Seeking Alpha

Transcripts | Healthcare

Biogen Inc. (BIIB) CEO Michel Vounatsos on Q3 2019 Results - Earnings Call Transcript

Oct. 22, 2019 4:40 PM ET | 2 Likes

by: SA Transcripts

Q3: 10-22-19 Earnings Summary

SEC *10-Q* *Slides*

EPS of $9.17 beats by $0.90 | Revenue of $3.6B (4.68% Y/Y) beats by $67.39M

Earning Call Audio

Subscribers Only

0:00:00 -1:21:08

Biogen Inc. (NASDAQ:BIIB) Q3 2019 Earnings Conference Call October 22, 2019 8:00 AM ET

Company Participants

Joe Mara - Vice President, Investor Relations

Michel Vounatsos - Chief Executive Officer

Al Sandrock - Executive Vice President, Research and Development and Chief Medical Officer

Samantha Budd Haeberlein - Vice President, Late Stage Clinical Development

Jeff Capello - Chief Financial Officer

Conference Call Participants

Umer Raffat - Evercore ISI

Phil Nadeau - Cowen and Company

Terence Flynn - Goldman Sachs

Geoff Porges - Leerink

Michael Yee - Jefferies

Cory Kasimov - JPMorgan

Geoff Meacham - Bank of America

Brian Abrahams - RBC Capital Markets

Matthew Harrison - Morgan Stanley

Ronny Gal - Bernstein

Jay Olson - Oppenheimer

Paul Matteis - Stifel

Operator

Good morning. My name is Jessa and I will be your conference operator today. At this time, I would like to welcome everyone to the Biogen Third Quarter 2019 Financial Results and Business Update. [Operator Instructions] I would now like to turn the conference over to Mr. Joe Mara, Vice President, Investor Relations. You may begin your conference.

Joe Mara

Good morning, everyone and welcome to Biogen's third quarter 2019 earnings conference call. On today's call, we will be discussing our Q3 results as well as an update on our Alzheimer's program aducanumab including our plan to file in the U.S.

Before we begin, I encourage everyone to go to the Investors section of biogen.com to find the earnings release and related financial tables, including a reconciliation of the GAAP to non-GAAP financial measures that we will discuss today. Our GAAP financials are provided in Tables 1 and 2 and Table 3 includes a reconciliation of our GAAP to non-

GAAP financial results. We believe non-GAAP financial results better represent the ongoing economics of our business and reflect how we manage the business internally. We have also posted slides on our website that follow the discussion related to this call.

I would like to point out that we will be making forward-looking statements which are based on our current expectations and beliefs. These statements are subject to certain risks and uncertainties and our actual results may differ materially. I encourage you to consult the Risk Factors discussed in our SEC filings for additional detail.

On today's call, I am joined by our Chief Executive Officer, Michel Vounatsos; Dr. Al Sandrock, EVP, Research and Development and our Chief Medical Officer; Dr. Samantha Budd Haeberlein, Vice President, Late Stage Clinical Development and our CFO, Jeff Capello.

Now I will turn the call over to Michel.

Michel Vounatsos

Thank you, Joe and good morning everyone. I will start by giving you an outline of this call since we are announcing both Q3 results and news on aducanumab. First, I will review the recent news on aducanumab. Next, I will provide the key highlights of a strong quarter. Al and Samantha will then provide additional details on aducanumab and progress across the rest of our pipeline. Jeff will discuss our financial performance for Q3 and I will close before we open the call for questions.

This is an important day as we are announcing that based on discussion with the FDA, we plan to submit a regulatory filing in the U.S. for aducanumab. If approved, aducanumab will become the first therapy to reduce clinical decline in Alzheimer's disease and the first therapy to show that removing amyloid beta can lead to better clinical outcomes. This is an important milestone providing hope for patients, physicians, caregivers and families around the world. It is also important to highlight that the path taken in the pursuit of discovering and developing breakthrough treatments is not always direct and straightforward. As you know in March, we announced our decision to discontinue the Phase 3 EMERGE and ENGAGE studies for aducanumab in Alzheimer's disease based

on a pre-specified futility analysis. In retrospect the result of our futility analysis was incorrect. Based on what we know now it is clear that the pre-specified futility criteria did not adequately anticipate the effect of all the variables in these trials.

So, what happened? First, the decision to stop these trials relied on an earlier and smaller dataset comprised only of patients who had the opportunity to complete 18 months of treatment as of December 26, 2018. At that time, the futility analysis predicted that the trials were unlikely to meet the primary endpoint upon completion. Futility analysis are common in large studies and they use statistical modeling to attempt to predict the outcome of the studies based on a number of pre-specified assumptions and criteria. There are multiple methodologies that can be used for futility analysis and the methodology we use was a well accepted approach. However, based on what we have learned, we know now that the futility analysis did not adequately account for the effect that the earlier enrollment in ENGAGE had on patients overall exposure to high dose aducanumab.

Second, in the months following the discontinuation of the studies, our team has continued to analyze the vast set of clinical imaging and biomarker data that the studies have generated. In addition to further analysis of the dataset which informed the futility analysis we also gain access to an analyzed additional data, including data on patients who completed treatment after the cutoff date for the futility analysis as well as data for patients who did not complete the full duration of the study. Once we became aware of the potential implication of this larger dataset, we consulted with external advisors followed by the FDA with a Type C Meeting in June as we began conducting further analysis. Third, the new analysis of the larger dataset, which was conducted in consultation with the FDA, showed that aducanumab had a dose-dependent effect on the underlying pathology as measured by amyloid-PET imaging and reduced clinical decline in patients with early Alzheimer's disease as measured by the pre-specified primary and secondary endpoints. Based on the second type C meeting held with the FDA just yesterday, we believe this data support regulatory filing.

Beyond aducanumab, we are hopeful about the implication of these results for similar approaches targeting amyloid beta, including BAN2401. Looking forward, we plan to submit a regulatory filing in the U.S. in early 2020 and we will continue dialog with

regulatory authorities in international markets, including in Europe and Japan. Most importantly, we have a deep commitment to the patients' community starting with those who participated in our clinical trials. With the support of the FDA, we aim to offer access to aducanumab as soon as possible to eligible patients previously enrolled in the Phase 3 studies, the long-term extension of the Phase 1 PRIME b-study and the Phase 2 EVOLVE study. We will work towards this goal with the regulatory authorities, principal investigators and the institutional review boards with a sense of urgency. I know this development is unexpected for all our stakeholders, including the many patients involved in our clinical studies and their families, our investigators, our investors and our employees. And I am sure you have a lot of questions. We were also surprised when we initially learned about the potential implication of these additional data, but our surprise quickly turned to the hope that we maybe in the position to offer Alzheimer's patients the first step to reduce clinical decline in this devastating disease. We are humbled and honored by this opportunity and we are committed to following the science and doing the right thing for patients.

