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MRK - Q4 2016 Merck & Co Inc Earnings Call

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PRESENTATION

Operator

Good morning. My name is Darla and I will be your conference operator today. At this time I would like to welcome everyone to Merck's Q4 and full-year 2016 sales and earnings conference call. (Operator Instructions)

Thank you. I would now like to turn the call over to Teri Loxam. Please go ahead.

Teri Loxam - Merck & Co., Inc. - IR

Thank you, Darla, and good morning. Welcome to Merck's fourth-quarter and full-year 2016 conference call. Today I'm joined by Ken Frazier, our Chairman and Chief Executive Officer; Rob Davis, our Chief Financial Officer; Adam Schechter, President of Global Human Health; and Dr. Roger Perlmutter, President of Merck Research Laboratories.

Before I turn the call over to Ken, I'd like to point out a few items. You will see that we have items in our GAAP results such as acquisition-related charges, restructuring costs, and certain other items. You should note that we have excluded these from our non-GAAP results and provide a reconciliation of these in our press release.

We have also provided a table in our press release to help you understand the sales in the quarter for the business units and products. I would like to remind you that some of the statements that we make during today's call may be considered forward-looking statements within the meaning of the Safe Harbor provision of the US Private Securities and Litigation Reform Act of 1995. Such statements are made based on the current beliefs of Merck's management and are subject to significant risks and uncertainties.



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If our underlying assumptions prove inaccurate or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements. Our SEC filings, including Item 1A in the 2015 10-K, identify certain risk factors and cautionary statements that could cause the Company's actual results to differ materially from those projected in any of our forward-looking statements made this morning. Merck undertakes no obligation to publicly update any forward-looking statements.

You can see our SEC filings, as well as today's earnings release, on Merck.com.

With that, I would like to turn the call over to Ken Frazier.

Ken Frazier - Merck & Co., Inc. - Chairman & CEO

Thank you, Teri. Good morning, everyone. In 2016, we drove growth across many areas of our portfolio, which enabled us to exceed our EPS commitments for the year. Looking forward, we remain confident in the ongoing performance of our key in-line franchises and core brands, as well as the growing momentum behind our pipeline and major product launches.

Business development remains an important priority for us, as we are committed to building on our current portfolio and pipeline. We continue to seek the best scientific opportunities via acquisitions, partnerships, and collaborations at the right financial valuation with particular focus on augmenting our early- to mid-stage pipeline.

As you are all aware, we're operating in a period of significant volatility and uncertainty, including the current political and policy environment in the United States. Merck, however, remains steadfast in our mission to produce biomedical innovations that save and improve lives. We believe our broad and balanced portfolio will enable us to weather these uncertainties and positions us well to deliver long-term value to shareholders.

Earlier this week, along with a small group of industry CEOs representing pharma, I participated in an initial meeting with President Trump. We discussed how we can work together on areas of common ground such as reforming our country's tax code, removing outdated and counterproductive regulations that drive up costs and hinder biomedical progress, and using market forces like competition and choice to make medicines more affordable and accessible to the patients who need them, all with the ultimate goal of stimulating greater innovation and growth on the part of US-based companies. I came away encouraged by the open and constructive dialog of this first meeting and we look forward to working with the administration and Congress to develop an advanced solution that will achieve this goal.

In closing, we remain committed to investing in R&D and to discovering and developing transformational medicines and vaccines that create significant therapeutic and shareholder value. While planning in the current environment has its challenges, we believe we've put forward reasonable expectations for 2017, which Rob will discuss next in more detail. We will stay focused on driving the performance of our core business, advancing our late-stage pipeline, including expanding the use of Keytruda, our foundational immuno-oncology agent, and executing on our key launch products to maximize long-term growth.

And with that, I'd like to turn the call over now to Rob.

Rob Davis - Merck & Co., Inc. - EVP, Global Services & CFO

Thanks, Ken. Good morning, everyone. I'll make a few remarks on our full-year and fourth-quarter 2016 results as well as provide some commentary on our 2017 guidance. My remarks will focus mainly on our non-GAAP financials.

2016 reflected a year of strong execution and disciplined resource allocation. We delivered full-year revenues of \$39.8 billion, which was in the upper end of our original guidance range. This represents top-line growth of 1%, or 3% excluding the impact of FX, and was driven by new product launches such as Keytruda, Zepatier, and Bridion, as well as growth in the Januvia franchise, vaccines and our Animal Health business, somewhat offset by generic competition.



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We were able to reallocate costs from other areas of our portfolio to support these growth drivers, resulting in full-year 2016 operating expenses that were generally flat to 2015 with higher R&D expenses offset by a decline in marketing and administrative expense. As a result, the Company delivered a leveraged P&L for full-year non-GAAP EPS of \$3.78, exceeding our original 2016 guidance and representing 5% growth over the prior year, or 7% excluding the impact of exchange.

Now turning to the fourth quarter. Despite significant headwinds in the fourth quarter from generic competition for Zetia, Cubicin, and Nasonex in the US and Remicade in Europe, we were able to deliver sales and EPS that were roughly flat on an ex-exchange basis. Total company revenues of \$10.1 billion in the quarter were flat versus prior year, excluding a 1% negative impact from foreign exchange.

Our Human Health business decreased 1%, excluding exchange, while our Animal Health business grew 7% excluding exchange. Recall that our Human Health sales in the third quarter included an approximately \$150 million benefit from the pull-forward of customer purchases from the fourth quarter, due to the timing of shipments in Japan in anticipation of the ERP go-live.

