian Rommel  
Ph.D., Global Head of Research and Development, Pharmaceuticals, Bayer AG  

So neurology and rare diseases are a new area for Bayer and this will be primarily led by our efforts and access to these modalities of cell and gene therapy at AskBio and BlueRock, and you will learn today so much more, and in particular Seth will share with you the first data of the completion of the phase I and our next step.  

It is the opportunity, and that’s why we live in this unprecedented time of innovation, where we can for the first time deliver restorative medicine to neurodegenerative diseases where there are no current therapeutic options. And what is more an innovation story and meaningful to patients, if you can envision to have a one-time treatment and a long-time durable even cure outcome for patients. This is all relatively new technologies. We are aware of this, but we have a commitment to make this work, and that is also basically reflected in our current pipeline.  

I just want to give you a bit of a preview. You will learn so much more in a moment, but yet it is a remarkable progress already, considering that this is a new area and the time that we began to work together with BlueRock and AskBio is very, very recent still in history. I also find remarkable and want to inspire you with this part. By moving these programs into the clinical phase, we don’t stop investing in next-generation approaches, to become the leaders in genetic medicine and become the leaders in stem-cell based cell therapy.  

Now, a quick word on immunology because you may say, ‘Why are you further expanding?’ First and foremost, we see a strong unmet need and a great opportunity with the technologies we have to succeed with precision medicines in this area. In addition to this, I would prepare you for that I think the next decade there will be exponentially data growth in the areas of autoimmune and inflammatory diseases, which is driven by an evermore increasing understanding of the underlying biology of diseases, access to genetic data. We will see a much better molecular understanding of diseases, which leads to subpopulations, and we will make an impact there. Stefan is distracting me.  

In addition, before I stop, immunology plays an important role in all other diseases. So either the immune system causes a disease or it participates, accelerates, strengthens a disease and immunology, the way that the immune system reacts in patients, can also get in the way of succeeding with your therapies, and when you commit to modalities like gene therapy and cell therapy, for us not to have the expertise, capabilities and a stronger commitment to immunology would be a mistake.  

So I think, in honesty, we’re a little bit in a catch-up mode, but there we will accelerate immunology and that you will see also from Aleks from Vividion. We have a unique opportunity to move now, with a proven approach, into the undruggable space in immunology because we all know, in certain particular autoimmune diseases, there are the KRASs, the β-catenin from oncology. They exist in this disease biology as well, and we will have the courage to take them on.
So I think I’ll stop here and give it now to Aleks. It’s a pleasure for me to hand over to you. It’s been a tremendous experience working with you, and, as I said, I’m so excited to be here today with you.

**Vividion Therapeutics: Removing the Boundaries of Druggability**

**Aleksandra Rizo**

M.D., Ph.D., President and CEO of Vividion Therapeutics

Good morning, everyone. Thank you for coming today. Thank you for being online with us and willing to hear about the progress that Vividion, together with Bayer, has made over the past years. Now, what I’ll talk today is about the so-called – or I call it the frustration rate of 10% of drugs being available to patients due to the limitations in current small molecule drug discovery technologies. I will talk a little bit about how we believe that, with our chemoproteomics platform, we have the potential to change this.

I will also talk even more, even though you heard enough maybe from Stefan and from Christian, how we work together with Bayer, how we leverage resources and how we really make the best out of the two worlds, and I will end up talking a little bit about our platform, focusing on the most advanced projects that we have, and of course I’ll be very proud to share and perhaps a couple of times mention that we are going to be entering the clinic by the end of the year with our first homegrown asset.

So just a couple of facts about Vividion – we are a San Diego-based small molecule and drug discovery company, but we are really excited to be at this pivotal stage of transition into a clinical stage company. Our founders are, as you could see them here, from the Scripps Institute, and we have built our company on the decades-long research efforts from all of them. Ben is involved even today, almost on a weekly basis, he speaks with our scientists. You may know that he was awarded the Wolf Prize in Chemistry in 2022, and this is the precursor for the Noble Prize, so we are rooting for him and keeping our fingers crossed there.

The operations were initiated in 2017, and what’s interesting, really, to note is that the founding scientists, the number-one scientist, is today’s CSO of Vividion. We have now grown to about 200 employees, and we’re headquartered – we have offices and labs based in San Diego. Now, Vividion was acquired by Bayer in 2021, and we are now a wholly owned and independently operated entity.

I joined Vividion in 2022. As a drug developer who’s lived a life both in big pharma and small biotech, I can tell you that I strongly believe that there is no one company that can bring breakthrough transformational medicines to patients alone.

This is why I strongly believe that Vividion, while keeping the entrepreneurial spirit, backed by Bayer, with all the resources and all the knowledge and know-how in small molecule drug discovery, can make a huge impact for patients.

Now, let me start talking just a little bit right about the past and about the huge discoveries that have already been made by discovering or getting us to acknowledge that there are hundreds of
proteins out there that are causing disease. We call them also disease targets. But I already alluded to the fact that only for 10% of those we have drugs nowadays. Now, what does this mean in reality? If you’re a physician just like me, it’s really unbelievably frustrating knowing that, of the 10 patients that will come today in my clinic, I’ll have a drug only for one patient. So how can this be and how can we move the needle? What can we do and how can we change the landscape?

Now, this is where Vividion is coming in. We are pioneering a new way in drug discovery and we do believe that we have the potential to remove the boundaries of druggability, and we are using our strong expertise in chemistry, mass spectrometry, targeted biology. We’re guided by human genetics and we’ve built our chemoproteomics platform that I believe has the potential to open up unprecedented therapeutic options for patients. I’ll talk a little bit more about that in a second.

So what you see on this slide is the 10% percent are on the left-hand side; the 90% that we hope to get to at some point – I’m not saying we are there but we hope to get to – is on the right-hand side of the slide. So, talking about the traditional way of making drugs, typically or in general, to have a good drug you need potency and selectivity, and to achieve these two characteristics in the past and even nowadays many companies are using the so-called reversible drug approach. Now, what this means is that, once you have the protein, you need a big, large surface between the drug that you want to have and the protein, and these are deep pockets that are very difficult to assess. With this approach, you can target certain types of protein classes, like enzymes or receptors, for example.

Now, moving to our approach, which is the so-called covalent or irreversible approach, the story is very different. We need very small shallow pockets because the surface that we need for our drugs to bind to the protein are much smaller, and the difference is that, with this approach, we have the potential to open new drug classes. So now – and you’ll see later also on my pipeline slide – we have developed drugs against transcriptional factors, against ubiquitin ligases, and this opens up the space. This gives the optionality to go broader and to go bigger.

Now, what is the uniqueness of our platform? Why do we believe that we could get there? And it’s based on these two key components that you see here, and I always say one is the chemistry; the other one is the assay. What do I mean by this? So when I say ‘the chemistry’, I refer to our small molecule custom-made library of covalent drugs, of covalent molecules, and then this one – so small molecule of covalent drugs. Now, these molecules are designed such that they are unreactive until they specifically reach the reactive cysteine on the protein target. So that’s number one.

And number two is the platform or how we are able to assay these small molecules on the proteins. And so here we use high-throughput very-high-resolution mass spectrometry, and we are able to, if you will, probe the proteins in their native state, and this is the key. This is the difference that enables us to find so many proteins in their physiological state because proteins are interacting with each other. There are signalling pathways that are occurring or signalling that occurs in the meantime, and so we are able to find those proteins at the right time when they are exerting their signalling and causing the disease. With this platform we are able to screen or to probe thousands and thousands of proteins at the same time. So this is the other uniqueness, the fact that we have this industrial way of screening proteins.

Now, talking just a little bit more about the platform, to tell you why do we believe that we are more efficient by the way that we are doing our screening – and it’s a very different approach. I just want to say this. It’s really orthogonal to the classical way of conventional drug therapies. And the key fact is that – or the key difference is that we can screen many, many targets at the same time. And the fact that we do not need to filter for druggable classes, like the enzymes or receptors that I mentioned, that are able to be drugged with conventional therapies – it’s the biggest advantage that we have.
So we are able to put many targets in screening. We are able to get hits on those targets and then prioritise and see which ones of those are the most undruggable or are the ones that are the most interesting for us to take to the clinic and address large patient populations with high unmet medical needs.

Now, contrary to this – just a little bit about the conventional approach – typically, while the source of targets is always the same, you have to really pick a target upfront that you believe in. You will be investing millions and millions of dollars to go through the screening and you will come with the data for one of those targets, and what’s the downside is that six, 12 months down the road you may actually realise that this is not the best target or you don’t have the best approaches to make a drug for that target.

Now, what you’re seeing on this slide is what a Vividion scientist can see from our chemoproteomics approach. So on the y-axis you’re seeing the thousands of the undruggable proteins out there and the undruggable targets. So this is on the y-axis. And then on the top, on the x-axis, what you see is drug by drug from our proprietary library, and what we are looking for is intersection, where our drug can hit one of the targets at that singular point, the highlighted one. So with our technology we are able to select drugs that are potent and selective at the same time.

Now, again, with most conventional screening technologies, you’re able to do this on a one target at a time. So the potential that you identify and that you speed up – it’s higher because of the industrial scale of capabilities that we have.

Now, a hit like the one that’s highlighted over there can rapidly kickstart an exciting first-in-class program, and, once we have that, once we have a viable and selective lead molecule, we are able to fine-tune, change properties and actually make drugs that have different modalities. This is another key component of the strong chemistry that we have in our company.

Now, on this slide let me focus on two key points. So let’s look just for a second at the curve, and what you can see is each dot on that curve represents an undruggable target that we have identified, and then you could see that, as we have been building our library, on the top, we are able to identify more and more targets, and this goes on. This graph also exemplifies our nice collaboration with our Bayer chemistry colleagues because at the moment we are expanding our library. We’re building perhaps one of the biggest libraries in the world, together with Bayer, and this will give us the potential and the capacity to add more and more and find more and more new undruggable targets now. And one very important point is this is how we remain competitive. This is how we keep on improving. This is how we are able to keep on finding new drugs.

Now, let’s talk a little bit pipeline. So, even though we are only a few years old, we have developed a couple of programs that are either first in class – and this is a key for us; there’s no me-too on our pipeline – or they’re best in class. And, just in line with what Christian was saying before, even though the platform is disease agnostic – we can find targets in any disease area that we would like to focus on – we’ve decided to be focused on oncology as one of the key pillars of Bayer, and we are also expanding, together with Christian’s group, in the immunology area. So this is really a strategic decision to focus on these two areas.

Now, what you can see here is that we have highly selective precision oncology drugs against known oncogenic mutations. Such an example is, for example, the kinase, the PPI inhibitor here, but we also have a – we are also focusing or we are able now to target transcription factors, and by this it opens up the space for much, much larger patient populations with high unmet medical needs, and that will be the case in immunology.
Another thing that you could see here is that we are utilising different modalities. So, if you just glance in the ‘programs’ column, you can see that we’re able to make inhibitors; we’re able to make activators to pathways; we’re able to do degraders as well. So, again, talk about the optionality that we are creating here. Now, because of the scale of the opportunity, and, I believe, the novel and, I would say, unique to some extent arm’s length merger with Bayer is strategically ideal for us. It allows us to accelerate development of all these exciting programs and get therapies to patients fast.

Now, let me just go back maybe one slide for a second. This doesn’t go back. Anyway, what I wanted to show you is that we – there we go. Thank you. So our pipeline is more advanced in oncology than in immunology, as you can see, and so our first programs that are going in the clinic are the NRF2 inhibitor and the STAT3 inhibitor, but what I will show you on the next two slides is how we are using or how we are able to modify these undruggable targets both ways and make their use in oncology and immunology at the same time.

So NRF2 is, I would say, a master transcriptional regulator. It regulates over 500 genes that are involved in oxidative stress, and under normal conditions NRF2 is depleted in the cells. KEAP1 is a ubiquitin ligase that actually degrades NRF2 and keeps it low in the cells in our body. Now, what we’ve learned is, if we keep on degrading NRF2, if we keep on having it low in our cells, if we inhibit the transcription with a NRF2 inhibitor, that way we can find utility of this drug in oncology, but, if we activate it and if we cause accumulation of NRF2 in the cells, we could use it and find applications in immunological diseases.

Now, based on the knowledge and the data that we have today in oncology, we believe that the best entry for us will be to go in squamous cancers, and here we are envisioning going into lung, oesophageal, head and neck and bladder cancer, and, in addition to that, we believe that we can open up the utility or even broaden the application further when we combine this with standard of care. Now, again, super-excited to be able to enter the clinic by the end of this year.

With our NRF2 activator now in immunology it’s a slightly different story. We believe that we’ve generated data in multiple colitis models and, as our first indication, we will be going in inflammatory bowel disease, both areas. You may know this. These are huge patient populations. We’re able to unlock potential, as we know that up to 3 million people nowadays, at least in the United States, are diagnosed with this disease. And we do have a potential for an IND by the end of next year.

Moving to our second target, STAT3, this is another traditionally undruggable target, we are able to make use of drugs both in oncology and immunology. In terms of our programs in oncology, we are envisioning starting study early next year, so we have a potential for an IND by the end of this year in LKB1 non-small cell lung cancer because LKB1 is the third-most prevalent mutation in lung cancer.

And then in immunology we believe that we really have a high potential or, I should say, a broad potential in psoriasis, psoriatic arthritis and IBD. The potential for an IND is also, like the NRF2 activator, by the end of that this year.

Now, with that, I will end my presentation. I’ll hand it back to Oliver, I think, who will take us through the Q&A session.
Questions and Answers

Oliver Maier

Absolutely. Thank you very much, Aleks. I think you’ve seen a lot of information, and we start with our first Q&A. Aleks, I think it would be great if you join me here on stage, and then I would like to ask Stefan and Christian, actually, on stage. We’re going to separate them, actually, on the table over there. I have lots of questions already on the livestream. Nevertheless, we obviously wanted to give everybody here in the audience first the chance to ask questions. We will have, because we have a livestream, two mics from Sebastian and, I think, Jamie over there so if you’d like to ask a question, please raise your hand, state your name and your company and then, if you like, also the person you’d like to direct the question to, and we’re going to start with Emily over here.

Emily Field, Barclays

Hi, Emily Field from Barclays. Thank you for taking my question. Just two, I guess, big picture questions. Stefan, you mentioned in your introduction an increasing focus on productivity. We get asked a lot from investors, ‘What’s the best metric to judge that with?’ and I was wondering if you could just give more context on how you’re seeing those productivity improvements at Bayer and what you’re using as a metric perhaps.