Now, let me review some financial highlights from the third quarter. Compared to the same period a year ago, Biogen delivered solid top line and bottom line growth. Third quarter revenues grew 5% to $3.6 billion. Third quarter GAAP earnings per share grew 17% to $8.39 and non-GAAP EPS grew 24% to $9.17. Now, let me briefly review our progress against our strategic business priorities. First, we continue to demonstrate resilience in MS and we remain focused on addressing the IP challenge with TECFIDERA, while also preparing for the expected launch of VUMERITY. Second, SPINRAZA revenues grew double-digits both year-over-year and quarter-over-quarter. Third, our biosimilars business continued to grow led by the recent launch of IMRALDI. Fourth, we continue to progress our pipeline with a positive readout on VUMERITY and the addition of two new clinical programs. And fifth, Biogen has continued to be disciplined and focused on capital allocation. As we have demonstrated, we are committed to maximizing returns for our shareholders while continuing to bring innovative therapies to patients, something that demands a thoughtful approach toward all our investment over both the short-term and the long-term.

Before turning the call over to Al, I would like to congratulate him on his new role as the Head of R&D at Biogen. I know, I speak for the broader Biogen family in expressing my confidence in Al as a scientist, as a clinician, and as a leader. Al is taking the helm at the time when I believe Biogen R&D has never been stronger. And I believe he is well equipped to continue driving Biogen R&D forward.

Al Sandrock

Thank you, Michel. Before diving in, let me first take a moment to say how excited I am, about the opportunity to lead the R&D organization here at Biogen. I'm extremely proud of the team for all the hard work that brought us to today's announcement on aducanumab, and I believe now more than ever, that Biogen is uniquely positioned to bring breakthroughs in neuroscience and transform the lives of patients with neurological disease. As Michel said, we were all surprised when we learned of the potential implications of the new analysis of a larger dataset from the Phase 3 studies of aducanumab. Following discussions with external advisors and the FDA, we have now come to better understand what happened, and even more importantly with the positive implications of the larger dataset may mean for patients, physicians and the broader scientific community.

To start, I will briefly summarize our current understanding of the Phase 3 data, before I turn the call over to Samantha, who will describe in more detail, the series of events and analysis that have led us to the current conclusions and status today. First, it is important to understand what the results – that the results you will hear about today, which we have analyzed in consultation with the FDA, are based on a new analysis of a larger dataset, than that which was used for the futility analysis.

Our primary learning from these data is that sufficient exposure to high dose aducanumab reduced clinical decline across multiple clinical endpoints. This reduction and clinical decline was statistically significant in EMERGE, and we believe that patients – that the data from patients who achieve sufficient exposure to high dose aducanumab in ENGAGE support the findings of EMERGE. After consultation with the FDA, we believe that the totality of these data support a regulatory filing. Importantly patients included in the futility analysis, were those who had enrolled early in the trials and those early enrolling patients

had a lower average exposure to aducanumab in large part due to two protocol amendments that occurred sometime after the start of the trials. These two protocol amendments were put in place precisely to enable more patients to reach high dose aducanumab, and for a longer duration. As a consequence, the larger dataset available after trial cessation included more patients with sufficient exposure to high dose aducanumab.

Moreover, differences between EMERGE and ENGAGE can mostly be accounted for by a greater level of exposure to high dose aducanumab in EMERGE due to multiple factors including the fact that ENGAGE started earlier and enrolled earlier then EMERGE, meaning that fewer patients in ENGAGE had sufficient exposure to high dose aducanumab, as well as other factors including differences in the degree of dose suspension due to ARIA. Taken together, we believe that these data and the associated extensive analysis provide compelling evidence that aducanumab reduces the otherwise devastating and inexorable clinical decline of Alzheimer's disease.

To expand further, I will now hand the call over to Samantha.

Samantha Budd Haeberlein

Thank you, Al. Let me now describe in more detail how we got here. It's important to first understand the design of the studies and how that evolved over time. EMERGE and ENGAGE were Phase 3 multicenter, randomized, double-blind, placebo-controlled parallel group studies, designed to evaluate the efficacy and safety of aducanumab in early Alzheimer's disease. The studies were identical in design. A full enrollment EMERGE included 1,638 patients and ENGAGE included 1,647 patients. Based on the data from the Phase 1b PRIME study of aducanumab, we believed that higher doses of aducanumab may be associated with improved clinical outcomes. However, as the incidents of amyloid related imaging abnormality or ARIA for short, the most common adverse event associated with aducanumab, also increased with aducanumab dose and occurred more often in ApoE4 carriers than non-carriers.

The Phase 3 study had a number of design elements, such as titration, dose levels and management with MRI to mitigate and manage the risk of ARIA. In addition, dosing of aducanumab was stratified by ApoE4 carrier status. The low dose was defined as 3

milligram per kilogram for ApoE4 carriers and 6 milligram per kilogram for non-carriers, whereas the high dose was initially defined as 6 milligram per kilogram for ApoE4 carriers and 10 milligram per kilogram for non-carriers. Results from the PRIME study for ApoE4 carriers titrated to 10 milligram per kilogram became available in August 2016. This data showed that the incidence of ARIA as well as discontinuations from treatment due to ARIA in ApoE4 carriers receiving aducanumab titrated to 10 milligram per kilogram appeared to be reduced as compared to the fixed dose cohort. Following this analysis, the protocols for the ongoing Phase 3 studies were amended such that the high dose in ApoE4 carriers would then be increased from 6 to 10 milligram per kilogram. Of note, in each study approximately two-thirds of enrolled patients were ApoE4 carriers, and the number of carriers was well balanced across each of the arms of both studies. Each dose arm had a titration period such that the maximum number of monthly 10 milligram per kilogram doses that any patient in the high dose group could receive in the 18 months study was 14. Moreover, the original protocol recommended that some patients with ARIA suspend their dosing and then restart and remain at a lower dose.

ENGAGE enrolled its first patient in August 2015 and EMERGE began enrolling approximately one month later in September, 2015. Two key amendments were made to the protocols during the conduct of the study. In July of 2016, we amended the protocol to allow patients with ARIA who suspended dosing to resume aducanumab treatment at the originally assigned dose. And then in March of 2017 as I mentioned, the protocol was amended to increase the high dose for ApoE4 carriers from 6 to 10 milligram per kilogram after titration. Taken together, these protocol amendments had the effect of allowing more patients to receive their target dose. Since enrollment in ENGAGE had begun and remained ahead of EMERGE, overall more patients in EMERGE were impacted by the protocol amendments and received the 10 milligram per kilogram dosing of aducanumab.

On March 21, 2019, we announced the termination of EMERGE and ENGAGE following the outcome of a pre-specified futility analysis. The futility analysis was based on efficacy data on all patients in the two trials who had enrolled early enough to have had the opportunity to have completed the 18 month study period by December 26, 2018. Futility criteria which were pre-specified in the statistical analysis plan would be met if both arms of both trials were predicted to have had less than 20% probability of being positive on the

primary endpoint at the end of the study. This probability used pool data from the two trials to predict the future behavior of the remaining patients. This is a well accepted statistical methodology for two trials that are identical in design, such as EMERGE and ENGAGE. However this pooling methodology assumes no large heterogeneity between the studies.