I should also note that fourth quarter Keytruda sales in the US include approximately \$40 million of revenue that had previously been deferred. Now that we have sufficient sales returns history, deferral is no longer necessary and the one-time adjustment was made in the fourth quarter.

Looking to the other parts of the P&L, non-GAAP gross margin was 74.8%, which was flat year over year. Full-year gross margin increased 30 basis points to 75.7%. Non-GAAP operating expenses of \$4.3 billion were slightly lower versus the fourth quarter of 2015, due to a slight decline in R&D mainly driven by lower licensing expenses.

Our non-GAAP effective tax rate was 23.3% this quarter, an increase of roughly 7 percentage points year over year, resulting in a full-year tax rate of 22.3%. Recall that the fourth quarter of 2015 reflected the full-year benefit from the renewal of the R&D tax credit.

Taken together, we earned \$0.89 per share on a non-GAAP basis, a decrease of 4% versus the prior year. Excluding the impact of foreign exchange, non-GAAP EPS decreased 1%. When looking at the year-over-year comparison, our fourth-quarter EPS was also negatively impacted by the pull-forward of customer purchases in Japan into the third quarter, which we had said was about a \$0.04 EPS favorable impact in Q3.

On a GAAP basis, we earned \$0.42 in the quarter, which includes a \$625 million pretax charge to settle the worldwide Keytruda patent litigation.

Now let's turn to guidance and our outlook for 2017. Launches of Keytruda and Zepatier, as well as strength in our in-line brands, including Januvia and our vaccines business, largely mitigate the headwinds that we anticipate this year from LOEs on an ex-exchange basis. We expect full-year 2017 revenues to be in the range of \$38.6 billion to \$40.1 billion, which includes an approximately 2% negative impact from foreign exchange using mid-January rates.

While there are many potential pushes and pulls across our business that our guidance range encompasses, for clarity, we would like to specifically mention that we have included risk-adjusted sales from the potential opportunity for a Keytruda indication based on the KEYNOTE-021G filing. We expect our 2017 product gross margin to moderately increase year over year, despite having to absorb the impact of a 6.5% royalty on our worldwide sales of Keytruda.

We expect operating expenses to increase year over year at a low single-digit rate, driven by an increase in R&D spending, coupled with marketing and administrative expenses that are anticipated to be relatively flat. The increase in R&D expense is a reflection of the investments needed to continue to fund Keytruda, along with the rest of our pipeline, at optimal levels to maximize potential long-term growth. We have made a significant effort to look across our portfolio to reallocate resources and we will continue this discipline and make appropriate trade-off decisions to balance near and long-term results.

Regarding tax, we expect the full-year non-GAAP tax rate to be in the range of 21% to 22%. We project average diluted shares outstanding of approximately 2.75 billion for 2017, reflecting a decrease versus the prior year, as we continue our share repurchase program.



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Taken together, we expect non-GAAP EPS to be \$3.72 to \$3.87, which reflects an approximately 2 percentage point negative impact from foreign currency at mid-January rates. Projected 2017 EPS growth would be flat to up 4%, excluding the impact of exchange. Despite the significant generic competition we face in 2017, our non-GAAP EPS guidance demonstrates growth at the midpoint versus 2016 and fully absorbs the impact of the Keytruda royalty to BMS.

It's also worth noting several items that will make year-over-year comparisons more difficult, especially in the first half of the year. While we are facing rapid erosion of sales from our product set of lost patent exclusivity, we will not get the full benefit of the ramp from new product launches, such as Keytruda and Zepatier, until the second half of 2017. In addition, the timing of customer purchases for Januvia will further contribute to the difficult comparison, particularly in the first quarter.

While we expect sales to build over the course of the year, we anticipate operating expenses will be somewhat frontend-loaded, driven largely by higher promotional expense for Keytruda and the phasing of clinical spend.

In summary, 2016 was another example of our commitment to delivering shareholder value through the prioritization of resources toward innovative products that will contribute to long-term growth. We expect this momentum to continue as we further innovate in our labs and invest behind our launches. We are confident the investments we're making today will realize continued shareholder value in the future.

With that I'll turn the call over to Adam.

Adam Schechter - Merck & Co., Inc. - EVP & President, Global Human Health

Thank you, Rob, and good morning, everyone. This morning I'll provide highlights in Global Human Health's performance for the fourth quarter and for the full year of 2016. My comments will be on a constant currency basis.

Global Human Health annual sales reached \$35.2 billion and grew 2%. All core areas -- oncology, vaccines, diabetes, and hospital and specialty care -- contributed to the growth. In the fourth quarter, sales of \$8.9 billion declined 1%. We were able to mostly offset the impact from LOEs in the quarter from growth products; from new products including Keytruda and Zepatier, but also from in-line products such as Januvia and our vaccine franchise.

I'll now highlight a few of our product launches in key franchises and I'll start with oncology.

We continue to execute well on the launch of Keytruda globally and we are confident about the opportunity we see for this important brand. In the fourth quarter, sales were \$483 million, driving strong full-year sales of \$1.4 billion. In the US, Keytruda fourth-quarter sales of \$311 million were driven by continued strength in melanoma, rapid penetration of head and neck cancer, and the launch of first-line lung.

Since our first-line lung approval in late October, we have seen a significant acceleration in PD-L1 testing in non-small cell lung cancer. Early data suggests that about two-thirds of new patients are being tested and the vast majority of first-line patients that are tested and also have PD-L1 greater than or equal to 50% are being treated with Keytruda.

