

Aducanumab for the Treatment of Alzheimer's Disease

US Food & Drug Administration
Peripheral and Central Nervous System Drugs Advisory Committee
November 6, 2020

Introduction

Alfred Sandrock, MD, PhD, Executive Vice President, Research and Development, Biogen

CI-2

Hello. My name is Alfred Sandrock.

I am a neurologist, neurobiologist, and head of R&D at Biogen.

It is my pleasure to introduce our presentation on Aducanumab for the treatment of Alzheimer's Disease.

CI-3

At Biogen, we are motivated by the profound need for new treatments for diseases of the nervous system. We see the heavy toll these diseases take on patients, caregivers, families, and society.

We are encouraged by the growing understanding of the pathophysiology of disease. Moreover, technological advancements offer new opportunities to develop drugs that can meaningfully alter the course of disease.

The need for new treatments is especially clear in Alzheimer's Disease, and it's what drove our development of aducanumab.

CI-4

About 15 years ago we intensified our R&D in Alzheimer's Disease. At that time, a theory was emerging that neurodegenerative diseases may be caused by the misfolding and aggregation of normal proteins, or their fragments, rendering them toxic to the nervous system. In Alzheimer's disease, human genetic and clinicopathologic evidence have implicated beta-amyloid, the principle constituent of amyloid plaques, as a key protein involved in its pathogenesis.

Certain peptide fragments of beta-amyloid are prone to aggregation, and when these aggregates form in the brain, they appear to be toxic to synapses.

Aggregated beta-amyloid may also cause neurodegeneration, perhaps by triggering the misfolding, aggregation, and accumulation of the protein tau, the principle constituent of neurofibrillary tangles.

Several companies have worked to develop drugs that target beta amyloid, including several anti-amyloid antibodies. Even though this research has not yielded new medicines, we are grateful to the investigators and the Alzheimer's Disease community for sharing and publishing the trial results so that we could learn from these pioneering efforts.

One learning was that certain antibodies that bound non-specifically to all forms of beta amyloid could not be dosed at levels high enough to safely engage its target in the brain. So, we limited our search to antibodies that specifically target aggregated forms of beta-amyloid.

CI-5

Aducanumab does exactly that.

It binds specifically to aggregated forms of beta-amyloid and recognizes amyloid plaques in brain tissue.

When transgenic mice were treated with Aducanumab systemically, the antibody was found to have entered the brain and bound to brain parenchymal beta-amyloid. When these mice were treated chronically with Aducanumab, there was substantial and dose-dependent removal of beta-amyloid pathology.

CI-6

We opened an IND for aducanumab in 2011 and conducted Phase 1 trials. By this time, data was emerging that the underlying pathophysiological changes of Alzheimer's disease can start decades before the onset of symptoms, suggesting that earlier intervention might be important.

Also, with the advent of beta-amyloid PET imaging, we realized that many patients in prior Alzheimer's Disease trials did not have beta-amyloid in the brain.

Thus, we took great care to enroll only patients in the early stages of Alzheimer's Disease who had beta-amyloid plaques, as visualized by PET scan.

In the Phase 1 trials, we found the dose-response relationship for removal of amyloid from the brain. Through the use of surveillance MRI scans, the Phase 1 trials also showed that ARIA, or amyloid-related imaging abnormality, was the principle side effect of aducanumab, and that its incidence was dose-dependent and more common in ApoE4 carriers.

At a dose of 10mg/kg - the maximum tolerated dose - aducanumab showed robust removal of beta-amyloid and reduced clinical decline, as measured by two clinical outcome measures.

In 2015, we began Phase 3 trials of Aducanumab under a Special Protocol Assessment with the FDA. These global trials tested the efficacy and safety of two dosing regimens

of Aducanumab. When data became available that the risk of ARIA to ApoE4 carriers was manageable, the Safety and Data Monitoring Committee agreed that we could amend the Phase 3 protocols to allow carriers to receive the target dose of 10 mg/kg. This was a critically important amendment, and the difference in timing of the implementation of this amendment at the clinical trial sites had an important role in the outcome of the trials.

In 2016, fast track status for Aducanumab was granted by the FDA.

In March of 2019 we conducted a pre-specified futility analysis, which led us to terminate the Phase 3 trials. In retrospect, it would have been more appropriate if futility had not been declared for those trials. When we examined all the data that had been collected up until March, which was considerably more data than used for the futility analysis, we saw that one of the trials was apparently positive.

In June 2019, we shared these data with the FDA and sought their advice. It was agreed that we would collaborate with the FDA to determine whether the Phase 3 trials were interpretable, despite the premature termination and whether there was evidence of efficacy.

This collaboration ultimately led to the BLA for aducanumab, which was submitted in July of this year.

CI-7

We believe that the data show that aducanumab provides clinically meaningful benefit by reducing clinical decline for Alzheimer's disease patients, and that this benefit outweighs the risks.

As such, we are seeking the approval of Aducanumab as an amyloid beta targeting antibody indicated to delay clinical decline in patients with Alzheimer's Disease in whom the presence of amyloid beta pathology has been confirmed. The recommended dosage is 10mg/kg administered as an intravenous infusion over approximately one hour every four weeks following a titration period.

CI-8

I would now like to introduce the speakers for the subsequent presentations.

First, Dr. Douglas Galasko will discuss the background of Alzheimer's Disease, and the substantial unmet need in this area.

Then, Dr. Samantha Budd Haeberlein will share an overview of our clinical development program, followed by our efficacy results.

Then, Dr. Karen Smirnakis will present the safety profile.

And finally, Dr. Anton Porsteinsson will complete our presentations with a clinical perspective on aducanumab.

I want to close by expressing our deep appreciation to the investigators, patients, caregivers, and the Alzheimer's Disease community for their contributions to the field of Alzheimer's Disease research and for their support of the Aducanumab clinical trials.

I now invite you to listen to the presentation by Dr. Galasko.

Disease Background & Unmet Need
Douglas Galasko, MD, UC San Diego

CU-1

My name is Dr. Douglas Galasko. I am a Neurologist and Professor of Neurosciences at UC San Diego.

I am a paid consultant to the sponsor, but I have no financial interest in the outcome of this meeting.

Today I will present to you the disease background and enormous unmet medical need in Alzheimer's disease.

CU-2

An estimated ~ 5.8 million Americans suffer from Alzheimer's disease, which is the 6th leading cause of death in the US.

Alzheimer's is a progressive neurological disorder, characterized clinically by memory loss, behavioral symptoms, and loss of ability to live a normal life

In advanced stages of dementia, patients become completely dependent on others

The disease is ultimately fatal in all cases, and,
There is no available treatment that alters the course of disease

CU-3

The clinical picture of Alzheimer's disease involves progressive decline in cognition, function and behavior.

The MMSE scores can be used as an approximate staging scheme. The earliest cognitive features are a deterioration in memory, learning, and executive function. Even in this early stage people may begin to lose their ability to drive, manage finances, or to enjoy complex hobbies - with a major impact on their autonomy and independence.

Early changes in behavior can include depression, withdrawal, and irritability.

The arrow on the left of the figure indicates the progressive loss of autonomy and independence for patients with Alzheimer's disease. All patients will become increasingly dependent on others for help and will eventually need 24/7 care.

On a personal level, loss of functional ability and changes in behavior are highly distressing for patients and caregivers, with a burden that continues to increase as the disease progresses. There is urgent unmet need for a drug that can intervene as early as possible to slow the deterioration and associated loss of autonomy.

CU-4

We now can model how pathological changes in the brain relate to the progression of Alzheimer's disease. The green curve on this schematic indicates the onset and progression of clinical decline.

Longitudinal studies of cognition together with fluid and imaging biomarkers in both sporadic and autosomal dominant Alzheimer's patients have contributed to these models.

Cognitive symptoms are preceded and accompanied by the build up of amyloid deposition, followed by tau pathology and structural brain changes.

The onset and symptoms of clinical impairment are heterogeneous. Early in disease, patients progress slowly, and then they accelerate.

Biomarkers and sensitive cognitive testing can be used to define prodromal stages as was done in the Phase 3 Aducanumab program.