And then also just the focus on moving to a US-centric model and also the discussion on continued development of small molecules ahead of the implementation of the IRA – why do you think that both of those decisions are right given that regulatory change?

Oliver Maier

Thank you, Emily.

Stefan Oelrich

So thank you for that question, Emily. First – and I will need your help here – obviously, for us, we’ve tried to retrofit, if you like, from a productivity perspective, our throughput model to get to something that will give us an improved output, but not just on quantity but also quality. But I’ve heard those stories many times. ‘We’re improving quality’, and what have you, but when you see the science today – I think that’s the testament to the quality and effect sizes that we’re looking for in terms of pipeline productivity quality-wise. But, quantity-wise, it needs to translate into something that, for a company of our size, I would think by the end of – and I need to tread lightly here, but by the end of this decade we should be able to get to double-digit IND productivity out of our pipeline. Please correct me if I have this wrong.

And, ultimately, the beauty of this is, when you look at the makeup of our priorities and you look at, for example, in the areas of cell and gene or when you look at some of the specialty cardiology or specialty oncology, we’re moving away from these broad outcome trials that take a long time and cost a huge amount of money, and we’re trying to actually increase the amount of shots on goal. With our traditional approach, we could’ve never been able to actually put through so much through our pipeline. When you look at the cost of asunexian or when you look at the previous
costs of a development like Kerendia or like Xarelto in its day, those are unthinkable with this type of productivity increase that we’re trying to get. So that’s how we measure this.

On IRA, of course, we’re following IRA closely. Now, the beauty of this is, when you have almost no presence of molecules that are exposed to IRA, it lives so much better. That is obviously going to change, but, when you still look comparatively at the value of, let’s say, the four main markets that you will have in the world, Europe, China, Japan and the United States of America, I see – from our vantage point, I see no change or decrease in attractiveness of the US business. That being said, you will need to remain competitive. On the small molecule side, you need to take this into account as you look for the returns that you want to get to, but, when you take the approach that we’re taking, for example, in Vividion, we believe that we have a unique capability to address some of these targets. That will give us tremendous advantage also as we move forward both in effect size but also in the type of the molecules that we can actually ultimately patent and create uniqueness around.

So I’m not necessarily fearful of IRA going to change all of that. I believe in the attractiveness of the US market, and IRA does not change that. Let’s not forget, when we talk already macro, the macro picture is that the United States of America spends roughly 18-19% of the overall wealth of this country is invested into health, and of course that gives also a superior opportunity to add innovative drugs that help to curb overall healthcare expenditures, and I would also hope that in the coming years and years, as science progresses, the value of what we contribute as an industry will also be even more recognised than it is currently in legislation. For the US, this is a key industry in terms of innovation and in terms of helping patients, but also in terms of economic wealth to this nation so I’m not pessimistic at all about our industry here in this country.

**Oliver Maier**

Christian, you want to add something?

**Christian Rommel**

You know what? With IRA, I have to say, when you meet the R&D team at Bayer, we are drug hunters, and cancer does not know there’s IRA. So we will continue to commit to doing the right thing to create value for patients. If there is a mechanism and target that requires the right modality, we will swing for that. In addition, there is one thing that we have to deal with: when we enter the clinical development phase, what kind of disease type and patient population are we pursuing in order to establish proof of concept versus a longer-term strategy? There is a twist to this that we have to put our heads together, but I want to bring home we do what we need to do in order to create value for patients and then for the business. Cancer does not know there’s IRA, and we’re not bending over to that.

**Oliver Maier**

Thank you, Christian. I think there’s one more question from Pete over there

**Peter Verdult, Citi**

Aleks, just a clarification. I believe, prior to being acquired by Bayer, you had partnerships with, I think, Roche and others. I just wanted to clarify, on 037 and 038, are these Bayer-owned assets or are they part of the prior collaborations?
Aleksandra Rizo

What I presented today is all Bayer, 037 and 850.

Christian Rommel

You know what? I don’t want to miss an opportunity to say that the collaboration was Roche has been very successful, and I think we met or exceeded all the expectations from this partner so far, but we are here today to talk about what we can do at Bayer, but it gives create validation and support to the value that Vividion can provide. Thank you for asking this.

Stefan Oelrich

Feel free to ask that question to our Roche friends.

Aleksandra Rizo

Even with the Roche programs, we do bring value for Bayer. We earn milestones for each of those programs as we advance them.

Florent Cespedes, Société Générale

Good morning, Florent Cespedes from Société Générale. Two big questions – first, regarding the inflammation, your programs you have in this field, we know that you have products already on the market which are pretty potent. So what would be the element of differentiation when you will enter in these markets? I have off the top of my head psoriasis, which is quite competitive, but if you could elaborate on that.

And the second question is on the library. You were mentioning the unique library you have. Could you elaborate a bit on the intellectual property behind? If there is an intellectual property, what is protected or is it really the uniqueness of the molecule you have in your library?

Oliver Maier

Do you want to start with that one, Aleks?

Aleksandra Rizo

With the second one?

Oliver Maier

Yeah.

Aleksandra Rizo

Yeah, sure. I can start and then we can tag-team on the immunology one. So it is proprietary; it’s custom built. There’s no such library in the world. So it’s molecule by molecule built by Vividion.
We own entirely the library and have the IP properties, so, yeah, we are very protected on that. We’ve taken care of that.

In terms of immunology and how are we going to be differentiated, it goes back to the fact that we are focusing only on first in class. So it’s absolutely undruggable never-entered-the-clinic targets that we will be focusing on with the potential to address really multiple large patient populations. I don’t know if you have anything to add.

**Christian Rommel**

I think you will agree with me that some of the medicines out there in the autoimmune inflammation space are very successful yet they don’t serve all the patients. I think it gets lost on us that there is also resistant mechanisms. That creates an unmet need, and many of the therapies – or the patients would also deserve kinder medicine, so maintain the effect size or improve, but also improve on safety.

So I’ll leave you with one thing. And you’ve been introduced to the first time – and I find it amazing that you share so much today – if we master KEAP1 for inflammation, we may have a mechanism that works like steroids without any of the liabilities, and don’t tell me there wouldn’t be value in that.

**Oliver Maier**

Great, I think I can squeeze in one question we’ve received from the livestream, and that came from Michael Leuchten from UBS, and I think it’s directed to you, Stefan. It’s on elinzanetant. ‘Your elinzanetant peak sales aspiration seems cautious relative to the market characteristics you outlined. What are the key variables that matter in your view to the sales potential?’

**Stefan Oelrich**

So thank you for that question, Michael, and I hope to respond better to your needs by significantly upping the peak potential once we have the data because that to me is the limiting factor. What we’re seeing so far – and I think that’s going to be key – is a good safety profile. So we currently have one entrant in the class that has some liver monitoring so we’ll have to see if that is needed with our compound, and then we’ll have to see, on the double mechanism of action, if that shows additional clinical benefit like, for example, some of the signals that we’ve seen in phase II on improved sleep quality because vasomotor symptoms are not the only thing that bother women in the menopause, and menopause is not just defined by vasomotor symptoms. We think that we’re going to be very effective there too.

So it’s those three: effective to treat these symptoms; b) a clean safety profile to the degree possible; and, thirdly, potentially an additional effect that we’ve seen signals for in our phase II. So we’re super excited about elinzanetant. I was with our US affiliate until yesterday, and the excitement is building inside of our commercial organisation because we’re nearing launch and they clearly see the incredible potential. You saw the amount of women that would be eligible for such a treatment, and we went through the treatment path as I was talking to our folks here in New Jersey, and it’s mind boggling. If you really could unlock this, then obviously the potential would be much greater than €1 billion peak sales.

So stay tuned. We don’t want to say anything before we see the data because, let’s not forget, we have some experience in launching also assets into menopause that were based on hormones, and
this is not an easy place to go to. So if the data is good, I think we have an incredible opportunity, so I hope you’re as excited as I am to uncover those data at the end of this year. Thank you, Michael, for the question.

**Oliver Maier**

Thank you, Stefan. Any more question here…? Otherwise we have time for maybe one more, and then otherwise I’ll squeeze one in. I have one more from – the name is not mentioned. Hold on. Let me see. Here we go. Aleks, that’s one for you. To what extent is your approach also applicable to TAs outside of oncology and immunology? Could you, for instance, come up with targets or compounds in other TAs of interest?

**Aleksandra Rizo**

Yeah, absolutely. I alluded to that a little bit. So the platform is disease-agnostic, and what that means is that we could be screening targets in any therapeutic area. We’ve decided to focus – it was a strategic decision to focus on oncology and immunology, but can we find targets in cardiovascular? Can we do other rare diseases? Yes.

**Oliver Maier**

Great, I think we are perfectly on time. I’m very impressed. Thank you so much. So I think we’re going to have a 10-minute break, a bio break, do emails, grab coffee, and then we’re going to be back here in 10 minutes, and then Dominik is going to start his presentation on oncology. Thank you so much.

[Break]

**Driving Leadership in Focus Areas of Oncology**

**Dominik Ruettinger**

M.D., Ph.D., Head of Research and Early Development for Oncology, Pharmaceuticals, Bayer AG

Welcome back, everyone. Thanks for listening in, for those online. What I’m going to do over the next 15-20 minutes is show you the oncology refresh and our strategy and take a look at a couple of portfolio programmes that we are excited about. In a way, Alex, from Vividion, has already started the oncology section, so this is a wonderful foundation to build on. I’ve been with Bayer – and you heard that from Christian and Stefan – for a good 18 months, joining from Roche Genentech. I get the question, ‘Why did you make that move?’ It’s really about the growth story, you know, like a 160-year-old giant rising and deciding to do something big in oncology.

So that’s in a nutshell, but there are a couple of other things that I found fascinating and that really supported my decision. One is patient-centricity, and we’re hearing that a lot, but I can give you an example in just a second, after this slide. So what I’m going to tell you today, or show you today, is around our refresh strategy in oncology. So we’re basing that on what we framed as precision drug development. The whole idea is to identify the most promising programs, in terms of targets, but
also in terms of commercial viability, as early as possible. And, obviously, take no-go decisions just as fast. I’ll show you a little bit on what we believe will happen, in terms of future patient populations, and what our focus is, derived from that knowledge. It will be around expanding the pool of druggable targets.

So one way to do it is Vividion’s approach, to turn undruggable into druggable. Other ways are identifying new targets, of course. We will definitely need kinder medicines – and I’ll show you an example of why we think that is so important – and we will have to address treatment resistance much more than we think about it today. For that, we’re building an R&D portfolio in oncology at Bayer rapidly. It is based on three scientific focus areas: so, targeted alpha therapy, what we call precision molecular oncology, so that is genetically driven disease, and next-generation IO, we call it, so where we take a clear focus on first-in-class and best-in-class opportunities.

So now, this picture was taken about two weeks ago, at a patient engagement event. And that is what I mean with using the patient as an anchor and as a starting point for what we do in drug development. Two patients – Harry, he’s kind of representing today’s patient population. He’s 58 years old, has two kids, was diagnosed with oesophageal cancer, advanced stage of disease at first diagnosis. He did have his tumour sequenced and also did the staining for HER2. So he’s now on a clinical trial, but we learned and listened carefully; he gave us that story of he had to swallow up to 20 different pills a day, which is hard, if you went through first-line chemo radiation for your oesophageal cancer. So these are what we mean with kinder medicines as well. So it’s not just the tolerability.

Merel represents a very different patient group, and we will see many more of these patients going forward – 46 years old, metastatic lung cancer, mum of two little children at that point. So her tumour tested positive for ROS1 rearrangement, and she’s been on treatment for seven years, so chronic treatment. You may want to remember that when I speak to future patient populations in just a second. So what we’re doing is serving today’s patient populations and being ready for future populations, and that’s why we need to understand these populations very thoroughly.

So now, on your left, I don’t have to tell you much about the opportunity in oncology. So the unmet need, I think, is a bit more clear. You will hear me speak a lot about differentiation in that context, that’s really what’s in the unmet. You know it’s going to be one of the largest and fastest growing segments in the pharmaceutical industry. And fascinating is the disruptive innovation, currently – what’s happening is unprecedented innovation at unprecedented speed. And, again, expanding the target pool is one of the examples, but also the incredible amount of data that we’re generating from different sources that we then integrate and analyse. And Christian gave you the example of AI-based approaches that really helps us tackle that amount of data, but also to recognise patterns within that.

On your right is the Bayer strength; there’s a lot to build on in oncology. Obviously, six marketed assets speaks to the commercial capabilities and the launch experience, speaks to certain tumour types that we’re covering with these assets. And the scientific-clinical expertise, just a couple of examples. What I need for a successful R&D organisation are certain ingredients; one is access to multiple different treatment modalities, and you’ve heard the examples of small molecules, protein therapeutics, chemoproteomics from Vividion, targeted alpha therapies. But there’s more experience at Bayer than I’ve seen at other companies. Targeted alpha therapy – wonderful example of a treatment modality that can kill any cancer cell, regardless of pre-treatment or mutational status. So I’ll speak to that in just a second. And then the experience in certain tumour types that comes with marketed assets, of course, but also in terms of the prediction of tumour types that we’re going to see more often going forward.
One part of the strategy is going to be, we will be doubling down wherever an internal strength meets an external opportunity, okay. So our focus areas – targeted alpha therapy, precision molecular oncology, and next-generation IO – and we will be looking in certain tumour types: GU, GI, lung cancer. Doesn’t mean we’re not developing in other tumour types if we find a really good fit to our drug development paradigm. The way you read the chart on your right is, basically, we looked at the unmet need, patient number, and the size of the bubble of indicates the broad sales at a certain point in time. And, obviously, we are looking to play in the upper right quadrant; these are the focused tumour types.

So now, very important slide, because we need to understand what’s happening 10 years from now. Phase I to launch is still more than nine years across industry, in terms of our development timelines in oncology. So we need to know – we need to be ready, by the time we launch, for that patient population. We will see more cancer patients, no doubt – that’s epidemiology, ageing patient population – but we will also see patients being much younger at the first diagnosis, so the early-onset cancers. We will also see more patients that are diagnosed earlier in their disease, and we will see certain tumour types come up in incidents – so, GI, GU, lung cancers.

On your right is our conclusion and what we’re going to focus on. So kinder medicines, we heard that a couple of times. Remember Merel, our patient, seven years on treatment, she spoke to a grade two fatigue. That means she can rest but it doesn’t do anything to her fatigue – seven years. So we really have to pay better attention and come up with kinder medicines. Higher selectivity for the target will help us in that sense. I’ll give you an example of our EGFR/HER2 exon20 insertion program in just a second, that has a high selectivity for the target over the wild-type receptor, resulting in better tolerability.