Outside of the US, melanoma continued to be the primary driver of sales of \$172 million in the quarter. In addition to the nearly 60 markets in which we have melanoma approvals, launches are underway in second-line non-small cell lung cancer in more than 50 markets. We're working through the reimbursement process for each country and we expect a meaningful contribution in 2017 from second-line lung as many of these countries come online. We will also begin reimbursement discussions on first-line lung as we gain additional approvals outside of the US.

Of note, we're looking forward to launching in Japan where we've recently been approved for first-line, second-line lung, as well as melanoma. This is only the beginning of opportunity that we see for Keytruda in 2017 and beyond.

Similar to melanoma and head and neck cancer, we are committed to building a leadership position in lung. We're moving forward with additional investment to leverage our unimpeded position in first-line lung, and as you may have seen, we've recently initiated a consumer campaign in the



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United States. We're also looking forward to further broadening the opportunity for Keytruda with three PDUFA dates upcoming in just the first half of 2017 and we expect even more to come.

Now I'll move to primary care. The Januvia franchise grew 4% globally in the fourth quarter, driven by strong performance in the US where sales grew 12% due to increased volume and some customer buy-in.

TRx trends remain strong in the US with growth of over 3% in the fourth quarter. We've now seen more than 10 consecutive quarters of volume growth in the US.

Outside of the US, sales declined slightly due to the unfavorable impact of customer shipment timing in Japan. For the full year, the franchise generated sales of \$6.1 billion or 2% growth. We remain encouraged by the underlying volume trends in the US and around the world for Januvia and we continue to see opportunities to grow our diabetes franchise.

We have maintained very good managed care coverage in 2017, though this access comes with higher discounts and rebates, as we've said before. Despite this increased pricing pressure, we remain confident in the franchise.

Our vaccine business grew 2% in the fourth quarter to \$1.7 billion, with the increase primarily driven by Pneumovax and Gardasil. Full-year sales also grew, increasing 10% to \$6.2 billion, with Gardasil, pediatric vaccines, and Pneumovax all delivering double-digit growth.

Gardasil sales in the fourth quarter grew 9% to \$542 million on another strong quarter in the US. Sales for the full year increased 14% as we continue to transition sales to Gardasil 9 around the world. We expect a rapid transition to the two-dose regimen in 2017, and that will have a negative impact on sales in the US, but we are confident in Gardasil 9 over the long term.

In addition, we completed the termination of our vaccine joint venture in Europe with Sanofi in the fourth quarter, and we have fully integrated our vaccine operations as of January 1.

Moving now to hospital and specialty care. Sales grew 2% to \$8.1 billion for the full year. Fourth-quarter sales of \$1.9 billion declined 3% as the decline in Remicade continued to accelerate and Cubicin sales were subject to generic competition in the US. These declines were partially offset by contributions from launch products, including Bridion and Zepatier.

Bridion had another strong quarter with nearly 50% growth, driven by strong uptake from the launch in the US as well as continued demand in Europe, the emerging markets, and Japan. Surgical trends support the increased use of Bridion and we are excited about the opportunity we see for Bridion in 2017 and beyond.

We also continue to be encouraged by the progress made with Zepatier in its first year of launch. Sales were \$229 million in the quarter. In the US we've continued to gain market share and remain focused on driving greater utilization across the public and private plans in which we have gained access. Some of these formulary wins had effective dates of January 1 and they are expected to meaningfully contribute to our results in 2017.

Outside of the US, we are encouraged by the initial uptake following recent launches in Japan and the EU late in the fourth quarter. We are pleased with the reimbursement discussions that are still ongoing across Europe, as well as the expansion of reimbursement criteria in several large markets.

All together, Global Human Health delivered solid results in 2016. While we'll have to contend with the significant impact in 2017 of revenue from the loss of US exclusivity for several large brands, including Zetia, Vytorin, Cubicin, and Nasonex, we will continue to execute on the opportunities we have in front of us.

We are committed to building our leadership position for Keytruda around the world and we'll continue to prioritize resources behind key franchises like Januvia and vaccines and we will maximize other product launches, such as Zepatier and Bridion. This, together, will position us well for years ahead.



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With that, I'll turn the call over to Roger.

Roger Perlmutter - Merck & Co., Inc. - EVP & President, Merck Research Laboratories

Thanks, Adam. As Ken, Rob and Adam have outlined, the fourth quarter was an important one for Merck Research Laboratories. Much of the excitement in the fourth quarter resulted from accomplishments in our oncology programs.

First, in late October, we received FDA approval for the use of Keytruda in second-line non-small cell lung cancer in patients whose tumors exhibit greater than 1% of cells expressing PD-L1, as determined using our companion diagnostic. This represents a meaningful broadening of the utility of Keytruda in the second-line setting and was based on results from our KEYNOTE-010 study showing improved survival in patients receiving this therapy as opposed to those who received traditional chemotherapeutic intervention.

Follow-up data from KEYNOTE-010 presented at the International Association for the Study of Lung Cancer meeting in December provided strong evidence for durable Keytruda-induced responses in patients who completed two years of therapy. Dr. Roy Herbst, presenting these data, noted a doubling of overall survival in Keytruda-treated second-line lung cancer patients as compared with what was achieved using traditional chemotherapy.

Also in late October the FDA approved Keytruda for the first-line treatment of non-small cell lung cancer patients whose tumors contained 50% or more tumor cells expressing PD-L1. This approval is based on our KEYNOTE-024 study, which was presented at the European Society for Medical Oncology meeting in Copenhagen and published simultaneously in the New England Journal of Medicine.

Compared with traditional platinum doublet therapy, Keytruda's treatment in this setting resulted in a 60% improvement in the overall response rate and a 40% reduction in the risk of death. Moreover, Keytruda treatment was associated with a lower rate of serious adverse effects than was observed in the chemotherapy treatment arm.

