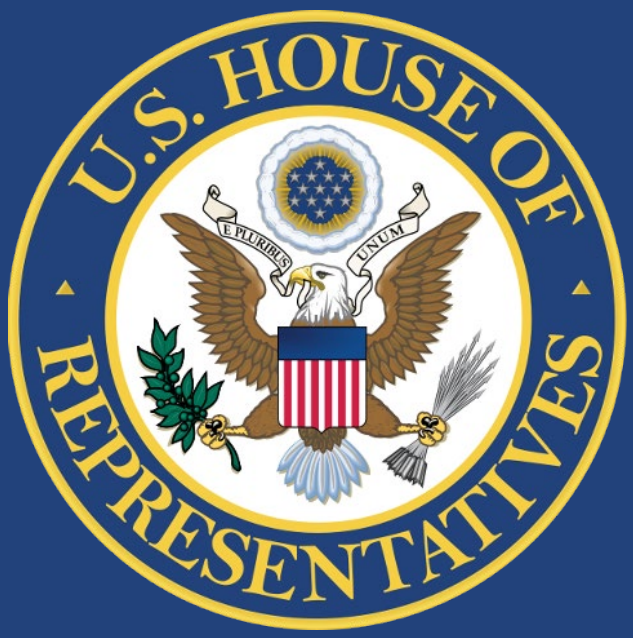

Aduhelm Investigation

Food and Drug Administration

Selected Investigation Documents

Committee on Oversight and Reform and Committee on Energy and Commerce
U.S. House of Representatives
December 2022

Document #	Citation	Short Description
1	Food and Drug Administration and Biogen, *Collaborative Workstream: Meeting Record* (July 2, 2019).	July 2019 Kickoff Meeting Minutes
2	Food and Drug Administration, Medical Policy and Program Review Council, *Medical Policy and Program Review Council Meeting: BLA 761178, Aducanumab for the Treatment of Alzheimer's Disease* (Mar. 31 and Apr. 7, 2021).	March and April 2021 MPPRC Meeting Minutes
3	Food and Drug Administration, *Internal Review of FDA-Biogen Interactions for Aducanumab BLA, Findings and Analysis* (May 30, 2021).	May 2021 FDA Internal Review (Selected Pages)

Collaborative Workstream: Meeting Record

Date	02 July 2019			
Attendees	**FDA**	**Attendance**	**Biogen**	**Attendance**
	Billy Dunn, Director, Division of Neurology Products (DNP) & Acting Deputy Director of Office of Drug Evaluation, I	☒	Samantha Budd Haeberlein, Vice President, Clinical Development	☒
	Eric Bastings, MD, Deputy Director, DNP (Apologies) & Acting Director of the Division of Neurology Products	☐	[redacted] Clinical Development	☒
	Nick Kozauer, Associate Director, DNP & Acting Deputy Directory of the Division of Neurology Products	☒	[redacted] Biostatistics	☒
	Ranjit Mani, Clinical Reviewer, DNP	☒	[redacted] Clinical Development (Apologies)	☐
	Kun Jin, Biostatistics Team Leader	☒	[redacted] Clinical Development	☒
	Tristan Massie, Statistical Reviewer	☒	[redacted] Drug Safety	☒
	Kevin Krudys, Senior Clinical Analyst, DNP	☒	[redacted] Biostatistics	☒
	E. Andrew Papanastasiou, Regulatory Project Manager, DNP	☒	[redacted] Biostatistics	☒
	Sue Jane Wang, Associate Director, Office of Biostatistics Acting director for biomarkers analysis	☒	[redacted] Biostatistics	☒
	Jim Hung, Director, Division of Biometrics I	☒	[redacted] Biostatistics	☒
	Brian Trummer, MD, PhD – Neurology Fellow	☒	[redacted] Translational Sciences Biomarker	☒
			[redacted] Biostatistics	☒
			[redacted] Biostatistics	☒
			[redacted] Biostatistics	☒
			[redacted] Biostatistics	☐

Collaborative Workstream: Meeting Record

			[redacted]	
			[redacted] Development Imaging	☒
			[redacted] Pharmacometrics	☒
			[redacted] harmacometrics	☒
			[redacted] Clinical Program Leadership	☒
			[redacted] Medical Writing	☒
			[redacted] Safety	☐