Early therapeutic intervention has the greatest promise to preserve cognition, function, and autonomy.

CU-5

Now let's dig a bit deeper into the pathology –

Amyloid beta is enzymatically cleaved from a precursor protein and released from neurons as peptide fragments, such as Abeta 1-40 or 1-42.

Abeta is cleared from the brain by bulk flow and by cellular pathways. In Alzheimer's disease extracellular amyloid aggregates, forming oligomers, fibrils, and eventually large insoluble plaques.

Amyloid pathology promotes pathways leading to the phosphorylation and aggregation of tau, leading to its build up within neurons.

This pathological cascade triggered by amyloid leads to dysfunction in neuronal and synaptic activity, inflammation, and neuronal death.

CU-6

Increasing age has the largest known impact on risk of developing Alzheimer's disease

While, the strongest known genetic risk factor is the apolipoprotein E 4 variant, or “ApoE4”. One copy of ApoE4 increases the lifetime risk of developing Alzheimer’s disease by 2-4-fold, while two copies increases risk by as much as 10-fold.

Autosomal dominant mutations with young age at disease onset account for approximately 1% of patients with Alzheimer’s disease. The mutated genes are highly penetrant and directly related to Abeta production and clearance.

Therefore, in both familial and sporadic Alzheimer’s disease, clinical, pathological, and genetic studies all implicate amyloid production and/or clearance as important factors

CU-7

There have been many therapeutic approaches to targeting amyloid pathways, including production, clearance, and aggregation. Over the last 20 years, there have been advances in antibody development and clinical trial design and tools that enable us to achieve success.

Aducanumab is among a later generation of anti-amyloid antibodies which has benefited from these learnings.

First, the Target – by targeting aggregated forms of A β with specificity and high-affinity, Aducanumab provides an opportunity to disrupt the pathological cascade that leads to the clinical symptoms of Alzheimer’s disease

Secondly, when to treat - Therapeutic Approaches to target amyloid may be more successful if initiated earlier in disease, prior to extensive neurodegeneration.

Dr. Budd-Haeberlein will explain more in the next presentation about these points.

CU-8

Approved therapies for Alzheimer’s disease dementia are limited to the cholinesterase inhibitors and, for patients in moderate to severe stages, the N-methyl-D-aspartate antagonist, Memantine

These therapies provide a modest effect on cognitive symptoms, and only for a limited duration of time.

There are no therapies approved for earlier stages of disease, such as MCI due to Alzheimer’s disease.

And these symptomatic treatments do not impact brain pathology.

CU-9

In summary, we are dealing with a disabling and ultimately fatal disease. As the population ages, and with advances in longevity, the importance of Alzheimer’s disease will continue to grow.

The economic burden of Alzheimer's disease is enormous, including direct medical care costs and unrecompensed time on the part of caregivers. Nearly 1 of every 5 medical dollars in the US spent on Alzheimer's disease

Researchers have estimated that delaying the onset and progression of Alzheimer's disease by just 2 years may result in a reduction of over 20% of the global burden of Alzheimer's disease by the year 2050

Aducanumab, has the potential to slow clinical decline, extending the time people can live with conserved cognitive abilities, preserving autonomy in activities of daily living, and lessening behavioral symptoms.

Thank you. And now I'd like to invite you to view Dr. Samantha Budd-Haeberlein's presentation of the clinical development program for Aducanumab.

Clinical Development

Samantha Budd Haeberlein, PhD, Senior Vice President, Head of Neurodegeneration Development Unit, Biogen

CD-1

Hello, my name is Samantha Budd Haeberlein. I am Head of the Neurodegeneration Development Unit at Biogen. I have been working for more than 20 years in the biopharmaceutical industry on the discovery and development of potential new therapies for Alzheimer's disease.

CD-2

The data from this program demonstrate that the proposed dosing regimen of Aducanumab reduces the clinical decline of Alzheimer's disease.

In Summary, the three studies will show that, Study 302 is a positive study, with robust, internally consistent results.

Study 301 is a failed study, but the reasons for the differences between the studies is sufficiently understood.

And, importantly, a subset of patients in Study 301 who had sufficient doses of 10mg/kg had a consistent effect.

Study 103 is an independent study, providing supportive evidence of effectiveness.

I will start by addressing the discovery of Aducanumab.

CD-3

In Dr Galasko's presentation we heard about the pathophysiology of Alzheimer's Disease and the amyloid pathway.

Aducanumab was designed to reduce the progression of Alzheimer's disease by interrupting and removing beta-amyloid pathology.

Aducanumab was developed based on the hypothesis that healthy elderly individuals or patients with cognitive impairment but a stable clinical course were mounting an immune response and generating antibodies against the pathogenic misfolded proteins involved in Alzheimer's disease.

Hence, if isolated and sequenced, these antibodies of human origin could have potential as therapeutic agents. Memory B cells were collected from elderly individuals and selected for their ability to produce antibodies that recognized aggregated forms of beta-amyloid with high specificity and selectivity. This approach yielded a Human IgG1 Monoclonal Antibody that is highly selective for aggregated beta-amyloid.

Aducanumab specifically targets and binds to oligomeric and fibrillar forms of beta-amyloid

This leads to the clearance of beta-amyloid plaques, the reduction of downstream pathology, and the preservation of synaptic and neuronal function.

Such an approach is expected to alter the course of disease rather than only addressing symptoms.

Aducanumab is not the first candidate to target the amyloid pathway, however, aducanumab benefitted from the learnings from earlier Anti-Abeta programs, and differs from them in several important ways, including molecular characteristics and clinical trial design features.

CD-4

Aducanumab is differentiated from the first generation of anti-Abeta antibodies: Unlike the first generation, aducanumab specifically targets the neurotoxic aggregated forms of beta-amyloid, and it retains full effector function.

In addition, aducanumab clinical trials implemented key design elements to improve the ability to assess efficacy in Alzheimer's disease: The Aducanumab program enrolled patients at the early stages of cognitive symptoms— and who had their diagnosis confirmed by testing for the presence of beta-amyloid pathology via PET imaging

We believe that at this early stage of disease the patients have less neurodegeneration, and that slowing progression at this stage could offer greater clinical benefit.

The trials also included clinical outcome measures sensitive to early symptoms.

Importantly, in 2014, with data from Study 103, aducanumab was the first of this generation of antibodies to demonstrate Proof of Concept before initiating Phase 3

Accordingly, aducanumab is the only program to have read out with positive results in Phase 3.

Let's look more closely at the discovery and development background of Aducanumab.

CD-5

Anti-Abeta antibodies can be differentiated based on their molecular characteristics, which in turn contribute to their binding specificity towards different forms of Abeta

Shown here is the crystal structure of aducanumab together with the Abeta peptide – Aducanumab has a very shallow and compact binding cleft that makes only few contacts with the Abeta peptide. Which is very different from other anti-Abeta antibodies.

This characteristic, in conjunction with others, contributes to the selectivity of aducanumab towards aggregated forms of beta-amyloid

Beta-amyloid presents as different forms along the aggregation pathway, from monomers into oligomers, protofibrils, and elongation of protofibrils into fibrils. Monomers do not seem to have detrimental effects in the brain, while aggregated forms have consistently been shown to be neurotoxic. Monomers are also found in the periphery and can divert binding away from the brain.

Biophysical data further show that aducanumab directly interferes with the aggregation pathway, and reduces the formation of oligomers, one of the highly toxic forms of beta-amyloid.

CD-6

Preclinical studies have confirmed the selectivity of aducanumab towards aggregated forms of beta-amyloid.

This dot blot preparation shows that aducanumab (in the left most column) shows high binding to aggregated forms of beta-amyloid (oligomers and fibrils), and has low affinity for non-pathogenic soluble monomers (no binding in the red box), which differs from a first generation antibody in the adjacent lane of the blot

In a mouse model of Alzheimer's Disease, aducanumab treatment over 6 months showed dose-dependent reduction in soluble and insoluble beta-amyloid pathology in the brains of these mice, with maximal effects at doses at, and above 10mg/kg

These pre-clinical data confirmed aducanumab's ability to target and remove a key pathology of Alzheimer's disease.