At the time of the futility analysis, EMERGE was trending positive, while ENGAGE was not. We did not understand the drivers of these different results. While we did know that the protocol amendments could have had differential effects on the two studies, due to the relative timing of enrollment. We did not anticipate the magnitude of the effect this would have on the data. Following the discontinuation of EMERGE and ENGAGE, additional data from these studies became available, namely the 2,066 patients who had the opportunity to complete the full 18 month study period by March 20th as well as all 3,285 patients who had enrolled in the trials in what's known as the intent to treat or ITT population. Importantly, once we had applied the pre-specified statistical analysis to the larger dataset, we were excited to see that EMERGE met its primary endpoint on CDR Sum of Boxes or CDR-SB. CDR-SB scores are obtained through clinician interviews of patients and caregivers and assess three domains each of cognition and function, namely memory, orientation judgment and problem solving, community affairs, home and hobbies and personal care.

Specifically in the intent to treat population, patients from the high dose aducanumab group showed a 23% reduction in clinical decline from baseline in CDR-SB scores at 78 weeks with a p-value of 0.01. The corresponding results in the opportunity to complete or OTC dataset was also 23% with a nominal p-value of 0.03. The low dose group also had less decline on the CDR-SB than placebo. However, the differences were smaller than in the high dose group and did not attain statistical significance. In EMERGE, patients on high dose aducanumab also showed a reduction in clinical decline as measured by the pre-specified secondary endpoints. Specifically, we saw a 15% reduction in clinical decline as measured by MMSE with a p-value of 0.06, a 27% reduction in clinical decline as measured by ADAS-COG13 with a p-value of 0.01 and a 40% reduction in clinical decline as measured by ADCS-ADL-MCI with a p-value of 0.001. A small numeric advantage for low dose over placebo was observed on all endpoints except for MMSE, MMSE and ADAS-COG measures of cognitive performance in domains relevant to Alzheimer's

disease such as memory, orientation and language. ADCS-ADL-MCI on the other hand is a caregiver rated assessment of activities of daily living, including conducting personal finances, performing household chores such as cleaning, shopping and doing laundry and independently traveling out of the home.

In ENGAGE, the primary endpoint was not met though the low dose showed results similar to the low dose of EMERGE. Results of the ITT and OTC analysis of the secondary endpoints in ENGAGE showed no statistically significant differences in decline on MMSE ADAS-COG13 or ADCS-ADL-MCI compared with placebo. However, small numeric advantages for the low dose of a placebo were observed on these endpoints. In addition to the clinical data, we observe supporting data from multiple biomarkers, imaging of amyloid plaque deposition in both studies demonstrated that treatment with aducanumab resulted in a dose and time dependent reduction in amyloid plaque burden compared to placebo with p-values less than 0.001. The magnitude of reduction in the high doses is similar to that seen in the Phase 1b study. aducanumab also demonstrated an impact on CSF biomarkers of tau pathology. A statistically significant reduction on CSF phospho-Tau levels was observed in EMERGE and ENGAGE with a dose proportional response in EMERGE. aducanumab produced a numeric reduction in CSF total-Tau levels in EMERGE and ENGAGE with a dose proportional response in EMERGE. Although the primary and secondary endpoints were not met in ENGAGE in post analysis, the subset of patients who received sufficient exposure to 10 milligram per kilogram aducanumab in this case, at least 10 doses of 10 milligram per kilogram showed similar results to the comparable population from EMERGE, in terms of both amyloid plaque reduction and reduced clinical decline on CDR-SB.

The safety and tolerability profile of aducanumab in EMERGE and ENGAGE was consistent with previous studies of aducanumab, with the most commonly reported adverse event being ARIA-E and headache. Although the underlying cause of ARIA-E is not well understood, it is likely that the MRI signal of ARIA-E is due to increased extra cellular fluid. The majority of patients with ARIA-E did not experience symptoms during the ARIA-E episode and ARIA-E episodes generally resolved within 4 to 16 weeks, typically

without long-term clinical sequelae. We plan to present further details on the new analysis of the larger dataset from aducanumab at the C Type Meeting in December, which we plan to webcast.

So to summarize, first, across multiple clinical endpoints, the larger aducanumab dataset demonstrated a statistically significant reduction of clinical decline in early Alzheimer's disease patients in EMERGE, and we believe that data from a subset of ENGAGE support these findings.Second, exposure to high dose aducanumab was important for efficacy and differences and exposure to high dose aducanumab largely explain the different result of futility analysis and the new analysis of this larger dataset as well as the different results between the two studies. Finally, following consultation with the FDA, we believe it is reasonable to submit a regulatory filing for aducanumab based on these data.

As Michel and Al mentioned, the past that brought us to today was long and complex. We will be working with our investigators to redose eligible patients who had previously participated in the aducanumab clinical trial, and we look forward to working with the FDA as well as regulators around the world to find a path to make the drug available to patients. Most importantly, we envisage a future where physicians may finally have an option to offer patients to help reduce clinical decline in Alzheimer's disease.

I'll now turn it back over to Al.

Al Sandrock

Thank you, Samantha. We believe that these positive results for aducanumab represent a turning point for patients, caregivers, physicians and scientists in the fight against Alzheimer's disease. More broadly, we believe these results represent an inflection point in neuroscience drug development and validate our core strategy, by demonstrating the removal of aggregated forms of amyloid beta can result in improved clinical outcomes, we believe these results have positive implications for BAN2401, a distinct antibody that also targets aggregated amyloid beta that we are currently evaluating in a Phase 3 study in early Alzheimer's disease in collaboration with Eisai.

More generally, we believe these data may have positive implications for additional assets in our portfolio that target the casual pathobiology of neurodegenerative disease, particularly those validated by human genetics. These include our Tau directed assets for Alzheimer's disease and primary tauopathies, our alpha-synuclein antibody for Parkinson's disease and our SOD1 and C9ORF targeting antisense oligonucleotides for ALS. Given our depth of expertise, our deep and interconnected neuroscience pipeline including nine additional readouts expected by the end of next year, we believe that Biogen is uniquely positioned to capture the opportunity in neuroscience, and potentially deliver a suite of breakthrough therapies for diseases of the nervous system.

With that in mind, let me now review the highlights across the rest of our pipeline in the third quarter. Starting with MS, this quarter we announced positive top line results from EVOLVE-MS-2, a Phase 3 study of VUMERITY or diroximel fumarate, a novel oral fumarate for relapsing remitting multiple sclerosis compared to TECFIDERA. The remedy was statistically superior to TECFIDERA on the studies pre-specified primary endpoint, the individual gastrointestinal symptom an impact scale with a p-value of 0.0003. The proportion of patients who discontinued due to GI adverse events during the five-week treatment period was 0.8% for VUMERITY and 4.8% for TECFIDERA. Of note, discontinuation rate for TECFIDERA is similar to that observed in the Phase 3 studies of TECFIDERA in which 4% of patients discontinued due to GI events. Earlier this month, Alkermes received a tentative approval from the FDA for VUMARITY. We are working with our Alkermes and the agency to secure final approval as quickly as possible.

Moving to TYSABRI, previous analysis of real world data from the US TOUCH registry demonstrated that extended interval dosing of TYSABRI reduced the risk of PML by between 78% and 99% in this population. However, whether extended interval dosing preserves the efficacy profile of TYSABRI remains an open question. To this end, at last month's ECTRIMS meeting, we presented data on the efficacy of extended interval dosing with TYSABRI using data from the TYSABRI Observational Program. After propensity score matching, the results indicated that there was no significant difference in annualized relapse rate or risk of relapse between the two groups. And we recently completed enrollment for the Phase 3b NOVA study of TYSABRI, a two year randomized prospective trial that will directly compare the effectiveness of every six-week dosing versus the

approved every four-week dosing regimen after at least one year of standard dosing. Also this quarter the EMA updated the labels of AVONEX and PLEGRIDY to remove pregnancy contra-indications, and where clinically needed to allow use during pregnancy and breast feeding in women with relapsing MS. With these updates interferon-beta therapies are the only MS Therapies in Europe that can be considered for use in MS patients throughout the full course of pregnancy. This is important, given that women are diagnosed with MS at least 2 to 3 times more frequently than men and women are often affected during their childbearing years.