Outline Agenda Kick off meeting July

Agenda attached

Meeting Purpose/Goal

Kick Off Meeting to discuss Collaborative Workstream with introduction of team members at FDA and Biogen

Goal of Collaborative Workstream

- Three overarching themes to address
  1. Analyze the impact if any that early termination of the studies may have on the ability to interpret the data.
  2. Identify which data from #1 should be used to look further into 301 & 302. Does 302 remain robust / is there data from 301 that is supportive/explanatory/concerning?
  3. Based on the outcomes of #1 and #2 above; which option (out of the 5 proposed by the Agency) does the data support

Aligned mission to move workstream forward as rapidly as possible. Reminder that Alzheimer's disease is a critical public health issue. We always need to maintain scientific rigor and equipoise. This team should feel proud to be driving this endeavor forward.

Decisions

Collaborative Workstream operating model

Established Leadership team (LT)
- FDA: Kevin R, Tristan M, Andrew P
- Biogen: [redacted]

- LT team to meet twice weekly to define work & align work to be done (starting week of 08 July 2019)
- Weekly update call to Dr. Dunn and Dr. Budd from LT (starting week of 08 July 2019)
- All email communications between Biogen team members and FDA team members to copy LT
- Communication and ways of working practice to be reviewed periodically
- Potential to have informal F2F meetings as needed

Collaborative Workstream: Meeting Record

- First wave of workstream – 'virtual completion studies 301 and 302'
  - Evaluate how we are going to apply modeling/simulation to the completion of the trials. Determine appropriate dataset(s) for virtual completion simulation of trials

Actions

Task	Due Date	Accountable	Status
Provide FDA with cross functional team members and key contact for Biogen's biostats team [redacted] (primary contact for FDA) [redacted]	02 July 2019	[redacted]	Completed with this meeting record
List of Biogen completed / ongoing analyses (excel tracker)	05 July 2019	[redacted]	Pending
literature regarding stochastic curtailment sent to Biogen	02 July 2019	Sue Jane Wang	Completed 02 July 2019
First Leadership Team (LT) call to be scheduled on 08 July 2019 and include FDA and Biogen stats teams to discuss completed and future analyses	02 July 2019	[redacted] Andrew	Meeting scheduled
FDA stats team meeting to consider ways to address virtual completion of trials, output to be communicated to workstream	05 July 2019	FDA Stats team	Meeting pending
[redacted] /Kevin R to communicate via email to exchange/share ideas on PK/PD analysis completed	05 July 2019	[redacted] to initiate communication	Pending
Second LT Meeting to be scheduled for Wed/Thursday 10/11th July	10/11 July 2019	[redacted] /Andrew	
Meeting with BD/SB to be scheduled for Thursday 11th July		[redacted] /Andrew	

FDA & Biogen Collaborative Workstream, Kick off meeting 11.00 – 1.00 July 2, 2019

FDA Attendees:	**Biogen Attendees:**
Billy Dunn, Director, Division of Neurology Products (DNP) Eric Bastings, MD, Deputy Director, DNP (absent) Nick Kozauer, Associate Director, DNP Ranjit Mani, Clinical Reviewer, DNP Kun Jin, Biostatistics Team Leader Tristan Massie, Statistical Reviewer Kevin Krudys, Senior Clinical Analyst, DNP E. Andrew Papanastasiou, Regulatory Project Manager, DNP Sue Jane Wang, Associate Director, Office of Biostatistics Jim Hung, Director, Division of Biometrics I	Samantha Budd Haeberlein, Vice President, Clinical Development [redacted] Clinical Development Biostatistics Global Regulatory Sciences [redacted] Clinical Development Clinical Development Drug Safety Biostatistics Biostatistics Biostatistics Biostatistics Translational Sciences Biostatistics Biostatistics Biostatistics Biostatistics Development Imaging Pharmacometrics Pharmacometrics Clinical Program Leadership Medical Writing

Topic	Notes	Anticipated outcome
1. Hello/welcome/ introductions	• All individuals to introduce themselves and describe their background, skills, and (for Biogen) what role they have played in the ongoing analyses & the role they will have in the collaborative workstream	• Teams to connect, talk to each other, will be working together to create and inspire ideas and approaches for analyses.