The next step was to translate these results to patients.

CD-7

The aducanumab clinical development program includes 8 studies, which have enrolled more than 3600 patients, with some for longer than 6 and a half years... thereby generating approximately 5000 patient-years exposure to aducanumab.

Studies 103, 301, and 302 were conducted over an 8-year span.

Study 101 was a first-in-human study in Alzheimer's patients that evaluated single ascending doses.

Study 103, the proof-of-concept study began in 2012, with results available in 2014. The results from study 103 informed the design of studies 301 and 302 that began in 2015.

All three studies included a long-term extension phase, in which all patients receive aducanumab.

CD-8

Let's review Study 103, the Proof of Concept Study

CD-9

Study 103 was a randomized, multicenter, 12-month double-blind, placebo-controlled study in patients with early Alzheimer's Disease with 4 fixed doses in a cohort design, each including 14 doses of Aducanumab

The primary objective was safety and tolerability, with assessment of pharmacokinetic and pharmacodynamic effects.

The study was powered for the change in brain beta-amyloid as measured by PET at week 26.

Clinical measures, the Clinical Dementia Rating Scale sum of boxes (CDR-SB) and the Mini Mental State Examination (MMSE) were exploratory endpoints.

The study included patients with early symptomatic Alzheimer's Disease with a baseline MMSE of 20 to 30 inclusive.

As discussed, patients needed to be positive for the presence of beta-amyloid pathology at study entrance.

This was the first such study to ensure diagnostic accuracy with pathology.

CD-10

In Study 103, Aducanumab demonstrated dose- and time-dependent reduction in beta-amyloid plaque as measured by PET. On the left are selected beta-amyloid PET images from the different dosing cohorts.

On the right are the mean changes from baseline over time, quantified in a composite of 6 brain regions. The grey line depicts beta-amyloid plaque in placebo patients, which is manifestly present, and does not change at this stage of disease

The aducanumab dosing arms had dose-ordered and significant reductions in beta-amyloid plaque at Week 26 and week 54 in all groups. Maximal reduction was seen in the 10 mg/kg dose group at week 54.

The titration group had a reduction in beta-amyloid plaque consistent with the average cumulative doses at the time of the PET measurement.

These results confirmed that aducanumab was acting in patients, as it had in preclinical studies - by binding to and reducing the levels of brain beta-amyloid. When Study 103 read out in 2014, aducanumab had the largest reduction in beta-amyloid plaque of any of the anti- A β antibodies.

CD-11

In addition to removing beta-amyloid plaques, aducanumab showed dose-dependent reduction in clinical decline by week 54 as measured by the clinical outcome measures: CDR-Sum of boxes and MMSE.

Although the study was not powered to detect an effect on clinical outcomes, the differences from placebo were nominally significant for the 10 mg/kg dose.

As such, aducanumab was the first development program in which Proof-of-Concept – namely an effect on clinical measures - was demonstrated prior to beginning phase 3.

CD-12

The results from Study 103 across multiple doses show a strong correlation between brain beta-amyloid reduction and reduction in clinical decline.

As shown by the regression line, the greater the mean reduction in beta-amyloid, the greater the reduction in clinical decline, here as measured by the CDR-sum of boxes.

This correlation supports the hypothesis that aducanumab reduction in clinical decline is via reduction of beta-amyloid plaque

CD-13

Study 103 provided key design elements that were implemented to improve the probability of succeeding in Phase 3.

The first three elements focused on enrolling the right patients. Baseline MMSE scores in Phase 3 were changed to 24 to 30, narrower than in study 103 to reduce variability in outcomes.

Study 103 confirmed external validation that the CDR-Sum of boxes was sensitive to changes in this population who have early emerging symptoms and slow decline.

And confirmed that assessing beta-amyloid pathology was important for accurate diagnosis of this early symptomatic population.

10mg/kg, was identified in study 103 as the most efficacious dose, and selected as the target dose for the Phase 3 studies,

ARIA, an adverse event that will be described in the presentation by Dr Smirnakis, was shown in study 103 to be dose-dependent and occurring in the first doses of the study. Dose titration was therefore added to the Phase 3 studies to reduce the incidence of ARIA

Each of these factors was taken into consideration in the design of our phase three program. In the next presentation we will review the Phase 3 study designs and efficacy results.

Efficacy

Samantha Budd Haerberlein, PhD, Senior Vice President, Head of Neurodegeneration Development Unit, Biogen

CE-1

Hello, I'm Samantha Budd Haerberlein, Senior Vice President and Head of the Neurodegeneration Development Unit at Biogen.

In this presentation, I will discuss the design of our phase three trials and the efficacy results that were observed.

CE-2

The Phase 3 studies were identical in design, randomized, 18-month, double-blind and placebo-controlled.

The Studies enrolled 3,285 patients and were conducted at 348 clinical sites in 20 countries.

Patients were in the early symptomatic stages of disease where symptoms are still limited. Patients were defined as Mild Cognitive Impairment or (MCI) due to Alzheimer's Disease, and mild Alzheimer's Disease dementia; and had a baseline MMSE of 24 to 30 inclusive, and a CDR-Global scale score of 0.5. As with Study 103, all patients were confirmed for the presence of beta-amyloid pathology by PET.

Two dosing regimens were compared versus placebo, with a 1:1:1 randomization.

The primary endpoint was the CDR-Sum of Boxes. Secondary endpoints measured additional aspects of cognition and function. There were sub studies to assess biomarkers of target engagement, and disease pathophysiology.

The primary and secondary endpoints were selected to provide meaningful evaluations for these early symptomatic Alzheimer's patients.

CE-3

Five clinical endpoints were used in the phase 3 studies to assess aducanumab's effects on distinct and important symptoms of cognition, function and behavior.

Each scale is validated and widely used in early Alzheimer's disease and cover the full scope of symptoms experienced by patients with Alzheimer's disease

These scales differ methodologically and provide different perspectives, including inputs from

- expert clinical judgements based on patient's examination and caregiver input
- patient and caregiver reports,
- And, objective cognitive performance-based tests

Together, the scales capture a range of important dimensions and with minimal overlap in what they each measure.

The primary efficacy outcome measure, CDR-Sum of Boxes, is an integrated scale that adequately and meaningfully assesses both daily function and cognitive effects in early Alzheimer's disease patients and is acceptable as a single primary efficacy outcome measure.

CE-4

The patients enrolled in these studies are reflective of the early Alzheimer's disease population, and in terms of demographics, were balanced between the treatment groups.

CE-5

The target dose for Phase 3, based on both preclinical data and study 103 results, was 10mg/kg.

The Phase 3 studies were designed such that - as in Study 103, 14 doses of 10 mg/kg would be given.

To reduce the incidence of ARIA, the target dose was preceded by a 24-week titration phase.

And, given the emerging understanding of ARIA, a low dose was also included.

Additionally, both low and high dose, were stratified by ApoE 4 gene carrier status, with ApoE4 carriers receiving a lower dose.

CE-6

In the low dose group, ApoE4 non-carriers were titrated to 6 mg/kg; and ApoE4 carriers were titrated to 3.

In the high dose group, the ApoE4 non-carriers were titrated to 10 mg/kg throughout the study, whereas, initially, ApoE4 carriers were titrated to the lower dose of 6 mg/kg.

Part way through the studies, we learnt from Study 103 that ApoE4 carriers could be safely titrated to 10mg/kg. Therefore, the protocols were amended in consultation with our DMC and global regulators such that all patients in the high dose arm would receive 10 mg/kg. This amendment is referred to as protocol version 4.

With ApoE 4 carriers being approximately two thirds of the study population, this change directly impacted actual dosing in the high dose arm.

The median cumulative dose after the protocol change was 153 mg/kg, a 32% increase.

Dosing did not change in the low dose arm during the study.

CE-7

Enrolment of patients in the studies took 35 months.

Study 301 began one month ahead of Study 302 and remained ahead in enrollment throughout the study.

In March 2017, when Protocol Version 4 was signed, Study 301 had 200 more patients enrolled. The signing of a protocol amendment happens at a point in time. However, implementing a change across 20 countries, hundreds of sites, and multiple ethics committees takes time.