We spoke to the druggable pool of targets – making the undruggable druggable, but also finding new targets. We believe there will be new targets, in the early disease setting, for example. And then we need modalities that can kill cancer cells regardless of their pre-treatments, mutational status, so the problem of resistance, alright. And the disease-centric drug development I mentioned focuses on those tumour types, where the unmet need sits going forward.

This is, if you wish, the strategy, how we’re going to do this, in one slide. Okay, we call this precision drug development. Everything we do starts with the patient, as I told you, and then the right target. What we mean with the right target is, we’re only going to take programs forward where we see a true vulnerability or dependency of the tumour. So it has to matter if you module that target. We know the shortcomings of drug development in oncology pretty well. Usually there is a lack of the target disease link and safety surprises is a problem, and there is no predictive biomarker. So we really have little idea of what the patients are that are most likely to benefit And if you reverse that, we don’t know the patients that we should not be treating, okay, expose them unnecessarily to treatment.

So we’re going to look at the right target, establish the target disease link, only go for assets where we have a defined patient population, and we need to be able to measure the impact of what we do. So target modulation biomarkers are very important. Now this is almost like modality-agnostic, in a manner, right. So that’s where the broad range of modalities comes in at Bayer. So we will then use the fit-for-purpose modality and all of this will be driven by value and differentiation. So we do want to know, is there a price at the end of the finish line? I’m an R&D guy, but there’s nothing more rewarding than seeing your drug that you brought to launch actually being used by physicians and patients.

So now, quick look at the current oncology portfolio across all stages of development. As you can see, it’s a very balanced portfolio – balanced in the sense of the modalities – so we’ve got to work
on this. You will see, for example, speaking of IRA earlier, so we will see more biologics coming up, and just to have the right balance there – alpha therapy, biologics, small molecules. Balance, also, in terms of partner programs versus full in-house developments. And then, also, across our scientific focus areas. The boxed programs are the ones I’m going to give you a bit more detail on; I picked three out of the area of precision molecular oncology and next generation IO. And then I’m going to speak, at the end, a little bit about our excitement on targeted alpha therapy.

So, first one, the way I’m going to do this, there’s two slides per program. One gives you a bit on the current status and the key hypothesis. That’s so important. I heard someone say that successful drug development is really mastery of the fundamentals, and I could not agree more to that. So our EGFR/HER2 exon20 insertion program is one where the unmet need is beyond doubt. So these patients do worse, okay, than other – they have, more frequently, brain mets. They have a median PFS – so progression-free survival – of about six months. So they simply do worse. That’s a poor prognostic marker, if you wish. So now, the unmet need is clear.

Differentiation of our molecular – we have a reversible inhibitor here, again speaking about safety. But the key hypothesis is the selectivity over the wild-type receptor, and I’ll show you a piece of data in just a second. This molecule actually targets classical mutation – mutations that are acquired after first line treatment – so you can see that here, C797X, for example. But it also has a very strong activity against HER2 insertions, which is very important as well, as there’s no approved drug for these patients. Current status – this program entered in the clinic in October end ’21. We’ve completed dose escalation and are currently recruiting expansions specifically for different subsets, and anticipate that to be fully recruited, still, this year.

So just one piece – a key data here, in vivo model this is our EGFR exon20 lung cancer model. The black curve basically shows you the control, and then you can see the blue one is our compound in comparison to competitors. So that’s pretty equal there. On your right, in terms of tolerability, this is sustained, where we look for intact, wild-type signalling, okay. So the brownish stuff is good. So the more you have – the more intact your wild-type signalling is, the less side effects we expect. Okay, so then, the control and our molecule basically leaves that pretty much intact, whereas other molecules that we tested in comparison don’t.

So next is a truly first-in-class opportunity. It’s a kinase diacylglycerol kinase, that is involved in activating T-cells, so two steps mainly. It’s around priming T-cells to a certain antigen, so that the T-cell recognises the antigen; and then recovering, reactivating, silent T-cells, so tumour resident, in an anergic state, T-cells. So that’s the key hypothesis. We block the kinase; there’s an overexpression of diacylglycerol and the T-cells are activated. So that obviously has huge potential. This goes all the way to first line; it could overcome resistance to immune checkpoint inhibitors, where we know that durable benefit is actually rather the exception than the rule, so huge potential across many tumour types.

And the first isoform, DGKzeta, entered the clinic end of last year, and we are really excited to have the second molecule, which targets a different isoform of the kinase. You may ask, ‘What’s the difference?’ We expect different levels of T-cell activation, so that’s the difference. You may even want to combine these two molecules. There is a combination potential with checkpoint inhibition, for example, so multiple ways to play with this asset, huge potential – obviously durability will be a key readout for us on this program.

Again, one key piece of data in vivo model again, showing both the monotherapy and the combination with an anti-PD-L1 antibody, and I think the green line here speaks for itself. It shows what we like to see in a survival curve as a tail – as a durable response in a cure in this pre-clinical setting, so excited to see data coming up. Both programs will be in those escalations in 2023.
So next example – and we picked this because this is an antibody. It’s glycoengineered, so that’s the differentiation. The target is an interesting one. Chemokine receptor 8 is expressed on regulatory T-cells, but on those that are tumour-resident. It’s usually not expressed on peripheral Tregs – on cutaneous Tregs. You may be familiar with Treg-targeting approaches. This is not a new field, as such, but Tregs seem to be one of the dominant mechanisms in terms of creating an immunosuppressive state at the site of the tumour.

Again, the key hypothesis – if we get rid of these cells, we will see a more immune-permissive state locally, so the molecule is differentiated – does exactly what it’s supposed to do. This is a program that also entered the clinic end of last year, so this is still in dose escalation. Huge potential, and if you match that against our precision drug development paradigm – I just want to mention that – in IO, it will always be an indirect link of the target and the disease. We’re not targeting the tumour; we’re targeting the immune system, so there has to be more to these programs, such as the first-in-class potential or at least a best-in-class potential.

Key pieces of data – an in vivo growth curve again. This is a MC38 mouse model, so it’s an immune-responsive colorectal cancer model. You can see for yourself in terms of, again, the monotherapy activity and the combination with a PD-L1 antibody, but the fascinating data is on your right. That shows survival – for the pinkish curve, the 80% survival, these animals are actually cured. They have durable responses and do not relapse with their tumours.

Now, two more slides on targeted alpha therapy and why we’re so excited about it. The scientific rationale of an alpha particle inducing a DNA double-strand break that the cell can really not repair is fascinating in itself, but there is more to it. Remember what I told you about the rising importance of treatment resistance in our patients that, let’s say, start their cancer career at the age of 40, 45 or something – they will see multiple lines of treatment, so we will need modalities or approaches that work regardless of potential treatment resistance mechanisms. This, from what we have seen so far, is definitely one of them.

There’s another effect that is called the crossfires effect, so basically the payload goes to the target-positive cell and usually, if it was an ADC or something, it would only kill this cell. The crossfire effect basically describes that a radioligand kills neighbouring cells as well, regardless of if they are target-positive or not, so very important for us – short range, high energy. That’s the principle of an alpha-emitter, so it does not do damage to adjacent healthy tissue.

Then of course the combination potential – we have four examples. Really interesting data in the combination with darolutamide (NUBEQA) in the preclinical setting – application possible across many hard-to-treat tumour types. We are, like many others, interested in prostate, but this is something that has potential in many really hard-to-treat tumour types.

Now you may say, ‘2013, approval of Xofigo – what happened since?’ What we have likely underappreciated is the need for multiple iterations, and this is, by the way, true for any scientific approach – the need for multiple iterations. The middle cartoon shows you that this is a four-component molecule, so we have a targeting moiety; we have a linker; we have a chelator, and we have a payload, and every element makes a huge difference, so possible permutations are many.

Now what we’re doing is we’re going to be much faster in this iterative process. We are going to take more approaches and test them faster, and another thing that we’ve done probably not enough is pay attention to the targeting moiety. Many of our previous programs – by the way, all of them showed clinical activity, so this approach works, but many of them were based on full-length antibody approaches as a targeting moiety. We are now switching, and you may have seen the
bicycle collaboration that we announced, so we are now looking at ratios. It’s the same principle – our collaboration there.

So we’re looking at new targeting moieties. They all look at the same principle. We need an optimal tumour penetration, tumour retention, and the fast elimination from the body to avoid side-effects as much as we can of this approach. Multiple durations, new targeting moieties – we have also worked on the other components and are well underway, I would say, to have the best molecule for hard-to-treat tumours. On your right, seven pre-clinical programs, and we expect two programs to enter the clinic very soon. Overall, our pipeline is very dynamic, so the remaining six months of 2023 we anticipate three clinical entries, so lots of things happening in the oncology portfolio here.

With that, I hope I showed the precision drug development approach and how much discipline it will take to follow that, and how that can increase our productivity significantly. The need for expanding the target pool, kinder medicines and the importance of resistance mechanisms, and for that we are building a world-class pipeline right now and that is, to close the loop, the key reason why I joined Bayer. Thank you very much and, with that, handing over to Maria Borentain.

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**Shaping new Treatment Paradigms in Cardiovascular Diseases**

Maria Borentain

M.D., Head of Cardiovascular and Renal Clinical Development, Pharmaceuticals, Bayer AG

Thank you, Dominik. It’s always very difficult to go after Dominik, by the way, and I realise that I am very happy I wasn’t in high school with Dominik. What I would like to share with you today is really what we will be focusing in cardiovascular in the future and how we want to tackle development in this area. Let me start by the key points that I would like to make today.

First of all, you know all cardiovascular diseases remained a huge unmet medical need, and we will need to find solutions for many millions of patients living with cardiovascular diseases in the world. Secondly, and you would have guessed by now, cardiovascular has been and remains a key area for us and will build on our strong heritage to continue to bring innovative therapies to patients. Thirdly, and you’ve actually seen from Christian, we will be shifting our strategy to a three-pillar approach, something that we called value pools. These are areas with high unmet need, areas we think we could make a tremendous difference versus standard of care and bring innovative therapies to patients in need. These priorities are targeting rare diseases, working in subpopulations, and disrupting large indications. Lastly, our focus in cardiovascular includes selected areas in nephrology and acute care.

Let me tell you how we plan to unlock the strong potential of the future cardiovascular market to continue our success story. As you agreed and you know, the unmet need remains high and disease continues to grow at a steady pace. We have a number of exciting emerging trends that are happening under our eyes in cardiovascular. First, of course, is these new drug modalities that will allow us to unlock undruggable space. Secondly, through data science and advanced analytics, and particularly multi-omics, we will further disease understanding. Of course, digital solutions are
important for us and are enabling a facilitating of all aspects of clinical development. We talk about Bayer. We are really well positioned to meet the future challenges of this area, and that’s thanks to our experience, our capacity to innovate and our integrated capabilities and footprint.

And we have already with Kerendia a very exciting launch, and we are coming to new opportunities in the late-stage development, and, of course, we want to break new ground in thrombosis prevention with Asundexian, but what really will change the paradigm in cardiovascular will be to find which patients will be responders to a certain mechanism. Our external collaborations, but particularly our collaborations with the platform companies, will help us make this jump into the future of precision cardiology. As a cardiologist, I’m extremely happy and very honoured to work for Bayer, a company that has this longstanding track of success in cardiovascular, but not only that; this decades-long experience and knowledge that has been accumulated is essential to make that jump into precision cardiology.

We aim to sustain our leadership. As you see, we are among the top global market leader in cardiovascular, and what that means for us in R&D is that our medicines are impacting and bringing hope to millions of patients around the world. And we aim to build on that in our current market and drive our midterm growth with our potential blockbusters Kerendia and Asundexian. We have an industry-leading integrated capabilities from discovery and R&D to commercial, and this integration and constant feedback loop from bench to bedside, to market and back, would allow us to leverage those insights from clinical trials and market to inform R&D, and obviously, we envision to build on that to consolidate and transform our pipeline to meet patients’ needs.

In order to address the high cardiovascular disease burden and drive our long-term growth, we have established a number of priority areas, and we are back at the value pools, and let’s see what we mean by that. These three value pools are rare diseases, subpopulations of larger indications and disruption in large indications. These are areas where we think we could make a difference with high unmet need, where we could be substantially better than standard of care and deliver superior therapeutic options to patients in need.

Rare diseases tend to have the highest unmet medical need with no treatment options, or very few of them. While the numbers of patients are relatively small, the value added could be considerably high. This is also an area where we could be extremely innovative in terms of clinical trial designs and execution.

Now, let’s talk about subpopulations of larger indications. The goal here is find those mechanistically homogenous forms of the disease with the same response signature, meaning patients will respond in a homogenous way that would lead to better treatment effect, would lead to more predictive response, which means less non-responders, less adverse effects and potentially a more positive probability of success with potentially smaller trials. And we are working on the subpopulations in heart failure and chronic kidney disease.

And, of course, disruption in large indications means that when we find a therapy that will disrupt large established market with a new standard of care, we will be very happy, and we’ll take it forward, like we are doing right now with Asundexian, that is meant to change the paradigm of thrombosis prevention. Again, our ambition is to deliver transformative medicines that will bring value to our customers.

And here it’s similar to what you’ve seen in oncology. The focus of today will be on the two compounds on late-stage development, Kerendia and Asundexian, and we will go into some details of the earlier pipeline, but what I would like to bring your attention to is if you go down into the
pipeline, you’ll see more variety of drug modalities. And this is pretty exceptional actually, I would say, in cardiovascular. Even a couple of years, several years ago, we wouldn’t have seen that.

So let’s start with Kerendia. So finerenone – that has been approved recently, as you know, for chronic kidney disease in type 2 diabetes. It’s meant to be a foundational therapy in multiple indications, literally a pipeline in a pill. Now, Kerendia has a differentiated profile versus other compounds in this class and its differential structure and mechanism of action actually leads to what you see on the table, the high potency that Kerendia has, high selectivity, and particularly, I would like to draw your attention to the more balanced tissue distribution between the kidneys and the heart, with potentially a more protective effect on the heart.

This has been validated with gene expression models in preclinical models and cell models where we see that finerenone is actually acting on expression of genes that are involved in profibrotic and pro-inflammatory pathways and that’s very important – keep that thought – we’ll see why we think it’s important for the future of Kerendia.

This mechanism has already panned out in chronic kidney disease in type 2 diabetes, and you’ve heard from Stefan the launch in this indication. This was based on maybe the largest clinical trial program to date in diabetes with chronic kidney disease called FIDELITY. And you can see here the results on the composite cardiovascular outcome and the composite kidney outcome, where we achieved significant reductions.

