Q4 2020 Earnings Call

Company Participants

- Anne White, President of Lilly Oncology
- Dan Skovronsky, Chief Scientific Officer
- Dave Ricks, Chairman and Chief Executive Officer
- Joshua Smiley, Senior Vice President and Chief Financial Officer
- Kevin Hern, Vice President of Investor Relations

Other Participants

- Andrew Baum, Analyst
- Carter Gould, Analyst
- Chris Schott, Analyst
- Dan, Analyst
- David Risinger, Analyst
- Geoff Meacham, Analyst
- Gregg Gilbert, Analyst
- Kerry Holford, Analyst
- Ronny Gal, Analyst
- Seamus Fernandez, Analyst
- Steve Scala, Analyst
- Tim Anderson, Analyst
- Umer Raffat, Analyst
- Vamil Divan, Analyst

Presentation

Operator

Ladies and gentlemen, thank you for standing by, and welcome to the Lilly Q4 2020 Earnings Call. At this time, all participants are in a listen-only mode. Later, we will conduct a question-and-answer session. (Operator Instructions) And as a reminder, your conference is being recorded.

I would now like to turn the conference over to our host, Vice President of Investor Relations, Mr. Kevin Hern. Please go ahead, sir.

Kevin Hern {BIO 20557573 <GO>}

Good morning. Thank you for joining us for Eli Lilly and Company's Q4 2020 Earnings Call. I'm Kevin Hern, Vice President, Investor Relations. Joining me on today's call are Dave Ricks, Lilly's Chairman and CEO; Josh Smiley, Chief Financial Officer; Dr. Dan Skovronsky, Chief Scientific Officer; Anne White, President of Lilly Oncology; Ilya Yuffa, President of Lilly Biomedicines; and Mike Mason, President of Lilly Diabetes. We're also joined by Sara Smith and Lauren Durfy of the Investor Relations team.

During this conference call, we anticipate making projections and forward-looking statements based on our current expectations. Our actual results could differ materially due to a number of factors, including those listed on Slide 3. The additional information concerning factors that could cause actual results to differ materially is contained in our latest Form 10-K and subsequent Forms 10-Q and 8-K filed with the Securities and Exchange Commission.

The information we provide about our products and pipeline is for the benefit of the investment community. It is not intended to be promotional and is not sufficient for prescribing decisions. As we transition to our prepared remarks, a reminder that our commentary will focus on non-GAAP financial measures, which exclude the financial contribution from Elanco during 2019, and present earnings per share as though the full disposition via the exchange offer was complete on January 1, 2019.

Now, I'll turn the call over to Dave for a summary of our 2020 results.

Dave Ricks {BIO 16504838 <GO>}

Thanks, Kevin. On our guidance call in December 2019, we provided a framework for how we are thinking about the 2020 to 2025 period, noting our expectations to continue to deliver top-tier revenue growth and operating margin growing into the mid-to high 30s while continuing to increase R&D productivity. As we met with investors throughout 2020, it was evident that while there was good insight into management's expectations for the next few years. Investors were increasingly focused on our ability to grow in the second half of this coming decade.

In the past two months, we have begun to deliver answers to that question, with positive data for LOXO-305, tirzepatide and donanemab, each with a chance to significantly improve patient outcomes in areas of high unmet medical need. We believe these are three of the most important and exciting pipeline assets in our industry and provide meaningful support for Lilly's growth potential beyond 2025.

Together with Verzenio data in early breast cancer last summer, we have significantly reinforced our growth prospects for the midterm and upgraded them for the long term. While these readouts drive incredible momentum for our future, I am also pleased with the way that we delivered in a complex and challenging 2020. Our 2020 revenue enabled us to exceed our midterm revenue goal of 7% CAGR from the years 2015 to 2,020.

Turning to the quarter. Revenue grew an impressive 22% versus Q4 2019 or 20% in constant currency. This strong percentage points despite continued pricing headwinds and demand pressure from the effects of COVID-19.

Excluding bamlanivimab, revenue grew over 7% for the quarter. Key growth products continue to drive this volume and our revenue, now representing 55% of our base business. We continue to advance our productivity agenda in Q4 as the combination of strong revenue growth and modest operating expense growth drove significant margin expansion. Our non-GAAP operating margin was approximately 33% with and without COVID-19 therapies, an improvement of roughly 650 basis points versus Q4 2019.

With continued margin expansion for the quarter and full year, excluding the impacts of COVID-19 on our business in 2020, we would have achieved our midterm operating margin as a percent of revenue goal of 31%. We're proud to have delivered nearly 1,000 basis points of operating margin expansion since 2016.

In addition to the strong business performance, we achieved multiple pipeline milestones since our Q3 earnings call. These include the positive results I noted for LOXO-305, tirzepatide and donanemab; the FDA granting emergency use authorizations for bamlanivimab and baricitinib to help patients with COVID-19; the submission of empagliflozin for heart failure in people with reduced injection fraction in the U.S., Europe and Japan. This is done in collaboration with Boehringer Ingelheim; and the submission of Verzenio in early breast cancer in the U.S.

During Q4, we put our growing operating cash flow to work, announcing a 5% increase in the dividend for the third consecutive year, as well as continuing to pursue external innovation to augment future growth prospects with the acquisition of Prevail Therapeutics. This acquisition adds a promising new modality for Lilly by creating a gene therapy program that will be anchored by Prevail's portfolio of clinical-stage and late-preclinical-stage gene therapies across Alzheimer's, Parkinson's, dementia, ALS and other neurodegenerative disorders.

Moving to Slides 5 and 6. You'll see a list of key events since our last earnings call. In November, we announced that Arti Shaw, our Senior Vice President and Chief Information and Digital Officer, will retire in the first half of this year after 27 years of service to Lilly. She's been an invaluable member of our Executive Committee and a leader who really models our values. In addition to leading the development of our digital information strategy, she has developed and mentored talent throughout the organization and demonstrated a deep care for the patients we aim to serve. I want to thank Arti for her many contributions to Lilly.

And now, I'll turn the call over to Josh to review our Q4 and full year results.

Joshua Smiley {BIO 19888026 <GO>}

Thanks, Dave, and good morning. Slide 7 summarizes our non-GAAP financial performance in Q4 and 2020. And as Dave mentioned, revenue increased 22% this quarter compared to Q4 2019 and increased 7%, excluding bamlanivimab sales. Gross margin as a percent of revenue declined 130 basis points to 78.6%. Excluding the impact of bamlanivimab revenue and the related manufacturing costs, gross margin as a percent of revenue was 79.9%, in line with Q4 2019 performance.

Moving down the P&L. Operating expenses grew 3% compared to the same quarter last year. Marketing, selling and administrative expenses were down 8% as reduced activity due to COVID-19 and productivity measures offset investments in key growth products. R&D expenses increased 16% driven by investment in COVID-19 therapies. Net of COVID-19 expenses, baseline R&D was relatively flat, and total operating expenses decreased over 5% compared to Q4 2019.

Operating income increased 53% compared to Q4 2019 as revenue growth far outpaced expense growth, resulting in operating income as a percent of revenue of 33% for the quarter. Excluding the impact of COVID-19 therapies, operating income grew 34% in the quarter, and the operating margin for our base business was 32.7% for Q4.

Other income and expense was income of $477 million this quarter compared to income of $206 million in Q4 2019 driven by investment gains on public equities. As we in our Q3 earnings call, beginning in 2021, we will exclude the gains or losses due to equity investments from our non-GAAP measures. We have posted a supplemental investor workbook for Q4 on that basis to enable you to have an apples-to-apples comparison as we move into 2021 and compare to 2020 non-GAAP performance.

Our tax rate was 14.4%, an increase of 180 basis points compared with the same quarter last year, driven primarily by net discrete tax items in both quarters. At the bottom line, net income increased 58%, while earnings per share increased 59%. Net of COVID-19 therapies, net income and earnings per share increased 43%.

