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EDITED TRANSCRIPT

NOVOb.CO - Novo Nordisk A/S to Announce the Decision to Enter the Phase 3 Development in Alzheimer's Disease with Oral Semaglutide Call

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PRESENTATION

Operator

Hello, and welcome to Novo Nordisk's Conference Call. (Operator Instructions)

Today, I'm pleased to present Karsten Munk Knudsen, CFO. Please begin your meeting.

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Thank you. Welcome to the Novo Nordisk conference call regarding our decision to initiate Phase III trials within early Alzheimer's disease and an update on our R&D Tier 1 strategy. My name is Karsten Munk Knudsen, and I'm the CFO of Novo Nordisk. And together with me today on the call, I have Mads Krogsgaard Thomsen, our Chief Science Officer; and Martin Lange, our Head of Global Development.

We will present for around 15 minutes, followed by 30 minutes Q&A.

The next slide, please. As you know, the future is uncertain, and we might be making predictions around the future and especially when we talk about the pipeline. There will inherently be the uncertainties in this case.

Next slide, please. Roughly a year ago, we launched our strategic aspirations for the company towards 2025. And today, we will be covering our quarter end call innovation and therapeutic focus, again, with the discussion around our decision to enter Phase III development with oral semaglutide in early Alzheimer's disease, which is a serious chronic disease with high unmet needs.

Before we dive into this, let me put a few words on the Emisphere deal, which we closed last week. Afterwards, Martin will explain the rationale for initiating development within Alzheimer's.

Last week, we closed our Emisphere acquisition price of USD 1.8 billion. With the acquisition, we have now full control of the SNAC platform and hence, are not liable for future SNAC-related royalty payments, and we have full access to the technology platform, which we'll be using for future pipeline projects, and we'll come back to that in a short while.

The financial impact for the SNAC acquisition is as follows. Our operating profit for 2020 will not change compared to the guidance we issued in conjunction with our third quarter results. So we are basically reiterating our 5% to 8% constant exchange rate operating profit growth. Our tax rate is expected to be slightly impacted. And we still maintain our guidance range of 20% to 22%, but compared to the 20.2% we realized in the first 9 months, now you should expect us to be more in the middle of our effective tax rate range for the full year.

Our free cash flow, where we guided between DKK 34 billion and DKK 39 billion, will be reduced by the acquisition price. So you should expect our free cash flow for the year, the range, to be roughly DKK 10 billion lower than what was guided in conjunction with our Q3 announcements.

For 2021, operating profit will be impacted by -- negatively by less than 1%, driven by amortizations, offset by eliminated royalty payments. In the medium term, the acquisition is expected to have a neutral to positive net impact on operating profit. And with this, over to you, Martin, to cover our decision entering early Alzheimer's disease.

Martin Holst Lange - *Novo Nordisk A/S - SVP of Global Development*

Thank you very much, Karsten. So as already mentioned (inaudible). Thank you very much, Karsten. As already mentioned, we based our decision primarily on 2 major points, the first point being that, as we've already discussed, Alzheimer's disease is a serious disease with a substantial unmet need. It's devastating to the patients. And importantly, it's also devastating and debilitating to otherwise well-functioning families, and it is associated with a substantial burden for societies. In a recent study published in U.S. with U.S. focus, it was estimated that the 2020 cost associated with treatment of Alzheimer's disease is to the tune of USD 300 billion. And these are only the direct costs, indirect costs, such as lost hours of work for associated families and/or patients, it is to the tune of USD 250 billion on top of this. So a substantial unmet need for patients, families and society.

Our second basis, obviously, the scientific data that we have, both in the preclinical as well as in the clinic. We have real-world evidence studies, we have RCT studies, and we also have an ever-growing pool of non-clinical data that have supported our decision.

As stated in the announcement, we expect to initiate the Phase III program during first half of next year, testing the 14-milligram oral -- dose of oral semaglutide versus placebo.

Next slide, please. So a few words on the overall Alzheimer's disease, it's -- constitute a segment of the proportion of dementia, which is an ever-growing problem and challenge in -- across the globe. This is not a disease specifically for developed countries, but basically a global issue that we see is growing. Today, more than 15 million patients globally have a diagnose of dementia. This is expected to more than double over the next 30 years. Alzheimer's disease is a subsegment of this, constituting approximately 60% of patients with dementia. So the overall Alzheimer's population is constituting approximately 30 million.

As I'll come back to in the next slide, Alzheimer's disease is preceded by what we call mild cognitive impairment. Approximately 55 million people are estimated to suffer from mild cognitive impairment due to Alzheimer's pathology. Currently, there is no treatment approved or available to modify the disease to delay disease progression. A couple of drugs are approved as symptomatic treatment in already-established Alzheimer. But otherwise, we are back to the substantial unmet need.

I think it's important to acknowledge that this unmet need is coming on the background of a very large attrition in drug development, where we have seen approximately 99% of all development programs fail, some of them in Phase II, but also a great number in Phase III. This obviously increases our challenge. It adds to the risk that we see, despite the fact that we believe that we have good data to support us in our decision.