Based on that, we are progressing Kerendia to all patient populations of chronic kidney disease, and we are very happy that we have two ongoing studies. One is FIND-CKD in patients with chronic kidney disease due to other causes than diabetes. That’s ongoing and will read out in 2026. And very excited about a study that we just announced this week at ADA – we investigate finerenone in CKD in type 1 diabetes, a disease that has been neglected for so long and I could tell you the medical community is extremely excited about that.

And we are very happy about the progress that we make in our heart failure program in HFpEF with Kerendia. Now, this is an area again with very high unmet need. It is the fastest growing cardiovascular disease and many patients, despite progress that has been made, remain at unacceptable high risk for cardiovascular mortality and hospitalisation.

But why do we think that Kerendia (finerenone) could work in heart failure with preserved ejection fraction? Now, coming back to the biological property of this drug that show really a more differentiated effect on the myocardium and the heart, we’ve seen extremely compelling data on cardiovascular outcomes from the adjacent populations, which are chronic kidney disease in diabetes. And you could see on the right-hand side, the top panel, the composite of cardiovascular death and heart failure-related hospitalisations that has been shown in FIGARO-DKD, the cardiovascular outcome trial, to be extremely significant. And we have a very promising, albeit preliminary, data from a study in heart failure, with reduced ejection fraction where we’ve seen compelling data.

So, with that, let’s move to the next area that’s extremely exciting for us, which is our accelerated approach to disrupt thrombosis prevention with Asundexian. So I think you’ve heard by now, and Stefan really mentioned that very well, a significant proportion of patients today are not treated due to the fear of bleeding. So to address this remaining unmet medical need, we think Asundexian is really what will make the change in this area and let me tell you why we think this is an extremely innovative drug.
And talking about and you know, of course, haemostasis and thrombosis. Haemostasis is the physiological clot formation that the body employs to seal an injured vessel, for instance, and to stop bleeding. Thrombosis is something that’s pathological, that leads to an exuberant clot formation and these two pathways actually have been thought to be so intricately linked that any attempt to decrease thrombosis was thought to lead to an increase in bleeding.

Now, recent advances in understanding of the coagulation cascade led us to believe that these mechanisms could be distinct. And you can see on the cartoon on the left-hand side, factor XI sits on a very crucial place on the thrombosis amplification, meaning that the pathway, the contact pathway, by the way, that leads to this thrombotic pathological event that leads to build up of clots in the vessel, disrupt the blood flow and lead to thrombotic events. Therefore inhibiting factor XI seems to be a strategy that will remove that part of thrombosis build up but leave the haemostasis intact, meaning the body’s ability to stop bleeding intact.

And factor XI has many validated targets. It’s a genetically validated target and we’ve demonstrated in the – and you could see that in the literature, that patients that genetically lack factor XI are somehow protected from having ischemic events, particularly ischemic strokes without increasing bleeding. And, on the contrary, the other spectrum, patients that have a genetically increased factor XI have more risk of ischemic events and particularly cardioembolic events.

With that, this mechanism we think has been validated in our phase II program PACIFIC. And you can see on this slide, it’s something you’ve seen already last year when we presented the data, PACIFIC-AF and PACIFIC-STROKE. In PACIFIC-AF, we’ve seen a significant reduction in bleeding versus the standard of care apixaban that has been given at standard doses. And in PACIFIC-STROKE we’ve seen no increase in bleeding versus placebo on top of antiplatelet therapies. And if you look, and it’s a post-op analysis, the rate of recurrent stroke and TIA in patients with any extra or intra-cranial atherosclerosis, those who are at higher risk of having recurrent events, has been reduced significantly.

And based on this important program PACIFIC, we have designed the phase III program, OCEANIC, that comprises of two studies, OCEANIC-AF in atrial fibrillation and OCEANIC-STROKE for secondary stroke prevention. Both studies are ongoing. They will recruit more than 27,000 patients worldwide across 40 countries. This will be probably one of the biggest endeavours that Bayer has ever undertaken. OCEANIC-AF will enrol 18,000 patients. The primary endpoint will be stroke and systemic embolism and will read out in the second half of 2025.

OCEANIC-STROKE will look at Asundexian versus placebo on top of antiplatelet therapies and the primary endpoint would be the recurrence of ischemic stroke. Readout, similarly, in the second half of 2025.

Okay. So, with that, let’s go into more, earlier pipeline and I would like to introduce some of our exciting, very promising assets that we think we disrupt many indications. Starting with this one, which we are developing for chronic kidney disease, and we’ll try to position in some populations. So everybody knows about nitric oxide, the importance of the nitric oxide and its pathway through soluble guanylyl cyclase and cyclic GMP on many pathological processes in the body. The deficit of this pathway leads to ischemia and organ damage in heart and kidney.

So why we are excited about that, now, soluble guanylyl cyclase has been core to Bayer research for more than two decades and has led to two important approvals, Adempas in pulmonary arterial hypertension and Verquvo in heart failure. These two molecules are sGC stimulators that act by binding to an iron-containing haemoprotein that sits on the surface of the soluble guanylyl cyclase.
Recent research by our scientists led to the groundbreaking discovery showing that we could modulate soluble guanylyl cyclase on a different manner through a heme-independent pathway. Why is this important? Well, in conditions of high oxidative stress, for instance, in diabetic nephropathy or in diabetic retinopathy, for instance, the soluble guanylyl cyclase loses its heme molecule and the stimulators become inactive. By modulating and by its heme-independent mechanism, soluble guanylyl cyclase activators represent a new class of drugs that could be transformational and disease modifier, because they act in these high oxidative stress conditions.

And so I would like to talk about our sGC activator platform, and we have here in this slide the data from the front-runner called runcaciguat. On the left-hand side you could see the preclinical data in animal models of CKD where we have seen survival improvement in proteinuria and improvement in renal function in diseased animal.

But why we are so excited, by the way, it’s because of the phase II CONCORD study which we have just presented at the European Renal Association last week. It’s a study in patients with type 2 diabetes and chronic kidney disease and other forms of chronic kidney disease. And you could see here that proteinuria has been dramatically and probably in an unprecedented manner, decreased – more than 40% reduction in patients with diabetic nephropathy. And that’s, more importantly, in patients that have a maximised treatment with RAAS inhibition, ACE or ARB, and, more importantly, in patients with or without sGLT2 inhibitor. And we know the importance of proteinuria, that more and more it’s considered to be an extremely important risk factor for progression of CKD, but as well for cardiovascular events. So we are extremely excited about this compound, and we hope to bring it to clinic in the near future.

The sGC activator oral BAY328 is actually the follower of runcaciguat of the data that I showed on the previous slide. And this compound has shown similar efficacy in preclinical models and because of its improved PK profile, BAY328 will be the compound that will be continued in the clinic.

Now, let’s move, switch gears now to alpha 2-antiplasmin, BAY301. We are again in the thrombosis area. This is a field of high unmet medical need. You all know what an acute thrombotic condition could represent and how dramatically the lives of patients suffering from acute ischemic stroke or pulmonary embolism can become and the high societal burden.

We have a new modality. We are very excited about this new way of driving thrombolysis in patients with these acute thrombotic conditions. Now, if you look at the cartoon on the right-hand side, you could see here the plasmin, which is the main protein that degrades clots and you all know about tPA, this is the tissue plasmin activator that exists. It’s the only class of thrombolitics that we have today for patients that have an acute stroke or a very small population – subpopulations of patients – that have a pulmonary embolism. And tPA is used globally but we all know the important – while it’s a very effective thrombolytic, it’s associated with a very high risk of bleeding, and particularly intra-cranial bleedings that might be extremely catastrophic.

So with our mechanism, by targeting alpha 2-antiplasmin, we think that we have a more precise and more fine-tuning way of modulating plasmin to degrade the clot than the tPA route that will lead to efficacy without increase in bleeding. And our data actually from preclinical setting, we see the efficacy that’s similar to tPA but without increasing bleeding.

And with that, let me talk for really one minute about another exciting approach in a rare indication, which is Sema3A for Alport patients. Alport syndrome is a rare kidney disease, genetically defined disease, where patients at a young age lose their kidney function and end up in dialysis or need a kidney transplant. Sema3A, or Semaphorin-3A, is a molecule that by increasing the signalling, it’s
contributed to the pathophysiological mechanism of this disease. And what we have shown is that
the increased signalling of this molecule leads to tissue degeneration, an impaired regeneration,
progressive loss of kidney function in proteinuria and our data in a preclinical model of Alport
show clearly by targeting with a monoclonal antibody of this molecule would lead to significantly
decrease in proteinuria. And with that, I guess we could start our Q&A session with Dominik.
Thank you very much.

Questions & Answers

Oliver Maier

Thank you, Maria. Fantastic listening to you. Thank you, Dominik, for all the insight. I think we’re
going to have another 10 minutes for Q&A, so please raise your hand if you have a question.
Otherwise, I have a couple of questions actually on the stream online, which I will squeeze in. We
start with Emily again. Ladies first, here we are.

Emily Field, Barclays

Thank you. Emily Field from Barclays. Yeah, maybe just a follow – and I’m not going to
pronounce this right – but the drug in the CONCORD study.

Maria Borentain

Runcaciguat.

Emily Field

And apologies if I missed this in your remarks, but you’re not taking that into phase III, and just
how is the follow-on molecule then expected to be an improvement?

Maria Borentain

So the follow-on molecule has an improved PK profile that will allow us to give it once daily,
which is a tremendous improvement for patients. And we think that this molecule that are
structurally some – not exactly the same structure – but structurally related, and with the data that
we have in preclinical models showing the same efficacy we could accelerate the development and
move it directly to phase IIb.

Florent Cespedes, Société Générale

Good morning. Florent Cespedes from Société Générale. First, a question on cancer, radiotherapy.
Could you share with us which tumour types you will target first in your development program?
And I know it’s a bit early days, but about the manufacturing capacities, will you have enough
when you have to scale up for broader clinical program and also for the commercial? So that’s for
the cancer question.

And then I have a question on cardio. It will be on OCEANIC-AF. Are you targeting a superiority
or the same efficacy as your comparator and what could be the different scenario here? Thank you.
Maria Borentain

Shall I start with the cardiology? So obviously, in this arena and you know very well that previous clinical trials, mega trials, that have tested factor X inhibitor versus Warfarin, the classical strategy is to go for non-inferiority and to test superiority. So today, with the statistical techniques that we have we could do that with preserving the – with alpha control in an alpha control setting and without losing power.

Dominik Ruettinger

Certainly. Of course, you guessed the tumour type from our two frontrunners, which is PSMA as a target, so that’s prostate cancer, obviously. Others where we have not disclosed the targets, but I can speak to tumour type and then let you guess on the target is hepatocellular carcinoma is one that we’re very interested in. Small-cell lung cancer is one and then we have the additional targets that allow us to target a broad range of tumour types and, in particular, hard-to-treat tumour types and that could include tumour types like pancreatic cancer, for example.

In terms of the manufacturing, it’s an interesting question, because once we’ve figured out the best molecule with our iterative process and new targeting moieties, the logistics and the application locally at hospitals, you’re probably familiar with the just-in-time drugs, as we call them, and that is a bit of a euphemism. There’s a lot of logistics behind it. So that is in place, and this is one of the things where Bayer has a clear stronghold. This is where experience and expertise come in, so I think it’s safe to say that that is on track.

Oliver Maier

Thank you, Dominik. I squeeze in a couple actually from the livestream and then from the Zoom and then it’s Pete. It’s a question for you, Maria, from Michael Leuchten from UBS again. Regarding BAY328, is this your thinking this will become an add-on to Kerendia on CKD?

Maria Borentain

Well, this is a very different mechanism of action, so indeed, it could be given on top of standard of care, and we indeed expect to give it on top of Kerendia.

Oliver Maier

Okay, great. And then, Dominik, I have two questions for you from Richard Vosser from J. P. Morgan. On the CCR targeting, Tregs, have you seen any single-agent activity and, more broadly, do you think you need to see single-agent activity for ultimate success in oncology?

Dominik Ruettinger

So wonderful question. This is a program that entered the clinic only end of last year, so this is still in dose escalation, so it’s way too early to speak about anti-tumour activity. That’s not even a primary objective of that part of the phase I study, so simply too early to say that. For what it’s worth, in terms of preclinical model, we did see single-agent activity in hard-to-treat preclinical models, so translatability limited with a cautionary note, but that is remarkable. Let’s see how that translates into the clinic.
In terms of the development path for this molecule, it certainly does include combination development, just to be very clear, in terms of the CDP for this molecule.

**Oliver Maier**

Thank you, Dominik. There’s one more from Richard and I’ll just weave it in too. ‘Can you give more details on the targeting modality for the targeting radiotherapies? You said antibodies have toxicity, which I think are liver related.’ That’s what Richard says. ‘Are you using peptides or other modalities? If you’re using peptides they’re limited targets, so how are you going to differentiate from competitors?’

**Dominik Ruettinger**

Yeah. So again, excellent question. Remember when I told you – I heard the livestream wasn’t all working – but basically what I said was tumour penetration, tumour retention and fast elimination from the body. So it’s not only liver that we’re interested in. Kidney tox is a big challenge; not for us but for the field in general. So the trend we’re seeing across the field is the size of the targeting moiety decreases. So from a full-length antibody, which is at about 150 kilodalton, we’re now going down to sizes like 2 or 3 kilodalton, so very small.

A good example is the approach that Bicycle is taking. Basically, what we’re using there is – and that’s really why it’s called ‘Bicycle’. It’s a chemical scaffold of – and that has around eight to 12 amino acids around it. So basically what that is we can play with affinities. It’s a peptido-mimic, if you want. So basically it has antibody properties, but we can manufacture it as if it was a small molecule. So that is the beauty of that approach, but there are other approaches. That’s just one of multiple that we’re interested in.

**Oliver Maier**

Great, thank you, Dominik. Thank you, Maria. I think there’s one more question from Pete.

**Peter Verdult, Citigroup**

Thanks. Pete Verdult. Three questions, please. Dominik first. Just – we all know that ADC is the hot area. We’ve seen what companies are willing to pay for those assets and the market’s very focused on the upcoming lung trial in a matter of days. So could you just provide a candid assessment of Bayer’s ADC capabilities and how you’re going to play catch-up?

And then, Maria, just two for you, please. Just to be clear, 142, is that going back into phase II or is there a chance that you might push that straight into phase III? And then my last question to Maria on Asundexian, could you just provide an update on the recruitment rates and any high-level comments on the event rates you’re seeing across the program versus the powering assumptions? This relates to the OCEANIC program. Thank you.