Moving to Slide 8. You can see these same non-GAAP measures for the full year. In spite of the ongoing demand impact from the pandemic, we grew the top line at 10% or 6% excluding bamlanivimab. Excluding COVID-19 therapies, our operating margin expanded by 300 basis points contributing to 30% EPS growth while continuing to invest behind our newer products and pipeline.

On Slide 9, we quantify the effect of price rate and volume on revenue growth. As mentioned earlier, worldwide revenue grew 20% in constant currency during Q4 driven by strong volume growth of 24%, partially offset by price. Foreign exchange had a modest impact on revenue growth. U.S. revenue grew 31% compared to the fourth quarter of 2019 and 7% bamlanivimab. For the base business, volume growth of 11% was led by Trulicity, Taltz and Verzenio.

Pricing was a 5% drag on U.S. revenue growth this quarter driven primarily by increased rates to maintain excellent access, partially offset by modest list price increases, largely for diabetes, and to a lesser extent, by changes to estimates for rebates and discounts for Taltz, which was driven by the access win at ESI.

Segment mix was not a major driver of U.S. price performance in the fourth quarter as increased utilization in more highly rebated government segments was offset by lower utilization in the 340B segment primarily for Trulicity and Humalog. Like Q4, the full impact of price was also a headwind of 5%, consistent with our 2020 expectations for a mid-single-digit net price decline in the U.S. While the midterm price trends are stable at

present, given the increasing variability in payer mix, we expect to see quarterly variability in our U.S. price impact during the course of 2021.

Moving to Europe. Revenue grew 12% in constant currency driven by 9% volume growth and a favorable impact from price. Volume growth was led by Alimta, Trulicity and Taltz. We're pleased with the continued uptake of our key growth products across Europe and are looking forward to continued strong growth in 2021.

In Japan, revenue decreased 10% in constant currency driven primarily by decreased volume in post-patent expiry products, Cialis and Forteo, as well as by a modest pricing headwind due to the government-mandated price decreases that went into effect in March 2020. Japan is experiencing the impact of countercyclical patent expiries with Cialis, Strattera and Cymbalta LOEs impacting growth in 2020 and likely in 2021.

In China, revenue grew 31% in constant currency driven by 57% volume growth driven by Tyvyt and partially offset by pricing concessions for the government-sponsored programs, which drove Tyvyt significant volume growth. We are excited about the momentum of our China oncology business, and we are looking forward to continued growth for Tyvyt and the launch uptake for Verzenio. We're also pleased that Trulicity and Olumiant were added to the NRDL as of January 2021.

Revenue in the rest of the world increased 6% in constant currency driven by strong volume from Trulicity and Olumiant as well as three percentage points of growth coming from bamlanivimab sales to Canada. The same information for our full year revenue is at the bottom of the slide.

As shown on Slide 10, our key growth products continue to drive impressive volume growth. These newer medicines delivered nearly 14 percentage points of growth this quarter, with bamlanivimab also contributing roughly 14 percentage points of growth. The strong volume growth in our key products was partially offset by post-LOE products as well as by reduced Trajenta royalties from the restructuring of our alliance with Boehring Ingelheim. This impact will sunset as we move into 2021.

Slide 11 highlights the contributions of our key growth products. In total, these brands generated over $3.6 billion in revenue this quarter, making up 55% of our base revenue. Amidst the ongoing challenges presented by the pandemic, we are encouraged by the performance of our key growth products in 2020. Trulicity grew 23%, adding nearly $1 billion last year to finish with over $5 billion in revenue while outgrowing the GLP-1 injectable class in revenue while outgrowing the GLP-1 injectable class in the U.S. and exiting 2020 with a nearly 47% share of total prescriptions amidst the reacceleration of growth for injectable GLP-1s.

Taltz grew 31% to nearly $1.8 billion in revenue, outgrowing the U.S. market in both dermatology and rheumatology and entering 2021 with best-in-class access that provides a strong foundation for long-term growth. Jardiance crossed $1 billion in sales for Lilly's share revenue in 2020, ending the year at nearly 60% of total SGLT2 prescriptions in the

U.S. and driving encouraging growth for the class, as we look forward to the regulatory action for FrEF and the readout for HFrEF this year.

And Verzenio revenue grew nearly 60% in 2020 to over $900 million, significantly outgrowing the CDK 4/6 class growing six percentage points in total prescriptions while nearly doubling new-to-brand share of market on the heels of positive data readouts for overall survival in metastatic breast cancer in 2019 and early breast cancer in 2020. Our key growth products will continue to drive Lilly's strong growth outlook in 2021.

On Slide 12, we provide an update on capital allocation. In 2020, we invested over $8 billion to drive our future growth through a combination of business development, capital expenditures and after-tax investment in R&D. In addition, we returned approximately $3.2 billion to shareholders via dividends and share repurchases. As mentioned earlier, we also announced a 15% dividend increase for the third consecutive year, demonstrating our confidence in the outlook for the Company.

We are focused on utilizing the strong cash flow our through both internal and external sources, as highlighted by the recently completed acquisition of Prevail Therapeutics. We will remain active in assessing bolt-on acquisitions or in-licensing, where we can create shareholder value and enhance our future growth prospects.

Turning to our 2021 financial guidance on Slide 13. We are affirming our non-GAAP guidance, and we've updated our GAAP guidance to reflect the impact of the Precision Biosciences, Merus and Asahi Kasei agreements, which with reported earnings per share for 2021, now expected to be in the range of $7.10 to $7.75. The impact of the recently completed acquisition of Prevail Therapeutics will be updated on our next quarterly call and will only impact Lilly's GAAP guidance for 2021. There will be no change to our 2021 guidance for R&D expense or non-GAAP EPS as a result of this transaction.

As we move into this New Year, and as we noted on our guidance call, we continue to experience suppressed demand due to the pandemic with several key therapeutic classes still below our pre-COVID baseline. We remain committed to ensuring we are doing our part to limit COVID-19 exposure for physicians, patients and our employees as cases surge in the U.S. and around the world. At present, most of our HCP interactions in the U.S. and many other major markets are virtual.

While this may have a near-term impact on new-to-brand performance, we continue to believe our approach is the appropriate posture as we support health care professionals navigating the ongoing pandemic and driving broad vaccination to enable a return to normalcy for health care systems in the second half of the year. In addition, our year-end 2020 inventory build was approximately a $120 million higher than Q4 2019, which was driven by 2019 having a lower-than-typical year-end stocking. This primarily impacts our diabetes products as well as Taltz and Alimta. We anticipate this inventory will burn off in Q1 2021 like normal historical patterns.

As I noted on our guidance call, we also experienced significant COVID-19-related stocking benefit of roughly $250 million in Q1 2020. Given those divergent year-over-year

inventory trends, we expect inventory patterns will have a negative impact on revenue growth and operating margin expansion in the first quarter of 2021. Despite these challenges, we remain confident in our full year outlook for 2021 and have increased confidence in our mid- and long-term outlook given our recent high-quality pipeline readouts.

So, now I'll turn the call over to Dan to highlight our progress on R&D.

Dan Skovronsky {BIO 15349505 <GO>}

Thanks, Josh. We had an exciting start to 2021 as we read out positive results for gentimab in the Phase 2 Trailblazer Al study. Lilly has spent more than 30 years dedicated to finding solutions for Alzheimer's disease, and we are proud of our progress in advancing the science and providing hope for patients and their families suffering from this devastating disease.

On Slide 14, you can see our key takeaways from this exciting trial. We are encouraged by the strong efficacy results, where in a relatively small study, we overcame the scale of the study with precision on patient enrollment and a very potent and effective plaque-clearing drug, becoming the first-ever disease modification study to hit statistical significance on its primary endpoint, with a slowing of decline by 32% relative to placebo as measured by the integrated Alzheimer's Disease Rating Scale.

ADAS is a clinical composite tool, combining two well-accepted measures in Alzheimer's disease: ADAS-Cog 13 for cognition; and ADCS IADL, Instrumental Activities of Data Living, for function. While the study was not powered for assessing multiple endpoints, we're very encouraged by the consistent improvements observed on all pre-specified secondary endpoints for cognition and function compared to placebo though ganitumab did not reach statistical significance on every secondary endpoint.