Next slide, please. A few words on the underlying pathology. The underlying events preceding a clinical diagnosis of Alzheimer is an establishment of amyloid plaques. This leads to following accumulation of tau tangles. And importantly, and potentially also, a gating event is increased inflammation in the brain. It's exceedingly important to understand that these events, in particular the amyloid deposits, is taking place several years up to 20 years before the clinical manifestation of the disease. This obviously needs a chance -- a diagnostic chance for treating precision, but it also allow us to look at diagnostic and prognostic models to anticipate which patients would be the right patients to include in both clinical trials and for regulatory purposes. But it's also important to understand that once patients manifest themselves with clinical symptoms, both in the early stage of mild cognitive impairment but also in the later stage of downright dementia, the underlying pathology is very, very progressed.

Mads will come back to specifically where we intend to direct our clinical activities in this disease stage. But again, important to understand that the underlying pathology allows us to diagnose these patients in a proactive way, which is a support for us in our regulatory purposes.

Next slide. Now as we've already discussed, we have a large pool of evidence to support us in our decision. We have a number of randomized controlled trials. I want to highlight, and I'll come back to that, first of all, our post-hoc assessments of our cardiovascular outcome trials with our GLP-1 analogues. In an assessment of those, we see a 53% lowering of the risk of having a dementia diagnosis if patients are on a GLP-1 analogue versus placebo. This is a substantial decrease that obviously encourages a lot.

But importantly, we also see a substantial systemic anti-inflammatory effect of the semaglutide. As I already mentioned, we now believe that the inflammation part in the brain is an important pathway towards the development of Alzheimer's disease. And having a drug that, in the case of semaglutide, has the potential of decreasing inflammation by up to 50%, is an important variable in this space.

We have also seen studies demonstrating less decline in cerebral glucose metabolism. This is demonstrated in some, but not in all studies. I'll come back to that right now because a lot of you have mentioned the ELAD study, and also believe that our primary sort of evidence for making this decision was the ELAD study. I hope to convince you that's not the case. First of all, because the ELAD study is only 1 piece of the puzzle. And second of all, the ELAD study is associated with a few caveats and biases that does not allow us to fully compute on the ELAD study. First of all, the ELAD study is not in the same population as we intend to investigate in our Phase III program. And second of all, the impact of specifically COVID-19 on the ability to collect data led to some missing data in the assessment of ELAD. Therefore, it's maybe not surprising to see that ELAD failed on the primary endpoint, but I think it's actually encouraging to see that on specific and relevant endpoint, both on cognition, but also brain pathology as assessed by MRI, we actually see positive outcomes of the ELAD study.

Finally, I think this is important in the discussion of the mechanism of action. We've seen a recent study, granted small study in obesity patients, demonstrating that memory function is improved on GLP-1 treatment, independent of weight loss, suggesting that the effects of GLP-1 treatment in this space is not necessarily correlated to metabolism or weight loss, but more to the anti-inflammatory and improved atherosclerosis effect of GLP-1.

I come back to the real-world evidence. And specifically, we have seen a number of preclinical very encouraging data suggesting that the mechanism behind GLP-1 improvement in this phase is substantial. I've mentioned the decrease in both peripheral but also central inflammation. We've seen, in several animal models, a decrease in neural inflammation. We've seen improvement, obviously, in cardiovascular space. We've seen improved synaptic viabilities. And that basically leads to a decrease in our animal models' amyloid deposition, phospho-tau deposition and improved memory function in animals -- animal models of dementia. All in all, very encouraging data.

And this, supported by -- next slide, please, again, our RCT and our real-world evidence data. I've just mentioned the pool of our RCT data, our cardiovascular outcomes data. A total of 15,000 -- almost 16,000 patients being randomized to either receive GLP-1 analogue or placebo. We accumulated 47 events of a dementia diagnosis, and what we see is that we have an approximately 50% reduction in risk of a dementia diagnosis with the GLP-1 analogue versus placebo. This is strongly supported from what we see in our real-world evidence data. We've seen in a Danish registry that we have, in 1 year, an 11% lowering risk of a dementia diagnosis. However, in a 2-year period, we see a 25% risk reduction. This is based on almost 0.5 million Danish patients. And is supporting by almost the same reduction over a 2.5-year period in the Truven claims database with approximately 300,000 patients.

As I showed in the previous slide, there are more data, real-world evidence data available. I want to point out a recently reported database study using the FDA database, the [Fair] study, again, with a large patient number, and specifically, this time in Alzheimer's disease, demonstrating a 60% reduction in risk of getting an Alzheimer's dementia diagnoses. So all in all, we believe that we have good data to support our decision, both on the clinical side, but certainly also on the nonclinical mode of action side. And this makes us so confident that we are now in a position to announce our Phase III initiative. Very happy to leave the word to Mads now.