Turning to our progress in neuromuscular disorders, at last month's Congress of the European Pediatric Neurological Society, we presented new interim data from the open label shine extension study of SPINRAZA in children with later onset SMA. Now, including data on patients up to 15 years of age followed for up to six years, this analysis demonstrated that in star contrast to the natural history of SMA patients with Type 2 SMA treated with SPINRAZA demonstrated improvements in motor function as assessed by the Hammersmith Functional Motor Scale Expanded and patients with Type 3 SMA treated with SPINRAZA demonstrated stable Hammersmith scores and improvement in distance walked. No participants discontinued treatment due to adverse events. And no new safety concerns were identified. Taken – Taken together, these data again underscore the robust durable efficacy and well-established longer term safety profile of SPINRAZA across a broad range of SMA patients. Also this quarter we published data from the nurture study of SPINRAZA in pre-symptomatic infants in the journal neuromuscular disorders. Data from the nurture study showed that all patients treated with SPINRAZA were alive and achieved the ability to sit without support, non required permanent ventilation, 92% achieved walking with assistance and 88% achieved walking independently.

Given SPINRAZA is well-characterized safety profile, we recently announced a Phase 2/3 DEVOTE study to evaluate whether a higher doses of SPINRAZA can provide even greater efficacy than the currently approved dose. Our review of PK/PD data suggested individuals with higher CSF concentrations of SPINRAZA achieved greater improvements in CHOP INTEND and motor milestones. As with any therapy that is developed to address high end men need, companies who lead need to continue to continually explore ways to optimize their treatment. Building on the success of SPINRAZA, we aim to build a broader

neuromuscular franchise including ALS. At the meeting of the Northeast ALS Consortium held earlier this month, we presented new data on neurofilament levels assessed in the Phase 1/2 multiple ascending dose study to a person, our antisense oligonucleotide targeting SOD1 in patients with SOD1 ALS.

As a reminder, previous data from this study showed that treatment with 100 milligrams of tofersen was associated with a statistically significant reduction in CSF SOD1 protein levels and trends toward slowing of clinical decline as assessed by three independent measures relative to placebo. This new analysis of the same population showed the baseline neurofilament levels in both the plasma and CSF were correlated with baseline disease activity. And treatment with 100 milligrams of tofersen reduced levels of neurofilament in both plasma and CSF. These data further highlight the concordance across datasets generated in this study, including target engagement, clinical and neurofilament data and thus illustrate the potential for an antisense oligonucleotides to target genetic drivers of neurodegenerative disease. In movement disorders, we continue to advance to Phase 2 study of BIIB092 or gosuranemab, an antibody targeting extracellular tau in PSP with data expected by the end of the year. In this Phase 2 – if this Phase 2 study is positive, we believe we would be in a position to file for regulatory approval. In Parkinson's disease, we continue to progress the Phase 2 study of BIIB054, an antibody targeting extracellular alpha-synuclein. We expect data from the one year placebo controlled period of this study including data on safety, as well as neuro imaging based assessment of striatal dopaminergic transporter density in the second half of next year.

Also this quarter, as we work to build further depth and movement disorders, we dosed the first patient in the Phase 1 study of BIIB094 an antisense oligonucleotide targeting leucine-rich repeat kinase 2 or LRRK2 in Parkinson's disease. Toxic gain of function mutations in LRRK2 constitutes the most common genetic cause of Parkinson's disease representing approximately 5% of all Parkinson's disease cases. In addition to LRRK2s role in familiar Parkinson's disease, data from the literature suggests that LRRK2 gain of function may also contribute to the pathogenesis of sporadic Parkinson's disease. As a

result, this Phase 1 study will include Parkinson's disease patients with or without verified mutations in LRRK 2. Importantly BIIB094 leverages the same RNase H media degradation mechanism utilized by tofersen.

With the addition of BIIB094 to our pipeline, we are now advancing ASOs targeting the most common genetic cause of Parkinson's disease, two genetic causes of ALS and taupathology, which underpin several primary and secondary tauopathies including Alzheimer's disease. And we aim to build further depth across our ASO pipeline, as we continue to emphasize our focus on genetically validated targets and defined patient populations. In acute neurology, we continue to advance the Phase 3 study of BIIB093 or IV glibenclamide, for cerebral edema caused by large – large hemispheric infarction or LHI. As a reminder BIIB093 blocks SUR1-TRPM4 channels that are hypothesize to mediate brain edema following LHI. Given that these channels are also hypothesized to mediate expansion of Hematoma and Perihematoma edema associated with brain contusion, this month we dosed the first patient in a Phase 2 study of BIIB093 for brain contusion. Approximately 280,000 patients are hospitalized due to head trauma annually in the United States. And we estimate the contusions occur in approximately 25% to 35% of these patients. There are no pharmaceutical agents approved to mitigate contusion expansion, which is associated with worsened clinical outcomes. The primary objective of this new study of BIIB093 will evaluate the proportion of patients with brain contusion, who exhibited an expansion in contusion volume over the course of a 96 hour infusion of BIIB093 versus placebo. Importantly, we believe that the shared pathophysiologic features of LHI and brain contusion exemplify the interconnectivity of neuroscience that we are leveraging as we continue to increase the depth and breadth of our pipeline. This also highlights our strategy to produce – to pursue multiple indications for a given asset, particularly once we believe safety has been adequately established.

And finally, in our Alzheimer's disease portfolio, this quarter, we completed enrollment in the Phase 2 study of gosuranemab in early Alzheimer's disease. And we continue to advance the Phase 1 studies of BIIB076, a distinct anti-tau antibody and BIIB080 an ASO aimed at reducing the expression of tau in the central nervous system. Taken together with the positive results of aducanumab, we believe that no other company is better positioned to deliver breakthrough therapies for Alzheimer's disease. Overall, this was a

historic quarter for Biogen and for the patients, caregivers, physicians and scientists around the world, who have been waiting decades for a therapy that can reduce the clinical decline of Alzheimer's disease.

With that I will turn the call over to Jeff.

Jeff Capello

Thanks, Al. Good morning, everyone. I will now review our financial performance for the third quarter of 2019. As Michel mentioned earlier, we had a strong financial performance in Q3 2019. Total revenues for the third quarter grew 5% year-over-year to approximately $3.6 billion, while GAAP earnings per share increased 17% and non-GAAP earnings per share increased 24%, both compared to the prior year.