The consistency across time points and across statistical methods was very encouraging, particularly the disease progression model, which is becoming more accepted by the scientific community. In addition, we saw rapid and deep amyloid plaque clearance for ganitumab-treated patients who, on average, showed an 84 centiloid reduction of amyloid plaque at 76 weeks compared to a baseline of 108 centiloids. Since below 25 centiloids is a negative amyloid scan, this means that the average ganitumab-treated patient had a negative scan by the end of the study.

Finally, the safety profile was consistent with observations from Phase 1. Amyloid-Related Imaging Abnormalities or ARIA were observed, which is consistent with plaque-clearing antibodies. In the ganitumab treatment Group, ARIA E occurred in 27% of treated participants with an overall incidence of 6% of patients experiencing symptomatic ARIA E. We look forward to sharing the full results of Trailblazer AS at the ADPD 2021 virtual meeting on March 13, and we plan to have an investor call at 11 a.m. on March 15.

We hope to reproduce and extend these exciting findings in our second pivotal donanemab trial, TRAILBLAZER ALS 2, an 18-month study which began enrolling patients last year. At present, the study is expected to complete enrollment later this year with

nearly twice as many patients as the first TRAILBLAZER trial. We'll be engaging regulators to finalize the patient numbers and statistical plans for TRAILBLAZER 2, and we hope the exciting results from TRAILBLAZER 1 will increase patient interest and expedite enrollment.

TRAILBLAZER 2 was designed last year prior to TRAILBLAZER 1 data. And while the design is similar, at that time, we incorporated a few differences, including CDR sum of the boxes was moved to the primary endpoint for this larger trial, while ADAS becomes a key secondary endpoint. We added a high tau group and we include a blood-based screening for enrollment using the P-tau biomarker. We look forward to sharing the TRAILBLAZER-ALZ data and discussing next step for ganitumab with regulators.

Moving to Slide 15. As we discussed in-depth on Tuesday's call, there've been a number of developments for our COVID-19 antibodies since our last earnings call, which I will highlight only briefly now. In November, the FDA granted emergency use authorization for bamlanivimab as a treatment for COVID-19. We also submitted a request for EUA for bamlanivimab and antisemab together, which remain under review based on Phase 2 data from the BLAZE 1 trial.

Since the EUA for bamlanivimab, we've shipped approximately 1 million doses. We will have over 1 million additional doses available through mid-2021 for use around the world. This week, the U.S. government committed to purchase 500,000 of those additional doses by the end of March. Should any EUA be granted for bamlanivimab and etesevimab together, we expect to be able to supply in collaboration with Amgen up to 1 million doses of antisemab for administration with bamlanivimab together by mid-2021, with 250,000 doses available already in the first quarter this year.

In just the past eight days, we've shared Phase 3 data from the BLAZE 2 prevention trial where bamlanivimab showed up to an 80% reduction of risk of COVID-19 for nursing home residents; Phase 3 data from the BLAZE 1 trial for eisemanab together with bamlanivimab, which showed a 70% reduction in hospitalization or death among high-risk COVID-19 patients, providing further support for the EUA request for their joint administration.

Importantly, there were no COVID-19-related deaths in the antibody treatment arms from these two pivotal data sets. After having seen these results, Lilly has decided we will no longer conduct placebo-controlled studies in high-risk patients.

Initial results from the ongoing BLAZE 4 Phase 2 trial provide viral load and PK/PD data, which demonstrated that lower doses, including bamlanivimab 700 milligrams and tiseramab 1,400 milligrams together, are similar to the 2,800 milligram doses of those antibodies administered together.

We expanded the BLAZE 4 trial to also evaluate the administration of bamlanivimab AB with VER-7831 in collaboration with Vier and GSK, reinforcing our commitment to collaborate across the industry to treat current and future strains of COVID-19.

And yesterday, we received authorization from the FDA to update preparation and administration instructions in response to feedback from frontline nurses and doctors to enable flexibility, which can reduce infusion times considerably. These updates can shorten infusion times to as little as 16 minutes.

We're pleased with the potential impact our neutralizing antibodies can have, and we're working diligently to make them available to patients around the world. While the exciting progress with donanemab and the COVID-19-neutralizing antibodies has dominated Lilly's news in the past few weeks, we have continued to robustly advance the rest of our pipeline.

Slide 16 shows select pipeline opportunities as of January 27. Positive movement since our last earnings call includes the submissions Dave noted for Jardiance and Verzenio, the submission of Olumiant for the treatment of COVID-19 in Japan, the initiation of a Phase 3 trial for empagliflozin in post-myocardial infarction patients.

The movement of two pain assets into Phase 2 and the introduction of eight new Phase 1 assets, including our first clinical assets from two new modalities for Lilly: the siRNA molecule, ANGPTL3 from our collaboration with Dicerna and two gene therapy molecules from Prevail. In fact, we ended 2020 with a total of 17 new Phase 1 starts for the year, surpassing 2019's total of 16 first human doses, which was the highest number of new clinical starts for Lilly in a decade.

Considering the significant challenges we faced in 2020, including temporarily stopping the initiation of new clinical studies, this is a remarkable achievement. It speaks to the resilience and determination of our R&D organization during challenging times.

Moving to Slide 17. We show a final tally of how we finish 2020 versus the key events that we expected to occur. Since our guidance call in mid-December, we had submissions for selpercatinib for non-small cell lung cancer in Japan, Jardiance for heart failure for reduced ejection fraction in the United States and Verzenio for early breast cancer in the United States.

The sea of blue checkmarks emphasizes the sheer quantity of pipeline advancements in 2020. However, my take away from the year past is that I'm delighted with the quality represented here, including potentially practice-changing data for type 2 diabetes, for hematologic tumors; for early breast cancer, the launch of a first-in-class RET inhibitor; as well as the emergency use authorizations for two medicines to help address the COVID-19 pandemic. We're proud of the significant achievements delivered in 2020.

As we transition into 2021, I'd like to note that Josh Bilenker will be leaving his position as CEO of Loxo Oncology at Lilly to explore other interests and endeavors. We're grateful to Josh for his contributions to human health, both at Loxo and in his time with Lilly. We look forward to working with him in a consulting role.

I'm very pleased to announce that Jacob Bernardin is assuming the CEO role, continuing to work alongside Nisha Nanda and David Heyman, ensuring leadership continuity in

maintaining the strategy and operating model for Loxo Oncology at Lilly. Jake is a very highly talented leader, and this move allows him to continue to grow his responsibilities for the benefit of Lilly and Loxo.

Moving to Slide 18. You can see the expected events for 2021, including the donanemab data and upcoming disclosure I previously mentioned. A number of other major readouts are expected this year, including the remainder of the tirzepatide Phase 3 program, where we are looking forward to building on the SURPASS 1 data we disclosed late last year.

The Phase 2 readout for zagotenemab, our anti-tau antibody for early Alzheimer's, in a trial similar in design to the TRAILBLAZER trial that just read out; several to the TRAILBLAZER trial that just read out; several to the TRAILBLAZER trial that just read out; several potential Phase 3 readouts in immunology; and the results of empagliflozin for HFrEF.

Based on the recent high-quality pipeline data readouts for ganitumab, tirzepatide and LOXO-305, we entered 2021 optimistic by the impact these assets could have on patients. And we're focused on discovering and developing more new medicines to help patients.

Now I turn the call back over to Dave for some closing remarks.

Dave Ricks {BIO 16504838 <GO>}

Well, thanks, Dan. Before we go to Q&A, let me briefly sum up the progress we made in 2020. 2020 was a remarkable year as Lilly worked to fulfill its purpose in new and important ways. In addition to many contributions in the fight against the global pandemic, our business grew 10% in 2020 driven by strong volume growth from our key growth products launched since 2014. These products now account for more than half of our revenue for the first time.