The importance of the KEYNOTE-024 results was highlighted by the recommendation for approval by the European Committee on Human Medicinal Products in mid-December with subsequent EC ratification just a couple of days ago. Keytruda was also approved by the Japanese Ministry of Health, Labor and Welfare, based on the KEYNOTE-010 and -024 results, on December 19. In each of these cases, Keytruda is recommended at unit dosing, 200 milligrams given by intravenous infusion every three weeks, which simplifies patient management.

With each passing month we are learning more about the potential of Keytruda to improve treatment for patients suffering from cancer. Since our last earnings call, we received three new breakthrough designations from the FDA for the use of Keytruda to treat malignant disease.

First, in patients whose tumors, irrespective of histology, are found to have evidence of DNA repair defects, as demonstrated by so-called microsatellite instability. Our US filing for this indication was accepted with a PDUFA date of March 8.

Second, for treatment of urothelial malignancies, based on data from our KEYNOTE-045 study. And, third, we received breakthrough designation for the treatment of primary mediastinal B-cell lymphoma, a relatively rare tumor where Keytruda monotherapy may have a meaningful impact.

Finally, we received a priority review for our files supporting the use of Keytruda in the treatment of relapsed or refractory classical Hodgkin's lymphoma. The PDUFA date for this US submission is March 15.

Beyond monotherapy, the FDA has also accepted our file supporting the use of a combination of Keytruda with more traditional chemotherapy, as described in our KEYNOTE-021G study. Here in first-line treatment of patients with metastatic, non-squamous, non-small cell lung cancer, irrespective of PD-L1 expression, the combination of Keytruda with pemetrexed and carboplatin therapy yielded response rates of 55% and a near doubling of progression-free survival. The FDA has granted priority review for this filing with a PDUFA date of May 10.

Filings for US supplementary biologics licensing approvals for Keytruda are expanding logarithmically, which, together with our worldwide supportive filings, contributes to the enormous workload that we are experiencing in clinical research and regulatory affairs. I've said before that



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Keytruda is changing the landscape of cancer treatment, representing a fourth pillar, if you will, beyond surgery, radiation therapy, and traditional chemotherapy that provides hope for further progress in the treatment of malignant disease. We are currently supporting more than 430 studies of Keytruda in various settings, including an ever-larger fraction of combination protocols using novel immune modulators as well as traditional chemotherapeutic agents.

Beyond oncology, we continue to support very active programs in metabolic disease, cardiovascular disease, neuropsychiatric illness, and the development of improved vaccines. Many of these programs will begin to deliver results in the middle of 2017.

The REVEAL study, testing whether anacetrapib reduces cardiovascular events in at-risk patients already optimally treated with statin therapy, should provide data sometime after midyear. At around the same time, we will also see Phase 3 data from verubecestat, our beta secretase inhibitor, which we hope will delay progression of dementia in patients who already have mild to moderate cognitive impairment. A second Phase 3 study testing the use of verubecestat in patients with prodromal disease is now fully enrolled. I look forward to providing updates on these and other programs as the year progresses.

Now I'll turn the call back to Teri.

Teri Loxam - Merck & Co., Inc. - IR

Thanks, Roger. Darla, we will move on to our Q&A portion of the call. If I could ask the analysts to please limit your questions to just one or two so that we can get as many people in as possible, that would be appreciated.

Darla, we'll go to Q&A, please.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) David Risinger, Morgan Stanley.

David Risinger - Morgan Stanley - Analyst

Thanks very much. So, I guess I'd like to start just by asking a high-level question. Ken, could you just talk about how the meeting with President Trump concluded and the next steps that you expect from the administration?

And then, Roger, most physician experts are skeptical that FDA will approve the Keytruda chemo combo based upon the small Phase 2 data set with no overall survival benefit. What do you think the naysayers under appreciate about your chemo combo application and the likely FDA assessment? Thank you.

Ken Frazier - Merck & Co., Inc. - Chairman & CEO

This is Ken Frazier, Dave; thanks for the question. It's important to recognize that this was a first meeting with President Trump. In this meeting we got a lot of issues on the table; the President was really clear that his ultimate goal is twofold: one is to create US jobs and the second one is to ease the cost burden on patients. But he was also quick to say he recognizes the importance of this industry and he doesn't want to interfere with the incentives in the marketplace for us to continue to take risks and make the kinds of investments that are needed to discover and develop long-term innovation.



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We also talked, as you know, about reform and taxes, even regulation, ensuring that we have the right kinds of negotiations around value-based healthcare. Where we decided to go from there is that we would have regular check-ins after that. We don't have a second meeting today established on his calendar, but we said that we would continue to have regular check-ins to ensure that there was good communication between us and the administration.

Obviously, the administration is focused on repealing and replacing the ACA and they are very early in those thought processes also. And we will continue, along with our colleagues at PhRMA, to reach out to both the administration and Congress to ensure that our interests are represented and that patients continue to have access to high-quality and affordable healthcare.

Roger Perlmutter - Merck & Co., Inc. - EVP & President, Merck Research Laboratories

And, David, this is Roger. With respect to -021, it's worth recognizing that the KEYNOTE-021G results confirmed with respect to response rate the prior monotherapy study that is cohort C of KEYNOTE-021. So in essence, this is the second study. I think the data stand on their own.

The fact that the results we are seeing with respect to response rate and progression-free survival -- and at this point there is no separation in overall survival -- is unsurprising in a way because, first of all, follow-up is really quite short, six months, and secondly, because there is a substantial amount of crossover between the two arms. These data represent, to my knowledge, the first controlled data comparing a combination with chemotherapy and, as a result, I think are quite significant. I will not predict how an FDA or any regulatory agency will respond to those data, but I do think the results stand on their own.