Patient consents to Protocol Version 4 took place over more than 18 months. Because Study 301 was ahead in enrollment, the protocol amendment influenced dose for more patients in Study 302 than in Study 301.

Studies 301 and 302 included pre-specified interim analyses to predict whether continuation of the studies would be futile. These analyses were pre-specified to be based on the first 50% of patients to complete each study, those patients were enrolled in the period noted by the grey box.

Most patients included in the futility analysis were therefore enrolled too early to be influenced by the increased dosing in protocol version 4.

Having now covered the key design features, we next focus on the outcome of the futility analysis.

CE-8

Here are the results for the pre-specified futility analysis. According to the pre-specified approach, the predictions met futility criteria, defined as a less than 20% probability of both studies reaching statistically significant differences at the final analysis. Consequently, the studies were terminated in March 2019.

As is often done after termination of a study due to futility analysis, we looked at the complete data to see what we could learn.

We found that two key assumptions in the prediction did not hold, and therefore the futility analysis did not accurately predict the future results.

The first assumption is that the outcomes in the two trials would be similar, therefore using pooled results to represent the future unobserved data would be appropriate in the calculation of conditional power.

However, as shown here, the results in the futility dataset showed an 18% reduction versus placebo for the high dose arm in Study 302; but, in study 301 the results favored placebo by 15%. That is, the studies had divergent results, breaching the assumption of similarity. Unfortunately, this was not realized until after the studies were terminated. After the futility announcement, and in response to an FDA request, the conditional power was re-estimated for the individual studies.

This post-hoc assessment using non-pooled approach showed 302 would not have met futility criteria.

CE-9

The second assumption that did not hold was that the treatment effect would not change dramatically over time in the studies.

We did expect some increase in the treatment effect due to the increase in dosing from protocol version 4. And the pre-specified futility criteria were adjusted to reflect this, however the magnitude of change was greater than expected, especially in Study 301.

As shown here, the treatment effect increased in Study 302 from minus 18% to minus 22%, and Study 301 changed from 15% to 2%, no longer having a marked worsening versus placebo.

CE-10

The Futility Analysis included only patients with the opportunity to complete the week 78 primary assessment by the cut-off date of Dec 26, 2018, which was approximately 50% of patients

When futility was declared on March 20th of 2019 the datasets contained much more information. In the nearly 3 months between data cut-off and futility, the percentage of patients with a week 78 assessment increased to 66 and 60%, in studies 301 and 302 respectively.

The patients who did not complete by March also provided considerable additional information – at week 50, 89 and 86% of patients had assessments, and all patients in both studies had a week 26 assessment.

This larger dataset of data collected prior to March 20th showed an apparently positive Study 302 with a reduction in clinical decline compared with placebo.

Given these findings, and in view of the high unmet need for a treatment to slow progression in Alzheimer's disease, Biogen sought a meeting with the FDA seeking their advice on how to proceed. With the unusual divergent results, Biogen and the FDA concluded that it was imperative that more work be done to understand the results. This work was done as a collaboration between Biogen and the FDA.

Among the first outputs of this collaboration were that the trials should not have been terminated, that the data collected prior to the futility declaration in March were valid and suitable for interpretation, and that study conclusions should be based on these data.

Important to this conclusion was the strict adherence to pre-specified and blinded approaches to maintaining the integrity of the data throughout and after the futility analysis.

CE-11

With those conclusions, we now focus on the outcomes from the final analyses.

We begin with Study 302

CE-12

The primary outcome measure was CDR-Sum of boxes.

The CDR is rated following structured caregiver interview and patient examination by an expert clinician who is blinded to treatment and does not participate in any of the other endpoints. It is a quite coarse measure, with changes needing to be substantial for detection.

The CDR-SB is a zero-18 point scale, covering the full range of symptoms, all the way to complete dependence (unable to dress / needing to be fed / doubly incontinent).

The patients in Study 302 as we have discussed are at the earliest stages of symptoms and were 2.48 points on CDR-SB at baseline.

Study powering assumed an average decline at week 78 in the placebo group of 2.0 points on the CDR sum of boxes. The observed mean placebo decline was 1.74 points, which was within the anticipated range, and similar to that of contemporary clinical trials in this patient population.

CE-13

Study 302 high dose met the primary objective of difference from placebo in mean change to Week 78 on the CDR-Sum of boxes.

The high dose arm had a 22% reduction in clinical decline versus placebo, with a p value of 0.0120.

The low dose arm had an intermediate 15% reduction in decline, which is indicative of a dose response relationship.

The primary analysis is based on the ITT or intent to treat population on data up to 20th March 2019.

We used an MMRM analysis as pre-specified, and as agreed with the FDA in our Special Protocol Assessment.

All observations prior to March 20th, 2019 were included in the primary analysis, regardless of intercurrent events. This approach is consistent with the intention to treat principle.

CE-14

We conducted additional pre-specified and post-hoc sensitivity analyses that demonstrated the robustness of the results on the primary endpoint.

On the left are the results just described – the ITT data up to 20th March.

In the middle is the same analysis on the patients who by the 20th March had the opportunity to complete the week 78 visit (which was 60%).

Because the non-completing patients are excluded, the rate of missing data in this analysis is low. Results, at 22% reduction of decline in the high dose arm – are the same as the primary result, indicating that the MMRM approach used to account for administrative censoring in the primary analysis was appropriate.

The next results are from the “uncensored” ITT dataset which includes assessments after 20th March. Including these off-treatment data from the safety follow up visit, which was up to 18 weeks after the final dose, added about one hundred assessments per arm at week 78. These results, at 25% are again consistent with the primary results.

Therefore, results of Study 302 on the primary endpoint are consistent across the three datasets, with significance retained in each dataset.

CE-15

Additional sensitivity analyses demonstrated that the results of Study 302 were not impacted by missing data.

Censoring data after intercurrent events i.e. data after early withdrawal, or a change in concomitant medications, yields an estimate as if all patients adhered to the initially randomized medication. The result, at 25% is again similar to the primary result.

The second set of sensitivity analyses, these two plots to the right, address the missing at random assumption inherent to the primary MMRM model. These analyses make more pessimistic assumptions about what results would have been following early withdrawal. For example, jump to reference is the most conservative method. It assumes that patients who withdrew early, immediately lost benefit from study treatment and progressed as placebo.

These alternative ways of analyzing the data result in minimal attenuation to the treatment effect, with 20% effect in each analysis, and statistical significance being preserved.

Therefore, the missing data due to patients' early withdrawal from the studies did not compromise the validity of the results

CE-16

The CDR-Sum of boxes is an integrated scale that assesses both daily function and cognition. Shown here are the six individual domains of the scale.

Each domain measures key activities of daily life and functioning and so they are important to patients and caregivers.

Even in our early symptomatic patient population, in the placebo group we observe decline on all 6 domains over the 78-week study duration.

In the high dose aducanumab group, a reduction is seen in each domain, indicating that the overall CDR-sum of boxes score is reflective of effect across all of the domains.

CE-17

Now we focus on secondary endpoints recalling the primary endpoint on the left. The family-wise Type I error for testing of multiple endpoints for the 2 doses was controlled as per the pre-specified approach. According to that approach:

The high dose arm met all secondary endpoints, which were ordered MMSE, ADAS-Cog13 and ADCS-ADL-MCI.

Hence, aducanumab reduced clinical decline across multiple assessments which cover broad aspects of cognition and function.

The reductions in decline ranged from 18 to 40% versus placebo, with the high dose reaching significance in every case.

In each endpoint the low dose result is intermediate to high dose... again, indicating a dose response relationship.

CE-18

The MMSE and ADAS-Cog13 are measures of patient cognitive performance.

The ADCS-ADL-MCI in contrast is an assessment of change in functional state over time, given by the clinical rater to the caregiver.

The names of the items listed in the chart reveal that these cover basic activities of daily living and assess real world conditions of patient and care-givers everyday life.

Questions for each item assess whether an activity requires supervision or physical help. As such, this measure tracks with progression to loss of independence.

The results for Study 302 on the 18 items is shown here, and where, in the placebo group we observe decline on all items over the duration of the study, and, where, a reduction is seen in all items in the aducanumab high dose group.