We continued our productivity journey, delivering nearly 300 basis points of operating margin expansion for our base business. We made significant progress on our innovation based strategy, with LOXO-305, tirzepatide and Verzenio early breast cancer readouts, delivering potential category-changing data. While January's donanemab top line success was a first in Alzheimer's. With EUAs for bamlanivimab and Olumiant to combat COVID-19 and bolt-on acquisitions of Dermira and Prevail book ending the year, the past 12 months have been an exceptional example of Lilly's success in leveraging internal and external innovation.

We returned nearly $3.2 billion to shareholders via the dividend and share repurchase, and we will have another meaningful dividend increase, which we announced in December, reflecting significant confidence in the ongoing strength of our business. All of this was accomplished against the headwind of a pandemic that is still raging. While the New Year does not free us from that near-term challenge, our long-term outlook has never been stronger.

This concludes the prepared remarks and I'll turn the call over to Kevin for the Q&A.

Kevin Hern {BIO 20557573 <GO>}

Thanks, Dave. We'd like to take questions from as many colors as possible. So we ask that you limit your questions to two for follow-up. Tony, please provide the instructions for the Q&A session and then we're ready for the first caller.

Questions And Answers

Operator

Thank you, ladies and gentlemen. (Operator Instructions) Our first question comes from the line of Geoff Meacham with Bank of America. Please go ahead.

Q - Geoff Meacham {BIO 21252662 <GO>}

Okay, thanks. Morning, everyone. Just have a couple. Dan, on donanemab, I know you're planning on having regulatory discussions, but beyond expanding TRAILBLAZER-ALZ 2, is it reasonable to start a third study just to expand the safety database in the treatment experience? And then, Josh, you mentioned you're still seeing commercial impact from COVID, what would you say are the franchise's that were mostly affected in 2020? And maybe just review your assumptions for normalization of some of those in 2021? Thank you.

A - Dan Skovronsky {BIO 15349505 <GO>}

Thanks, Geoff. Your question is whether we'd consider starting a third donanemab study to improve the safety database. No, we haven't considered that at present. Of course, as we said, our next step is to discuss the dataset we have with regulators. I think if we determine that we need more patience, the place to do that is a TRAILBLAZER-2 study. With respect to additional studies, I think there could be opportunities to explore other populations and we're working through those possibilities right now, but we don't see that that necessary for this current population.

A - Joshua Smiley {BIO 19888026 <GO>}

Thanks, Geoff. I think when we look across our therapeutic areas, it's relatively consistent at this point that we're still not quite back to new to grand prescriptions in key areas, like immunology, pain and diabetes, although the diabetes numbers are looking stronger as we get here into January, but I think we're still seeing some suppressed demand. Physicians have, I think, in most markets has figured out how to see patients safely, and we're seeing nothing like what we saw back in April and May, in the U.S.

So, I think we just have to be cautious as we get into the first quarter and realize that the more complex treatments have some higher degree of variability against them and that includes starting new patients in areas like migraine. I think maintenance has been good throughout the pandemic. So, we do expect it, as we get through the first half of this year, we'll see returned to fully normal levels, but I think it's fair to assume that in the first quarter, we'll still be, in many of the therapeutic areas a little bit below pre-COVID baselines in terms of new prescription starts.

Q - Geoff Meacham {BIO 21252662 <GO>}

Okay. great.

A - Joshua Smiley {BIO 19888026 <GO>}

Thanks Geoff.

A - Dave Ricks {BIO 16504838 <GO>}

Probably referring Geoff as well as Durham, because I think that one also, you see some suppression in new patients starts, not affecting our share anything but just the overall volume in the category.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Dave. Geoff thanks for your questions. Next caller, please.

Operator

Thank you. Our next question comes from Tim Anderson with Wolfe Research.

Q - Tim Anderson {BIO 3271630 <GO>}

Thank you. Couple on donanemab. Investors are naturally wondering what the odds are that you could file for approval based on this first Phase 2 trial. To me, it seems highly unlikely given the size of the trial and the different subgroups, but just wondering, if you can share your latest thoughts on that?

And then, Dan, your view of the need to continue to knock down what is sometimes described in the industry as toxic oligomers which is what you might achieve by giving monoclonal chronically well after patients have already seen plaque normalization?

A - Joshua Smiley {BIO 19888026 <GO>}

Hi, Tim, we'll go to Dan for both of those.

A - Dan Skovronsky {BIO 15349505 <GO>}

Tim. So your first question is on the possibility of approval from a single study in Alzheimer's disease. Look, we, in general, we don't disclose our back and forth with FDA or other regulators. In this case, of course, we said that next steps are discussions with regulators. So clearly that hasn't happened yet. Still, we understand the regulatory threshold traditionally has been adequate and well controlled trial that means more than one trial.

In this case, we have a single, adequate and well controlled trial in Alzheimer's disease. As I said, it's not been the standard in this area. Of course, in other disease areas, notably in oncology, drugs can be approved from a single trial, usually, that's an accelerated approval. Usually, it's a group that's well defined by pathologic characteristics and

biomarkers. Usually, there's dramatic pathologic response as well as clinical outcomes. Of course, that's also true in the case of this dynamic trial, but again, oncology is quite different than Alzheimer's disease.

Your second question was on the question of toxic oligomers. It's long been unclear what is the toxic species of a beta, is it monomers and oligomers is a plaques. This antibody was designed to be exquisitely specific for amyloid plaques, we don't think it binds oligomers. And thereby the efficacy -- therefore the efficacy we see here seems to imply that it's the plaques that are the toxic species rather than the like oligomers. However, we can't rule out that these two things are in equilibrium with each other and perhaps by clearing plaques, you do remove oligomers as well.

Q - Tim Anderson {BIO 3271630 <GO>}

Thank you.

A - Kevin Hern {BIO 20557573 <GO>}

Tim, thanks for your questions. Next caller, please.

Operator

Next question comes from the line of Umer Raffat with Evercore. Please go ahead.

Q - Umer Raffat {BIO 16743519 <GO>}

Hi, thanks so much for taking my questions. Dan, in prior studies, the ADAS endpoint the composite they use in donanemab. It didn't correlate very well with CDR some of the boxes, but I did find it interesting that the most recent expedition three trials for solanezumab did have high concordance between this new composite versus CDR from the boxes.

I guess what I'm wondering is how should we be thinking about whether ADAS versus CDR some of the boxes correlate closely and that or is it more a function of the more recent trials where CDR does in fact correlate very closely with ADAS? I'm thinking about that heading into your donanemab trial.

The other one I had is, you have this tau antibody Phase 3 coming up this year. Maybe if you could remind us how's this tau MAb similar or different than some of the other ones because the progress on this target has not been quite good to date. And I saw your fall was pushed out a little bit as well, but it'd be very helpful to have any color. Thank you.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks Umer.

A - Dave Ricks {BIO 16504838 <GO>}

Thanks Umer. It's Dan. Umer, for your first question on ADAS and its correlation with CDR. Look, when we think about an endpoint for any clinical trial, there's really two things that

make an endpoint, a good endpoint. One is the statistical validation behind it. So in other words, is it reliable across different patients across different time points, across different trials, we put together a lot of data that support that.

Second, isn't meaningful for patients. And in this case, of course, we believe that that's inherently true. This is a composite of two things that are widely used, both thought to be important in meaningful it has Cogs and activities of daily living, obviously activities of daily living inherently meaningful for patients.

Now, why do we pick ADAS versus CDR to be the primary outcome of the study? That should be obvious, it's because ADAS would be more sensitive for measuring decline and therefore more sensitive for measuring a drug effect. That's based on all of that statistical validation data that we did.

If ADAS and some of the boxes were perfectly well correlated then ADAS couldn't be better, couldn't be more powerful. And yet, I'm telling you that our assumption going into this trial was that it would be. So of course, different outcomes will have some correlation, but they won't be perfectly correlated.

Based on what we saw in this trial, I think we haven't changed our thinking on outcomes, and we still think ADAS is a very valid and important outcome for Alzheimer's trials. Of course, that's a discussion to be had with regulators in the scientific community.

With the zagotenemab, this is our anti-tau antibody. Just as donanemab was a different type of anti-amyloid beta based on its specificity for plaque, zagotenemab is a different kind of anti-tau antibody. It's highly specific for aggregated tau.