FDA 1

2. Outline and purpose of the Collaborative Workstream	• Dr Dunn & Dr Budd outline the direction & thematic goals that we wish to achieve	• Ensure team is aligned to purpose and direction of collaborative workstream.

3. How the Collaborative Workstream will operate	• Collaborative Workstream Leadership Team (LT)
	  ○ FDA: Kevin, Tristan, Andrew,
	  ○ Biogen: [redacted]
	• Identify Working Group (WG)
	• Frequency of team interactions
	• Means of communication
	• Resource allocation
	• Record of work
		• Agree frequency of team interactions
		  ○ LT – 2x weekly calls, additional as needed
		  ○ LT + specific WG members – as needed
		  ○ As possible weekly LT update for Budd/Dunn (call)
		• Decide next meeting date – LT to convene by phone (without Budd/Dunn) early week of July 8; LT to update Budd/Dunn by phone no later than July 11
		• Agree means of communication – calls as above; emails can be exchanged that can involve as many of the WG as needed but should always include LT
		• Agree means of documentation of statistical analyses and modeling/simulation
		• Agree how Biogen can apply resources to joint investigative questions
		• Agree and identify Biogen support for record of meetings

4. First wave of workstream – 'virtually complete the 301 and 302 studies'	• Team to discuss ideas on how to virtually complete the trials – modeling/simulations (max, min, mean, multiple runs of each, novel ideas)	• Goal: identify primary data set(s) to work with following virtual completion exercise • Agree scope of work, timelines & resources
5. ACTION ITEMS	• Any questions on data transfer • Any questions on key analyses to date / outputs provided	• Ensure collection and timely resolution of actions
6. **AOB**		

FDA 1

Medical Policy and Program Review Council Meeting:
BLA 761178, Aducanumab for the Treatment of Alzheimer's Disease (OB, ON, OCP)
March 31 and April 7, 2021
Discussion of the data supporting the effectiveness of Aducanumab

Background

In the United States, more than 6 million people over the age of 65 years suffer from Alzheimer's disease (AD), and it is the sixth leading cause of death. Current treatment options for AD are few, have modest and symptomatic effects, and do not target the underlying pathology. The two pathological hallmarks of AD are the presence of beta-amyloid plaques and tau tangles within the brain.

Aducanumab, a human monoclonal antibody developed by Biogen (Sponsor), is thought to slow the progression of AD by binding to and removing beta-amyloid aggregates. Aducanumab was the first antibody demonstrated to lead to robust removal of amyloid plaques, as measured by positron emission tomography (PET). The Sponsor presented two phase 3 studies (301 and 302) and one phase 1 trial (103) in support of the efficacy of aducanumab. Studies 301 and 302 were multicenter, global, double-blind, placebo-controlled studies of identical design that were intended to evaluate the efficacy and safety of aducanumab. Study 103 was a smaller, placebo-controlled dose-ranging clinical trial conducted in the United States in a population that overlapped with that of 301 and 302.

Studies 301 and 302 enrolled patients with mild cognitive impairment due to AD and mild AD dementia with a PET scan positive for amyloid-beta at baseline. Patients in both studies received a 'low' or 'high' dose of aducanumab stratified on their apolipoprotein E (APOE) ε4 carrier status. The primary endpoint was the change from baseline in the Clinical Dementia Rating-Sum of Boxes (CDR-SB) score. Both studies included cognitive assessments as secondary endpoints. In a futility analysis of approximately 50% of subjects conducted in December 2018, Studies 301 and 302 were found to meet prespecified futility criteria and were terminated in March 2019.

Between the December 2018 data cutoff and the termination of Studies 301 and 302 in March 2019, per-protocol collection of blinded data continued as planned.