**Dominik Ruettinger**

Maria, are you going to start again?
**Maria Borentain**

Yeah, sure. So, well, we are very happy about the progress of our OCEANIC trials. We are on track. The trials have started, as you know, last December and we are progressing as planned, so no, no surprises there. We’re enrolling the right patient population.

With regards to – I think you mentioned it’s BAY328, right? So that’s the molecular that you’re – so actually we have already completed a phase I, and we’ll progress directly to phase IIb, based on data from runcaciguat.

**Peter Verdult**

Just a clarification, this was the runcaciguat follow-on. Is that going straight into phase III or is that going back into phase II?

**Maria Borentain**

So the runcaciguat, as I said, we won’t progress further. We’ll continue with the follower, which has an improved PK profile.

**Peter Verdult**

That’s going into phase II or into phase…?

**Maria Borentain**

Phase IIb, yes.

**Dominik Ruettinger**

So then, on the culture question, ADC is clearly a hot field – by the way, a wonderful example where the iterative process was so important, where some companies, competitors, really worked many, many years to come up with the right molecule, the right payload to antibody ratio in these variables for ADCs. Bayer actually is monitoring that. We have experience in that field, so we have worked in this field before, so active monitoring is our approach there.

Currently, there are a couple of disadvantages versus targeted alpha therapy as you’re probably aware. I spoke to the crossfire effect, so an ADC will kill a target positive cell but not a target negative cell. Alpha therapy does not. There’s no need for internalisation of the antibody, so it will – if it binds to a cell, it will kill it. So we believe there’s a true differentiation versus ADC, which doesn’t mean they cannot coexist, just be very clear.

**Oliver Maier**

Great. I think 10 minutes are over for the Q&A, so thank you, Maria. Thank you, Dominik, for the Q&As and for the answers especially. And with that, it’s my great honour to hand it over straightaway to Seth Ettenberg, CEO from BlueRock. Seth, the floor is yours.
BlueRock Therapeutics: Leading the way in PSC Therapies

Seth Ettenberg
Ph.D., President and CEO of BlueRock Therapeutics

Thanks, Oliver. Appreciate it. Hello all, and good afternoon. Good morning. We’re making the transition now, and it’s clear from today’s conversation with my colleagues that you’ve been having, and also if we look at the world around us, that science and drug development – this is a multidisciplinary sport now, yeah. We need many different of us in the in the team to get this done, and today is just a great example of that. And Christian, where are you? I even include you in that multidisciplinary team as well, so bear with me.

You’ve heard from many of my colleagues today talking about our enthusiasm, our excitement about the data that we’re sharing with you today. I’m going to put a challenge out to you in your chairs and for those of you online, which is to remember where you are today. I’m going to tell you about a new frontier in science and I’m going to then validate it with human clinical data releasing of top line data just today. I can’t tell you how excited I am to represent that after decades of work, and you will remember this moment, I hope, as you follow us for the years to come and the progress that we make.

There was a new frontier in medicine, as you all know, for the chimeric antigen receptor T-cells that made it through clinical development and now are on the market with miraculous efficacy for patients in haematological cancers. This bore out a new way for us to think about medicine. I’m here to tell you that BlueRock, with our partners at Bayer, are on the edge of a new frontier in cellular medicine and that is the ability to broaden well beyond haematological cancers into other indications and other cell types that weren’t yet possible to our industry and that we’re doing this with a pluripotent stem cell-based therapy. I’ll describe to you what I mean by this in the coming slides.

Today, I want you to take away three things from me. The first thing I want you to take away is that our commitment to Parkinson’s Disease in collaboration with Bayer, and we’re doing this through the advancement of our lead medicine that we call bemandanepcel.

In addition, if going after Parkinson’s Disease and creating a first regenerative medicine weren’t enough, we’re then looking to enter the clinic with our very next medicine called OpCT-001 in collaboration with our partners at Opsis, into photoreceptor disease and this is to restore vision to patients with primary photoreceptor disease as our second IND to enter the clinic.

And then finally, what I want you to take away is that we, together, along with – are coming into the Bayer family as we were acquired, that this led to the change, and what we’re inspiring to do is to change the way that we’re approaching medicine for both patients and for the treating physicians. And that we are committed to this by replacing the cells that are lost to disease, or their function is lost to disease in the ageing process. So, to start, it’s important just to make a recognition that by moving into cellular therapies, we’re going after diseases that currently unmet medical need is not treating these intractable diseases, and if you listen to the statement that I just made, the cells are lost. We can’t drug these cells back to life. We can’t give them a signalling pathway – they’re gone. This is evident by the number of cell therapy trials that you see going on in the world right now, and beyond that for the number of late-stage cell therapy trials, that leads to an increasing in market share and/or commercialisation of these products. This is clearly one of the
fastest growing areas, or the promise for one of the fastest growing areas, in the pharmaceutical industry, but let’s be really clear, there are still challenges for this field ahead.

So the first one that I want you to take away and think about is streamlining or optimising supply chain and logistics. We’re not bringing a pill to the pharmacy and moving it over on the shelf, we’re delivering a living medicine. The second one behind that is patient and caregiver support. The ability to educate the patients and the PR’s and the treating physicians that we’re bringing this medicine to, of what the difference is for a living medicine and what the difference is for the treatment paradigm. And then, lastly, we need to think about innovative payment solutions. Clearly, we’re all aware of and understand this, and we need to make sure that as we approach this, that we think about getting access to as many patients as possible that have a need for these medicines.

So at BlueRock, with our partners at Bayer, we are a leader in pluripotent stem cell biology, and I tell you this because we’re just now the team to bring this forward. We have the commitment, and you heard many – Aleksandra describe earlier today of that best of two worlds. The ability to take an innovative, bold step forward based on the science that we understand, and have the leverage or the force multiplier of a global and heritage company like Bayer to be there with us and help us in every step. We were initially founded back in 2016 by Leaps – Bayer Leaps – along with Versant, and we stand on the shoulders of giants that were the founders of our company and the founders of the projects that you’re going to hear me talk about. Since then, we have expanded our capabilities and we exist across four different sites and three different countries, and we’re continuing to grow our capabilities to deliver these medicines from the initial concept at the bench all the way through the clinic and eventually to the market, as you’re going to hear me talk about.

But the aim is to create cellular medicines that replace lost cells, as I’ve said. So I want you to think about this in a really simple, yet technically bold endeavour. Think about your Microsoft Word application on your computer right now. There’s a tool within that application that allows you to search for a keyword or a phrase and then replace that keyword or phrase throughout the document. That’s exactly how I want you to think about BlueRock Therapeutics. We study diseases for where which the cell is lost or its function is lost to the body, and we then carefully curate, create a well-defined and well-characterised cellular product that is then frozen and delivered to the clinic, and replace that very cell within the body. It sounds like science fiction, but I’m here to tell you and to share data with you – in fact, we’re doing just this.

To understand BlueRock’s strategy as we go about cell therapy, I want you to focus sort of on the bottom half of this slide. As you follow this graph and look through the bottom half, what you realise right away is that we are talking about an allogeneic cell therapy approach, and what I mean by allogeneic is that we take donor material from a healthy individual and then we make the ability to use that source to treat many different patients with the very same singular source. Now, this is in opposition to, or different from, what many of the early commercialisation products were, which are autologous cellular therapy products, where you take the product from the affected individual, modify it in the laboratory, and then bring it back to that same individual, which is logistically challenging, but also has both cost implications, scaleability implications, and reproducability issues. We believe we solve many of those problems, and the goal to solve many of those problems, with an allogeneic approach.

Now, this is a new endeavour. There aren’t allogeneic products like this on the market, whereas the autologous have been very effective. Pluripotent stem cells, on the other hand, these allow us, if you will, the source material. Pluripotent stem cells allow us an indefinite source material, as opposed to an adult-harvested source material which as the name is so to speak, we take this material from an adult which then limits the types of cells that we can do it, and also is very challenging to expand in the laboratory. So pluripotent stem cells allow us to do this indefinitely.
We can grow these in large vats, in industrial processes, and we can do this indefinitely from a single source material. You can think of us just like you would of a master cell bank in a biologics project or an antibody project. We can have that same master and working cell banks to go back to reproducibly over and over again.

When we develop these cell therapies, we also need to think about how we deliver these then to the patient, this living drug to the patient, and for BlueRock Therapeutics, for the indications that I’m going to speak to you about today, we have to invest and take careful attention to deliver safely to the location for where these cells must exist in the body, and so we do this often by surgery and by delivery device, which is an integral part of our product portfolio. As we work to bring these therapies into the clinic, BlueRock is focused on the disease to link an unmet medical need, and as I share with you the pipeline you’ll go back to this hypothesis, and one manner in which we can treat diseases is to take this blank canvas cell that I spoke about – the ability to reprogramme an adult cell, blank canvas – and then differentiate it into any cell type within the body. Now, you can imagine as we differentiate these into the cell type of the body, we can go after and focus on diseases where the cells are lost. Parkinson’s disease is a perfect example of just such an occasion, as is cardiomyocytes, with the loss of muscle cells within the heart. So these are part of our focus in differentiation.

We also can then, with advanced genetic engineering, we can manipulate the genomes of these cells to bring a therapeutic payload or modality to them that they don’t normally have from nature. And you could imagine we can now focus on areas of oncology, as we do, but also add enzymes – very complicated proteins to make within a manufacturing facility – to go after metabolic diseases or autoimmune diseases. As you think about BlueRock and the building of the capabilities to enter into this brand-new space, I want you to break those capabilities into three sort of separate areas. The first then is what is core to our foundation, is the ability to source that donor material and to reproduceably create these master cell banks in a reproducible manner, and to then be able to make multiple different cell types. The second, which is key to our success and that I will validate for you later in the slides as they come, is the ability to deliver these cells to the clinic, and then eventually into the market.

And third, as I mentioned, going from clinic into further development, we need to be able to make this product at a commercial and reliable scale, and we’ve already begun to do that in our partnership with our colleagues in Berkeley, California, at the probably first ever time where we’ve tech-transferred the production of dopaminergic neurons – a program that I’m going to tell you about with bemdaneprocel – at commercial scale in a commercial facility. And this is a bold new endeavour for us, and certainly for our colleagues at Bayer. Now, as I mentioned before, science and drug development, this is a team sport now, and that plays through in just our own strategy and how we go about striving towards our mission of continuing to push the envelope of science. We have ongoing partnerships in many different areas and many different aspects. I’m going to focus on just one of those off of this slide today, and tell you about our relationship we just recently announced with Rune Labs, as well as Emerald Innovations.

Now, these companies are digital health technologies that allow for either wearable or contactless digital health technologies that will follow our patients, and in this case in a non-interventional study. About 50 patients within the United States will be using these devices, that we hope will ease the burden of collection of information in Parkinson’s disease from the patients’ perspective and allow us to capture real-world data in a continuous and unbiased manner. Now, we think this is going to help our product within Parkinson’s disease, but you can imagine that these applications go well beyond our own, and will ease the burden of reporting for many different patients across our portfolio if we use these technologies, and we believe that partnerships like this help us and maintain our ability to stay on the leading edge of our technology.
I use this slide to introduce you to our pipeline. We cover four different disease areas mainly of focus. They’re very reminiscent of what you’ve heard today from Christian, which is neurology, cardiology, immunology, oncology. That seems to be our theme, that they hover near each other. And additionally, in a relationship that I’m going to tell you about now with Opsis – a wholly owned subsidiary of FujiFilm – our first endeavour into photoreceptor precursor cells in primary photoreceptor disease, what we call OpCT-001, and this is meant to be our next clinical asset. So what is primary photoreceptor disease? Well, it’s a collection of inherited retinal diseases, where the mutation in these diseases lead to the loss of or the dysfunction of the rods and cones of the eye.

Now, as I previously mentioned in our pipeline, we focus on areas of unmet medical need where we can replace these cells, and clearly in this disease setting this is a high unmet medical need. There is really no treatment paradigm for the vast majority of these patients, and we simply watch and wait while the patients go from limited vision to complete legal blindness. And there’s many genetic causes that lead to this, and in fact we’ve seen the advent – and you’ll hear later from Jude – the advent of AAVs, allowing us to go after specific genetic mutations to restore some of these cells, but what we’re doing is mutation agnostic. We’re bringing cells that have the entire genome, that can then go into the entirety of this IRD population – at least, that’s the goal of our endeavour – and allows for us to replace both the rods, that allow for vision within low light, or the cones, for vision within bright light, to give these patients and restore vision to these patients.

So our ambition beyond OpCT-001 is actually to go after many different indications, as we start to replace the cells within the eye, and what I want you to take away is that OpCT-001 is a pluripotent stem cell derived receptor progenitor cell, that goes into the eye as a progenitor and then forms into the rods and cones, these two separate cell types within the back of the retina. So I’m sharing with you for a first time and also our goal of restoring vision, which is grounded in really exciting pre-clinical data that I’m sharing with you here and will continue to share with you, from our partners at Opsis. And where what you can see is by the placement of these cells within the back of the retina in several different animal species – here, is a rat – where as long as we look into these animals, and the latest date we’ve looked is nine months, you can see that not only is the geography and the placement of these cells correct, but how they’re behaving in terms of moving the appropriate proteins, known as rhodopsin or opsin, to their right location within the cell, indicative of the fact that they’re functioning correctly.

We’re excited about the potential of this therapy, of course. It’s an incredible step within science and drug development, to be able to be privileged to be able to go after and think about this moment, and we’re looking to filing this IND within the next 12 months.

So let me change pace now and really start to talk to you a little bit about why I’m so excited to be here in front of you today, and shift gears and talk about Parkinson’s disease. Now, given that this is the second most common neurodegenerative disorder in the world, it’s likely that most of you in this room have met someone or know of a family member that is suffering from a neurodegenerative disorder – and what you’ll know from that is that this is a devastating disease. It’s a progressive disorder, and what we mean by that, it’s progressive because there’s a progressive loss of the dopaminergic neurons within the brain of these patients. The loss of these cells, which normally these cells produce dopamine that allows for really critical brain functions that often display as movement disorders. However, in Parkinson’s disease, when that patient first shows up to the clinic and first gets diagnosed with their neurologist, they’ve already lost 60% of the cells that are dopaminergic neurons, and what happens over the disease setting is they continue to lose these cells to the disease.

Now, there’s a wonderful treatment in the early stage of this disease known as Levodopa and Carbidopa, and this is the standard of care, and patients in fact get quite a bit of benefit from this
treatment early on in the disease setting, but both the patient and the doctor know from that moment on that there will be a progressive loss of efficacy of that drug type, and eventually the patients will no longer respond to this drug, and there are quite some side effects that come along with an ever-escalating dose. And so, as a result of this, there is significant unmet medical need in a longer term and, what we are hoping for, regenerative ability to replace these lost neurons to the patient. And in fact our vision is that these patients begin to think of themselves not waking up as a Parkinson’s patient, but for waking up and to begin to live their life again.