Operator

Steve Scala, Cowen.

Steve Scala - Cowen and Company - Analyst

Thank you very much. Two questions, both on Keytruda. On KEYNOTE-189, do you expect PFS to read out before OS? And, if yes, how long after the initial PFS will OS assessment be likely? Roche said yesterday on their call that they could get a simultaneous readout from their chemo combo trials.

And the second question is the FDA put a pembrolizumab study sponsored by NCI in glioblastoma on hold due to an adverse event. Can you provide more color on what signal they saw? Thank you very much.

Roger Perlmutter - Merck & Co., Inc. - EVP & President, Merck Research Laboratories

Right. On KEYNOTE-189, we could get a simultaneous readout; it's really sort of a function of the magnitude of the treatment effect, so I can't speculate on what exactly we're going to see for KEYNOTE-189. But, again, it's a comparison that looks at the ability of a combination with chemotherapy to have a meaningful treatment effect, and if there is an overall survival benefit of substantial magnitude, we'd see it.

Again, I think one should keep in mind that crossover does occur in these studies and more and more we will be seeing the impact of crossover. We are in the process of evaluating that because there are some interesting issues with respect to the sequencing of Keytruda therapy and chemotherapy and the impact that has on results. So there's a lot of information we are going to get out of -189.

With respect to the study on hold that you mentioned, that study actually is not on hold and that's a misstatement in clinicaltrials.gov. I believe they are busy correcting it, but it's not on hold. It's -- what was seen in the study is, we believe, of course, what you would expect to see in grievously-ill patients who have intracranial malignancies and there is really nothing represented in that study. So nothing to pay attention to really I think.



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Operator

Tim Anderson, Bernstein.

Tim Anderson - Bernstein - Analyst

Thank you. Going back to KEYNOTE-189, unless something has changed, my understanding is that PFS is the only primary endpoint for that trial, which makes it unique, if true, because all of the other I-O combo trials by other companies have PFS and OS as co-primaries. So I'm trying to understand the rationale behind this.

Is it so you can put more dedicated alpha only to this primary endpoint, or does it say you're worried about the crossover hurting OS potentially or what?

And then another question on KEYNOTE-042, so another monotherapy trial but this time I think it's an all-comers. And I believe you're supposed to have that in early 2018.

Might you change the cut-off for the primary analysis to widen it beyond -024, but not maybe go as low as 1%? I would imagine to keep the momentum going you don't want to have the negative trial on your hands, so how might you address -042?

And then last question, just on CTLA-4 combo, is that still something you might be considering, or with Bristol's increased caution, could that not be something you pursue?

Roger Perlmutter - Merck & Co., Inc. - EVP & President, Merck Research Laboratories

First of all, with KEYNOTE-189 not much to add to what I've said previously. Again, we are expecting that there will be a meaningful impact of crossover in all future studies because of the widespread appreciation of the value of Keytruda therapy and the desire, on the part of physicians and patients, to gain access to that when they have progressive disease.

The impact of crossover will depend upon its timing and also the sequencing phenomenon that I mentioned. PFS is a sensible endpoint in that context, and that contributes to our study design.

With KEYNOTE-042, you should expect that study to go to completion. We are eager to understand whether we -- the superiority that we demonstrated in -024 vis-a-vis traditional doublet chemotherapy applies across the totality of patients, lung cancer patients beyond those who just have PDL-1 expression in 50% or more of cells. So that study is going on.

I have no expectation. In general, we don't change the endpoints of our studies once we've embarked upon them. We think hard about them and we try and get those endpoints right at the beginning. We could, in principle, do that, but I see no reason to at the present time.

And with respect to combinations with immunotherapies, including those directed at CTLA-4, we remain interested in the broadest possible set of combinations that can have beneficial impact for patients. And that includes immunotherapies, not just CTLA-4, but other things as well.

My expectation is that with time we will see that treatment regimens are more and more personalized. I do not expect that one size will fit all here and that every cancer patient will receive the same combination, whether it's chemotherapy or immunologic manipulation. My feeling is, though, that Keytruda will prove to be foundational in these settings because of its very broad impact in a wide variety of different tumor types at different stages of disease, as we've shown.



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Operator

Geoff Meacham, Barclays.

Geoff Meacham - Barclays Capital - Analyst

Hey, guys. Good morning; thanks for the question. Rob or Adam, you mentioned including -021G in the 2017 outlook. Can you speak more qualitatively about your expectations for the MSI indication or for broader monotherapy use beyond the 50% cut point?

And then, Ken, you've talked in the past about biz dev being a priority I think for over a year now. Is there a tipping point to put it into action, be it, say, valuation expectations from sellers or tax policy or ACA? Thanks.

Adam Schechter - Merck & Co., Inc. - EVP & President, Global Human Health

Hi, Geoff; this is Adam. With regard to -021G, so as you know, right now Keytruda is approved first-line use in patients that have PD-L1 greater than or equal to 50%. Assuming that -021G gets put into the label, we anticipate that that would open up the non-squamous lung market, so we would have patients that are negative in PD-L1 all the way from PD-L1 of 1% up through greater than 50%. So it certainly would open up the rest of the market.

The way I would think about it, though, is that, from what we can tell, physicians will be much more apt to use the combination in patients that they deem to be relatively healthy. They are going to evaluate it patient by patient and see where they believe that the combination of the two would outweigh potential side effects and so forth. So I think, initially, it will be used in patients that are relatively healthy and those where they would be thinking about using Alimta anyway.