Now, we think that's particularly important in the case of tau because there's a lot of soluble monomeric tau, and tau antibodies, like any other antibody, not much of it gets in the brain. So if you have a lot of monomer and a little bit of antibody, it could sop up all of your antibody and not have left to go after what we think is the more important species, aggregated tau.

So, we'll have to wait and see. Of course, this is a field that is younger than anti-amyloid therapies, but we've taken a lot of things we learned from anti-amyloid, applied them to anti-tau, and we're quite looking forward to getting that data later this year.

Q - Umer Raffat {BIO 16743519 <GO>}

Thank you.

A - Kevin Hern {BIO 20557573 <GO>}

Umer, thanks for your questions. Next caller, please.

Operator

Our next question comes from the line of Steve Scala with Cowen. Please go ahead.

Q - Steve Scala {BIO 1505201 <GO>}

Thank you. Two questions. Investor expectations are quite high for donanemab in terms of sales potential. Lilly knows the full data for TRAILBLAZER and also the largely failed A-beta antibody landscape better than any other company. Based on what you've said, including that donanemab will be a driver in 25 3 30, it sounds as though you are fully comfortable with these multibillion-dollar expectations. Is that the conclusion you want to leave us with?

Secondly, LOXO-305 looks like it could be best-in-class in oncology, and the safety looks favorable. Has Lilly rolled out non-oncology indications for 305, potentially MS, or perhaps for the sister BTK that you also have? Thank you.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Steve. We'll go to Dave for the first question and then Dan for the second one.

A - Dave Ricks {BIO 16504838 <GO>}

Yes. Steve, I mean, we don't comment on analyst models or forecast, and we never would. So I can't directly answer your question. I guess what I can say is, we've invested in Alzheimer's for 30-plus years and spent a lot of money, as you point out, mostly failing, because there's a huge unmet medical need, and we believe that investment is justified based on the size of market.

But we're not able to say today, donanemab is the answer, has a path to market, et cetera. We're not saying any of that. We're looking forward to the ADPD presentation coming up. The field will survey that data and make your own conclusions. And we need to talk to the FDA in a formal way about the path forward, and then we'll get to sales forecast later, but it's just not possible to answer a question like the one you asked.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Dave. Dan?

A - Dan Skovronsky {BIO 15349505 <GO>}

Okay. The second question, more straightforward. LOXO-305 is a really uniquely specific reversal BTK inhibitor with great drug properties. That's why it's generating such remarkable data in oncology. You're asking a question that we thought a lot about, which is, could this also translate to being a highly differentiated molecule in immunology?

I think in this case, we would not pursue the same molecule. I think this is down the road far enough in oncology. This will be an oncology molecule. But you raised the question of whether we'd be interested in generating a sister molecule, as you said, for immunology indications. That's certainly something we are considering.

Q - Steve Scala {BIO 1505201 <GO>}

Thank you.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Dan. Steve, thanks for your questions. Next caller please.

Operator

Our next question comes from the line of David Risinger with Morgan Stanley. Please go ahead.

Q - David Risinger {BIO 1504228 <GO>}

Yes, thanks very much. Congrats on the update. I have two questions, please. First, when do you expect to have clarity from the FDA on whether Lilly can file with the single small Phase 2 trial on donanemab? And then second, would Lilly consider changing the primary endpoint for TRAILBLAZER 2, which is currently CDR sum of boxes?

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Dave. Dan?

A - Dan Skovronsky {BIO 15349505 <GO>}

Okay. Thanks, Dave. Your first question is on the potential for filing, which I think we addressed before. We haven't had those discussions with the regulators. Of course, we move quickly to understand the data and schedule discussions with regulators around the world. As I said before, the regulatory standard is adequate and well-controlled trials, so two trials there. But certainly, we'll be interested to hear what regulators say.

Q - David Risinger {BIO 1504228 <GO>}

Thank you.

A - Kevin Hern {BIO 20557573 <GO>}

And the second one is, can you see the change over the primary endpoint?

A - Dan Skovronsky {BIO 15349505 <GO>}

Oh, yes, yes. Sorry, Dave. So the second question there is would we change the endpoint. Yes, of course, we can consider it. I think we look at the totality of data that we get from TRAILBLAZER 1, and that will inform our decisions, as well as conversations with regulators. But so far, we haven't seen anything that leads us to make that decision to change it.

Q - David Risinger {BIO 1504228 <GO>}

Thank you.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Dan. Dave, thanks for your questions. Next caller please.

Operator

Next question comes from Terence Flynn with Goldman Sachs. Please go ahead.

Q - Dan {BIO 1934179 <GO>}

Hi, this is Dan on for Terence. Just one from us. On LOXO-305 that you could discuss if you believe there's a path to filing for approval on the Phase 1/2 data? Thank you.

A - Kevin Hern {BIO 20557573 <GO>}

Yeah, so, we'll go to Anne White for that one.

A - Anne White {BIO 20764375 <GO>}

Well, thanks, Terence, for the question. And we're obviously very excited about the data, both in CLL and CL. And so we do have ongoing discussions with the FDA regarding the potential for accelerated approval. Obviously, in this place, the single-arm accelerated approvals for heme malignancies can be challenging. And so that really require -- was going to require further discussions with regulators. So we can't commit yet on submissions, timing or which indications, but be assured that we'll continue those conversations.

And we couldn't be more excited about the data, as Dan mentioned. I think this molecule really started as a molecule focus on C41 mutations, and then as we saw the data and the performance in the broader populations remarkable. So, we'll keep that with conversations going, and we'll keep you posted.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Anne. Dan, thanks our next question. Next caller please.

Operator

Thank you. Our next question comes from the line of Chris Schott with JP Morgan. Please go ahead.

Q - Chris Schott {BIO 6299911 <GO>}

Great. Just one on donanemab and then just one other one. What are your thoughts on the high-tau population? I guess just based on what you saw from TRAILBLAZER, is there a strong rationale the drug could also work in some of these patients? And maybe just give us a sense of what percent of patients in TRAILBLAZER 2 we should expect to come from that group?

Then my second question was just did make some changes to your 340B program reimbursement last year. Maybe just remind us the scope of that business in your portfolio. And have there been any either challenges or push backs with the implementation of that? And how we should be kind of thinking about 340B as we go through 2021? Thank you.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Chris. We'll go to Dan for the first question and then Josh on 340B.

A - Dan Skovronsky {BIO 15349505 <GO>}

Got it. Thank you, Chris, for the question about the high-tau population. A notable feature of the TRAILBLAZER trial is that we excluded patients who had too much tau in their brain. We believe that people who have the highest tau or it's spread throughout their brain are past the point of no return at least for an amyloid-directed therapy.

Of course, as we fully analyze this data, and hopefully, even in time for the upcoming presentation, we'll understand what we're seeing in this current data set with respect to baseline tau levels predicting response to therapy, as we see that, that could lead us to be either more excited or less excited about including high-tau patients in TRAILBLAZER 2 study. And so that is something that is still very much open. As we see that dataand understand it, we could think about changing the design there.

In terms of the percent of patients that are impacted here, it sort of depends on how you cut it. If you start with all of the early Alzheimer's patients, plus -- mild AD plus MCI, that's about 4.5 million in the U.S. and double that in Europe and Japan combined. Many of those patients with amyloid negative. We've shown that before. So you take about one-third out for that. A small fraction of them will be amyloid positive but no tau at all. We didn't include those patients. And then a slightly larger fraction will be in that tau high group.

So once you've excluded all those patients, we've said it's sort of 30% to 45% of that mild AD to MCI population that would meet these enrollment criteria in TRAILBLAZER 1.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Dan. Josh?

A - Joshua Smiley {BIO 19888026 <GO>}

Chris, on 340B, what we said is if you look over the last 10 years, the 340B segment has been among the fastest-growing, certainly across the industry but for our business as well, and it rivals the size of Medicaid in our U.S. business, so about 10% of the business now. Of course, the change we made was to go back to the legislated intent and to provide the discounts to the actual hospitals that provide care and to exclude contract pharmacy that have grown overtime And when we look at that business, it's probably about half of the businesses in these contracted pharmacy. So that's where we've made the change, to not provide the pricing there.