Overall, our MS business delivered revenues were approximately $2.3 billion in the third quarter of this year, including OCREVUS royalties for approximately $188 million, growing 2% versus the prior year. Global MS revenues in Q3, 2019 were stable versus the prior year with OCREVUS royalties and the total number of patients on our MS products globally continued to grow in the low single-digits versus the prior year. U.S. MS revenues in Q3, 2019 were impacted by a decrease in channel inventory of approximately $30 million compared to a decrease of approximately $5 million in Q3, 2018 and a decrease of approximately $30 million in Q2 2019. Global third quarter TECFIDERA revenues increased 3% versus prior year, as TECFIDERA delivered strong global patient growth of approximately 8% year-over-year. In the U.S., TECFIDERA revenues were flat year-over-year as TECFIDERA share of total prescriptions remained relatively stable compared to the last couple of quarters. Outside the U.S. TECFIDERA performed very well again in Q3 2019 with continued volume increases across all large European markets and Japan versus the prior year, somewhat offset by pricing pressure in several European countries.

Q3 global Interferon revenues including both AVONEX and PLEGRIDY decreased 10% versus Q3 2018, due to the continued shift from the injectable platforms to oral or high efficacy therapies. TYSABRI worldwide revenues increased 3% versus the third quarter of 2018. We were pleased with this growth into TYSABRI revenues as it continued to perform well in the high efficacy segment. In the US, we grew TYSABRI revenues 4% year-over-year, as we continue to maintain stable TYSABRI share of total prescriptions

compared to the last couple of quarters. Outside the US, we grew TYSABRI 2% driven by volume growth in several markets and favorable timing of shipments somewhat offset by pricing pressures. Overall, we were pleased with the execution of our MS franchise and the continued strong performance of our MS business in the third quarter. We remain focused on maintaining resilience and MS market leadership.

Let me now move on to SPINRAZA. Global third quarter SPINRAZA revenues increased 17% versus prior year, and 12% versus the prior quarter to $547 million. In the third quarter SPINRAZA achieved year-over-year and quarter-over-revenue growth both in the US and outside the US, driven by continued patient growth across both mature and new markets. And we now have approximately 9,300 patients on SPINRAZA, including the expanded access program in clinical trials. In the U.S. revenues increased 6% versus Q3 2018 and 3% versus Q2 2019. The number of patients on therapy in the U.S. increased 3% as compared to the end of the second quarter of 2019. And importantly, we continue to make strong progress with adults. The largest patient segment with the number of adults on SPINRAZA growing 8% compared to the prior quarter, which is a third quarter in a row with upper single-digit growth. As a reminder, Zolgensma is competing in a limited portion of the market, specifically the approximately 5% of SMA patients were under 2 years old. Within that segment, we have begun to see some impact on SPINRAZA performance.

Outside the U.S., revenues increased 27% versus Q3 2018 and 21% versus last quarter, driven by strong performance in established markets such as EU and Japan as well as key markets in both Latin America and Asia Pacific. We were pleased to see double-digit patient growth versus prior quarter outside the U.S. and we are now approved in over 50 countries. Additionally, we recently dosed the first SPINRAZA patients in China. Overall, we were pleased to see continued patient growth across the larger mature markets and continued rapid uptake from our recently launched markets.

Given our expected continued patient growth and execution across many global markets, our established product profile and the significant market opportunity, we remain optimistic about our SMA business. In our biosimilars business, we generated $184 million this quarter, growing 36% versus prior year driven by IMRALDI. We estimate that we now have approximately 180,000 patients of biosimilars in Europe. Total anti-CD20 revenues in the

third quarter increased 16% versus the prior year, primarily driven by OCREVUS royalties. Q3 OCREVUS royalties benefited by approximately $10 million due to adjustment related to prior periods. We continue to expect RITUXAN revenues to be impacted by the entry of biosimilars in the U.S. beginning next month.

Total other revenues in the third quarter decreased 26% versus the prior year driven by the decline in our manufacturing services revenues due to our divestiture of the Hillerod plant. Importantly we continue to see geographic diversification of our revenue base, driven by growth in MS revenues outside the U.S., the continued market expansion of SPINRAZA and our growing biosimilars business. In the third quarter approximately 41% of our product revenues came from outside the U.S. versus approximately 37% in Q3 2018 and 32% in Q3, 2017. We aim to continue capitalizing on global growth opportunities, both our current commercial portfolio and our pipeline of products.

Let me now turn to the expense lines on the P&L. Q3 2019 gross margin was 88%, an improvement versus both prior year and prior quarter, which were both 87% due to favorable cost of goods sold, product mix and higher margin contract manufacturing. Q3 GAAP and non-GAAP R&D expense were both 15% of revenue. R&D expense included approximately $58 million in trial closeout costs for both elenbecestat and BG00011. Q3 GAAP and non-GAAP SG&A expense were both 15% of revenue. Q3 GAAP other expense was $27 million and non-GAAP other expense was $23 million. In the third quarter, our GAAP tax rate was approximately 12% and our non-GAAP tax rate was approximately 16%. Compared to Q3 2018, our Q3 2019 GAAP tax rate benefited from the remaining amount realized from U.S. corporate tax reform, the change in our tax profile in Q2 2019 and recently enacted tax reform in Switzerland.

In the third quarter, we repurchased approximately 3.1 million shares at an average price of $233 for total value of approximately $718 million. As of September 30, 2019, we had approximately $3.4 billion remaining on our 2019 share repurchase authorization, which now brings us to our diluted earnings per share. In the third quarter, we booked GAAP EPS of $8.39, an increase of 17% versus the prior year and non-GAAP earnings per share of $9.17, a 24% increase versus the prior year. We generated approximately $1.7 billion in net cash flows from operations in Q3. We ended the quarter with approximately $6.3 billion in cash and marketable securities and $6 billion in debt.

I will now turn the call back over to Michel for his closing comments.

Michel Vounatsos

Thank you, Jeff. To summarize, first, the positive clinical results for aducanumab position Biogen to potentially lead the fight against Alzheimer's disease. Second, these data validates Biogen strategy to focus on an interconnected neuroscience pipeline and productization of target supported by human genetics. Third, our base business continued to deliver solid performance in Q3 2019, driven by strong execution against our strategic priorities. Between now and the end of 2020, we expect continued progress as we aim to build a multi-franchise portfolio including nine additional mid to late stage data readouts, the expected launch of VUMERITY in the U.S. and submitting the regulatory filing for aducanumab in the U.S. while continuing dialog with regulatory authorities in international markets, including in Europe and in Japan. I am proud of the Biogen team for not being deterred by history of disappointment in the pursuit of Alzheimer's therapies and more so for continuing their work of analyzing the clinical trial data with unprecedented focus and intensity even in light of an apparent futility results. This work reflects Biogen's steadfast determination to follow the science, tackle the biggest challenges and do always the right thing for the patients. Finally, what is most important today is that in consultation with the FDA, we are excited to be moving ahead and preparing for regulatory filing for aducanumab on the ground of positive clinical results. And we will be redosing eligible patients from our Alzheimer's trials as quickly as possible.

This is a major step in the fight against Alzheimer's disease and an important inflection point for Biogen's neuroscience mission. We believe now more than ever that our core focus on neuroscience will enable us to maximize the value for all our stakeholders. First and foremost, for the patients as well as for our shareholders as the leader in neuroscience, we believe that no other company is better positioned to continue to deliver breakthrough therapies for diseases of the nervous system. We will continue to execute on our cost strategy to build a multi franchise portfolio across our core and emerging growth areas. We are inspired by the progress we have made in tackling Alzheimer's disease and the broader scientific implications of the positive clinical results for aducanumab.