After that, we believe that it will go into patients that are relatively healthy where they are not necessarily thinking about Alimta, but they might start to use Alimta in combination for Keytruda to treat those patients and get better results. And then, lastly, over time we think that even in patients that are less healthy, they will probably, after having a lot of exposure to the combination, begin to use it in those patients as well.

Ken Frazier - Merck & Co., Inc. - Chairman & CEO

Yes, so thanks for the question. You know, I'll start by saying that valuations have come down and that has caused us to continue to look very hard at various options that we have across the marketplace. I would say you shouldn't infer from the fact you haven't seen a deal that we're not making every effort to try to do the right kind of deal for our shareholders in the long run.

We still have to find a willing seller and we still have to find a price where we think we can actually create value and that's generally the issue that we've actually encountered up until now.

I would also say with respect to your question about exogenous factors like tax policy and ACA that we feel like we have the firepower now, in terms of a strong balance sheet, to do the kinds of deals that we need to do across the entire spectrum of opportunities and assets. So I would just say we keep reminding you that BD is important to us because we want you to know that we are being very diligent and looking for the right deal at the right valuation.

Operator

Mark Schoenebaum, Evercore ISI.



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Mark Schoenebaum - *Evercore ISI - Analyst*

Hey, guys. Teri, the question with two parts and one subpart. In the -- I'm just wondering -- but they are simple. Roger, can you just remind us what your development strategy is in the squamous lung cancer setting for frontline?

And then number two, I'd love to hear, Roger, your thoughts on Alimta versus ABRAXANE in particular, but just other chemos. Do you think the chemo is -- ultimately the choice of chemo is going to matter very much?

And then the impact of the solanezumab failure on your thinking about the A-beta hypothesis. You've been very -- made some very interesting statements. You've thought a lot about this, the A-beta hypothesis and made some memorable statements. I'm just wondering what you think of the solanezumab trial data.

And also thanks to Teri and the team for all the help that she gave my team while I was out. Thank you.

Teri Loxam - *Merck & Co., Inc. - IR*

Thanks, Mark.

Roger Perlmutter - *Merck & Co., Inc. - EVP & President, Merck Research Laboratories*

Right, so a number of questions, Mark. Thanks for that. First of all, we do have a squamous frontline study, which will be coming out in -- we expect sometime in 2018, the first part of 2018; KEYNOTE-407. And our expectation is that we will be able to demonstrate the same kind of effect in first line with squamous, but time will tell.

As far as chemo combinations are concerned, it is early days. We -- if you look at the -021 program, you can see that there were improvements in response rates in a variety of different settings in combinations with different therapies and, of course, our colleagues at Roche have demonstrated combination results with chemotherapy using their PD-L1 antibody.

So I think that over time we're going to find out that there are probably a lot of things that work in combination fairly well. Certainly preclinically that's what we see. Combinations with radiotherapy, chemotherapy, immune manipulations, a variety of kinds including vaccinations, oncolytic viruses, and then, of course, our recent interesting data that we have in combination with IDO1 antagonists with our colleagues at Incyte.

So all of that suggests that there are going to be many different combinations and there will be quite a lot of customization over time. And, as I say, I don't think that one size will fit all in that regard.

And finally, with respect to the results from Lilly, the disappointing results with solanezumab, again, I don't think that that speaks specifically to the validity of the A-beta hypothesis, or the general hypothesis that processing of amyloid precursor protein into toxic -- potentially toxic peptides contributes to the pathogenesis of Alzheimer's dementia and other dementias. I think the data -- the genetic data are very clear that, in general, one associates an increase in processing -- as a result of which alleles one inherits of the precursor protein itself or of the beta secretase, one associates increased processing with a higher likelihood of progressing to dementing illness during life.

The question is, if we block that, if we phenocopy a reduction of beta secretase activity, will that reduce progress of dementing illness or the likelihood of becoming demented? And how early do we have to do that?

And, of course, that's what we're testing with our beta secretase inhibitor, verubecestat, which is an excellent beta secretase inhibitor. We can dramatically reduce beta secretase activity and reduce the levels of A-beta peptides in cerebrospinal fluid. The question is: Are we getting in early enough? And time will tell.



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Operator

Vamil Divan, Credit Suisse.

Vamil Divan - Credit Suisse - Analyst

Thanks so much for taking my questions. I just had a couple here.

One, you talked a little bit about the BACE and the CETP data you'll have later this year. Are there any other data readouts that you'd highlight as being important or from the pipeline perspective that maybe people are under appreciating beyond BACE and CETP and I guess beyond the KEYNOTE-189, which also has been discussed here?

And then my second one, if you could just maybe provide a little bit more of a breakdown in terms of the percentage of the Keytruda sales in the fourth quarter that came from each of the different indications, especially in the US where obviously you're getting more of the lung impact so far. Thanks.

Adam Schechter - Merck & Co., Inc. - EVP & President, Global Human Health

Yes, so let me start with the Keytruda numbers. And again the data is not perfect, but it'll give you a rough estimate. So the total sales were \$483 million globally: the US was \$311 million, rest of the world was \$172 million. A rough estimate for the US is that about 40% of the sales were melanoma, about 30% of the sales were in lung cancer, about 15% in head and neck, and then 15% in all other categories.

Roger Perlmutter - Merck & Co., Inc. - EVP & President, Merck Research Laboratories

Right. So, Vamil, there's a lot of data coming out over the next year, and, of course, there's a very substantial amount of Keytruda data that we'll be seeing, which we've already mentioned relates to the enormous breadth of indications. So that's the first thing.