Now, we do have a process where those contracted pharmacy can apply and we've said for insolence, as long as they can demonstrate that they're passing on the entire pricing that they're still eligible to participate. When we look at all that together, we knew that that's where we implemented in September. We knew there would be challenges, and we're seeing those challenges come, but I think in terms of patient impacts, we haven't

seen much yet. So, we're seeing the fact that the discounts are being provided as per our change, but we don't think it's impacting patient care at this point.

So everything we're seeing so far is consistent with the decision we made. We knew it would be a difficult decision to implement. We knew there would be some customer concerns. We knew there'd be legal challenges, but I think what we saw in the fourth quarter is consistent with the guidance we've given for 2021, which is that we would expect this portion of the 340b program to moderate in growth and provide a two to three point price tailwind for us in 2021. So I think we're on track for that at this point.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Josh. Chris, thanks for your questions. Next caller please.

Operator

The next question comes from the line of Seamus Fernandez with Guggenheim. Please go ahead.

Q - Seamus Fernandez {BIO 7525186 <GO>}

Great, thanks. So I just wanted to follow up on the one donanemab question, which is, Dan, can you just give us a little bit of color on the magnitude of blinding in this study, given the fact that patients obviously had almost absolute clearing of their amyloid plaques? And your confidence that the behavior of the placebo arm was consistent with the benefits of monitoring both tau and amyloid?

And then the second question, just wanted to get a bit of an update on Verzenio and how Verzenio is tracking relative to your expectations. I think we're starting to see fits and starts, I guess, to some degree in terms of capturing incremental market share. But directionally, it seems positive. Just trying to get a sense of where Lilly thinks the uptake could go in metastatic disease? And then, how ultimately an approval of the adjuvant opportunity can impact sales or your market share going forward? Is that really the big driver? Or are you already seeing meaningful changes in metastatic market share? Thanks so much.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Seamus. We'll go to Dan for the first question and Anne for the second.

A - Dan Skovronsky {BIO 15349505 <GO>}

Yeah. Thank you, Seamus, for those very thoughtful questions focused on that blinding of the study. We said before that TRAILBLAZER 1, we carried this study out with the quality that we typically use for regulatory pivotal studies, fully blinded, double-blinded study.

You raised the possibility that there could be some unintentional unblinding as a result of amyloid clearance. We don't see that that's possible. Patients don't know or feel the clearance of amyloid in their brain directly. And investigators wouldn't have seen that the results of the PET scan themselves.

The other potential in any Alzheimer's study for in over blinding is ARIA E because sometimes that is something that can cause a side effect. And we commented on the 6% of patients that had symptomatic ARIA E or so. I think that's certainly an important analysis, I think, in every study in Alzheimer's disease is to look at the drug effect with and without ARIA patients. And certainly, that's something that we hope to have complete and be able to share in March.

And then finally, you asked about the behavior of the placebo arm. That's a great question. Really, when we saw this data that was the first thing I wanted to look at. Sometimes, you have small studies that look promising. It's because your placebo arm did worse than typical. And here, we said -- we've communicated a high level of confidence and encouragement based on the data. So that excludes that possibility. This placebo arm is not behaving aberrantly. That's not what's driving the effect.

Again, we'll get into the details of that in March, but very, very pleased with the performance of the placebo arm here.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Dan. Anne?

A - Anne White {BIO 20764375 <GO>}

Yeah. Thanks for the question on Verzenio. So as you noted, 2020 was really another year of very positive and clinically 2020 was really another year of very positive and clinically meaningful data for Verzenio. And then our shares, as a result, I think, continue to improve.

While obviously, no CDK is yet approved in the EVC setting, we do think that this readout is particularly drew attention to the market class. So that said, we're really confident that the current trends are a result of our strong execution and our focus on NBC and then the -- particularly logistically significant OS data, which a key competitor in the space didn't have.

As we compare Q4 '19 to Q4 '20, it was really a remarkable period of growth, as you said, for Verzenio. We saw TRx increase of 6% worldwide revenue growth of 57% and U.S. growth of 36%. And what we're hearing pretty repeatedly now from thought leaders is that they're seeing more and more that Verzenio is a differentiated agent.

So obviously, we've shared that in MEMS, we feel we have higher CDK4 activity than -- versus others, differentiated continuous dosing, a monotherapy indication, and then obviously, the data that we saw in MONARCH 2 with the primary endocrine-resistant population. So I think all of that is really playing into the growth that we're seeing in the MVC market. And so, we'll expect to continue to see our growth -- our share market grow in that space.

On the adjuvant side, as Dave and others mentioned, we did submit to the FDA in other areas at the end of last year. So we look forward to regulatory action later this year. This market size is significant in the fact that it's probably an additional 50% if you match our

entry criteria, 50% increase to our current metastatic market in this high-risk adjuvant population. So that's significant.

And what's also significant is the duration of treatment will very likely will be longer than a metastatic setting. So patients in the study are treated for 24 months. And right now, we're seeing patients stay on for months on average in the study. And many of the patients are still on study, so I think that number will continue to get longer. So that duration of treatment offers upside as well. But we're incredibly excited about the data. We're looking forward to bringing it to patients as soon as possible. Thanks for the question.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Anne. Seamus, thanks for your question. Next caller please.

Operator

Next, we go to the line of Andrew Baum with Citi. Please go ahead.

Q - Andrew Baum {BIO 1540495 <GO>}

Thank you. A couple of questions. First, on donanemab. On the issue of whether potentially donanemab could be submitted on the back of the Phase 2 data set that you have. Could you talk to your level of preparedness, particularly manufacturing, given the anticipated demand, but also to the P tau blood test that will potentially be used to define the patients? I'm just trying to understand where you at because there is a scenario by which you could be on the market sooner than perhaps that many may believe. And that's an open observation rather than reflecting any particularly personal view.

And then second for Anne, could you talk to your BTK inhibitor 305? I know you're hiring medical liaisons already, which in hematology would suggest that you're optimistic about being able to file in the second half. From your understanding of the community nature of practice for CLL, given the very high tolerability of the drug and the strong efficacy even without a randomized trial, do you believe that this drug could take significant market share in the first BTK refractory or intolerant setting? Thank you.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Andrew. We'll go to Dan for the first question and Anne for the second.

A - Dan Skovronsky {BIO 15349505 <GO>}

Yeah. Andrew, you raised an excellent question on all the work that needs to be done to prepare for ganitumab. We actually initiated manufacturing preparedness before we had this data. So, this is something we do at Lilly. We always prepare for success. And so at the same time, that our manufacturing colleagues we're ramping up the anti-COVID antibodies, we asked them to also prepare for donanemab.

So that is well underway, and I like what's going on, the progress we're making in manufacturing there. The diagnostic ecosystem also needs work. We started that both ramping up imaging and proceeding along with opportunities to bring the phospho-TAL

blood test to more patients. That's both underway, again, started before we had this data and then, of course, is useful whether we're successful in coming to market or whether any other anti-amyloid drug comes to market. So, those are preparations that we're certainly taking.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Dan. Anne?

A - Anne White {BIO 20764375 <GO>}

Yeah. Thanks for the question on 305. So with the MSL population, it's important to remember, this arm of our company talks about the work that's going on in our -- across our portfolio. So this is not just related to 305, but we have other assets in the portfolio that may be heading in this space. So I wouldn't read too much into that, its normal operations to make sure that we're covering the portfolio. But obviously, they do get many questions about 305, the excitement that's out there in treating physicians.

And importantly, we have a number of large Phase 3 trials that are starting as well. And as you know, that field force helps us identify high-quality rates to include in those programs. As far as CLL, obviously, the story there is incredibly exciting, and we do think that we have a real contender here. Particularly what we're interested in seeing is what has been seen in the past, certainly in the area of oncology, is that drugs that have a meaningful treatment effect on the same target pathway in patients who have relapsed tend to have sometimes an even more pronounced effect in that first-line setting.