CE-19

The neuropsychiatric inventory or NPI-10 was included as a tertiary endpoint.

The NPI-10 assesses behavioral symptoms in Alzheimer's Disease, things like anxiety, agitation and aggression, and depression.

These are symptoms that can be very troubling for patients and their families.

In Study 302 there was a dose-dependent reduction in decline on NPI-10 with a nominally significant 87% difference versus placebo for high dose.

The NPI scale also captures caregiver distress; caregivers of patients in the high dose aducanumab group reported an 84% less burden compared with caregivers of patients who received placebo.

CE-20

Moving now to look at the biomarker results.

Brain beta-amyloid was measured in a subgroup of more than 1000 patients using the same beta-amyloid PET tracer and methodology as Study 103.

And similar to what we saw in Study 103, in Study 302 there was a dose-dependent reduction in brain beta-amyloid plaque levels, with a nominal p-value of 0.001.

The magnitude of these changes was similar to the corresponding results in Study 103.

CE-21

In addition to effects on brain beta-amyloid plaque, Aducanumab showed significant, dose-dependent effects on biomarkers of down-stream pathology.

Here, phosphorylated Tau, a biomarker of Alzheimer's specific pathology measured in CSF shows aducanumab dose-dependent, and nominally significant reduction.

A higher cumulative dose of aducanumab was associated with a greater reduction in CSF phospho-Tau levels.

The two clusters of blue squares at 56 and 98 mg/kg for the low dose are expected and is a result of the 3 and 6 mg/kg dosing for ApoE4 carriers and non-carriers.

This reduction in CSF phospho-Tau is consistent with downstream modification of tau pathophysiology.

CE-22

Further, Total-Tau, a biomarker of neurodegeneration measured in CSF shows aducanumab dose-dependent, and nominally significant reductions.

A higher cumulative dose of aducanumab was associated with a greater reduction in CSF Total-Tau levels.

This reduction in CSF Total-Tau is consistent with downstream modification of neurodegeneration.

CE-23

A Tau PET sub study was conducted in both Studies 302 and 301 to evaluate the effect of aducanumab on neurofibrillary tangles as measured by the radiotracer 18F-MK6240 (a quantitative measure of cerebral neurofibrillary tangles of tau).

The composite regions of interest were prespecified and were formed based on stages of tau pathology (and in Alzheimer's disease does not directly overlap with those of beta-amyloid pathology).

The placebo group demonstrated an increase in Tau SUVR as expected, in the medial temporal, temporal and frontal composites, indicating accumulation of tau pathology over time.

Aducanumab resulted in dose dependent reduction, and for the high dose nominally significant reductions in Tau SUVR in each of these composite regions.

CE-24

The largest magnitude of Tau SUVR reduction was observed in the medial temporal composite. Both dose groups produced a nominally statistically significant reduction relative to baseline, suggesting a reduction of tau pathology in this brain region.

A higher cumulative dose was associated with a greater magnitude of reduction in Tau SUVR.

These findings are notable since this is the first reported evidence of an Anti Abeta immunotherapy having an effect on downstream tau pathophysiology as demonstrated

by two independent modalities (CSF and Tau PET imaging), and in their respective subgroups.

CE-25

The effects of Aducanumab on beta-amyloid and clinical outcomes are separated temporally, therefore correlations assessed at a cross-section in time may show little to no relationship even with a strong underlying causal relationship.

Based on individual patient outcomes, there is a weak to moderate correlation between beta-amyloid reduction and clinical outcomes at Week 78 (0.19 – 0.29).

The correlation between beta-amyloid reduction and lowering of phospho-Tau in CSF is at 0.52 – a stronger correlation between the more precisely measured biomarkers.

Phospho-Tau in turn is correlated with clinical outcomes.

Collectively, the various imaging and fluid biomarker results are consistent with a direct effect of aducanumab on lowering brain beta-amyloid pathology with a subsequent effect on reducing tau pathology and neurodegeneration.

CE-26

Results of subgroup analyses on clinical endpoints and beta amyloid pathology showed a high degree of internal consistency.

Sixteen prespecified subgroups encompassing demographic and disease-specific characteristics were assessed

On clinical endpoints, a numeric advantage of high dose versus placebo was seen in 79 out of 80 comparisons, including all 16 of the comparisons on CDR-SB, the primary endpoint.

All of the subgroups had a significant advantage of high dose versus placebo on reductions in beta-amyloid PET.

CE-27

Underlying the biomarker and clinical outcome results is a relationship between dose, exposure and beta-amyloid reduction.

A population PK/PD model was developed to describe the relationship between exposure to aducanumab and brain beta-amyloid plaque removal, as measured by PET. A strong and consistent relationship between aducanumab exposure and beta-amyloid removal was found.

The exposure-beta-amyloid removal relationship is illustrated here, where the mean beta-amyloid profiles for the 3 mg/kg, 6 mg/kg, and 10 mg/kg titration regimens differed substantially.

Additionally, we assessed the consequences of a representative dose interruptions due to ARIA. An interruption in dosing has a prolonged influence on brain beta-amyloid plaque removal, including at the Week 78 primary endpoint and beyond. Therefore, in addition to magnitude and duration, the consistency of dosing is also an important factor in the degree of beta-amyloid removal.

CE-28

In the previous presentation we looked at the group-level correlation between beta-amyloid reduction and the reduction of clinical decline in Study 103 – now here we have added the data from Study 302.

The regression line continues to show a strong correlation between beta-amyloid reduction and the reduction of clinical decline. The Spearman's partial correlation, controlling for study, based on these group-level outcomes is approximately 0.9.

CE-29

Putting all these pieces together: Study 302 is a robustly positive study which

Dose-dependently slowed the natural progression of Alzheimer's disease as shown on the primary efficacy endpoint, all 3 secondary efficacy endpoints, and the tertiary efficacy endpoint.

The breadth and magnitude of effect in the high dose, as seen by multiple measures, is clinically meaningful.

Moreover, these benefits were observed in patients with a limited baseline severity, against a background of minimal expected disease progression over this timeframe.

The primary and secondary endpoint results were robust to departures from missing data and normality assumptions. And benefit was observed... across a broad range of pre-defined, relevant subgroups.

The clinical effects of aducanumab are supported by substantial treatment effects on biomarkers, objective measures of Alzheimer's disease pathophysiology

CE-30

Now turning to Study 301

CE-31

Study 301 did not meet its primary or secondary objectives, with each of the high dose comparisons versus placebo not statistically significant.

The results for the low dose group were, however, similar to the corresponding results in Study 302.

Because Study 301 was not positive, some results presented for 302 are not relevant. For example, there is no need to assess the internal consistency of the treatment effect in subgroups.

CE-32

As in Study 103 and 302, a time and dose-dependent reduction in beta-amyloid plaque is seen in Study 301.

The mean reduction in low dose was similar to the corresponding results in Study 302.

However, the mean reduction in the high dose group was 16.5% less than in Study 302.

It is important to note that the mean cumulative dose in the high dose group of study 301 was 109, compared with 118mg/kg in 302. This was associated with a 16.5% smaller reduction in beta-amyloid compared with 302 high-dose data - shown here in the dotted green line.

Given that beta-amyloid PET is responsive to the exposure levels of aducanumab, the smaller reduction in beta-amyloid for the high dose arm in Study 301 was an important finding.

CE-33

The high dose group in Study 301 also had a smaller effect on the disease biomarkers than in study 302.

Reductions on phospho-Tau in CSF were of similar magnitude in both high and low dose at week 78 and did not reach statistical significance.

Results in the low dose group were, however, similar to study 302.

The scatter plot for this study shows only a slight reduction in CSF phospho-Tau levels with higher cumulative dose.

CE-34

On Total-Tau in CSF, a numerical decrease was observed in the high dose group at week 78 but did not reach statistical significance.

No apparent association was observed between cumulative dose and change in CSF Total-Tau levels in Study 301.

CE-35

Now adding Study 301 results to the correlation graphic of beta-amyloid and CDR-Sum of boxes.

The low dose group in Study 301 is in line with the other studies.