So our phase I trial that we announced earlier today, this was a multi-centre, open label phase I trial. It’s a small trial, about 12 patients in a low dose and a high dose cohort. We enrolled these 12 patients to receive bemdaneprocel, and the ones that were able to receive this were patients that were still getting some benefit from Levodopa/Carbidopa, but were suffering from lack of benefit from that, meaning that they still are experiencing inadequate relief from their motor symptoms. To receive bemdaneprocel, the patients went through a one-time surgical treatment for which we make two burr-holes, one in each side of the head, and then we place a cannula three times into three different locations on each side, and we do this with two things in mind.

First, to reduce the number of impact we’re having on the number of holes or cannula placements when within the brain, but we also do this to get the best coverage of the area that we know the dopaminergic neurons need to be within that patient. And so we do this with a mindset of decreasing the risk for the patient, but also increasing the coverage area of the cells, and our custom approach allows for this to happen, but we’re using standard practices and standard equipment that are already in neurosurgical practice.

So today it’s an honour, it’s a privilege, for me to be in this moment, because I get to represent what is the last 20 years of our scientific founder putting in investment and time to get to this moment today, and what I’m going to share with you today is that we’ve just released really just the top line results from the study. As you know, a phase I study, its primary objective is safety and tolerability, and what I can tell you is that for all 12 patients we’ve met this primary objective. We had little to no major safety issues in all 12 of the patients. The secondary objectives, of which there are several, we’ve met feasibility of transplantation, and beyond that we have evidence of engraftment and dopamine production from these cells, and we can do that by following the patients with a Fluorodopa PET. Now this is an incredible, significant milestone ahead, not just for BlueRock, not just for our Bayer colleagues that we’re involved with, but really for our patients, because dopamine and the release of dopamine is the sine qua non. This is how we diagnose patients, is the loss of this signal over time.

And so we’re going to share, as is appropriate, the extent and the details of our data in an upcoming conference, The International Conference of Parkinson’s disease and Movement Disorders in Copenhagen in the end of August, and encourage you all to come see, and look at the details of that data as we share it with both our community and with the PIs in our study. So I know that I’m giving you a task, which is to remember this moment. I’m also going to tell you that we’ve made great progress. We’ve made incredible progress for where we wanted to be. Reporting out these phase I results, what I haven’t mentioned that I’ll mention now is that we’re also now in the planning stages and we will initiate our phase II study, which will allow us to be in a controlled setting with a control arm study for phase II in the first half of next year. We are committed to making a change in Parkinson’s disease with this approach, and because of that we have a program right behind DA01 that we call DA02, and we’ll tell you more about that in the time that comes forward.

And finally, watch for us as we file the IND into OpCT-001, and initiate our first in-human study in the next 12 months. And I didn’t have time to tell you about, but a project that’s near and dear to
both our colleagues in Bayer in Germany as well as our own team, where we’ve demonstrated already proof of concept in large animals, the ability to replace cardiomyocytes into infarcted or heart failure models, translatable models, and we look to file the IND for this in the near future. So with that let me stop. Let me pass the baton over to my buddy, Jude Samulski, who I know you will enjoy time with him, as I always learn every time Jude’s up on the stage. So, Jude, over to you.

**Aklepios BioPharmaceutical: Pioneering AAV-Based Gene Therapies**

R. Jude Samulski  
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It’s very interesting being here. This is my first time doing something like this. My Bayer colleagues get very nervous when they ask me to get in front of people, because I must tell you that I’m not an employee of Bayer. I’m the founder of AskBio. I’m a professor at the University of North Carolina, and I’m a consultant and CSO for the company, so I don’t have any objective of trying to sell you anything or convince you of anything. At the same time, when I look out here and I see a lot of kids – I call you kids because if you were born after 1978, you weren’t even around when I started on this project, and I still am working on what I would call my thesis, which was to make a viral vector and correct genetic diseases. So as I talk forward, everything I’m saying it’s irrespective of what I think, it’s irrespective of what Bayer thinks, this is happening and it’s going to continue to happen, and I’m fortunate that I’ve been able to be in it from the beginning and still participate.

First question you ask is, ‘Oh, how long will he stay, blah, blah?’ No, forget it, I’m a ten-toe-up type of researcher. When I’m laying on a slab with my toes pointing up, that’s the day I’m done. But just to share with you where we’re going with this, let’s think about it from the perspective – you’ve heard some phenomenal science today. If you didn’t catch it guys, it’s a very simple message. You can take a single target and run your million compounds against it, or you can run a million compounds against a million targets. It’s a no-brainer. And I think where Seth was going is where everybody realises. I went to the Mayo clinic last week, and all I heard was everything that wasn’t working – my hearing, my eyes, and so forth. No one told me that, ‘Oh yeah, we’re going to make this better.’ It was all, ‘You were here, you’re now here, you’re going to be down here before it’s over.’

And if you take that and put it in context, there’s eight billion people on this planet, and if you think about it, over the next hundred years, eight billion people will die. Irrespective of what else we talk about, likelihood is over a hundred years all of them will pass away, so you’re really getting down to, if you’re going to live, what’s your quality of life, and what is it that you can participate by getting back to life? And so I’ll share with you our AskBio objectives and mission and try to do it in a very simple way. The last thing I’m going to tell you, I owe homage to Anastasia, Simone and Thomas because they put up with my prima donna type attitude, but I hate these slides. I think they’re an insult. One time, I had to get up in front of the senators, and they said, ‘Oh, use pretty pictures, simple concepts, and aim for the mentality of a 13-year-old,’ and I have to tell you guys, these slides aren’t that much better so don’t take it as an offence, but now that I’ve insulted my Bayer colleagues and you guys, I’ll go ahead and start talking about why I’m here.
Everybody has the same pitch – this is a great market, it’s an unmet need, robust therapeutic pipeline. Like I said, it’s irrespective of what I think. You have to look at this from the reality of what’s happening at this point in time and history. This is the most conservative group you could imagine projecting what they anticipate is going to happen, and it’s very clear by 2020 they anticipate more than 200 INDs, they’re looking at 10 to 20 gene therapy and cell therapy drugs being approved, and they’re going to add 50 additional reviewers just to handle the onslaught. So, like I said, it doesn’t matter what I think or say, this is coming from our regulatory community, which probably sees the tsunami of activity and they’re bringing it to our attention in a very conservative statement. I will take credit that they bring attention to it, it’s because of this development, and I was fortunate enough to be in the lab that started that activity.

Look at the data – and you don’t have to listen to the FDA – the data’s right there. The number of phase I/phase II trials are growing exponentially, and the potential cells – which I don’t really have any interest in, it’s part of where you guys live – is concomitant with what’s going to happen with these things. The more important thing is look at the ones going into phase III, and then start watching what’s been happening in the news. You heard about haemophilia. You just heard about Sarepta getting an approval. It’s a tremendous win for the families. They wobbled from a research perspective, but it’s irrelevant. We’re moving down a path that’s going to get trodden over and over again.

This is the part where you’re supposed go, ‘Oh, Jude’s amazing. What is the expertise that lets you stand up here and say why we are leaders, why we’re better and so forth?’ It’s because we made every fricking mistake you can make along the way, and learned the hard way that this is not an easy science. We were the first to clone AAV. We were the first to put it into a patient’s brain. We were the first to put it in intrathecelly. We were the first to put it in DMD patients and so forth. So what does that mean? It’s like winning the Super Bowl. Next year, everybody wants to know, ‘What are you going to do next?’ So we were the first to do all of this, but in the end what it did was it gave us a really, really exceptional early insight in what’s required to make this work, and that’s what I will share with you right now is these pillars.

The technology is self-explanatory. You need to have that in order to go forward, but what I think a lot of people didn’t appreciate was the importance of manufacturing, and that showing that you could help a kid or cure disease was irrelevant if you couldn’t produce it for the masses out there. And we look at this as a springboard from going from orphan diseases to more general diseases, that manufacturing becomes even more critical. And everybody’s in this phase of clinical development and learning how do you do gene – how do you do these types of trials and have them successful. You heard Stefan bring up the point about doing these massive trials and how they’re going to try to focus them down and make them more specific, which saves money and so on. We’re talking about maybe 10 patients, and after that you’re getting a decision to go forward or not, and so it’s a really different mindset on how you approach this.

Let me share with you what we did. This is called Pro10 cell line. It stands for 2010. This is nine years before Zolgensma got approved, seven years before Luxturna got approved, 23 years before the Sarepta got approved. We were focusing on if we can’t make the material, it’s not going to be of any value. The reality that you have to accept is that if Sarepta has a drug that’s approved and the patients and the parents can’t get access to it, they’re going to throw bricks through your window. They’re not going to tolerate an answer not being available, so production becomes absolutely the platform that you have to have. This was generated to be novel, and it works really, really well, but we have to live in the real world. What’s going to happen, there’s going to be stable packaging cell lines that are like monoclonal antibodies. This is where we lean on our Bayer colleagues, who’ve been producing proteins forever at this level. We have to transition, so when we find something that
works, we’ve got a make a producer cell line that can produce enough to cover the patients around the world.

Talk about inducible promoters, and all that simply means is like a light switch. We have small molecules we can throw in and it turns things on, and then turns things off. If you can envision having a production system where the cells are growing continuously, and then you’d put in a small molecule to produce your reagent. That becomes a really important, invaluable asset because that density above which you can grow cells in continuous bioreactors. I share with you this last one because this is the first example where we made plasmid DNA that’s used to produce virus that goes in the patients, that was all biochemically synthesised. It was not put in a bioreactor at any step. So you’re seeing a conversion of the old formats of doing everything in bioreactors moving into more of a biochemistry perspective. Do not be surprised. Long after I’m gone, this will probably all be done in a test tube where you’re generating these therapeutics, and not so much in the 2000 litre bioreactors that we’re all familiar with.

Okay, this is where I overwhelm you with the technology stuff. Mother Nature gave us these serotypes of AAV. This is like the flu – every year it’s a different version. There’s about nine or 10 that are commonly used. We started playing around with the receptors on the surface, which is like changing zip codes, and we actually had viruses that could change where they were going. Instead of going to the liver, they went to the brain and so forth. The first one ever approved to go into patients was generated by our lab and used by AskBio for Duchenne Muscular Dystrophy. Similar to the jargon you heard from Aleksandra about libraries, we now don’t have to wait for Covid and infect 350 million people to find out which one’s going to come out next. We can do this in the laboratory and select from many, many, many variants that never existed in nature and have phenotypes attached to them that are unheard of. This is not unique to AskBio. It’s not unique to Bayer. Everybody’s doing this, so from a technology perspective, delivering capsids and making new ones is a very simple – high school students in my lab actually generate new variants.

The power of this is do you have the ability to design them to go to the right target tissue, get them to produce in production system, and then more importantly to deliver the payload in a very safe – this is again an experience factor. I put this in here, and you’re not going to be able to appreciate it and I don’t want you to, but I want you just to hold onto this thought. Regulating promoters is going to be the key to this field going forward. Oh, thank you. See how humble they are? I love it. If you put a gene in someone’s body right now – the first experiments were done with viral promoters – they were on all the time, but we knew viruses work because they infected humans and their genes turned on. We eventually got confident enough to switch to what we called constitutive promoters, where it stays on all the time, and now we’re in a new era where we use what’s called tissue specific promoters, where it only comes on in the tissue that you’re at work in it.

So think about it from this perspective. One would be that if viral promoters are a power switch, all the lights come on instantly. The constitutive promoters is that when you turn them on it stays on day and night, and your cell type specific promoters are where the lights in the bathroom work by a separate switch than that in the living room. This regulated promoter is the ability to basically have like sprinklers and you can turn them on and off at will, and this gets back to the paradigm if you were taking small molecules like bare aspirin, you take it, it has a lifespan, and then it’s gone. This is now you’re the bioreactor, and when you take the small molecule, you’re turning on the bioreactor and then turning it off. This will be the area that dominates in this field.

I mean, we’re not naive. The early generation of the AAV vectors is similar to the early cell phones that were about the size of a shoebox. These are quickly being evolved to the traditional. It’s much thinner and easier to carry. But you’ll see a new generation of these lipid nanoparticles. You’ll see biological nanoparticles come out of this where they’re half virus, they’re half lipids. We will take
what Mother Nature evolved over millions of years and change them to reagents that work for us that are synthesised in a test tube. We’re doing this at AskBio, but as we’re no longer an AAV gene therapy company, we’re a gene transfer company, and so you have to keep moving with the technology and, again, all of this is dependent on production.

So what does this mean when you start getting really good at this and having a platform capability? We have areas of delivery in the brain, in the heart, and for the orphan diseases in which you’ll see it’s like over six/seven of them are in the clinic. Two of them are moving to phase II. Limb-girdle got the first patient done this week. Phase II, we’ve had conversations with the FDA, with approvals to move forward. I’ll take you through a handful of these, just so you can see the details, but what I wanted to make sure you walked away with is that we’re looking at this from balancing the see-saw. There’s 7,000 genetic diseases. If you put everybody that had a genetic disease in one country, it would be the third largest country in the world, so you can justify doing this forever, but the reality of it is when you learn how to develop these platforms in an orphan disease, you have the opportunity to springboard into a more popular pathway disease, and use the aspects that have been validated and have them optimised for a larger patient population.

So our monogenetic disorders are the obvious ones because you already know the answer before you start. If it’s haemophilia, it’s the clotting gene. If it’s muscular dystrophy, it’s the dystrophin gene. The only problem is delivery, and this is what we’re perfecting at this point in time. Once you have delivery, you can go after pathway diseases, because now the platform’s been established, and now you’re working on the science that’s giving you justification that this is the best approach to go after – Alzheimer’s, diabetes, heart failure, so forth and so on. And I’m going to just take you through an example so you can see the outcome of this type of technology.

This is a disease called Amino Acid Decarboxylase. It’s called Juvenile Parkinson’s disease. All the wiring is still there, and the body just switches off, and the point of it is can we effectively deliver the vector which will then deliver the payload to the target cells, express the protein, and turn the switch on. In this case, we had to come up with the delivery system surgically, the payload – or the molecular FedEx truck – is the vector, the promoter is the switch, the protein is amino acid decarboxylase. What it ends up doing is what you heard from Seth. It turns on the dopamine pathways, and this is what gives you movement and so forth. I’ll show you – this is a hideous disease because these children are frozen and there’s no movement except by the caregiver and the parents, and so you might imagine one night of doing this, but these children can live for an awful long time and as a result of that, they don’t do well in bright lights, they don’t eat well, they don’t swallow well, they don’t do essentially anything.