I would like to thank all the Biogen employees in particular, those who have been working tirelessly on the aducanumab program and the many more who will contribute to this critical priority over time. I am incredibly grateful for all the patients, physicians and caregivers who have dedicated so much time and efforts to our Alzheimer's clinical studies and advancing our understanding of this very complex disease. I would like to thank the FDA for their guidance, and independent scientific expertise throughout this process.

We will now open up the call for questions.

Question-and-Answer Session

Operator

Thank you. [Operator Instructions] Your first question comes from the line of Umer Raffat from Evercore ISI. Please go ahead.

Umer Raffat

Hello. If I may, I only have a question on aducanumab but it's got three parts, and given the significance of the news today, I would really appreciate if you could bear with us on it. So my three parts are as follows: first, I'm not attempting to correlate the two but Michael Ehlers departure ahead of this data announcement, just wanted to hear are those two things are related in anyway or not. Second, the implication in the data is that the high with insufficient exposure at the high dose, the second trial worked as well. But when we look at CDR Sum of the Boxes low dose actually looks more consistent than the high dose and also for patients that did not make it to the large opportunity to complete dataset, those patients actually especially in MMSE more consistent than the patients that did have a sufficient exposure. So I guess I'm just trying to understand how spot on is that finding on patients that had a sufficient exposure and those are the ones that drove efficacy. Thank you so much.

Michel Vounatsos

Thank you, Umer. This is Michel. Mike decided to leave the company on his own and I can cannot thank him enough for his many contributions over the past three and half years to Biogen. So, thanks, Mike. And at the same time I'm extremely confident in Al's leadership as a clinician too, as a scientist to take the helm at the time where the R&D portfolio never been as stronger, the team also and the capabilities.

Al Sandrock

Umar, this is Al Sandrock, and I will turn it over to Samantha later for follow-up. But look, your point is well taken, the low dose is consistent across ENGAGE and EMERGE, and that's because the particularly the second protocol amendment, really affected the high dose arm of – in the carriers. So in the low dose arm or in the protocol amendments had less of an effect and I think that's one of the main reasons for the consistency in the results across the two studies. I'll turn it over to Samantha for a follow-up.

Samantha Budd Haeberlein

Yes, that's correct. Umar you'll also see that in the high dose for ENGAGE that we do have a partial response on ADAS-Cog13, and the ADCS-ADL-MCI. And so the potential read that you have there on CDR-Sum of Boxes and MMSC is that these are potentially less sensitive as endpoints. So what Al said is that in the high-dose group we know that we have less doses than we – at the high dose than we had in EMERGE, and we also know that the studies were to some degree impacted by dose suspensions due to ARIA, so dosing is a complex combination of duration, magnitude and no interruptions.

Umer Raffat

Thank you very much.

Operator

Your next question comes from the line of Phil Nadeau from Cowen and Company. Please go ahead.

Phil Nadeau

Good morning. Thanks for taking my question. It's also, as you might imagine on aducanumab. I guess in two parts. First, if you pull the data from ENGAGE and EMERGE, would the pooled results still be positive on the primary endpoint and kind of related to that, could you give us some sense of what the differences between ENGAGE and EMERGE were in exposures at those high doses. It seems like the trials didn't start far apart, there's just a month, so kind of in response to the last question, you mentioned exposures rely on dose suspensions and whatnot. Can you give us some sense quantitatively of how different the patient populations at that high dose were in ENGAGE and EMERGE in terms of their exposure? Thank you.

Samantha Budd Haeberlein

Certainly. So the first part that if we pulled the outcomes on ENGAGE and EMERGE at the high dose essentially you'll get an intermediate effect, not much more complicated than that. But we are looking at these stand-alone studies as two independently identically designed studies. The second part of the question, which I had forgotten actually,

Phil Nadeau

Differences in ENGAGE and EMERGE,

Samantha Budd Haeberlein

Yes, so they started one month difference between the two studies, as I mentioned and they remained different throughout the entirety of the studies and that initial one month at certain periods of the studies in particularly through the protocol amendments was greater in the middle of the studies and more details around this will come at the presentation in CTAD.

Operator

Your next question comes from the line of Terence Flynn from Goldman Sachs. Please go ahead.

Terence Flynn

Hi, thanks for taking the question. Maybe two parts for me as well. Just wondering if you can share any additional commentary on the second Type C Meeting, did FDA agree that a single positive trial could be sufficient for approval or is that likely a review question? And then can you give us the rates of ARIA in the high dose arms of the two trials? Thanks.

Al Sandrock

Yes, hi, this is Al. It's generally our policy not to comment too much on the content of regulatory interactions. I will say though that they thought it was reasonable for us to submit an application to – for approval. So that's the main, that was the upside of the meeting.

Samantha Budd Haeberlein

And the second part of the question was on ARIA and high dose and that was consistent in incidence for the studies that we have previously reported, and we'll give more details on that at CTAD.

Operator

Your next question comes from the line of Geoff Porges from Leerink. Please go ahead.

Geoff Porges

Thank you very much and thanks for having Samantha on the call. It's very helpful. First, could you answer whether the analysis that you presented and presented to the agency has been independently verified. What confirmation of both the statistics and the results do you have? Secondly, do you have any intention or plans for a confirmatory pivotal trial to supplement these two trials? And then I hate to sort of push on the issue of the type, the FDA meeting but did the FDIC, the full analysis or did the FDA just here the company summary of the analysis? Thanks.

Al Sandrock

Let me with the last question and I'll let Samantha answer the first couple. First of all, the FDA did see the full analysis of both studies and I would also say that the only study we have planned right now is the redosing study and any further study, we'll update you as soon as we plan one.

Samantha Budd Haeberlein

Thanks, Al. Going to your first question, Geoff. Have we had independent review. As we mentioned, one of the first steps that we undertook was to engage external advisors to help us review this data and that did include independent statistical experts, but the data that we did take to the FDA as Al says was a full dataset, which was an analysis of the blinded data conducted using the same statistical analysis plan as we had originally planned for the end of the study. And the validity of the dataset was the first thing that we analyzed together with the FDA. To your second question on whether we are conducting another study. As we've mentioned, our next steps are twofold, one is the FDA indicated to us that it is reasonable for us to file these two studies, and for us to go ahead and put together a re-dosing study for the patients who were in previously enrolled studies of aducanumab.

Operator

Your next question comes from the line of Michael Yee from Jefferies. Please go ahead.

Michael Yee

Thanks. Thanks for the question. Appreciate it. Al or Samantha, I guess, just wanted to understand, ENGAGE a little bit more specifically in the high dose you appropriately say that there was a slightly negative trend overall in the high dose. But in the subgroup of exposure patients, which as you think about a third of it, they had a nice benefit. I guess the question is how do you think about the patients you did not have enough exposure, did they drive a strong negative trend? Are those patients at harm? How do you think about that since that's a huge majority of the patients and how is that explainable given the difference in EMERGE? Thanks.