And so that's the upside here that is the potential for LOXO-305 is that first-line setting. So this year, we're actually planning to initiate, as you know, four global clinical studies, and three of them are in CLL. And obviously, two of them are in the BTK-preta patients, but one is in that really in a head-to-head setting and looking at head-to-head with ibrutinib in CLL.

And obviously, this is a riskier study to do. We still feel very confident in the later-line setting, but we do have a belief that this molecule has a lot of potential in the first line, but hence, doing the trials. So obviously, as I said earlier, I can't comment on the regulatory likelihood. Those are ongoing conversations with the FDA. But regardless, we know that in this space, you need randomized clinical trials to really reach the patients that we wish to reach. And so that's -- the intention is to do those trials regardless.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Anne. Andrew, thanks for your questions. Next caller please. Our next question comes from the line of Gregg Gilbert with Truist Securities. Please go ahead.

Q - Gregg Gilbert {BIO 3565226 <GO>}

Thanks. On the COVID antibodies, Dave, I realize the latest data is quite fresh. But to the extent you're worried that there could be disconnect between the power of the data and the speed of uptake, is there anything that Lilly plans to do proactively to help move this along? I was intrigued by your comments on the prior call about some well-known

hospitals being slower than other hospitals to get trained and ready. And I think that was even from before this latest data set.

And then maybe for Josh, on that call, it sounded like the upper limit of $2 billion in your guidance is not necessarily set in stone if demand picks up. What's the practical limitation from a manufacturing standpoint as it relates to 2021 for the antibodies? Thanks.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Greg. And we'll go to Dave and then Josh.

A - Dave Ricks {BIO 16504838 <GO>}

Okay. Yes, I'll comment. Dan, jump in. I mean we've -- since the beginning, we've been working with health care systems and physicians across the country to enable uptake of the antibodies. I guess it's, in some ways, a test of what happens when you don't have the normal commercial preparation and rollout. This was done via government channels under an EUA. And you see big differences in adoption rates, and I highlighted that it seems to be an inverse relationship between the places you think about advanced medicine and who's actually using this.

One of those barriers clearly is conviction on the data. So, I'm really pleased with the data we announced in the last week, and I think it will, has to, increase conviction. And this is also -- there's a class effect here, too. And the fact that other antibodies are demonstrating promise in different settings adds to that data and I think will build confidence. So hopefully, that will change.

There's two endorsements as well we hope will change: one is NIH, the other is the Infectious Disease Society. That said, there's tons of practical problems with at scale, infusing people with COVID-19 that have been completely worked out by numerous health systems and not worked out by many, many others. So we work quite a bit with state departments of health, et cetera, to share those practices.

The best practice is chart flagging upon positive COVID-19 for at-risk patients, scheduling of appointments, dedicated facilities and staff for high-throughput antibody administration. Where that's happening, they're using a lot of material. And you can almost see actually a reduction in health care utilization. So we're actually running an experiment like that in New Mexico to actually prove it as well as with UnitedHealthcare. But I'm optimistic that we'll see the rate of use grow. It moved from about 20% in December to about double that now. We hope to see more progress going forward.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Dave. Josh?

A - Joshua Smiley {BIO 19888026 <GO>}

Thanks, Greg. So what we've said for this year is guidance range for COVID antibodies is $1 billion to $2 billion. And of course, there's a lot of uncertainty in that. Although with what we've announced this morning on the call, the next agreement that we've signed

with the U.S. government, it's probably high probability for $1 billion in the first quarter. That's just the purchase agreements that we already have.

I think then to get past that, we have -- based on what we've already committed to in terms of manufacturing, probably about another 500,000 banliminivab doses available in the first half of the year in monotherapy and one million combo. So if we sold all of that and it's weighted heavily towards the U.S. or high-income countries, you could get above $2 billion. But we don't have an EUA with the U.S. government or any other government for the combo yet, and there's a lot to still play out, I think, in terms of vaccine and where these products can be utilized.

If we get into the second half of the year, I think we can continue at the pace of production of million-plus doses available per quarter. I don't think the manufacturing piece is going to be as much of a barrier in the second half of the year if we stay on the course of vaccines and otherwise. So clearly, we could be above $2 billion for the year. But there's a lot of uncertainty, and we'll continue to monitor this number and provide updates as we have more agreements and more approvals.

Q - Gregg Gilbert {BIO 3565226 <GO>}

Thank you.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Josh. Gregg, thanks for your questions. Next caller please.

Operator

Next, we go to the line of Ronny Gal with Bernstein. Please go ahead.

Q - Ronny Gal {BIO 15022045 <GO>}

Good morning. Congratulations on nice result, and I will continue on the tradition of asking one question about donanemab and one other. So on donanemab, I guess the bar that you can see from the FDA is one kind of well internally correlated trial and data support elsewhere. When you look at your program, it looks like the support you could provide is from removal of plaque from earlier trials. And I guess the question for you is, is the understanding that plaque removal is related to clinical benefits solid enough that you can use that as early approval based elsewhere?

As for a non-donanemab question, I was going to go back to the 340B prices. The signs are increasing from data there might be an action on this issue before the end of 2021. I just want to kind of confirm that you have not assumed in your model got full impact for the entire year, but there is some sort of a partial year assumption or some sort of a partial impact that you've modeled in.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Ronny. We'll go to Dan and then Josh.

A - Dan Skovronsky {BIO 15349505 <GO>}

Yep. Thanks, Ronny. It's a really good question that you're asking, which is how strong is the biomarker evidence here? And how can that be used to support regulatory decisions? I certainly think that's the direction the field is going. So in other words, when I look across all of the trials that have read out, again, this is the first plaque removing antibody that has had a positive study that hit its primary endpoint on the pre-specified statistical analysis.

But even the other ones that didn't do that, when you look across the totality of evidence, you get a sense that there's a correlation between plaque removal in general and better cognitive performance. Here, we have probably the most significant plaque removal, the fastest, deepest plaque removal and a very meaningful clinical effect. So it's another point in this sort of dose response curve comparing amyloid plaque removal and cognitive changes across different trials.

As that gets filled out further and further by additional experiments, I think amyloid plaque removal could someday become an important surrogate that could aid in the regulatory approval of drugs. Are we there today? I don't know. That's a question for regulators and for the field and something that we certainly have believed in for many years and will continue to take up.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Dan. Josh?

A - Joshua Smiley {BIO 19888026 <GO>}

Thanks, Ronny. As I mentioned earlier, we've guided to a two- to three-point price benefit in 2021 as a function of the 340B changes that we've made. We've been very clear on 340B that the reason for the change is that we're providing discounts that patients don't get. And we want the program needs to be reformed and cleaned up. So our assumption is in 2021, there will be changes. Whether -- and as I mentioned earlier, we also have mechanisms for contract pharmacies to get the discounts. We want to ensure that patients' insulin can get the pass-through discount.

So we're assuming in our 2021 guidance that -- not a full financial benefit for the full year that there will be changes in modifications through the year, either as we try to work to ensure patients get the benefits of the discounts or if there are some administrative or legislative changes.

Q - Ronny Gal {BIO 15022045 <GO>}

Great, thank you.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Josh. Ryan, thanks for your questions. Next caller please.

Operator

Our next question comes from the line of Vamil Divan with Mizuho Securities. Please go ahead.

Q - Vamil Divan {BIO 15748296 <GO>}

All right. Thanks for taking my questions. So I also have a couple on the Alzheimer's theme. So one, just on the second Alzheimer's TRAILBLAZER 2, an issue we've seen with other CNS drugs, maybe not as much in Alzheimer's, but you get these positive results. Everyone gets excited. But then the second trial, you might have to manage more of the placebo response or improperly getting patients into the trial. So I'm just wondering if there's anything you're doing differently or more carefully to make sure for the second trial, you don't have patients who may be getting to the trial that otherwise shouldn't have? Or you say being to manage the placebo response, especially when the endpoint is a sort of clinical rating scale like a CDR sum of the boxes?