Mads Krogsgaard Thomsen - *Novo Nordisk A/S - Executive VP, Chief Scientific Officer, Head of R&D and Member of the Management Board*

Thank you, Martin. And next slide, please. So we have not taken this decision easily. We have liaised with the stakeholders throughout the globe, including regulatory agencies, the FDA, EMA, PMDA and CFDA even in China. And we have, of course, spoken to global trialists and key opinion leaders within the Alzheimer's space to make sure that we base the decision on as firm ground as possible in this very high-risk area of drug development.

Now what I'd like to show you on this slide is that in the shaded area, we have what the FDA calls stages 3 and 4 of Alzheimer's disease. And stage 3 is the one you can see on the left part of the shaded area, where you actually have not only neuropsychological impairment, but the emergence of subtle, but yet detectable also functional impairment in the human being suffering from this. And stage 4 is the first kind of category of overt dementia, known as mild dementia, even though it is by no means a mild condition. So these are the trials that have been included in the 2 global trials as it's been agreed with the regulatory agencies.

Now they have to be of the Alzheimer's type. That means that we will be declaring amyloid positivity either by a PET scan or a lumbar puncture to achieve cerebral spinal fluid, you can say, aspiration and detection of the A beta biomarker positivity. So these are Alzheimer's type patients.

And if you take the next slide, I can briefly show you the 2 pivotal trials that we've agreed upon with the agencies. These are 2 trials that in totality include 3,700 early Alzheimer's patients, and we are going to show or trying to show, sorry, superiority of oral semaglutide 14-milligram, today known as Rybelsus, versus placebo. There will be a randomization. And the trial's main phase is a full 2-year recruitment, where we dose escalate to 14 milligrams of either sema or placebo. And then there will be a confirmatory endpoint readout after 2 years, followed by a, you can say, to the physician and the patient, blinded extension phase, but open to certain members of the Novo Nordisk company, where we will then follow-up with a more hard outcome measure.

And I'll just describe what the endpoints more specifically are. The primary endpoint agreed with the agency is the CDR, also known as the Clinical Dementia Rating-Sum of Boxes score, where you essentially have 6 domains with a maximum score with increasing impairment of the patient up to 3, leading to a score of maximum 18, which is very severe dementia, almost death, I would say, at that stage. And that is the primary -- this is a score that is able to detect rather subtle changes and has a good inter-reader reliability and is fully accepted by the regulators as a primary endpoint. However, we also have secondary endpoints that include time to a diagnosis of dementia and also activities of daily living. In terms of the key inclusion criteria, I mentioned these were stage 3 or 4 category Alzheimer's patients, aged between 55 and 85. And one of the trials will be pure-play Alzheimer's type, either MCI or early dementia, whereas the other one will include around 20% with small vessel pathology. Small vessel pathology has recently emerged as a, albeit post-hoc analysis, as a point of intervention for semaglutide. So we know that small vessel pathology is clearly intervened in -- by semaglutide and this plays a role in what we call vascular dementia, where we will have around or above 20% with this pathology coinciding with Alzheimer's pathology.

The trial timelines are such that we will, during the first half of next year, initiate both of these pivotal trials, and they're expected to complete 3 to 4 years from initiation. The CDR, the Clinical Dementia Rating-Sum of Boxes scale, is explained on the right-hand side, but suffice to say that you have neuropsychological elements such as memory, orientation and problem solving, and you have more functional elements such as community affairs, homes, hobbies, personal care and the like. So this is a very holistic assessment of the patient's situation.

Moving to the next slide, I will just mention that, as Karsten alluded to, we've acquired the Emisphere Corporation, very recently closed it last week. And that means that Novo Nordisk is embarking on a strategy of global leadership within oral biologics of the future. And the only element that we'll touch upon today relates to the GLP-1 opportunity that this provides us with, more specifically, high dose of semaglutide for type 2 diabetes. But on the slide, you can also see that GLP-1 is being broadened out either in the oral form for cardiovascular protection in the SOUL trial or in injectable form in the SELECT trial for obesity. And we are trying to build bridges between the injectable and the oral versions of semaglutide with the endpoints that we have integrated in all these trials. Likewise, we will be doing semaglutide by the injection route for chronic kidney disease and for NASH, starting clinical trials during the first half of next year, and as discussed on this slide and during this presentation, Alzheimer's disease via the 14-milligram oral version.

But on the next slide, I'd actually like to update you on how we have decided to initiate a Phase III trial, a pivotal trial for high-dose oral semaglutide 25 and 50 milligrams in type 2 diabetes in order to allow patients who have been heavily treated on Rybelsus 14 milligrams for maybe years, but

at some point in time, will need intensification of their therapy, hence, the 25- and 50-milligram doses. The trial is somewhat reminiscent of the SUSTAIN FORTE trial that we did for 2 milligrams of injectable semaglutide. It includes 2 higher doses, and the amount of patients is rather high, 1,200 patients with type 2. The classic endpoint is changing hemoglobin A1c from baseline to week 52, with a follow-up where we also get readouts after 68 weeks, including on-body weight.