Al Sandrock

Thanks, Michael. I'll start. Look, I don't think – first of all there is a slight negative. I would say that that was just basically no effect. And then those who did not have the high dose, I would not say that they had a negative effect, in fact, in many ways, there was either neutral or positive effect. But I would point out this, you remember the 6 milligram per kilogram dose arm in PRIME, that everybody was wondering about. You always ask me questions about it. I remember, Michael, and we thought that was an outlier. Well, maybe that wasn't the outlier. Maybe that was true in that the 3 milligram per kilogram that looked like it was trending was the outlier. So in other words, what I'm saying is that there is a very sort of sharp dose response, if you will, you have to get to high dose of aducanumab and intermediate dosing at least in an 18-month trial is not enough.

Michael Yee

Okay. Thanks.

Operator

Your next question comes from the line of Cory Kasimov from JPMorgan. Please go ahead.

Cory Kasimov

Hey, good morning guys. Thanks for taking my question. I guess first just to ask Phil's question more directly, can you tell us yet how many patients got the 14 doses of 10 mg per kg in each study in the full dataset? And then as a follow-up, did you see any difference in ApoE4 carriers versus non-carriers, especially in the patients who completed after the futility cohort and would have had more exposure to the higher dose? Thanks.

Samantha Budd Haeberlein

Yes. So the first thing I want to mention is, in terms of the numbers of subjects who had the particular dataset that you're referring to more dose, more than 10 doses of 10 milligram per kilogram, there's more than a 10% difference between the two studies, but that's not the only parameter of difference that is important for dose. As I've mentioned, you need to achieve high dose for long enough, but also have no interruptions, and so that's a more complex calculation between the two studies.

Michel Vounatsos

ApoE4 versus non.

Samantha Budd Haeberlein

So your question regarding ApoE4 carriers versus non-carriers, the analysis that we've conducted to date has been on the entire studies. And as we've mentioned for EMERGE, we have a positive but we met the primary endpoint for the entire patient population and details of subgroups is something that will come to later. And we'll have details at CTAD.

Cory Kasimov

Okay, thank you.

Operator

Your next question comes from the line of Geoff Meacham from Bank of America. Please go ahead.

Geoff Meacham

Hey, guys. Thanks for the question and all the detail on aducanumab. Al, I just have a couple of regulatory type of questions all related. If half of the EMERGE achieved significance at the high dose and none of ENGAGE achieved it, is it you guys expectations that the PRIME study could count as one of the two pivotals? Second one is, does a conditional approval, pending another successful Phase 3 did that come up in the FDA discussion? And then third, have you had any discussions with the European regulators on the data? Thank you.

Al Sandrock

Let me start with the last question first. So we have just started to contact the European regulators that we haven't had any substantive discussions as of yet. In terms of the EMERGE and ENGAGE, I – we looked at – we look at ENGAGE in totality as a positive study that stands on its own. And remember, as Samantha said we use pre-specified primary and secondary outcomes, we didn't look at a subset. We looked at all the patients

and based on that, we believe the study met its primary endpoint and the secondary endpoints as well. I think that whether or not a single trial can be approved, there are circumstances where an FDA can approve a drug based on a single study, it's up to them to determine what those circumstances are, and so I'll just leave it at that and then I would say that ENGAGE, we believe, we showed the data for example in those who achieve sufficient exposure to 10 milligrams per kilogram. We do see evidence of efficacy. So I would say that EMERGE stands on its own, ENGAGE has supportive evidence, and I would also say that PRIME is supportive, it's a well controlled Phase 1b, some may call it Phase 2 trial, and we'll submit all the data.

Samantha Budd Haeberlein

Just to add there, Al, EMERGE is the study that met its primary endpoints. I think you said ENGAGE.

Al Sandrock

Did I say anything wrong?

Samantha Budd Haeberlein

Yes.

Al Sandrock

Yes. I get confused in times.

Operator

Your next question comes from the line of Brian Abrahams from RBC Capital Markets. Please go ahead.

Brian Abrahams

Hi there. Thanks for taking my questions. So a question, just a little more clarity on the ENGAGE study, for the subgroups of patients I guess for both ENGAGE and EMERGE with 10 interrupted – receiving 10 uninterrupted high doses. Can you talk about the baseline characteristics for the aducanumab verse placebo arms across both studies and

how well balanced those were? And then, can you maybe help us understand how feasible was it for patients? I guess, once the protocol – was protocols, were amended to remain on 10 uninterrupted doses or is the lesson here that if you do need to temporarily discontinue for ARIA or whatever reason you're probably best off not restarting the drug? Thanks.

Samantha Budd Haeberlein

So, thanks. Thank you for the question. I want to point out that the analysis that we conducted in close consultation with the FDA around determining who in ENGAGE did have a response were exploratory analysis. And any time that you look at a subset of patients who you have very important questions in regards to whether they are balance for the baseline characteristics. The studies overall, were very well balanced for all baseline characteristics and as I mentioned, ApoE4 status. But those subgroups are exploratory in nature and they help us understand that dosing is important for efficacy. And in the context of an 18-month trial, one does tend to see that you need a certain number of doses for clinical benefit of aducanumab. However, that's not the same as one would anticipate in a real world situation where an individual is taking aducanumab for an extended period of time, for a dose interruption would likely be of less significance.

Al Sandrock

Yes, I agree with Samantha. I think that dose suspension in the context of an 18-month study was – it could be problematic, because they didn't achieve enough of the high dose. But in clinical practice, we don't do 18 month treatment periods. We're going to treat patients for longer periods of time. And in that situation I think dose suspension may be acceptable in some patients.

Operator

Your next question comes from the line of Matthew Harrison from Morgan Stanley. Please go ahead.

Matthew Harrison

Great, thanks for taking the question. I guess a follow-up and sort of second question from me. So first one is, you've been talking about exposure and dose a lot. Could you just broadly comment on how many of these patients actually achieved all the factors that you were looking for and how easily you think that will be the case in clinical practice. And I guess, the related question to that is, dose exposure curve that you're sort of talking about Al. I mean, what were their characteristics that were different were the kinetics of the amyloid plaque reduction different in these subgroup of patients with the achievement of tau or amyloid reductions were they significantly different. I'm wondering what you think is sort of biologically happen to account for this steep dose exposure curve [indiscernible]?

Al Sandrock

These were good questions Matthew and we're still learning as we look at the data, but I would say this, the – even in MCI patient, if you look at the amount of amyloid in the brain, it's tremendous. It took 20 years to build that much up and in the context of an 18 month trial, you have to remove a large amount of amyloid. I think that's what distinguishes as you aducanumab and BAN2401, is that we can – it's safe enough to achieve the doses that allow us to remove a large amount of amyloid. And if you don't remove a large amount, you're not going to get an effect. Also there is a lag. You remove amyloid, and then there is a little bit of a lag for the clinical effect. We saw that in PRIME for example, where we did have some amyloid lowering of six months, but we saw no difference in the clinical outcomes at six months. It was – it took the 12-month time period to see – to start to see an effect on clinical outcomes. So in addition to a large amount of amyloid removal, I think you need to have a little bit of time for that, for that biological activity to have an effect on clinical outcomes That's what we see and I would say that if you look at the amyloid-PET results that was on one of the slides and those who had more than 10 doses of 10 milligrams, you can see that the SUVR score is very similar in ENGAGE in that subgroup of patients in ENGAGE to the EMERGE total dataset. So – and so again, what it says is that if you give it enough of the high dose, you can achieve a certain amount of amyloid removal and that certain amount is what's required to see the reduction in clinical decline in an 18 month study.