According to the presentation by the clinical reviewer, Dr. Krudys (Division of Neurology I; the Division), the analysis conducted on this more complete dataset indicated that 1) in the high dose cohort of Study 302, the probability of a type 1 error for all four endpoints is extremely small, 2) biomarker results support clinical observations, and 3) a dose-dependent relationship between aducanumab exposure and clinical endpoints was identified. The Division argues that a fundamental assumption of the futility analysis was not met; specifically, the assumption that the effects of aducanumab were expected to be similar in Studies 301 and 302. The Division, in collaboration with the sponsor, began an analysis of the data for 301 and 302, first to see whether the declaration of futility rendered the data uninterpretable, and once it was agreed that the data were interpretable after virtual completion of the trials was done using statistical modeling and simulation, further analyses were done to understand the discordant results of the two identically designed studies. In Studies 301 and 302, patients received one of two

aducanumab dosing regimens based on whether they are a carrier of the APOE ε4 allele. The rationale for this trial design was that surveillance magnetic resonance imaging (MRI) scans from the phase 1 trials revealed amyloid-related imaging abnormality (ARIA) as the principal side effect of aducanumab. The incidence of ARIA was dose-dependent and more common in APOE ε4 carriers. Therefore, carriers were enrolled in the phase 3 trials on a lower dose of the drug as a safety precaution. However, when data became available that the risk of ARIA to APOE ε4 carriers was manageable, the Safety and Data Monitoring Committee agreed that the protocol for the phase 3 trials could be amended to allow carriers to receive the target 'high' dose of 10 mg/kg. At the time this change in the protocol was made (Amendment 4) study 301 was farther along in enrollment than study 302 and therefore a larger number of APOE carriers in study 302 received at least 14 doses of the highest dose 10 mg/kg.

The same analysis showed that Study 301 failed to meet the primary endpoint of change from baseline in CDR-SB score and indeed the high dose aducanumab arm was slightly numerically worse than placebo on the primary, although there was a favorable trend that was comparable to the low dose in the ADAS-Cog13 and the ADCS-ADL-MCI.

The Division noted that certain results from Study 301 were consistent with those of 302. First, numerically favorable results were observed in the low-dose arm and were of similar magnitude to those observed in Study 302. Second, the results for two of the secondary endpoints in the high dose group were numerically, but not statistically, favorable and hence were not inconsistent with the results of study 302. In analyses intended to evaluate potential explanations for the discrepancy between studies, it was noted that there were some differences in the number of rapid progressors (n=4) in treatment arm of 301 compared to placebo arm. In addition an analysis of those participants that received $\geq$ 8 uninterrupted doses of 10 mg/kg, using propensity score matching to placebo subjects, suggested that both of these high dose subsets in 301 and 302 had comparable reductions on the CDR-SB compared to placebo. However, in this same analysis the results for the intermediate exposure to 10 mg/kg subset were discordant between Study 301 and 302. For these reasons, the Division argued that despite its failure to meet the primary endpoint, the results of Study 301 do not necessarily contradict those of Study 302.

Study 103 was primarily designed to evaluate the safety and tolerability of aducanumab. However, it included assessments of biomarker and clinical endpoints, and shared elements of Studies 301 and 302, including the requirement for a positive amyloid PET scan at baseline and blinded assessment of clinical endpoints. The results of Study 103 mirrored those of 302 in that a dose-dependent relationship was observed for brain amyloid reduction as well as clinical outcomes.

The Division's overall view is that the results of Study 301 do not undermine those of Study 302, and when considered as a whole, could potentially provide some support for the findings of efficacy in Study 302. In addition, the phase 2 Study 103 provides supportive evidence of effectiveness for aducanumab. In a presentation by the Office of Clinical Pharmacology, further evidence was provided that was considered by OCP to support the effectiveness of aducanumab. This included evidence of exposure-response relationships across all studies for CDR-SB, including Study 301 (although attenuated relative to Study 302), a group-level strong

relationship between the change from baseline in amyloid plaque by PET imaging and the change from baseline in CDR-SB, and a probability assessment to examine the likelihood that the efficacy findings across all doses and efficacy endpoints might have occurred based upon chance alone. OCP also showed data from other development programs with compounds with the same mechanism of action showing a relationship between reduction in amyloid by SUVR and clinical improvements on the CDR-SB. This assessment suggested that the likelihood that the results reflected a random outcome was extremely remote.