So after a single injection you can see the outcome is pretty transformative, and I think what we’re seeing here – this is why you don’t have to do 1,000 patients to find out if it’s working or not. You can basically get that outcome within a short number of individuals. I was talking to Cliff, who was basically telling me that his nine-year-old daughter was dancing, and he was able to watch her do a performance. So imagine when you go from a stage like this to get to a point where you can see something like this.

[Video shown]

Now, first let me impress upon you, there is like 92 of these children on the planet, and I’ve got 40 videos, because we’ve treated 40 of them now, that can convince you of how it works, but that’s not the point. I think the point you should be looking at here is that a platform has been developed, a surgical procedure has been established, delivery of a gene appears to function once it gets to the other side – how can we take that and apply it to another disease that may have a bigger impact on patients.
And this is where I leave you with this concept of this is our molecular FedEx truck, this is our promoter, now we’re talking about the cargo. For our AADC kids, we didn’t need to make a lot of this because there’s 92 of them. For Parkinson’s, Alzheimer’s and so forth, if you don’t have these types of carrier capability, again, bricks are going to come through the window because a solution is not of any value if you can’t get it out to the patients. nd so this is where the see-saw – and I show you this example – is we have strategically looked at indications that would use the same procedure, the same FedEx truck, the same promoter, just a different trans gene. In this case, we’re also looking at Parkinson’s.

We’re kind of in this relay where we hand off our success to Seth, who hopefully will meet the needs of the patients who have nothing that we can rescue, but what we’re doing is we’re putting back a gene product called GDNF, which will rescue whatever neurons are there and allow them to become healthy and potentially reinnervate and grow, and so through the same procedure, the same promoter capsid that we’ve been delivering this gene, and here’s some early data showing you in 18 patients over an extended period of time. They’re on a trajectory of they’re no longer showing their symptoms, they’re getting much better, and they’re persisting because this gene activity is there for the life of the cell. The value of this is that it can go forward with the same endpoints that have been established in the community with respect to Parkinson’s disease, and what I would just impress you with in looking at this – we’re now moving into phase II studies, and we’ve had our interaction with the regulatory, and they’ve accepted everything we propose for a phase II gene therapy for Parkinson’s. That’s pretty significant if you think about the amino acid decarboxylase and then springboarding to a large indication.

You may sit out there as analysts and say, ‘Oh, you’re competing against your other technology.’ Be grateful if you can have two drugs or two approaches to go after something as large as Parkinson’s. Now, we sat down and thought for a while and said, ‘What else can we do with this exact same package?’ and MSA came up – Multiple System Atrophy – another hideous disease that once you get diagnosed, within ten years you’re done. You go through horrific progression and disabellement, and the prevalence – it’s about 35,000 patients out there – but the importance of it is that you lose 76% of GDNF when you’re going through this disease state, so the logic is put it back in, just like we are doing for the Parkinson patients rescued at loss of this important protein. And so that’s the fundamental thought behind it. The strategic thought behind it is this could get approved very quickly, because there’s absolutely nothing near it. It could be an off-label drug that starts getting used for Parkinson’s before the Parkinson drug goes through all of its studies.

So there’s some strategy here that, again credit goes to our Bayer colleagues that are much more aware of how you can take these types of drugs and get the maximum use for patient benefit. I’ll show you the data that supports it. Again, this is looking at the loss of these alpha-synuclein build up in the target cells. And again, this is moving forward because of all the data that’s generated with the production. Same capsid, same promoter, same so forth. Limb-girdle: if you haven’t heard about the Sarepta, you’ve been living under a rock. This is going to go forward. This is another one of these muscle disorders. We had the experience of the program that Pfizer’s now in phase III. We partner with them for that. It will use the same capsid, the same muscle promoter, different gene, and we should see a positive outcome. Our first patient was dosed two days ago.

This was interesting because we went to the FDA with the tradition of phase I: safety, phase II – and they turned around and said, ‘No, let’s be proactive. You can do a pivotal trial if you set it up where you do some get placebo, some get dose, and then switch over halfway and measure these outcomes, because the outcomes are fairly obvious,’ and this is the numbers again. And I’m going to just stop by sharing with you our last one, which is congestive heart failure, being led by Roger Hajjar, and he’s had a long history of working in this area. We have a chimeric capsid that was designed that goes only to the cardiomyocytes and is delivering the I1C inhibitor mutant to turn on
the circuit genes for phospholamban, getting contractility. We’ve already done our phase I studies. We’ve gotten some positive results in those studies. We’re moving into our phase II. Again, that balancing between the see-saw is one of the things that I think AskBio has spent more time than most people trying to think about how can you maximise the use of these reagents.

So I will give you the obligatory ‘we work really well with Bayer’. We work really well with them. They’ve given us a phenomenal opportunity to move all of these things forward. As I mentioned to you, the expertise that we need going from producer cell lines to production is well established. The colleagues are phenomenal. The clinical trial designs are phenomenal. The immunologists are phenomenal. So we’re handing batons, often at the same time remaining very independent in how we drive these things forward. So for those who are looking to go into professions such as running for office, this is the last slide. Then it’s the take home message. The markets there, irrespective of what I’m saying, the field is moving forward, and I think the pipeline that we presented, six things in the clinic, a number of them going into phase II, it’s not rocket science to figure out the answers are going to be yes or no and what happens.

But don’t lose sight of this, this field is evolving very, very quickly, and if you’re not able to evolve with it, you got yesterday’s news and you’re trying to catch up, so I think one of the strengths of the AskBio community at the moment is we are constantly pushing the envelope. We’re the tip of the spear. We have a lot of support behind us to make it happen. I’m going to stop there because I think Chris is going to come up here and say, ‘We apologise for Jude’s bad behaviour. We wish he wasn’t here, but we don’t have a choice.’

**Concluding Remarks**

**Christian Rommel**

Ph.D., Global Head of Research and Development, Pharmaceuticals, Bayer AG

Thank you. You’re not that far off, because I thought this morning I really knew what I’m going to say now to conclude, yet listening to all of my colleagues, and also how Stefan started, I’m asking for your support to close our meeting differently. If I think of people, and when we met this morning I told you we’re telling you or we’ll share with you a new phase of R&D at Bayer, new phases, right – and I hope, and I know you’ll agree, that you have seen strong leadership. New leaders, and strong leadership. Charismatic people, even, with a sense of humour, and we referred to diversity and the power of diversity, and I think it was represented by new technologies, different approaches, modalities, but also who the people behind the invention and all the science.

We also shared with you that in R&D we have a new strategy, and strategy brings us a clarity. We shared with you which areas we want to play, and how to play. In addition to this, we shaped the pipeline. We’re clear on the priorities. We’re also clear of the job we have to do to meet everyone’s expectations, but we also shared, I think, some projects, some assets, that have a high potential to make an impact. You’ve seen new science and, I’m not repeating it, in new technologies. Also, I want to remind you that the foundation of all that we do has to be a culture and an operating system. So think back a little bit in history and where we’re going now. We have a new focus in therapeutic areas. We want to be stronger leaders in oncology. We have a plan to maintain leadership in cardiovascular. We have a unique opportunity to make an impact in neurology and rare diseases, by making restorative medicine reality for neurodegenerative diseases, and re-entering immunology.
Now, we also made clear to you that there are some very near-term opportunities with Asundexian and Elinzanetant and now I’m reaching out to you, and imagine if we get that right with Asundexian and Elinzanetant and, as we share with you the mid- and long-term strategy on the therapeutic area direction to focus on the highest unmet need and enabling our ambition by a novel and very much needed science and technologies, and I think that gives us the power of imagination. We are excited, and as Dominik said, this was a reason for many of us to join the company and to lead in this new phase. And doing this at the company, at Bayer, with 160 years of history, at multiple times making a big difference to patients, to humankind, there was always a need to reinvent yourself because you have to adapt to external factors. You have to capture new innovation, and I think we will remember the day today that we’re telling you our story, our new story. And it’s not only that we told you what we’re planning to do, we delivered proof points. You’ve seen new data. You’ve seen progress.

So thank you for your time. Thank you for your very good questions. I think you’re following us with interest, and I invite you to keep doing this because we’re going into a new phase at R&D at Bayer, and we are excited, and I am confident that we will make an impact.

**Oliver Maier**

Great. Thank you very much. I think we’re going to have a short break of 10 minutes, and when we come back, we have another 20/30 minutes for Q&A before we then have lunch. So thank you very much for a little technical break.

[Break]

**Questions & Answers**

**Oliver Maier**

Thank you very much and before we actually end the session today, we have another opportunity with the whole team, for some more questions. In the previous Q&A sessions, we start with the audience, and I chime in with some questions we have online. So, Florent, do you want to go first.

**Florent Cespedes**

Thank you very much. Florent Cespedes from Société Générale. Quick question on the, let’s say, overall portfolio. First of all, thank you very much for the great science and very interesting presentation this morning. But Stefan, a question on the – when we look at your early phase, or your project in development, could you talk a little bit about the risks you see with these projects, because, with great science, but, maybe, in new areas with a lot of uncertainties. So if you could give us some colour on this point.

And then, second question is about budget – a lot of assets, which means you will need some resources to fund these attractive projects. Would you, at some point, envisage some kind of out-licensing, some strategy that some other large companies are doing? Is it something that you could envisage to, let’s say, get some resources to fund some other more, let’s say, projects that are under areas where you are focused on? Thank you.
Stefan Oelrich

So, thank you for the question, Florent. It’s simple, when it comes to the risk, I think we’re, actually, in a way, quite well-balanced between a late-stage pipeline, which is either de-risked because halfway launched or waiting for additional indications, and the ones that we’re bringing in, hopefully, into an approval stage, also very advanced. So there is little risk on the late stage – well ‘little’ stage. I knock on proverbial wood saying that.

On the early stage, you’ve seen, today, the new Bayer Pharma. You’ve seen how we have changed. And yes, that comes with increased risk, which is why we’ve also said, we have to increase the shots on goal. Because if we continue to deliver the type of cadence that we’ve traditionally delivered coming out of our research, we’re not going to get there. As you increase the cadence, you either have the opportunity to spend more total, or to make your trials, your clinical programs, a little bit more leaner from a cost perspective. And I think we’ve said this too, today, that our goal is to aim higher, but at the same time, be more focused. And that will reduce our clinical development cost.

So we’re thinking about a throughput model which is, really, very different from what we’ve done in the past, where we went after these big, big populations, a little bit like we’re doing, still, with Asundexian now. So that’s the difference. That being said, when you look at the profile and the make-up of our company, we’re spending, today, 17% on R&D; we’re spending over 20%, or a little bit over 20% on SG&A. And I would hope that we will invert this with time, because we’re going to see – given some of the things that you saw today – a very different look and feel to our commercial footprint.

Now that’s more for the next decade than it is for this decade. But it’s going to start, slowly, to move in that direction. So we’re hoping to move our R&D expenses off sales, in a growing sales line, more towards 20%, rather sooner than later. But you have to give us a little bit of time because, in between, I have four – hopefully – four blockbuster launches in the US, and that doesn’t come for free. So we will, still, have to increase, in the coming three, four years, our SG&A percentage of sales and, at the same time, balance the R&D portfolio that you saw today.

Out-licensing is something that we will consider when someone else is better suited to do things than we are. So there are things in the rare disease space, where I think we have a world class platform, we may not always be the right commercial outlet for that. So we will consider commercial partnerships there. But in some of the large programs, you know that we decided, ultimately, to not partner Asundexian and not partner – for now – and not partner Kerendia, because we thought that we could pull it off ourselves. And I think that we’ve proven that, with Kerendia, we’re off to a good start even though we were out of the US cardiovascular scene, which is, arguably, not an easy market to be successful in.

So I think we’re going to balance those things out. But I think, to remember is, our goal is to increase our R&D expense in total – from 17 today to 20-plus with time – and to decrease marketing sales, once we’re through all of these launches. So when I say we’re through with these launches, we’re talking past ’27 probably.

Emily Field

Great. I have a question – I guess this is applicable for both AB1005 and then also DA01. Both your slides noted a potential – a patient population, Parkinson’s, of 1 million patients. So, obviously, very broad population – Carbidopa, Levodopa has been around for ever and very, very
cheap. So for each of these therapies, which would likely be very expensive, who would be the target Parkinson’s population within that broader patient set?

R. Jude Samulski

So for AskBio, it’s genetically determined, we have to go in in earlier patients, because once they lose those neurons, we don’t provide any benefit, we have to hand that over to the BlueRock community. So you’re looking at young patients that are showing early Parkinson diseases and, technically, difference between a Michael Fox-type life versus someone in their 60s and 80s going forward.

Seth Ettenberg

So maybe just to give you a perspective from BlueRock, I think you said this correctly, that Levodopa, Carbidopa are phenomenal benefit but for a short period of time. And I think what we’re talking about are patients that are in our trial that are no longer getting adequate control throughout the day and have multiple hours of what we call off time from their medication, even though they’re on. So that’s the population; we would consider that moderate. We are in very early stages, we’re in 12 patients. So where do we land eventually? You’re asking a really important question. We imagine, by who we’re testing in right now, that be a potential for 1 million patients. There’s a lot of need out there. There’s incredible need. And so, the safety profile, along with what we see in the coming next phase, will help to define what you’re asking.

Oliver Maier

Can I piggyback one on for you, Seth, because Michael Leuchten from UBS asked a question on the bemdaneprocel I knew I couldn’t pronounce it; it was close enough. Can you talk to the immunosuppression use being limited to 12 months, and why is it limited in time?

Seth Ettenberg

Sure. So, to be quite frank, we don’t know the right amount of immunosuppression or the amount, length of time. It’s something that we’ll probably need to test out, eventually, in a clinical setting because there’s no translatable model for that. But we based the rationale around previous tissue and cell transplants that have been done in hundreds of patients. And in that patient setting, what was demonstrated that is if you did a short period of time of immunosuppression – now, think of our immunosuppression like you do for organ transplant, but about half of that – so we can give the specifics at a later date. And that that immunosuppression and with that short a period of time, patients in those settings, from the previous trials, even at post-operative cadavers – so after they’ve succumbed to disease – demonstrated engraftment of cells even 20 years later. And so that short period of immunosuppression – remember, also, that we’re placing cells in the brain, which is, we call, a privileged, beyond the blood brain barrier, privileged environment, which isn’t to say that there are no immune cells or no surveillance in that area. But it’s different than the systemic environment.