And I would like to mention that the inclusion criteria, because this is an intensification regimen, calls for patients with an A1c between 8% and 10.5%, i.e., a relatively high baseline A1c and a body mass index in the overweight or obese ranges. And they have had to have stable doses of 1 to 3 orals before administration or integration into the trial.

So we expect to be initiating the trial during the first half. And the total trial completion will take approximately 2.5 years from initiation and will allow us to offer a oral version of semaglutide that can match even the high doses of the injectable counterparts that exist or are going to exist in the market.

So very, very exciting, and that leads me to the final slide that actually just summarizes what we've been speaking about, namely that we will conduct 2 pivotal Phase III trials with sema 14 milligrams oral versus placebo in early Alzheimer's patients initiated during the first half of next year in both cases because we do believe Alzheimer's is an area with a huge unmet medical need. We also believe, based on Martin's data, that the modes of action -- multiple modes of action of GLP-1 indicates a potential beneficial effect in this devastating disease, while acknowledging that there is, of course, a high-risk to this program due to the historic failure rate of 99% within Alzheimer's clinical development. And the other element we touched upon was the pivotal Phase III trial to upgrade our intensification of patients failing on, for instance, 14-milligram of Rybelsus or other products for that matter, with the use of 25 and 50 milligrams of oral semaglutide. And this is a trial that will assess the efficacy in patients, who need improved outcomes despite a long-standing type 2 diabetes, you can argue.

So with that final, over to you, Karsten, for moderating the session.

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Great. Thank you, Mads, and thank you, Martin. We're now moving into our Q&A session. And I kindly, as usual, ask all of you to limit yourself to 2 questions per caller.

And with that, operator, please take the first Q&A.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question is from Richard Vosser from JPMorgan.

Richard Vosser - *JPMorgan Chase & Co, Research Division - Senior Analyst*

First question, just on the cost of these trials, how should we think of the cost of the Alzheimer's trials and the higher dose trials? And what burden that would put on 2021 R&D spend and beyond? Some idea there, please.

And then second question, just on the dose chosen in the Alzheimer's trials and the oral route. I can clearly see oral would be convenient and 14 milligrams is the current oral dose. But why not go to a 2.4 milligram weekly high dose sema sort of dose to try and maximize the clinical effect. What's the evidence behind the choice of dose?

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Thank you, Richard. So I'll be covering your first questions on impact on our P&L. And Mads, if you'll take the choices we've made in terms of formulations, that would be great.

So Richard, first of all, in terms of cost of trials, this -- the cost we've built in here, we will contain within the guidance we've already issued and kind of the overall capital allocation that obviously covering both at our Capital Markets Day roughly a year ago and most recently, as part of the Q3 call, we're also discussing ratios into 2021. So clearly, we are we are pursuing a growth strategy and that growth strategy enables us to also make substantial increased investments into R&D. And you should expect that over time, we will gradually be expanding our R&D ratio, but the main driver of the increased investments in R&D comes from a growing top line.

We are not providing specifics on individual trial costs, but just to give you a magnitude for the investment into Alzheimer's, then over the next, say, 4-year period, then it will be in the mid-single digits of our total percentage of our total R&D budget that we're investing in this area. And then Mads, on the formulations chosen?

Mads Krogsgaard Thomsen - *Novo Nordisk A/S - Executive VP, Chief Scientific Officer, Head of R&D and Member of the Management Board*

Yes. First of all, Richard, it has to be said that we've done quite a bit of research into patient and physician preferences within early Alzheimer's disease. And these are patients who, in 8 out of 10 cases, will prefer an oral administration rather than an injectable because actually, when you have a mild cognitive impairment, you are still not as debilitated, of course, as later stages, where injections are maybe even more relevant. But I should also bear in mind, the PIONEER 4 trial, where actually, we showed that Rybelsus 14 milligrams given up against Victoza 1.8 milligram was statistically significantly better, both on glucose metabolic and weight-related parameters, really showing that everything Martin has run through on real-world evidence on meta analysis and whatnot, has been done with a drug that is actually inferior to what we are going into Phase III with. So I think it's suffice to say that we are happy with the dose chosen. And also, Richard, these are people aged 55 to 85. They are not with a BMI in the 30-something range that we are seeing for diabetes and obesity. So in terms of exposure, you should not be worried about the exposure in the relevant parts of the brain, in my opinion.

Operator

And the next question is from Martin Parkhøi from Danske Bank.

Martin Parkhøi - *Danske Bank A/S, Research Division - Senior Equity Analyst*

Also 2 questions. And it's actually the first one is a little bit same line as Richard, with respect to the choice of the oral formulation. Mads, could you maybe also discuss if there is also something with the patent life, given that, of course, the substance patent is going out at the same time in '31, but there are better protection for the oral formulation, potentially, is that also a reason? And also, given the fact that, of course, we know you have obesity and NASH Phase II in injections, but we also know that the production output of the oral formulation has been much better than you initially expected. So is that also a reason?