Samantha Budd Haeberlein

Yes, Al just add to that, on the question of numbers. On the graph that you've just referred to, you got the end numbers. So they were 147 for EMERGE and 116 for ENGAGE in that CDR-Sum of Boxes analysis. But the question you ask of how many patients have the precise criteria? Well there aren't precise criteria. Dose response is not binary. And so, given the levels of dose you have a different response and it's a bit of a sliding scale. So we have that exploratory analysis that we disclosed to explain what it is we learned around the importance of dose, but there is no perfect number of doses that are required, it's not binary.

Operator

Your next question comes from the line of Ronny Gal from Bernstein. Please go ahead.

Ronny Gal

Hi everybody. And thank you for taking the question. And I'm going to stay with aducanumab here. I'm just kind of struggling with the movement from the Interim Futility Analysis to efficacy with relatively small number of patients. Just looking at the number of completed that you have here in EMERGE, you move from 803 patients in the futility analysis to 980 patients in the treatment. So it's about 180 more patients. If we assume a third of those were on the high dose, 60 more in your total number of folks that you have amyloid beta that you calls got sufficient exposure is at the end of the trial, 127 I kind of wonder if there is just a very small number of patients that drove the entire movement. If you can discuss a little bit that issue of how many patients actually contribute to the difference between stopping the trial for futility and showing efficacy would be appreciated. And then I'm going to – if you don't mind going to throw my second one in and it will be different, not to kind of just for the variability. And do you have any way to protecting the highest dose TYSABRI from biosimilars through the first-generation products. If you can discuss that at all, I would appreciate it. Thanks.

Al Sandrock

Ronny, this is Al. My head is swimming even just with the first question. But, so I think first of all you should remember that in EMERGE even at the time of this utility analysis, that study was trending positive as Samantha said. And then we add those additional patients

and it didn't take that many now to then in the April dataset to see that – they had met its primary endpoint. And then I would also say that we also looked at the patients who had not completed 18 months, all the rest of the patients, which is roughly half the patients because we only looked at the first half, the first half of the enrollees for futility. So it's a large number of patients that we ended up looking at and I remind you that result that you saw in that slide was all the patients in EMERGE, who had been randomized, the ITT population and it was using the prespecified primary and secondary endpoints. And then I now forgot the second question.

Ronny Gal

Before you jump into that if you look at the slide that you had Slide 22, the number of patient aducanumab that you have there is the number of patients received enough dose. The questions from some of my peers, was how many patients got exposed and both the numbers that we're seeing on aducanumab on Slide 22 are the numbers we should be thinking about?

Samantha Budd Haeberlein

So I just want to recap that Slide 22 was a piece of exploratory analysis, it is not the subset, to be release are supported, it's just a particular analysis to emphasize the point that there are subjects in ENGAGE, whom if they do have sufficient dosing, do support the outcome of EMERGE.

Al Sandrock

I would also say Ronny that the, PET was done in a subset of patients to – so the numbers that you see on the left side, which is the amyloid-PET are from – the only the subset who got the PET imaging.

Ronny Gal

And the numbers on the right, that's still not the complete set, this is just a – some sort of a subset.

Samantha Budd Haeberlein

That's correct.

Ronny Gal

And the second question was around, high dose TYSABRI?

Michel Vounatsos

IP protection for TYSABRI.

Jeff Capello

So what we would say that Ronny it's Jeff, is obviously what we can see kind of what happens with regard to the Phase 3 trials that are going on with regards to biosimilars and we're supportive of biosimilars coming into the market. We obviously have biosimilars business. We just have to see how their products do and we'll deal with it when it comes.

Joe Mara

And probably we have time for about two more questions.

Operator

Thank you. Your next question comes from the line of Jay Olson from Oppenheimer. Please go ahead.

Jay Olson

Well, hi. First off, I want to congratulate you for hanging in there and delivering these aducanumab results today. This is very promising news for Alzheimer's patients and their families. And second of all, I want to thank you for taking my questions. Can you comment on the clinical meaningfulness of aducanumab's efficacy profile and how does it line up with your target product profile in terms of improvements in cognition and function. Are there any gaps in the profile as you know it now, and how do you know if you optimize the efficacy at the 10 mg per kick dose or would it make sense to test higher doses? Thank you.

Michel Vounatsos

Jay, I'll start and then Samantha will follow up. We believe it is clinically meaningful, we heard that anything above 20% is clinically meaningful as a neurologist being the first drug of its – of its kind we have no drugs right now that affect the clinical decline in Alzheimer's disease. This would be the very first. So anything North of 20%, we believe is clinically meaningful and I would also add that – in clinical practice. I think that MCI patients, will be – if approved though enjoy the benefit of living an more independent life for longer periods of time. If you look at that AD, the activities of daily living, It's a 40% effect and that's a caregiver assessment of whether or not that the patients can live independently, can do their household chores, etcetera so. That's all very clinically meaningful results.

Jay Olson

There's a question around the dose to 10 mgs?

Samantha Budd Haeberlein

Yes. So the question of whether we had achieved the correct dose. I think what we have learned clearly is that dose is very important, but that if individuals do receive 10 milligram per kilogram then they do have an efficacious response. I think the trials unfortunately were hampered by a number of operational and other implications that meant – that not enough patients got 10 milligram per kilogram, so we do believe that would be the correct dose.

Jay Olson

Great, thank you.

Operator

Your last question comes from the line of Paul Matteis from Stifel. Please go ahead.

Paul Matteis

Great, thanks for fitting me in. Really appreciate it. Within the high dose arm in the ENGAGE study, can you talk about the magnitude of plaque reductions you observed in patients who titrated all the way up to the highest dose versus patient who ever stopped at 6 mg per kg and I guess, does a differential magnitude of plaque reduction in those

patients that I'll tell the same narrative you're seeing on the difference in clinical outcomes? And then can you just tell us anything else about other measures of function in the engage subset of patients, who titrated all the way up to 10 mgs per kg? Thanks so much.

Samantha Budd Haeberlein

Thank you. So, to your first question in amyloid plaque reduction, we do believe that PET measurement of amyloid plaque reduction is a very sensitive tool of dose and you've correctly identified that ENGAGE at the high dose is showing a lower reduction than in EMERGE and we do believe that, that is a clear reflection of the lower doses that were achieved in that high dosing group in ENGAGE. And the second question was.

Paul Matteis

Other measures that function...

Samantha Budd Haeberlein

Other measures that function. Yes, so the exploratory analysis that we have demonstrated for you, we focused on the primary endpoint, and we do not have the same analysis for the functional endpoints, but you do have those results for the overall study where even in ENGAGE, we do have some response on the functional scores, albeit not statistically significant.

Joe Mara

Okay, thank you. And I'll turn it back to Michel for some closing comments.

Michel Vounatsos

So thank you all for attending our Q3 call characterized by the go-to file decision for aducanumab with the US FDA, but also with a solid performance for the quarter. Today is about hope and opportunity for the patients first but also for the shareholders. Have a good day.

Operator

Thank you. Ladies and gentlemen, this concludes today's conference call. Thank you for participating. You may now disconnect.