The second thing, of course, as we've talked about already, is we're going to be seeing data from the REVEAL study and from BACE. Beyond that, of course, you're going to be seeing additional data from our ertugliflozin data that is in diabetes -- type 2 diabetes.

We have a lot of data in the HIV setting and generally in infectious diseases. So both the doravirine Phase 3 data which should be presented relatively early in 2017, and we're going to be seeing a lot more information coming from, as well, the letermovir CMV data that you'll have a chance to look at, which could be quite important.

And, finally, there's data from our acquisition of Afferent in the chronic cough setting, this is our P2X3 antagonist, and that could be quite interesting. You'll have a chance to see some of those Phase 2b data as well. So a lot of data coming out in 2017.

Operator

Jami Rubin, Goldman Sachs.

Jami Rubin - Goldman Sachs - Analyst

Thank you. Just a question, maybe for you, Adam, on the -- what you expect for the uptake of chemo combo. Assuming you get approval, which we are, how do you see the uptake of Keytruda Alimta? Given that this trial was a limited trial, only 60 patients in the Keytruda arm, Keytruda chemo arm, we don't yet have overall survival.



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The question I'm -- the reason why I'm asking the question is that your own -189 will be reporting out just a few months later -- I don't recall how many patients are in the Keytruda chemo arm -- but also the Roche trial with about 1,100 patients, or 400 in each arm with PFS and potentially OS will be reporting out just again a few months later. Do you expect physicians to wait for the larger Phase 3 clinical trials? Or is your expectation that there is just so much pent-up demand that you would expect a strong uptake?

And then, secondly, there are still so many questions but the key debates have yet to be resolved. I think market expectations on I-O/I-O have changed, but we really haven't seen data yet. How are you thinking about Keytruda front-line lung and the competitive dynamic in 2018 and 2019 when, presumably, others will be on the market? Thanks.

Adam Schechter - Merck & Co., Inc. - EVP & President, Global Human Health

Hi, Jami. First of all, when you think about -021G, it certainly opens up the entire market for first-line for non-squamous patients. And once it's in the label, I think physicians will tend to use the product.

Our representatives will be able to promote it appropriately. They will be able to talk about the data and the information, and typically, the physicians will follow the label on something as important as first-line lung cancer where people don't have great alternatives. I think that we will be able to see physicians begin to use it as soon as we have the data in the label.

With regard to progression-free survival versus overall survival, remember, we launched melanoma with progression-free survival and we were able to get very rapid uptake there. I think physicians understand that having that in your label is going to make a difference. So I do believe that it will give us a lead in first-line lung, for sure, once the data are available and, obviously, once the second study is out there, then I think it's even going to help us further into the future.

As I start to think about I-O/I-O combinations, I'm glad that we're doing those trials, because we don't have all the information that we need to figure out exactly where the future is going to take us. But the good news is we're off to a great start. Hopefully we'll get -021G in the label, which will give us even a further head start in first-line lung.

Physicians will become very comfortable using Keytruda as the drug of choice in first-line lung, where it's approved and then, over time, I think we'll have a very solid position. And the trials that Roger and his team are looking at across I-O/I-O combinations will only be helpful as we learn more.

Operator

Tony Butler, Guggenheim.

Tony Butler - Guggenheim Partners - Analyst

Thanks very much. Two questions; one for you, Rob, on the operating expenses of some modest increase or expectations for some modest increase in 2017. I'm just -- I'm struck by the notion that even in the midst of Vytorin and Zetia's LOEs where that would, I would argue, free up some capital, you are still going to grow op expenses.

But, moreover, is that simply dependent upon what might occur with -021G midyear? Is it depending upon that approval or not?

And second, Roger, back to the notion of types of chemo that one might utilize with pembrolizumab. I was struck in clintrials.gov of your own CDK inhibitor, I think it's 7965, in conjunction with pembro I guess in malignancies in the -155 trial; but it may have utility in others. And just your thoughts around different mechanisms, more specific mechanisms than simply something like Alimta or paclitaxel. Thanks for your time.

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Rob Davis - Merck & Co., Inc. - EVP, Global Services & CFO

Tony, this is Rob; thanks for the questions. As we look at this, I think this really goes back to something we started talking about even back in the third quarter as we started giving some indications of what we saw coming into 2017.

Clearly, we recognize the need to pivot and try to manage expense in a year of patent expiries. However, we also recognize and, frankly, feel good about the fact that we have such a strong opportunity with Keytruda that to try to pull back on some of those important clinical studies -- as you know, we have over 420 studies underway -- for a product that clearly is starting to show it can be a leader in the space only to manage for the short term, we felt was not the right decision.

So we made a decision to still invest in R&D; that's why R&D is actually growing. We are holding SG&A relatively flat. And I think that's also important, because on the back of what's coming with Keytruda in first-line lung cancer and across the other indications it has, we want to make sure we're also investing for a successful global launch of those products.

As far as to the specific question of is this dependent on -021G, the answer is no. Obviously, we will adapt our spend depending on what we see happening throughout the year, but there's not a specific trigger tied to -021G. And I would point out that we will remain disciplined and continue to make the right decisions and resource allocations, so that we can, ultimately, in the long term get back to a leveraged P&L.

I think we're in a unique situation where we have such an opportunity we don't want to lose it. We're going to invest behind it, but we're going to do so in a disciplined way.

Roger Perlmutter - Merck & Co., Inc. - EVP & President, Merck Research Laboratories

And Tony, it's Roger. I think the general logic of this is that if we want to improve responses to Keytruda, we need to recruit more immune cells and lower the barrier to activation of those cells. That's kind of the general logic.