The Office of Biostatistics (OB) presentation concluded that the data does not demonstrate substantial evidence based on OB's interpretation of Studies 301 and 302. The statisticians also asserted the incorrectness of the probability of false positive simulations by the sponsor and OCP on several grounds: i) that they redefined false positive rate and elevated the importance of the secondary endpoints post-hoc, ii) that for their post-hoc false positive rate, adding more endpoints can decrease the p-value even when the treatment effects on the added endpoints are almost none, thus the strength of evidence is exaggerated by the post-hoc addition of endpoints, and iii) that due to the added complexity when considering multiple endpoints (or multiple dimensions) together, the simulations failed to include several false positive regions that should have been included and should have added weight to the probability; thus, that the probability of false positive at issue was severely underestimated.

In their presentation to the MPPRC, OB noted that based on the statistical plan, once the low dose was not statistically significant in Study 302 then further statistical analyses of secondary endpoints should have stopped. In addition, they noted that when focusing on the post-amendment 4 population, the low dose in study 302 had a greater change in the CDR-SB than the high dose in Study 302, calling into question that high dose is consistently associated with greater clinical improvement, one of the assumptions in the subgroup analyses in 301 that was used to explain why the results do not detract from the results of 302. In addition, because APOE non-carriers received high dose throughout the study they generally have higher dose exposure than APOE +; however, their clinical response was generally lower than APOE carriers in 301 and 302. With respect to dose and clinical outcomes, in 301, a comparison between the low and high dose after Amendment 4, showed that the change in CDR-SB was comparable, again calling into question whether dosing differences in the high dose cohorts of Studies 301 and 302 are an explanation of the discordant results.

The statistical reviewer also noted that there seemed to be a greater decline in the placebo group in Study 302 after Protocol Amendment 4 compared to Study 301 which may have contributed to the positive results in Study 302, although the Division noted that the decline in 302 was always below 2.0, which was the presumed decline for the power analyses.

The statistical division also had questions about the significance of the difference in the rapid progressors in 301 vs 302 as explaining the negative study.

The statistical division showed their analyses that there is little to no correlation between biomarker change and clinical endpoint change at the patient level in study 302. Also, at the study level, across studies the strength of the biomarker relationship to the clinical effect is limited and hinges on the smaller, shorter, weaker designed study 103. The statistical reviewer noted that the proportion of the clinical treatment effect explained by the change in the

biomarker at Week 78 for study 302 was numerically lower for the high dose than the low dose and the confidence interval for the proportion of the high dose treatment effect explained by the biomarker change does not exclude 0% explained by the biomarker.

OCP showed how such analysis at the patient level can be misleading even when at a population level there is a strong correlation, using the example of QTc prolonging drugs as an example. OCP and the Division reached a different conclusion regarding the strength of the association between the biomarker and the clinical effect in all three studies. OCP pointed out that the approach they have applied is the standard methodology.

With respect to Study 103, the statistical reviewer noted that the clinical endpoints were exploratory with no control for multiplicity and the pooling of the placebo arm for the analysis of the 10 mg/kg arm was not consistent with the randomization scheme. It was noted that there were a greater number of women and APOE+ patients in the pooled placebo group and in 103, the larger effect was seen in the APOE- patients rather than the APOE+ patients, as seen in 302.

MPPRC's input was sought on whether to approve aducanumab based on the evidence of effectiveness provided by these studies.

Discussion at the MPPRC Meeting

- Based on p-value for the primary endpoint, it was generally agreed that Study 302 was a positive study. However, it was acknowledged that the study had several issues such as a small absolute magnitude of effect (0.39 on a 18 point scale), early termination leading to a smaller dataset than planned, possible greater unblinding in the higher dose cohort due to greater incident of ARIA, somewhat greater placebo decline compared to that seen in Study 301, and limitations based upon the planned hierarchical testing strategy. Only a part of the study population completed the study (due to early termination), and all analyses thereafter were post hoc. Although some members considered potential unblinding as an issue, others did not express concern over it since the analysis done by the Division showed that the results were consistent in patients in Study 302 who experienced ARIA compared to those in the treatment group who did not, and that there was ARIA in the placebo group and all assessments were blinded. The statisticians expressed concerns with using the full alpha for this analysis.

- The trial design modification introduced by Amendment 4 introduces challenges in the interpretation of the data. Because patients with APOE ε4 were initially only given 6mg/kg, the APOE ε4 population had less opportunity to receive as many 10mg/kg doses. Had these patients been initially enrolled on the 10 mg/kg dose of aducanumab, the results may have provided more convincing evidence of efficacy.