However, the 301 high dose group does not fit the trend.

CE-36

Unlike Study 302, Study 301 failed to meet its primary or secondary objectives.

CE-37

Presented here is a summary of efficacy results for studies 301, 302 and 103.

The CDR- sum of boxes and MMSE were common to the studies.

The consistency of the results for these endpoints in the high dose of study 302 and the 10 mg/kg group of Study 103 is evident. As is the numerically favorable treatment effect in the low dose arms of Studies 301 and 302.

Dose-response is observed in Study 103 and in Study 302, on CDR-sum of boxes, MMSE and although not shown in the table, also in brain beta-amyloid reduction.

In the next presentation we will present the post hoc and exploratory analyses conducted as a collaborative investigation with the FDA to maximally understand the partially discordant results from Studies 301 and 302.

Understanding Why Study 301 High-Dose Arm was Discordant Samantha Budd Haerberlein, PhD, Senior Vice President, Head of Neurodegeneration Development Unit, Biogen

CR-1

Hello, I'm Samantha Budd Haerberlein, Senior Vice President and Head of the Neurodegeneration Development Unit at Biogen.

In this segment, I will present our understanding of why the Study 301 high-dose arm was discordant.

On initial review of the data, the FDA stated that a marketing application may be considered based primarily on the results of Study 302 as a single positive efficacy study.

It was stated that resources should be brought to bear on achieving a maximum understanding of the existing data, and in particular to investigate whether the results of Study 301 may have a role in supporting Study 302 or may be understood well enough to not detract from Study 302 (i.e., to not represent evidence that the drug is ineffective).

What we will review in the next slides are results of post hoc analyses conducted in collaboration with the FDA to understand the difference in results between these trials.

CR-2

To recap: the results in the two trials were only partially discordant:

The results were similar in the low dose groups, across clinical and biomarker measures.

The pharmacokinetic properties and pharmacology of aducanumab did not differ, indicating that the differences were not due to differences in the intrinsic biological activity of aducanumab.

Therefore, the discordant results are for the high dose arms on biomarkers and clinical endpoints.

CR-3

From our collaboration with FDA, we concluded:

That the demographic and disease characteristics did not differ, nor did the frequency, severity and management of ARIA

What did differ was that Study 301 had lower exposure to 10 mg/kg dosing. And, the results were also affected by an imbalance in a small number of rapidly progressing patients, which I will describe shortly

We will now examine these two main factors, beginning with dose.

CR-4

Our investigations confirmed that the high dose 10 mg/kg was important for efficacy

However, achieving sufficient and sustained doses at 10 mg/kg was influenced by multiple connected factors, including

- Missed doses or early study withdrawal
- ARIA management
- Change in the protocol for ApoE4 carriers

Our dose-exposure-response modeling showed an important interplay between magnitude, consistency and duration of dosing in removing brain beta-amyloid and on clinical efficacy

CR-5

Exposure to 10 mg/kg was lower in the high dose of Study 301 than in Study 302.

These charts – so called heat maps - are made up of individual lines recording the actual doses taken at each visit by each patient randomized to the high dose arm in Studies 301 and 302.

The dark blue shows a 10 mg/kg dose. Yellow is no dose. The lighter blue lines are the lower doses of 1,3 and 6 used in 24-week titration or when they appear after that period are the doses for those patients who continued on lower dose.

The heat maps illustrate that both studies have few patients with the full 14 doses of 10 mg/kg. This was only 29% of patients in Study 302, and 22% of patients in Study 301.

Further, the high dose in Study 301 had more patients with no or very low levels of 10 mg/kg (yellow lines).

We also see a lot of heterogeneity in dosing even though all these patients were randomized to the high dose regimen.

CR-6

If we look at dosing over time, we can see the impact of the protocol amendment: Because the amendment was implemented partway through the study, early on the high dose arms in both studies had lower exposure to 10mg/kg.

In the first 200 patients enrolled, the median number of 10 mg/kg doses in Study 301 was just 1 and was 4 in Study 302.

As the studies progressed, more patients had higher levels of dosing, such that by the end more patients in both studies received the full 14 doses of 10 mg/kg.

However, as we saw in the individual dosing charts, Study 301 had lower overall exposure to 10 mg/kg, particularly early on.

Hence, the importance of assessing whether patients in Study 301 who received sufficient doses of 10 mg/kg had outcomes similar to those in Study 302

CR-7

In the High dose group three subgroups created by stratified randomization and protocol amendment 4 had the opportunity for the full 14 doses of 10 mg/kg, they were

- ApoE4 non carriers at both the beginning and the end of the study
- And ApoE4 carriers after protocol version 4 was implemented.

In both studies, the weighted mean outcome of these 3 groups gave the same treatment effect of - 23%

This demonstrated that, on the basis of dose, patients in study 301 who had the opportunity for 14 doses of 10mg/kg had outcomes showing a reduction in clinical decline, and this was of a similar magnitude as Study 302.

Because these results are based on groups formed by randomization, standard statistical analyses were used.

We conducted additional analyses based on actual doses taken. These additional analyses were ALL post hoc. However, the methods employed differing assumptions, and each showed a consistent result, that patients in 301 who received sufficient doses had outcomes similar to 302.

CR-8

An additional factor in the difference between Study 302 and 301 was an imbalance in a very small number of rapidly progressing patients.

In this histogram of change to week 78 on CDR-Sum of boxes for all patients in both studies – rapidly progressing patients are in the far right, highlighted by the grey box.

The expected decline in this population is 1-2 points on the CDR-Sum of boxes. Patients with large declines are seen in clinical practice and so, we expected to see them in our studies. There is, however, no standard definition of these patients in the literature.

Using a post-hoc definition, across both studies 31 of the 3285 patients were classified as rapid progressors, based on having at least an 8-point change in CDR-Sum of boxes at Week 78. 8 points is four-fold greater than the upper end of the expected mean decline.

On detailed assessment, the rapidly progressing patients in the studies could not be defined by any single or unifying factor including adverse events or concomitant medications and did not differ in any baseline characteristics.

A review of literature and epidemiological studies were consistent with these findings.

CR-9

Each treatment arm in each study had either 4 or 5 rapidly progressing patients - including placebo - except for the study 301 high dose arm, which had NINE, twice as many as the other groups. This imbalance was especially problematic because all 9 were enrolled early in the study and were included in the futility dataset.

This imbalance in rapidly progressing patients influenced results for the high dose arm in Study 301. This forest plot shows the result for each dose group high/low on CDR-Sum of boxes with the bottom of each pair showing the results excluding rapid progressing patients. The purpose of this analysis was to get a simple illustration of the impact of the Rapid Progressors. It is not intended as a substitute for the primary analysis.

The low dose group in Study 301, and both dose groups in Study 302 all show minimal impact of excluding rapid progressors.

In contrast, excluding rapid progressors changed the magnitude of the treatment effect in the high dose arm of Study 301 by 8-percent relative to placebo. Across the primary and secondary outcomes, with rapid progressors excluded, results from the high dose arm of 301 were similar to the low dose arm in 301.

It is important to appreciate that this was a study of patients with early Alzheimer's disease where the vast majority of patients progress slowly. Four excess rapidly progressing patients with a change of 8 or more points have a significant impact. Not only did high dose 301 have more rapid progressors, they also tended to have the highest declines of 10 to 13 points.

CR-10

The totality of evidence generated by our collaborative investigation with the FDA concluded that we sufficiently understand Study 301 and that Study 301 does not detract from the persuasiveness of Study 302

Study 301 high dose arm clinical outcome was substantially impacted by lower exposures to the target dose of 10 mg/kg and an imbalance in a very small number of rapidly progressing subjects.

However, subjects in Study 301 who were randomized to dose regimens allowing the full 14 doses of 10mg/kg had pharmacological activity and clinical efficacy consistent with Study 302.

The underlying biological activity of aducanumab is similar in Studies 301 and 302, is well understood.

Simply put, an imbalance in rapid progressors and less exposure to 10mg/kg dosing drove the difference between studies. When these factors were not present, results from 301 were similar to 302. Nevertheless, 301 is a failed study. These findings do not add to the substantial evidence of efficacy from Studies 302 and 103 – but neither do they detract from that evidence.