And then the second question is on the type 2 diabetes with the higher doses and as you compare it with SUSTAIN FORTE and in SUSTAIN FORTE, you did not -- was not able to show superiority on-body weight at the treatment policy estimate. Do you think the study -- this study will be powered better, so you feel more comfortable to show superiority on both dose control and weight on the new higher doses?

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Excellent. Thank you, Martin. So first question on choice of formulation again, oral versus injectable. And then the design in type 2 diabetes with our high dose Rybelsus. Mads?

Mads Krogsgaard Thomsen - *Novo Nordisk A/S - Executive VP, Chief Scientific Officer, Head of R&D and Member of the Management Board*

Yes. I think a small correction to you, Martin. The IP protection for the injectable version runs until 2032 rather than '31, just a minor correction. And you are absolutely correct now that we have the patent estate on SNAC and we are constantly innovating new and better formulations with high bioavailability and so on and so forth, these will, of course, be seeking patent protection that, if applied for this year, will take us until 2040. And since Henrik Wulff, our Head of Product Supply, has managed to -- since we started the production plans for Rybelsus already now beefed up the overall output by 3 to 4 folders, so compared to the original plans, we have a situation where this is industrial scale protein manufacturing of a high GMP-grade and quality that is going to be very, very difficult to replicate for a competitor, both due to the sheer scale, but also due to all the patents that our innovations will hopefully lead to and are leading to, as we speak.

So we're really confident that we have made the right choice on the formulation. In terms of the diabetes trial, PIONEER PLUS. Two elements that differ slightly from the SUSTAIN FORTE. One is that the duration here is longer than SUSTAIN FORTE. And we know that the maxing out of body weight improvements does not take place within the first year, but actually slightly after the first year. So these patients are treated for longer. And the high dose 50-milligram with the tablet formulations being used is expected to provide a differentiation versus the existing Rybelsus 14-milligram, but that remains to be seen. And also the BMI, we are only above 25 in this one. And the weight in the SUSTAIN FORTE was not that high. I recall it has been only 91 kilos or something. So there's also the opportunity that the overall baseline weight is slightly high in this trial, but that remains to be seen, Martin, because we haven't recruited yet.

Operator

And our next question is from Peter Sehested from Handelsbanken.

Peter Sehested - *Handelsbanken Capital Markets AB, Research Division - Research Analyst*

It's Peter Sehested. I have 2, mainly to Mads. As you state, Alzheimer's is a disease that typically emerges 20 years before overt symptoms arise. And that sort of basically corresponds to just a couple of years before people are diagnosed with diabetes. Have you looked at the potential artifact that, for instance, looking at the Danish population based studies, you saw some beneficial impact from both GLP-1 and SGLT2 inhibitors? Have you looked into the artifact that the potential benefit of these drugs could actually be to the fact that they are used late in treatment and have been introduced to the market? A late competitor, for instance, been -- has been available for many, many years, et cetera, et cetera. So this artifact could be that patients have actually been on some kind of diabetes treatment for a long period of time, and then you just come in with a bit more power here and as to that, and how that could affect your -- the patient populations that you have chosen? That was sort of the number 1.

And following up on this, on the mechanism, that you actually -- you talked about inflammation, but since there has also seen some impacts with SGLT2 inhibitors, are you sort of working from that -- this is sort of the insulin hypothesis or glucose metabolism hypothesis? And again, how does your work here say on sort of how this correlates with the initial emergence of the biological changes in the brain?

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Great. Thank you, Peter. So Martin, first question, I think it is coming your way, which is especially linked to the timing of GLP-1 treatment initiation versus the initial onset and signals of Alzheimer's. And then the next question, Mads, on the mechanism of action and related to glucose metabolism. So Martin, if you'll kick it off.

Martin Holst Lange - *Novo Nordisk A/S - SVP of Global Development*

Thank you very much. So first of all, super good question. Obviously, something that we have also discussed ourselves. When we've been looking into the real-world evidence that we have in some of the studies, you're absolutely right. We also see effect of SGLT2s. And in some of them, we only actually see effects of GLP-1s. That being said, when looking broadly across the real-world evidence, the impact of glycemic control appears

not to be there. So independent of glycemic control, to the extent that we can correct for that, we don't see similar effects with all other glucose lowering drugs.

Second of all, just going back to our preclinical studies, we do see that the effects that we have appear to be glycemic control and metabolically independent, maybe Mads will come back to that.

And thirdly, we have data also from us, it's coming out showing that even at similar weight loss as compared to a placebo comparator, the effect of GLP-1 on memory function is significantly better suggesting that, again, the effect on cognition, on memory and on Alzheimer's disease appears to be metabolically independent, both on the glycemia control and also on the weight-loss level.

I think it's important to say also that in our clinical trials, and as Mads alluded to, we will also see patients with obesity and diabetes. So we will cover the spectrum as well.