- It was noted that once futility was declared, the study was closed, and the sponsor could have accessed the unblinded data before coming to meet with the Division. To address concerns about the Sponsor remaining blinded following the announcement of futility, the

Division investigated the Sponsor's data handling via an audit of sites common to Studies 301 and 302. The audit showed no evidence of problematic handling of the data. Additionally, the final analysis did not include data collected after the futility determination announcement in March 2019.

- One of the Council members noted that the overall mean treatment effect appeared small in magnitude. The Clinical Division noted that CDR-SB is designed such that any change on the scale represents a clinically meaningful change. The changes in the activities of daily living (ADCS-ADL-MCI) are particularly important and the 40% treatment effect is also a clinically meaningful change

- With respect to missing data, the statistical team did not agree that one could conclude that data are missing at random. MMRM implicitly imputes missing data from completers but there may not be enough overlap in model covariates between dropouts and completers due to changes in enrollment, especially with 70% missing (any model bias could be magnified and notably, some interactions between model covariates and study visit were nominally significant but not included in the primary analysis model).

- While the biomarker across all studies shows strong dose-related changes and there is a correlation in the positive study it was noted that selection of the SUVR convenience sample was based on patients who volunteered to be part of the sub-study. PET imaging was used to calculate biomarkers and was randomized between the three groups. The sub-study groups were consistent with the entire population.

- Although the effect size in study 302 was small, it was consistent and statistically significant. The absolute change from placebo translated across multiple functional domains, making it meaningful and robust. If clinical relevance was demonstrated, one Council member favored supporting approval.

Study 301

- There was consensus that Study 301 was clearly a failed study. However, there was some discussion on whether it could inform the totality of evidence.

- Despite negative result on primary endpoint, DN 1 argued that Study 301 did not directly contradict Study 302. They noted that the results in the low-dose arm were similar between Studies 301 and 302. Study 301 high dose had numerically favorable results for the two secondary endpoints, although not the MMSE. Patients with sustained exposure to the 10 mg/kg dose in Study 301 had results similar to patients in Study 302. The prespecified primary analysis for the high-dose arm yielded negative results (p=0.83). The concordance of biomarker and clinical outcome results in the low dose arms of 301 and 302, dose-response relationships in the two studies, and reliance on results supported by randomization during the exploratory analyses led some Council members to suggest that

301 did not detract from the persuasiveness of 302. However, others posited that the within-dose imbalances, highly complex (not univariate) correlation in the high dose, and multiple confounders reduced confidence in the data.

- The Division argued that contributions to Study 301 failing included a combination of factors, including power and exposure. A disproportionate number of patients with a rapid rate of disease progression were randomized into the high-dose arm, and patients did not receive the same exposure to drug in Study 301 as in 302. Besides this, Study 302 was initiated after Study 301 rather than concurrently, but the analyses were conducted with the assumption of concurrency. Additionally, it was argued that the primary efficacy analysis of study 301 was heavily influenced by a subset of pre-amendment outlier data. However, as noted above, the Statistical reviewer presented another perspective on the impact of the progressors in 301, noting that exclusion of 3 of the 4 outliers in 301 does not result in a change in the results. The committee did not discuss the selective nature of this perspective or the extensive discussion of the outlier issue in the background materials indicating that the study was sensitive to outliers across a range of cutoffs.

- The Office of Clinical Pharmacology argued that the impact of missing data on the overall study result is negligible for the exposure-response analysis because Studies 301 and 302 both followed a similar linear course of disease progression within the study duration.

Study 103

- Study 103 provided very useful information based upon prespecified clinical and biomarker endpoints. It indicated a dose-response relationship for brain amyloid reduction, captured several clinical outcomes, and provided compelling biomarker data. The pharmacodynamic effects provide important insights into the role of beta-amyloid in AD. However, the study was small and had many dropouts, which were later determined to be due to ARIA.

- The treatment effect of Study 103 was larger than that for Study 302. Several explanations were offered. Patients in Study 103 received 10 mg/kg from their first dose whereas those in Study 302 did not receive the 10 mg/kg dose until Week 24 (to mitigate ARIA). In a small subset of 302 patients who consistently received 10 mg/kg doses, the treatment effect was similar to that in Study 103. Similar reductions in brain amyloid were achieved at Week 54 in Study 103 and Week 78 in Study 302. Study 103 was conducted solely in the United States. The treatment effect in the United States population of Study 302 was larger than the overall treatment effect. Study 103 enrolled patients with more severe AD than Study 302, who therefore had greater scope for improvement.