And then my second questions are unrelated, but I guess partially related to Phase I. You mentioned that to more from where you terminated. I'm just wondering if you can share any details behind that decision.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Vamil. We'll go to Dan for both of those.

A - Dan Skovronsky {BIO 15349505 <GO>}

Yeah. Thanks, Vamil. It's a good point you raise. Of course, the placebo effect getting stronger in second trials is something that's been seen a lot in psychiatry and sometimes in pain studies. As you pointed out, I'm not sure it's such a strong effect in Alzheimer's disease.

One thing that encourages us here and I think would allow us to see a strong signal even if there is some of that here, is -- maybe two things that encourage us. First is the magnitude of the effect that we're seeing overall, which, as I said, hits test given in the small trial and TRAILBLAZER 2 is much bigger.

Second is the consistency across endpoints and time points and statistical methods. That gives us additional confidence as well. With respect to your second question, which was the tau more for the Alzheimer's program here with AC immune, we decided to pursue other promising tau from our candidates from AC immune's research platform. And therefore, we terminated this Phase 1 molecule. That's probably all we see right now.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Dan. Vamil, thanks for your questions. Next caller please. Our next question comes from the line of Carter Gould with Barclays. Please go ahead.

Q - Carter Gould {BIO 21330584 <GO>}

Good morning, guys. Congrats on the progress. Dan, I guess I keep up the trend of Alzheimer's first. I guess just can you talk first around your longer-term view towards combination approaches with donanemab, particularly with an anti-tau inhibitor? And

then you had good momentum across the pain portfolio in the quarter, and you've got a number of Phase 2 studies reading out with your epiregulin antibody. Any color there on your level of confidence? And if those data represent the key inputs regarding a get-go novocaine decision to Phase 3 or will you need additional Phase 2 work, longer safety data? And any commentary on how you see that coexisting with tanezumab if that's approved? Thank you.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Carter. Dan?

A - Dan Skovronsky {BIO 15349505 <GO>}

Great. Carter, two good interesting questions. So on combination of purchase for Alzheimer's, I do think that's what the future holds. One of the really neat things about donanemab is that we just treat until amyloid plaques are removed. This is not a drug that we anticipate patients will be taking for the rest of their lives. Once they're clear of amyloid plaques, we stop treatment with this drug. We know from prior data that plaques don't come back.

So you can imagine clearing a patient amyloid plaques and then treating them with another mechanism. That could be complementary, for example, in anti-tau drug or an immunomodulatory drug for Alzheimer's disease. So that's certainly something that we're considering and quite likely will pursue in the future.

Thanks for noting momentum in the pain space. This is an area that is just so underserved by the pharmaceutical industry. I think there's a variety of reasons including regulatory thresholds, that have held back investment in an area that represents one of the greatest unmet medical needs. This is why patients -- number one reason why patients see doctors because they're in pain. And we know the drawbacks to current therapies.

So we designed a platform pain study, which actually tests -- can test multiple molecules against multiple indications, And we can keep funneling molecules in and get results out. Depending on the strength of the efficacy here, that will inform next steps, but we're confident that this study is well designed to whether we have meaningful treatment effects or not.

Of course, a holdback in pain, as I said before, is the regulatory bar, which is heavily weighted towards safety. And typically, that takes a large number of patients to discharge. Certainly, tanezumab, a perfect example of that with so many patients studied and a well-understood signal here on both efficacy and potential safety that needs to be resolved for the FDA.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Dan. Carter, thanks for your questions. Next caller please.

Operator

Next question comes from Kerry Holford with Berenberg. Please go ahead.

Q - Kerry Holford {BIO 21698599 <GO>}

Hi, thank you. Just a couple left from me, please. Firstly, on Prevail. I wonder if you can talk however more about their decision to acquire here. What strategy is this particular gene therapy platform versus others? And when might we see the data readout for the lead assets? And indeed, when might we see these potentially come to market?

And then my second question is just more housekeeping in nature. You talked about a stocking benefit in Q4. I think it was $120 million. Could you detail which drugs that impacted primarily and whether you'd expect an unwind into the next quarter?

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Kerry. It's Dan for the question on the Prevail acquisition and then Josh on the stocking question.

A - Dan Skovronsky {BIO 15349505 <GO>}

Yes. Thanks, Kerry. We're really excited to have Prevail join Lilly. This is a really great gene therapy platform. Why we picked -- and a great team. Those are clearly two of the reasons why we picked Prevail. Also, I think there's just a natural synergy with the work we do at Lilly. We're extremely strong in neuroscience. We have a deep commitment to the space. And therefore, as we thought about what's our entry point into gene therapy, and we believe gene therapy will be an important treatment modality across therapeutic areas in the future, it made sense to enter gene therapy to begin our efforts here in neuroscience.

Prevail has got two exciting programs in the clinic already. One is for Parkinson's disease with GBA1 mutations, and it's a GBA1 gene transfer. There's a lot of phase validity to that kind of approach, and we're looking forward to seeing data from that. The other similarly well-validated target here in frontotemporal dementia with GRN mutations. And that's also, I think, exciting. In terms of time lines to market, I think it's -- these programs are still very early. We're just in the first few patients here, and we'll have to see what the data showed in port of those time lines.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Dan. Josh?

A - Joshua Smiley {BIO 19888026 <GO>}

Thanks, Kerry. Yes. On inventory, what we've said is if you look at 2020 inventory in the U.S. inventory levels versus Q4 of 2019, we're $120 million higher. We're not concerned about that. 2019 was an unusually low year when you just look at days of stock. So the $120 million is in line with our expectations.

But now as we look into Q1 2021, we do expect that $120 million will burn off. And it's across the portfolio. But as you would imagine, Trulicity is one of the products. We see a little bit extra in Taltz, and I think some of this is a function of the anticipation of increased

volume for Taltz as a function of the ESI win that'll go in -- that went into effect on January 1.

And we also see some on Alimta. We did see some purchasing patterns through the year in oncology. I think some of which was related to the pandemic and some delays in infused products, but those are probably the two biggest products where we see this on. So we would expect that $120 million to burn off in Q1 as it normally does.

The other piece, though, that we want to make investors aware is, remember last year in Q1 we saw a $250 million build in inventory on a worldwide basis. This was as customers were stocking up in anticipation of the walk-downs that were coming with the pandemic.

So I think if you put those two things together, the $250 million build last year and what we assumed to be $120 million burn this year, that's about $370 million of headwind when you just do year-over-year compare in growth, and that's -- could be up to six points or something. Again, it's not a concern to build into how we think about the year, but we do want to remind investors on that piece.

Now -- and I think throughout the year, we're going to have some strange compares. Remember that we sold $871 million in bamlanivimab in Q4, we expect to have significant sales this year as well. So we'll tease all that as we go through. But on the underlying base business, you should expect to see an inventory negative growth effect in Q1.

A - Kevin Hern {BIO 20557573 <GO>}

Thanks, Josh. Kerry, thanks for your question. And we'll go to Dave now for the close.

A - Dave Ricks {BIO 16504838 <GO>}

Great. Thanks, Kevin, and to the team. We appreciate everyone's participation in today's call, and of course, your interest in Eli Lilly. 2020 was a strong year for the Company, and we anticipate an important year in 2021. A lot of questions related to Alzheimer's today. We're excited about that as well.

But just a reminder, we have upcoming readouts for tirzepatide with sustained two, three and five over the coming weeks and months as well as a number of readouts this year in our immunology portfolio for baricitinib, lebrikizumab and mirikizumab in important indications.

The Company has a broad and diversified set of opportunities ahead for additional innovation for patients. With our strong lineup of marketed products as well and this industry-leading pipeline, we believe we continue to be a compelling investment.

So thanks for dialing in. Please follow-up with the IR team, if you have any additional questions and hope everyone has a great day and a great weekend. Take care.

Operator

Thank you. Ladies and gentlemen, that does conclude our conference for today. We thank you for your participation and for using AT&T conferencing service. You may now disconnect.