Mads Krogsgaard Thomsen - *Novo Nordisk A/S - Executive VP, Chief Scientific Officer, Head of R&D and Member of the Management Board*

Yes. And then on the other one, Peter, first of all, the preclinical work we've done, the animal models we've been using of accelerated senescence, et cetera, et cetera, they have all been done in the nondiabetic state, just a small notice. But in terms of why we are optimistic, albeit this is a high-risk endeavor, we acknowledge, then GLP-1 has shown a multitude of different activities that might all be relevant in Alzheimer's disease. Do bear in mind that the progression that Martin showed you happens over decades of life. They actually start being relatively specific with the A beta accumulation and fibro formulation, but then you have this spreading of a multitude of inflammatory phenomena in the brain, and that ends up also giving big neuronal damages and problems with transmission and so on.

And just let me remind ourselves that it is true that there is ancient resistance towards glucose metabolic effects in the brain, not towards other substrate, but only towards glucose metabolic effects in the brain. And that seems to be independent of whether or not you have diabetes or not in Alzheimer's disease. We believe this might be impacted by GLP-1, as we spoke about. And then there are numerous inflammatory mechanisms that we can only study in animals, but where microglia and other cells start reducing cytokines and damaging the synapses and the plasticity of the neuronal circuits in the brain, and we have shown animal models, a modulatory and inhibitory effect on this microglial activation. And of course, we will publish some of these data over time. We should also remind ourselves that GLP-1 is produced in the brain and is, de facto, a neurotransmitter in its own right. So by having sema enter into the brain, it might, in its own right, provide some neurotransmission improvement. And we've also seen in cell studies that autophagy, or cell death, is reduced and neural spouting is increased with the addition of GLP-1s to cell cultures. And even that tau-phospho relation can be decreased.

So there are many different elements here. Some are metabolic, such as glucose metabolism and blood flow improvements, some are more of an anti-inflammatory agent. We believe that might be a better shot on goal than having a very single mechanism of action that might be overruled by the multitude of cascades that kick into the different stages of Alzheimer's disease.

Operator

And our next question is from Peter Verdult from Citi.

Peter Verdult - *Citigroup Inc. Exchange Research - Research Analyst*

Peter Verdult, Citi. Just 1 on timing. Just in terms of base case planning, I realize that things can change, but what filing time line are you working to as it relates to Alzheimer's? Number two, just on capacity, the DKK 2 billion plant coming online in Clayton, you already mentioned that Henrik done a great job in terms of increasing production volumes. If your GLP-1 strategy, as a whole, is fully successful, including the high risk, high reward Alzheimer's, would that Clayton facility be able to meet the demand? Or do we need to think about the need for further expansion?

And then forgive me, feel free to give me a red card. It's my third question, but it's a quick one. In terms of the Alzheimer's study that you're running, over and above the inclusion and exclusion criteria that you've laid out in the slide deck, is there anything else we should be aware of in terms of, will it be a real for all comers population, a mix of diabetics, nondiabetics, high and low cardiovascular risk, is there basically any other inclusion or exclusion criteria we should be aware of?

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Great. Thank you, Peter, for these very relevant questions. And since it is Christmas, then I think it's a good time for taking 3 questions. So I'd say the first one on the trial design, both and timeline versus filing and inclusion criteria. I think, Martin, if you would take the deal on that one, and then I'll be covering -- and combine the 2, then I'll be covering the capacity expansion approach.

Martin Holst Lange - *Novo Nordisk A/S - SVP of Global Development*

Yes. So I don't really want to speculate specifically on the filing timeline. But if you imagine that 12 months recruitment period and a 2-year treatment period, and then obviously, we had to write it together, then you can sort of calculate from first half of next year. We -- I think Mads also mentioned the 3 to 4 years.

To your second point, actually, to your first -- third question, we do have, obviously, an exclusion criteria. But most of the exclusion criteria are to define the Alzheimer's disease. So we allow patients with diabetes, we allow patients with obesity. We also -- if they can participate in the study, allow patients with mild cardiovascular disease. So I don't want to call it a completely all common study, but fairly broad in an exclusion criteria.

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Great. Thank you, Martin. And then to your question on having sufficient capacity. And as you correctly allude to in that, then we're constantly working on improving our manufacturing and our efficiencies in manufacturing. And furthermore, then Mads and the team are also doing some very interesting work in R&D and CMC, also in terms of improving our oral platform. So what you should be expecting in terms of capacity and CapEx, I'd say, first of all, this is what we see as a positive problem because this is a top line-driven attractive growth from Tier 1. So we will be working on expanding our API manufacturing for GLP-1 in the years to come.

However, you should note that we expect to do so within our existing footprint. So this will be more, I would say, in line extensions in -- both in state of North Carolina potentially and in Kalundborg in Denmark. So you should expect a CapEx to sales ratio in still, I'd say, in the mid single-digit percentages.

Operator

And our next question is from Trung Huynh from Crédit Suisse.