Oliver Maier

Great, thank you Seth. I’ll squeeze another one in before Pete, you can ask the next question, because I think it makes sense, also, on base what we heard before from Stefan. I think it’s for you, Christian. It’s on the fact, why do we have two approaches for Parkinson’s? Is it related to
budgeting and resource allocations? And assuming both BlueRock and AskBio are successful in the early clinical development of products for Parkinson’s and heart failure, how likely is Bayer to progress both into later stages of clinical development? Can and will Bayer commercialise both, if both trials are successful? That was a long question, sorry.

**Christian Rommel**

So we signed up to provide new therapeutic options for patients suffering from Parkinson’s disease. And at the moment, we’re pursuing two approaches. We’ve heard that this is the second largest indication in neurodegenerative diseases, with a tremendous unmet need. So we envision, first, that if both programs work, there may be a different patient population that will be best suited either by the gene therapy or the cell therapy program. But for the near term, as we are in R&D, we will be data-driven, and we are encouraged by what we’ve seen today. But we are not done yet, right. So we have no reasons to stop, which is a huge success for the early phase of drug development. Now we have to bring the evidence and look at the data and make decisions. Right now, we are committed to pursue both for our strategic ambition to help patients with Parkinson’s disease.

**Stefan Oelrich**

And I’m going to take the commercial question because – this is not L-dopa, where we’re going to be distributing to a large group of physicians and hoping for them, based on our sampling programs, that they will prescribe it on the information that we’re going to provide. This is going to be, in both cases, an application that’s going to require neurosurgery. So we’re working on the devices that make this something that is doable in a specialised hospital setting. And we’re seeing, for now, the KOL community – the neurosurgical KOL community – really excited for both procedures to go forward with that. Don’t forget that in any major university hospital, they apply deep brain surgery – sorry, deep brain stimulation, sorry for that – deep brain stimulation, which is not that different from what we’re trying to do here, in terms of expertise.

So I see no reason why we could not commercialise both, in parallel. But that would be a dream come true. If we could really bring those two through all of the risks of the clinic into approvable products, because I think, then, we would rewrite history for Parkinson’s patients for sure.

**Pete Verdult**

Thanks. Pete Verdult, Citi. A couple of boring financial questions, first, for Stefan, and then a couple for Seth. Just ballpark, what percentage of the current $3-plus billion of R&D at Bayer Pharma is allocated to the platforms you’re very keen to show us today – so BlueRock, AskBio, and Vividion? That’s my first question.

**Stefan Oelrich**

Yeah, it’s obviously always hard to give you a percentage because a lot of this is brick and mortar, and now supporting the platforms. But if I look on the clinical stage part, I think we’re now thinking about one third of our investment goes into these three platforms. But it’s really hard to now start to segregate between what the old and the new one does, because a lot of the old supports the new. And we’re seeing that, if you take Vividion, for example, Vividion is pretty much what Bayer has always been doing but with a different twist. So it’s very, very close to what we do.

We independently operate these three, because we’re seeing that there’s a biotech spirit that we’re, by the way, now trying to bring into our labs and into our company, that is already there. So it’s a
real interesting integration model because we’re sort of trying to learn from them when it comes to being fast, being more breakthrough-oriented. We’re having this higher urgency that I think is already happening. And I can see how our internal troops – and you’ve seen Dominik and Maria here – they don’t want to stand behind the platforms. They are as good, and they are going to demonstrate that they’re as good, and we’re going to manage the funding depending on the quality of the clinical programs, for the most part.

Christian Rommel

May I add, Pete, so there may be a perception that with AskBio, BlueRock, Vividion, as they operate in an independent, autonomous manner, they also own their portfolios. But yet, at the Bayer level together we have one pipeline. And you expect from us that we make decisions, and trade-offs decisions, and resource allocation, from an overall one pipeline perspective, so we make sure we’re doing the right thing. Otherwise we would cannibalise each other, and that’s not the spirit.

Pete Verdult

And then, Seth, when we think about the story in Alzheimer’s – finally, in terms of the right patient, with a biomarker, doing the right trial, after all these years of failure, finally, we see some breakthroughs in Alzheimer’s. So when you think about phase two with BlueRock, are you going into an all-comers population, are you going into early stage, is there any biomarker work going on? And I’m sure the answer is no, but it’s only 12 patients and it was only for one year, but was there any cognitive data or anything you could point to in that phase I study that was encouraging? Or is it purely just safety and –

Seth Ettenberg

Sure. Let me first start with the beginning of your question around Alzheimer’s and push you over to Parkinson’s disease, because we’re in Parkinson’s disease. Yes, there were breakthroughs in Alzheimer’s recently, and approvals coming that are changing that paradigm, but really, remember there that it’s slowing the degeneration, it’s not altering the course. And so we’re talking about regenerative, altering the course. That’s the goal that we’re seeking.

You’re right, it’s too early. What I can tell you is that when you come see our data in August, at the end of August, and we begin to present this data, you’ll see the patient population. We were at two different sites – one in the US, one in Canada. For there, we have a slightly different age range, so that also speaks to the severity of the disease, the age range. And we’ll signal seek across that entire population. There is a bit of a biomarker, it’s not for disease, but the progression of loss of DopaNeurons that the FDA allows for, for diagnosis, which is for a Dopa PET, and not everyone receives that. And that PET signal is the loss of dopamine in certain regions of their brain, and those are exactly what we’re going to share with you later this year is the gain of signal in those regions of the brain. So your question’s right, I just don’t have the data for you just yet.

James Quigley, Morgan Stanley

Great, thank you. James Quigley, from Morgan Stanley. So I’ve got one follow-up to Pete’s question on the R&D allocation. So how are those decisions made, in terms of, from a top-down perspective, which program gets the funding? You sort of mentioned peak sales, but what else is there that could impact that allocation between the different platforms?
Christian Rommel

I have to pick you on this top-down, because we want to get away from that now, top-down. You see how we work together, how we present ourselves, I put a lot of – I don’t know whether you were in the room already – I put a lot of emphasis on this really different way of working. So let’s stay away from top-down as much as possible.

On the resource allocation, when we introduced our strategy and our focus on value, right. So very often, in R&D, you have a target product profile. But now we add, as early as possible, have the enter mind at the beginning of there is a value profile. And we allocate resources in are we strategically consistent? What is the PTS and what’s the chance of establishing new standards of care, superior standard of care, game-changing innovation, and so forth? And value will play a role into this. But this is what we do every day, and we want to do it together. So it’s not that I’m sitting in my office in Bayer and send an email. We get together, look at the data, look where the evidence is, and then we have to check some elements of this. But you’ve seen in our portfolio prioritisation that we took out 40% from phase zero – so it’s going to the clinic – to phase III, we took 30% out, because we didn’t think this would be value-creating. And that was a decision we take.

It gets me also back to, Florent, what you asked, with risk. I always think in two ways of risk; one is technical risk and one is the risk where we don’t pay enough attention. Will we actually create value, even if it’s going to work? Is there the price at the end of the finish line? And we signed up, all of us, to take, not risk, of knowing we will make an impact to patients and create value. And we would rather take risks technically, but we don’t want to take risk. And that comes back to, we need to do more innovation, we need to do breakthrough innovation. The incremental stuff, and emphasising technical productivity, has held back this industry. And that is, for us, a new beginning of putting way more emphasis on this.

Stefan Oelrich

And maybe just to complement that, I couldn’t agree more. So it’s really, it’s a value ranking, if you like, that informs the decision. When we come to the point that we have too much to develop and we’re too rich, then I think we will not be waiting for a long time for others to come knock at our door and wanting to partner some other things that we could not do right now. We have very few on that, but I think they will come, with time. And that’s a good problem to have, if it occurs. Don’t forget that we’re also aiming to increase the amount of money in our profile that we want to allocate to R&D with time, and that should continuously increase the shots on goal that we can take. I also told that there’s another three, four years in between where we have to launch our new products.

James Quigley

Thank you. And then, on the gene therapy side, Jude, you’re sort of indicating that maybe the FDA’s attitude may have relaxed a little bit, in terms of moving into phase II signal finding studies earlier. Is that the FDA taking a more relaxed view more generally, or is that partly because of, they understand the AskBio platform and what you can do and how that can work?

R. Jude Samulski

So I would be careful in how you interpret it. For this unmet need, these are the Jerry Lewis kids that we’ve all grown up listening to. This is the first time they have any hope, so I think it would be irresponsible for the regulatory community to say, ‘If you can’t meet these standards, seven years
of no integration risk factors,’ and blah, blah, blah, you would lose a lot of kids on the way. And I think what Peter Marks did was very brave, in basically saying, ‘We need to work with this community because this community has not had access to any opportunities.’ And I don’t think they’re going to change across the board. I think you’ll see the same rigour for where you have other alternatives, therapeutic-wise. But for these completely unmet needs, it’s almost not fair to ask them to play at that level because the resources aren’t there, the number of patients aren’t there. And the last thing you want to do is say, ‘We have technology to save your kid, but we can’t afford to do it because nobody will step up and go through all of the hurdles that have been.’

I have to tell you this, the FDA has worked with us from the very beginning, as partners, rather than as, they sit on one side and we sit on the other. Phenomenal group of individuals that are very passionate about this effort.

James Quigley

Maybe just one last quick one on BlueRock, in terms of the technology, in terms of – you had a slide up of the different stages of the technology. Where are you most specialised? What is it about your platform that is very, very difficult for others to copy?

Seth Ettenberg

Yeah, so there’s probably two areas that are important in biotech; one would be IP and the second would be know-how. And I would tell you that the foundation of the IP and the formation of BlueRock was both in-licensed and built, and so we stand on that IP and we’re creating more of it every day with what we’re doing, because it’s just not been done before. And the second half, especially in this field, is know-how – critical for the talent that we bring in and for the training that we’re giving them, because it just doesn’t exist in the community, and we can’t just simply replace those individuals.

And so, a critical aspect, and, to go more directly at that question would be to tell you about half of our team is involved in what we call process development and manufacturing, because that’s the key in being able to deliver a quality, reproducible, scalable product. And so, a special call out to that area.

Christian Rommel

It might be worth mentioning that at the present, you’re using a DNA or genetic-free engineering of cells, which is an art.

Seth Ettenberg

Yeah, so a couple of things to say there. One is, the reprogramming of cells is a DNA-free, footprint-free, RNA transgene that goes in, that allows us to reprogram. And then the cells that go forward are a non-touched genome. And also, important, because sometimes this gets missed, we’re not putting stem cells into people. We’re actually putting differentiated progenitor cells that are committed to their differentiation, and that complete that differentiation, importantly, within the individual, to allow it to integrate into either the neural network or the optic nerve. So those are keys to, and what I think is the power by our collective too, is that by taking these first steps, we are learning a tremendous amount out of the clinic, and we will be using that in the programs that follow. And each of these steps validate the next step that we take.
Oliver Maier

Thank you, Seth. Alex, I have one more question for you that come in online, if you don’t mind. Amongst the many hundreds of potential undruggable targets, why did you choose the NRF2 and the STAT3 as your lead targets and programs? What is it about these two pathways that make them particularly attractive?

Aleksandra Rizo

Sure. So we’ve screened hundreds of proteins, right, to come to the first two. And then we had a couple of good hits for NRF2 and STAT3 that we decided to move forward. But I think most important when we choose targets, in general, are how unique and how undruggable and how holy grail they are considered for the patients that we need to serve. So that is how we chose them, right. So we stayed within our platform and the strengths of our platform, and we linked the biology of the two targets that came first, and we took them both to the clinic. I should be careful.

Oliver Maier

Thank you, Alex. More questions here? If not, I have one more, actually, for Jude, because somebody is picking on all your experience in the sector. The history of gene therapy, Jude, has been mixed, with a fair amount of success in recent years, but also a fair degree of disappointment, right. Can you discuss why so many programs have failed and had setbacks, and what is it that AskBio is doing to ensure that your approach has a greater probability of success?

R. Jude Samulski

The question is an obvious one that’s happened, and the answer’s obvious. Are the animal models predicted, no problems? And every animal model, it’s a mouse, a rat, or haemophilic dogs, they all were rescued 100% completely. Then you step into the real world and deal with diversity and humans, and you find out that five people given the same drug don’t respond exactly the same. It’s not more complicated than that.

At AskBio, we’ve gone to a research effort that I think Christian’s supported. That’s what’s called a collaborative cross, which is where these founder mice – there’s nine of them that the industry uses, black 57, so forth – and they’ve been bred to generate a diverse group of offspring, so 164. And those offspring have now been inbred to generate lines. And so what you have is a family of tsars that have now generated a family of workers that have now generated a family of pedestrians. And in that setting, we are now seeing the same observations we see in patients. So we now have a link to say, ‘This patient responded, this mouse responded, what’s the genetics that supports that?’ That’s going to help, as you heard from Maria and everyone, narrowing us down to the patients that are likely to benefit and not just putting everyone in and keeping your fingers crossed.

Oliver Maier

Thank you, Jude. Any more questions here? Now that’s not the case, so, Stefan, Christian, any closing remarks from your end?
Christian Rommel

I personally learned a lot from Jude’s team and Seth’s team, at BlueRock and AskBio, the importance of the process development. And Jude, you taught us that many of the programs fail because the inability to take a construct from the lab into manufacturing and into patients. So it’s absolutely, of course, the patient, and then all the design principles, but the manufacturing is such a source of attrition and failure, and we were very impressed that both companies, from the beginning on – and we have nicely presented that today – invested and made that a priority. And we had a chance, now, to start working together. We very much supported and added strengths into the manufacturing capabilities. So if you’re not good at this part, I don’t know how much it helps to be so good at the front-load part.

Stefan Oelrich

So then let’s close it. There’s food outside, I’m being told, unfortunately not for those online, I have to say. We did not ship anything to your homes. Now, thank you for being here with us today. When I look at these six, here on stage, they represent the 6,000 that work for us in R&D. And they represent a different R&D than the very proud 160 years legacy of Bayer. They represent, hopefully, the next 160 years that we’re going to starting, as of today, if you like, with this different approach. It’s an approach where the quality of the output is going to be different; the areas in which we’re active are going to be different; and I hope the level of service that we’re going to bring to future patients is also going to be different in a positive way, really making a difference in people’s lives.

You heard Bill, in his introductory remarks, how much he was actually impressed with the pipeline that he found. And that’s because of these six and the 5994 that stand behind these six, because we want to make a difference in people lives every day and we believe in health for all and hunger for none. And I think that sets us apart as Bayer. So thank you for being here, and glad to have more small talk around some good food. So thanks, and see you soon.

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