When you look at indices of responsiveness to Keytruda, there are two things that clearly contribute, as has been reported by us and by others. First of all is mutational burden, so the representation of things that, in principle, immune cells could recognize, and the second is the pre-existing immune response, usually judged by something like PD-L1 expression or gamma interferon or something like that.

The combination with chemotherapy can improve immune responses just by releasing a lot of material from cell death and, in essence, cross-priming the immune system. So it can do that. It can improve responses through immunogenesis or it can more generally change the inflammatory (inaudible); all of those things are possible and the different chemotherapeutic agents can do those different things. So as we learn more about each patient and what the problem is that is required to achieve a better immune response, we should be able to harness those things better.

Maybe the answer is to increase mutagenesis in a particular patient and maybe radiation therapy is the best thing to use. Maybe, on the other hand, it's really a matter of tumor lysis to present more antigen. In which case, for example, directly cytotoxic drugs or cyclin-dependent kinase inhibitors might be good. So a whole variety of things to explore and we're trying to do that in a sensible and scientific way.

Operator

Alex Arfaei, BMO Capital Markets.

Alex Arfaei - BMO Capital Markets - Analyst

Good morning, folks, and congratulations on a strong 2016 and all the progress with Keytruda. A couple for Roger on the BACE inhibitor and the EPOCH study in Alzheimer's. Does the design and the statistical plan account for some of the potential limitations, such as not screening patients for beta-amyloid, and also including moderate patients?



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Also, to what extent -- can you give us an approximate breakdown about what we should expect in terms of mild and moderate patients in that study? And will you be looking at activity in those patients in a prospective manner as an endpoint, as opposed to the ad hoc analysis that we often see? Thank you.

Roger Perlmutter - Merck & Co., Inc. - EVP & President, Merck Research Laboratories

Right, Alex. So with respect to the first study, you're right; there was no imaging done for amyloid in the first study, in part because at the time of the start of the study that was not so easy to do. We did, however, try and pay attention to the representation of ApoE subsets by stratification, which will improve the representation of individuals who likely have amyloid-enhanced Alzheimer's by the traditional definition.

In terms of the study itself measuring the progression of cognitive improvement, it's a fairly traditional set of measures, and, roughly speaking, the representation of mild versus moderate is about 50%/50%. So we are eager to see the results; we will do a lot of subset analyses no matter what. And we're in a position, I think, because of the size of the study and the care with which the study was conducted, to get a lot of information. Fingers crossed, we're hopeful that we will actually see a positive result.

Operator

Gregg Gilbert, Deutsche Bank.

Gregg Gilbert - Deutsche Bank - Analyst

Thanks. First for Ken. You and your colleagues seem quite constructive post the meeting with the president. Just want to make sure you're confident post the meeting that there's not a proposal in the works to create some sort of bidding or direct negotiation process. I just want to make sure there's not a false sense of security building here. Not sure to what degree that came up, but perhaps you could go beyond just what you learned at the meeting on that front.

And secondly, for Rob on gross margin, is Keytruda gross margin still well above the corporate average, even after that new royalty burden? And is there anything else you'd like us to understand about product-specific gross margin as we think about the evolution of your gross margin this year and longer term as we model revenues for the different products? Thanks.

Ken Frazier - Merck & Co., Inc. - Chairman & CEO

Well, I'll start with the question that you asked. Obviously, we can't say what people in the Trump administration are thinking beyond what we heard in that meeting. And what we heard in that meeting I think gives us a lot of confidence that the Trump administration does understand the challenges associated with research-based pharmaceutical industry growth going forward.

What I heard from Mr. Trump was a concern less around the cost of drugs in the aggregate, but more around how patients need to be able to afford their co-pays and things of that nature. So, since that was the discussion in the meeting, we were thinking about, okay, we know that under the Part D benefit it's coming way under what was forecast. We know that substantial discounts are being negotiated by large players in the system. The question becomes how do we get some of that value to come to individual patients at the counter.

So the discussion went in that direction and I think that's a legitimate issue for American patients. We want to see how we can harness the private market to actually help patients afford their medicines more on an individual basis.

But we did not have a conversation in there that leads me to believe that they think the solution to that problem is secretarial negotiation. Now there will be politics around that; we know that there will be bills that are introduced in Congress calling for that, but the fact of the matter is I think that that is not perceived to be the solution to the problem.



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Rob Davis - Merck & Co., Inc. - EVP, Global Services & CFO

And with your question on gross margin, yes, Keytruda's gross margin, even with the royalty, is above, well above the corporate gross margin. And as we look at the mix of headwinds and tailwinds that drive gross margin going forward, growth in Keytruda is clearly one of the larger tailwinds for our overall gross margin into the future, even with the royalty included.

Teri Loxam - Merck & Co., Inc. - IR

Thanks, Rob, and, Darla, unfortunately, I think we're almost out of time here; Ken has got a few final words. But for any analyst that didn't get on the call with questions, the IR team is around throughout the day to answer those questions. And I'll let Ken finish off.

Ken Frazier - Merck & Co., Inc. - Chairman & CEO

I want to thank you all for being here this morning. If I could leave just one comment, we are extremely confident going into the future. I think you can see from our guidance that we are actually implying EPS growth, despite all the headwinds of loss of exclusivity and FX and the other challenges that we face. We're looking forward to our progress in first-line lung, to the -021G filing and things of that nature, and I think that we look forward to having tremendous opportunities going forward. So thank you very much.

Operator

This concludes Merck's Q4 and full-year 2016 sales and earnings conference call. You may now disconnect.

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