CR-11

With these conclusions, we have presented the basis for the substantial evidence of effectiveness of aducanumab

Study 302 is a positive study, supported by consistent evidence in Study 103.

Study 301 is not positive

These studies consistently demonstrate that sufficient exposure to 10 mg/kg aducanumab is effective at reducing the clinical decline in patients with early symptomatic Alzheimer's disease.

In the next presentation, my colleague, Dr. Karen Smirnakis, will present the safety elements of the BLA.

Safety

Karen Smirnakis, MD, PhD, MPH, Vice President, Head of Global Medical Safety, Biogen

CS-1

This is Karen Smirnakis, Head of Global Medical Safety at Biogen. I am a physician-scientist who has worked in biotechnology, academia and as a treating physician.

I will briefly summarize the safety profile of aducanumab with a focus on the integrated safety analysis of the phase 3 clinical trials.

CS-2

In the combined phase 3 placebo-controlled clinical trials, 2198 patients were treated with aducanumab, including 1033 in the 10 mg/kg dose group.

The total exposure to aducanumab, including follow-up time, exceeds 5300 person-years across all multiple dose studies.

This exposure exceeds ICH E1A guidance and enables a robust characterization of the safety profile of aducanumab.

CS-3

Overall, the safety profile in studies 301 and 302 was similar. This enabled pooling of the two phase 3 pivotal clinical trials for safety analyses.

At the top of this figure are the study-level treatment arms (low dose and high dose), with the corresponding dose level shown in the middle.

At the bottom of the figure are the integrated safety dose groups, based on target dose (3, 6, and 10 mg/kg).

This pooling strategy enabled a comprehensive evaluation of the safety of ADUCANUMAB, including safety at the proposed clinical dosing regimen.

Safety data was evaluated both by integrated safety dose groups, and by study-level treatment arms, yielding similar results from both analyses.

CS-4

Before I review the data, I would like to spend a few moments discussing ARIA. ARIA, an acronym for Amyloid-Related Imaging Abnormalities, refers to radiographic findings seen on brain MRI in the setting of treatment with antibodies targeting Amyloid beta.

MRI findings of ARIA include edema or effusion, called ARIA-E, and brain microhemorrhage or localized superficial siderosis, called ARIA-H.

In the aducanumab studies, CNS hemorrhages >1cm could also be reported as ARIA-H macrohemorrhage.

MRI findings or ARIA have been reported in clinical studies of many anti-A-beta antibodies. Although the underlying pathophysiology is not fully understood, both ARIA-E and ARIA-H are thought to result from increased cerebrovascular permeability as a consequence of antibody binding to deposited cerebral amyloid-beta.

In the phase 3 aducanumab studies, all radiographic events of ARIA were required to be reported as AEs, even in the absence of clinical symptoms. Therefore, the incidence of ARIA AEs in upcoming tables refers to the incidence of radiographic findings of ARIA. Any symptoms that were attributed to ARIA were captured as separate adverse events and will also be discussed.

CS-5

In this summary table of adverse events, placebo data is shown in the left column, and aducanumab data is shown by target dose group in the columns on the right.

Adverse Events were common in this patient population, being reported in 86 to 92% of all patients. The incidence of adverse events was similar across all treatment groups. The most common AE in the Aducanumab-treated groups was ARIA-E, which will be discussed in more detail in subsequent slides.

Overall, the incidence of SAEs was comparable between aducanumab treated groups and placebo, at ~13%.

The most common SAE that occurred more frequently with aducanumab compared to placebo was ARIA-E (1.3% in the 10 mg/kg group compared with less than 0.1% in the placebo group). Seriousness was assessed by the Investigator according to ICH criteria, which included medically important events, events that result in hospitalization, life-threatening or fatal events.

Fatal adverse events were uncommon and were balanced between the placebo group and the aducanumab treated group.

CS-6

Compared with placebo, the incidence of severe AEs was higher in the aducanumab groups. This was largely due to the incidence of severe ARIA events. As a reminder, the severity of ARIA was determined by the extent of radiographic involvement and does not refer to the severity of symptoms. Symptom severity was captured separately.

Additionally, more patients discontinued treatment due to an adverse event in the aducanumab groups compared with placebo. This difference was largely due to protocol mandated treatment discontinuation rules in the setting of certain types of ARIA.

CS-7

In this slide and on subsequent slides, we will focus on the aducanumab 10 mg/kg group, on the right, compared with placebo, shown in the left column.

This table shows those AEs that were reported with an incidence greater than or equal to 5% in the aducanumab 10 mg/kg group, and that exceeded the incidence in the placebo group by 2% or more.

Of these, ARIA-E, is the most common, followed by headache, brain microhemorrhage, fall, superficial siderosis and diarrhea. Most of these AEs were mild or moderate in severity.

Additional analyses, which I will discuss shortly, demonstrated a strong relationship between ARIA-E and events of ARIA-H brain microhemorrhage and ARIA-H localized superficial siderosis.

CS-8

ARIA risk minimization in the clinical trials consisted of several steps.

First, dose titration was utilized, as this has been shown to reduce the incidence of ARIA.

Dose titration to 10 mg/kg occurred over the first 24 weeks, with patients receiving 2 doses each of 1, 3 and 6 mg/kg before reaching the target dose of 10 mg/kg.

The second component of ARIA risk minimization was the use of routine brain MRIs. All study participants, regardless of symptoms, underwent a total of seven post-baseline MRIs during the placebo-controlled period, as shown by the dashed gray lines in this figure.

CS-9

The third component of ARIA risk management included dosing actions based upon the radiographic and clinical characteristics of ARIA.

Patients with mild radiographic findings of ARIA on MRI continued dosing and underwent monthly follow-up MRIs until the ARIA resolved. In the presence of symptoms, dosing was temporarily suspended.

Patients with radiographically moderate ARIA events temporarily suspended dosing, and underwent monthly follow-up MRIs until ARIA resolved, at which time dosing could be resumed. Patients with severe ARIA-E also temporarily suspended dosing, whereas patients with severe radiographic findings of ARIA-H permanently discontinued dosing.

CS-10

The incidence of ARIA-E in aducanumab treated patients is influenced by ApoE4 carrier status.

We previously noted that the overall incidence of ARIA-E in the 10 mg/kg target dose group was approximately 35%. In this same group, the incidence of ARIA-E in ApoE e4 carriers was 43%, whereas the incidence in non-carriers was ~20%.

CS-11

This slide shows a Kaplan-Meier plot of time to first ARIA-E.

Consistent with what has been previously observed with other anti-A-beta antibodies, ARIA-E typically occurred early in therapy, during dose titration or soon after reaching the target dose, with over 70% of first ARIA-E events occurring within 32 weeks of starting treatment.

Most events were detected on routine MRI scans, as illustrated by the steps early in the curve, and the incidence plateaued later in treatment, despite continued routine MRI monitoring. BUILD

During the long-term extension period, very few initial ARIA-E events were detected, despite continued MRI monitoring.

CS-12

The severity of ARIA-E events was based upon the extent of radiographic involvement.

In the 10 mg/kg dose group, 30% of ARIA-E events detected on MRI were mild in radiographic severity, while 58% were moderate and 12% were severe.

Importantly, 98% of ARIA events resolved on study, nearly 70% within 12 weeks, and over 80% within 16 weeks.

CS-13

The clinical impact of ARIA was assessed by the presence of symptoms, and the severity of those symptoms occurring during an ARIA event.

As shown in this table, approximately 75% of ARIA-E events were asymptomatic. Overall, 9% of aducanumab treated patients in the 10 mg/kg group experienced a symptomatic ARIA-E event.

The most common symptoms were headache, confusion, dizziness and nausea.

For those patients who had symptoms during an ARIA event, the maximum severity of symptoms was mild or moderate in 96% of patients.

Severe symptoms were uncommon and included rare reports of seizures. Overall, the incidence of seizures was balanced between aducanumab and placebo groups.

CS-14

We have previously noted that the incidence of ARIA-H brain microhemorrhage and superficial siderosis was increased among aducanumab treated patients in the 10 mg/kg group compared with placebo.