Trung Chuong Huynh - *Crédit Suisse AG, Research Division - Research Analyst*

I have 2, if I can. So just on your recruitment of the Alzheimer's patients. You noted that you're going with a PET scan or a lumbar puncture to identify that population. Does that limit the patients that you can recruit? And how easy is it for these types of patients to be identified, given that they have quite mild disease?

And my second is just a follow-up on Peter's capacity question. So on your ESG call, you said you now see a 3 to 4 fold improvement on sema's yield. Is that the ceiling? Or do you think you could potentially improve on that in the future?

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Thank you, Trung. So Mads, on our PET scans and Alzheimer's recruitments and whether that poses any limits to attracting patients into our clinical trials, if you take the first one.

And then on capacity, Trung, I think I'll field that one just from the get-go. Then for those of you who have followed Novo Nordisk over the years, then it's a Novo Nordisk classic to continue to improve productivity within existing footprints. So no, we have not reached the end. We are, on a constant basis, working on productivity enhancements and getting more out of our existing facilities. We have decades of experience in this field, and you should expect us to continue to do so, which is also why we expect to be able to stay within our current sites in terms of GLP-1 capacity. Yet, of course, invest in rebuilds and additional facilities, but still in our current footprint, as I called before. So Mads, on Alzheimer's recruitments and any limitations to attracting patients.

Mads Krogsgaard Thomsen - *Novo Nordisk A/S - Executive VP, Chief Scientific Officer, Head of R&D and Member of the Management Board*

Yes. Well, first of all, I think it goes right now without saying that there's been a lot of disappointments. And even though there is a sizable Alzheimer's pipeline out there, we have noticed a high level of engagement and enthusiasm from all the investigators and [cubing] in this we've been speaking to around the potential of semaglutide. So they are already, I would say, very eager to participate in the trial per se. Then you can say, what are the technological differences or difficulties in getting in there. We have 2 technologies for assessing amyloid positivity, one is the PET scanning technology where there are 2 particular PET ligands that can detect the A beta presence in the human brain via PET scanning. And they're based on Floor18 that we can, via a vendor, deliver on-site in such a way that despite the relatively short half-life of the radioligand, it is actually being produced just an hour or so before the PET scan. And even though each investigator doesn't have their own PET scans, then there are centers, for instance, in the U.S., where we don't use so much cerebrospinal fluid puncture for a number of reasons where this can clearly be done, and the investigators have access to these PET scanning sites without any doubt.

And we are making sure the ligands are made available via this vendor. And then in Europe and certain other countries, lumbar puncture to obtain cerebrospinal fluid for a, you can say, CSF biomarker assessment of A beta is fully doable, and you can say that's 1 of the 2 options, and we don't see any hinderances towards either one or the other of these 2, you can say, amyloid positivity assessments taking place in any of the countries.

Operator

And our next question is from Michael Novod from Nordea Markets.

Michael Novod - *Nordea Markets, Research Division - Director of Healthcare, Healthcare Analyst & Sector Coordinator*

It's Michael from Nordea. 2 questions, or 2.5 questions. So the first one, if you look at North America and Europe and you sort of funnel patients down to your inclusion criteria, is it possible to sort of give us a feeling of what the total size of number of patients you're looking at? And in that question, when you're going straight for Alzheimer's and not necessarily only type 2 diabetes and Alzheimer's, is this something that you will do alone? Or do you have the option to sort of co-promote this with an external party? And the second one, given the inclusion criteria in the 25- and 50-milligram oral Sema trials, is there a way that you can quickly bridge into?

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Great. Thank you, Michael. So a question around breaking on high dose to obesity. And then a question around the patient population. So Martin, if you take the all-patient population and the number of diagnosed patients, as we know it today. And Mads, you can talk to the bridging to obesity.

Mads Krogsgaard Thomsen - *Novo Nordisk A/S - Executive VP, Chief Scientific Officer, Head of R&D and Member of the Management Board*

Yes. So what we know today in U.S., as we see in Europe, which more or less correspond to what we intend to do in our clinical trials, we have a great number of trial sites outside of U.S., in which the label between the 2 administration forms. And we have some -- and we, of course, have to back that up by data from real-life kinetics that we do in some of these trials. That means that we want to bridge and have a really broad label with, over time, not only cardiovascular protection claims, but also hopefully, renal protection claims, and what have you, even NASH claims. The things we are doing in the trials, I showed you on one of the slides, we seek to bring as much as possible to a formulation variance of semaglutide substance.

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Thank you, Mads. And Michael, to your last question around on this at this point in time. However, still worth noting that with our GLP-1 franchise in most of our key markets, but needless to say, there are some that would need to be reached in some way or form when we, knock on wood, would potentially get to the market.

Operator

And our next question is from Simon Baker from Redburn.