In contrast, the incidence of ARIA-H macrohemorrhage was low and balanced between aducanumab and placebo groups.

CS-15

We examined whether there was relationship between ARIA-E and ARIA-H events in aducanumab treated patients.

Among aducanumab-treated patients, the incidence of ARIA-H was higher among those patients who had an event of ARIA-E compared to those treated patients who did not have an event ARIA-E. Patients who experienced both ARIA-E and ARIA-H typically had such events concurrently, meaning they were detected in the same MRI during the course of the ARIA event.

Among patients who did not experience ARIA-E, the incidence of ARIA-H was low and was similar between ADU and placebo-treated patients, at approximately 6-7 %. This reported incidence is consistent with the known background incidence of brain microhemorrhages and superficial siderosis observed in the Alzheimer's patient population.

CS-16

Lastly, compared with placebo, there were no differences in the aducanumab group in the incidence of:

- Abnormal vital signs
- EKG abnormalities
- Laboratory abnormalities
- Results on the Columbia suicide severity rating scale questionnaire
- Or immunogenicity

Serious hypersensitivity reactions associated with aducanumab infusion were rare, with an incidence of less than 0.1%.

CS-17

In summary, the safety profile of aducanumab is well characterized, based on more than 5300 person-years of follow-up for aducanumab-treated patients.

An MRI finding of ARIA-E was the most common AE among aducanumab-treated patients. In the course of the trials, our understanding of ARIA and its management has deepened.

- ARIA was mainly of mild or moderate MRI severity, and transient.
- In the majority of patients with ARIA, these events were asymptomatic.
- Among patients with ARIA, the majority remained on treatment or resumed treatment after a temporary dose suspension.
- Importantly, we learned that the risk of ARIA can be mitigated by MRI monitoring and dosing management.

Other AEs more common in the 10 mg/kg aducanumab group included headache, brain microhemorrhage, falls, superficial siderosis, and diarrhea.

CS-18

We are committed to further characterizing the safety profile of aducanumab in the post-marketing setting.

We will continue to collect safety data through routine surveillance and in the ongoing, long-term clinical study - EMBARK.

In clinical practice, as in the aducanumab clinical trials, ARIA risk mitigation will be important, and will include dose titration, the use of MRI monitoring, particularly during the early treatment period, and dose suspension as needed.

We recognize that if aducanumab is approved, ARIA will be a novel MRI finding and clinical entity for many clinicians and patients. Therefore, we are committed to educating prescribers, radiologists, patients, and their caregivers on the risk of ARIA and its management.

Thank you for your attention. In the next presentation, Dr. Porsteinsson will provide his clinical perspective on the data.

Clinical Perspective

Anton P. Porsteinsson, MD, University of Rochester Medical Center

CP-1

My name is Dr. Anton Porsteinsson. I am a Professor of Psychiatry, Neurology, Neuroscience, and Medicine at the University of Rochester, School of Medicine and Dentistry, and the Director of the Alzheimer's Disease Care, Research and Education Program.

I have centered my professional career over the past 25 years on the care and study of patients with Alzheimer's disease.

I am a paid consultant to the sponsor, but I have no financial interest in the outcome of this meeting.

I was a site principle investigator in the aducanumab phase 3 program, and it is a distinct honor to speak to you while representing the 348 clinical investigator sites.

I will lend a clinical perspective to the data and illustrate the clinical relevance of aducanumab.

CP-2

The Aducanumab studies enrolled patients with early symptomatic Alzheimer's disease, with roughly 80% of the participants having Mild Cognitive Impairment due to Alzheimer's Disease, and 20% having mild Alzheimer's Dementia at study entry.

These studies were designed to measure Aducanumab's impact on Alzheimer's Disease progression, in particular decline in COGNITION, FUNCTION, and BEHAVIOR.

Let me first bring your attention to the Clinical Dementia Rating Scale-Sum of Boxes or CDR Sum of Boxes, which was the primary outcome measure.

CP-3

The CDR sum of boxes has been VALIDATED to show disease progression in naturalistic longitudinal studies.

By design the CDR sum of boxes is established as a global scale to assess disease progression in dementia.

It involves semi-structured interviews, first of the study partner, and then of the patient. It uses direct and open-ended questions to assess 6 major domains of cognition and function.

This assessment is completed by an expert clinician who is blinded to other study measures and operationalizes this clinician's judgment, which means it is inherently clinically meaningful.

CP-4

But, how do these domain measures reflect a meaningful slowing of decline? Let's look at them individually.

Memory: reflects the patient's ability to accurately recall recent events, learn a short list of items, and recount important personal details. Aducanumab reduced decline of memory function by 28% compared to placebo over an 18-month period.

Orientation reflects the patient's awareness of time and place as well as ability to travel independently. Aducanumab slowed decline in this rating by 24%.

The Judgment and Problem-Solving domain captures the patient's ability to handle financial or business transactions, handling a household emergency and the like. Aducanumab slowed deterioration by 25%.

Community Affairs: includes working, driving, shopping, and going to functions outside of the home. Aducanumab slowed progression by 23%.

Home and Hobbies includes homemaking tasks and hobbies. Aducanumab slowed decline by 24% ...

...and finally, Personal Care: This includes getting dressed, personal hygiene, eating habits, and continence. Aducanumab slowed this functional loss by 15% relative to placebo.

These measures reflect core aspects of the ability to perform in our daily lives and maintain autonomy. Aducanumab made a noticeable and clinically meaningful difference in every domain.

CP-5

In addition to the 22% relative reduction in decline in CDR sum of boxes, Aducanumab slowed disease progression in two other well-validated assessments of cognitive status – the MMSE, which is widely used in the clinical setting, and the ADAS-cog 13.

Furthermore, the decline of functional autonomy, assessed by the ADCS-ADL-MCI scale, was reduced by 40% in patients who received aducanumab compared to placebo. Maintaining functional and behavioral abilities is at the heart of what most concerns patients and caregivers. A 40% reduction in functional decline translates into 7 months of preserved function for the average patient over the 18-month study period. Because of the disease modifying nature of Aducanumab, prolonged treatment would be expected to translate to even longer treatment benefits. This is clinically meaningful and significant particularly as 80% of participants had Mild Cognitive Impairment due to Alzheimer's Disease at study entry and may have the opportunity to maintain their functional autonomy.

And finally, the progression and emergence of new neuropsychiatric and behavioral disruptions, measured by the NPI-10, was reduced by 87% relative to placebo. Neuropsychiatric symptoms cause suffering, distress and isolation for patients and families. Patients with neuropsychiatric symptoms also tend to decline faster than those who do not have Neuropsychiatric symptoms.

CP-6

In addition to efficacy, we must factor in safety and tolerability when considering clinical relevance. Overall, for such long studies, we had remarkably low drop-out rates, which shows how committed the participants and sites were to the studies.

Outside of ARIA, there were very minimal differences in Adverse Events and Serious Adverse Events. These risks are manageable.

Regarding ARIA-E and ARIA-H, we have come a long way since I was one of the authors on the first paper describing these phenomena in 2012. We now have a good understanding of and clear guidelines for managing ARIA.

Physicians and other providers have developed great familiarity with infused biologics in multiple areas of medicine, and those management strategies are generalizable to this field as well.

CP-7

So why do we need aducanumab as a therapy for Alzheimer's disease?

First, Early diagnosis and treatment are feasible right now

You heard from Dr. Galasko about the urgent, unmet medical need in Alzheimer's disease. No therapies are currently approved for early stages of the disease, such as Mild Cognitive Impairment due to Alzheimer's disease.

Aducanumab clearly impacts underlying disease pathology, preserves cognitive and functional abilities, and reduces behavioral decline as shown on multiple outcome measures that are consistently positive for aducanumab over placebo.

Throughout the course of the study, aducanumab appears to slow the rate of decline and we would expect the effect to continue or even grow over time.

In conclusion, it's clear that treatment with aducanumab can provide a real, genuine, palpable and noticeable effect on the lives of patients with Early Symptomatic Alzheimer's disease. I look forward to having Aducanumab as a treatment option for my patients.

Thank you... This concludes our presentations