Simon P. Baker - *Redburn (Europe) Limited, Research Division - Head of Pharmaceutical Research*

Two questions. Firstly, just going back to the question on dosing. I fully get the preference for oral, but it's obviously very difficult to do a dose-ranging study ahead of greater spread of dosing within the study. And then second question, looking at the retrospective analysis in the patient registries. A lot of them talk about dementia. And presumably, that covers both your confident that the finding in those retrospective analyses is clean for Alzheimer's.

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Great. Thank you, Simon. So your question on additional doses, mads, if you will cover that in our Phase III trial design. And Martin, you spoke about the respective studies and signals between Alzheimer and vascular dementia. So over to you, Mads.

Mads Krogsgaard Thomsen - *Novo Nordisk A/S - Executive VP, Chief Scientific Officer, Head of R&D and Member of the Management Board*

Yes. So do bear in mind, Simon, that the dose of 14 milligrams of oral semaglutide is well-known and well documented from the entire 5-year program, albeit in people with diabetes. So since we know that there are no safety or tolerability concerns, we know from PIONEER 4 that it exerts more pharmacological action than does 1.8 milligrams of liraglutide, which I saw form the basis for a lot of the data that Martin was alluding to, there's no reason to include a number of other doses. We can, of course, include in the protocols, the ability of patients who, for some reason, might not be tolerating 14 milligrams equally well on a given occasion to titrate down and then go back to the dose again. This is normal in long clinical trials of 2 years duration, as we've also done it in our CVOTs, but there's no need to introduce a number of different doses with all the evidence that we already have behind the 14 milligrams of oral semaglutide. And then the other one, Martin.

Martin Holst Lange - *Novo Nordisk A/S - SVP of Global Development*

Yes, so really good question. And I think what you're alluding to is obviously when you do real-world evidence that there are a lot of data that you have access to, you have volume, but there are also data that you don't have access to. And 3 of the 4 real-world evidence that we've talked to today, we don't have a sort of differentiation on dementia diagnosis, we call it dementia. But we -- as we discussed in a data pool of almost 1 million patients, it's fair to assume that the 60% that constitute Alzheimer's in a broader population would also be present in those population. That obviously calls for us to evaluate is Alzheimer then the right place to be.

First of all, as Mads alluded to we, in one of our studies, look at both patients with Alzheimer's disease, but also patients with small vessel disease. And secondly, I just want to point your attention to the fourth of the real-world evidence studies. It's a 66,000-patient study conducted out of U.S. -- from the U.S. FDA database. And this is specifically conducted in patients with Alzheimer's disease. It's a retrospective study collecting data from 2004 to '18. As I said, 66,000 patients. And in those patients, all with Alzheimer's disease, an observed decrease is in risk of this diagnosis was observed to the tune of 64%. So strongly suggesting that GLP-1 analogues have a place not only in, so to speak, in the unspecified space of dementia, but specifically also in Alzheimer.

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Our next question is from Andrew Frost from UBS.

Andrew Frost - *UBS Investment Bank, Research Division - Analyst*

Two very quick ones for me. I'm just wondering how, the 3,700 recruitment number that you outlined earlier on, how does that compare to other recent Alzheimer's trials that we've seen? And then my second question, I think you showed some data earlier from the 2 registry studies that dementia risk seems to continue to drop as the treatment exposure continues. So do you have any indication of how far that benefit could go?

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Great. Thank you, Andrew. So Mads, our trial design and how that compares to the recent trials. And then I didn't fully get the second question, but Martin, assuming you got it, then I'll give that to you.

So my first -- because Martin is so young, he remembers much better than you and I do. Well, actually, you're young, too. Sorry. If we compare to aducanumab, the most recent we discussed project from Biogen ISI, then our trials are actually slightly larger than theirs. And we are using the same outcomes measures, the CDR-Sum of Boxes, et cetera. So you can actually say our statistical power, which we've calculated relatively carefully, should be in a really good place to show a clinical effect of oral semaglutide, pending, of course, that there is an effect, and that's what the trials are continuously starting next year. Then finally, Martin, on the real-world evidence studies.

Martin Holst Lange - *Novo Nordisk A/S - SVP of Global Development*

Yes. And I think I want to expand on the real-world evidence studies. And maybe also to other disease areas. There's no doubt we talk cardiovascular prevention, but also potentially in this space, the longer exposure, the better the patients seem to be off. We've made the same observation. And this is specifically also from dementia's point, I mean first of all, the 2 years is a reasonably lengthy study. However, we also do the extension because we want to make sure that we capture specifically what does exposure do, but obviously also because, as Mads alluded to, we want to be able to show an impact on the harder endpoints of time to dementia diagnosis.

Karsten Munk Knudsen - *Novo Nordisk A/S - Executive VP, CFO & Member of the Management Board*

Thank you, Martin. Thank you, Andrew.

This marks the closing of our Alzheimer's call and our R&D GLP-1 strategy update. In case you have any further questions, do not hesitate to reach out to Investor Relations, who are ready to field further questions. So without further ado, I would like to thank you for the interest and taking the time to listen-in into this call and wishing you all a peaceful holiday season.