- According to some Council members, data from Study 103 could be considered supportive early phase clinical data or mechanistic evidence and this could be used to support the

results from Study 302. Although others agreed, they also stipulated that it could be considered supportive only after a third AWC trial was conducted in light of study.

- One Council member argued that although Study 103 yielded compelling data, it was an early phase study and it is the success of early phase studies that prompts subsequent studies. It was argued by one Council Member that to allow a phase 1b study to be confirmatory evidence would be tantamount to rewriting the level-of-evidence standard.

Overall Considerations and Recommendations

- There was consensus that Study 302 was positive despite the complexities of its underlying data. It was not considered robust enough to be sufficient to meet substantial evidence of effectiveness on its own especially given a replicate negative trial.

- There was consensus that Study 301 was negative. However, some Council members considered the data obtained from this study to be informative, and not necessarily entirely conflicting with Study 302; other Council members were not persuaded that this was not in conflict with Study 302.

- Study 103 was positive but as a small study with many dropouts, it was not clear it was sufficient to provide the confirmatory evidence for 302 and regardless, with the results of Study 301, most did not think there was substantial evidence of effectiveness.

- Approval requires two AWC trials or one AWC trial and confirmatory evidence. Considering the compelling biomarker data from Study 103 and the consistency of aducanumab's pharmacological effects on β-amyloid, one Council member deemed the clinical development program for aducanumab as having demonstrated substantial evidence of effectiveness, but other Council Members considered that the evidence threshold for substantial evidence on clinical benefit had not been met. There was one proposal to consider how to grant AA, recognizing the preliminary data on effectiveness and leveraging AA to get confirmatory data.

Path Forward

- One Council member noted that if approved, this drug would potentially be used by millions of patients. For this reason, it was argued that it is critical that the decision for standard approval be made from a place of certainty on clinical benefit.

- However, most Council members did not agree that the evidence package met the threshold for substantial evidence of effectiveness for standard approval. Several Council members felt strongly that clinical benefit had not been established, others opined that the evidence was highly suggestive of benefit but agreed that substantial evidence for clinical

benefit had not been reached. One Council member pointed out that in this case the consequences of a type I error would be worse than those of a type II error, in that a false positive would result in millions of patients taking aducanumab without any indication of actually receiving any benefit, or worse, cause harm due to the relatively prevalent ARIA.

- In general, most Council members recommended a third AWC trial, the design of which would be based on the lessons learned from Studies 301 and 302, particularly the importance of exposure and could be done as efficiently as possible

- In contrast to other comments, one senior leader noted that given the huge unmet need, progressive irreversible disease, with patients waiting for treatments and willing to accept some uncertainty, that the group should consider the option of approval using AA, with a subsequent PMR study to confirm benefit. It was noted that this approach has been effective in oncology, providing patients access to potentially life-saving treatments without delay, while ongoing studies are intended to confirm benefit. There was no further discussion about the applicability of AA for aducanumab, as this option had not been presented or otherwise discussed.

Council Members

Peter Stein, OND
Jacqueline Corrigan-Curay, OMP
Patrizia Cavazzoni, CDER
Robert Temple, CDER
Gerald Dal Pan, OSE
Mark Levenson, OB
Issam Zineh, OCP
Judith Zander, OSE/OPE
Mary Thanh Hai, OND
James Smith, OND/ONDP/DCP
John Farley, OND/OID
Ellis Unger, OND/OCHEN
Aliza Thompson, OND/OCHEN/DCN
Steven Lemery, OND/OOD/DO3
Christine Nguyen, OND/ORDPURM/DUOG
Kayla Holman, Project Manager

Team Members

Billy Dunn, ON
Eric Bastings, ON
Kevin Krudys, ON/DN1
Tristan Massie, OB
Kun Jin, OB
Sue-Jane Wang, OB
Hsien Ming J Hung, OB
Yaning Wang, OCP
Gopichand Gottipati, OCP
Mike Bewernitz, OCP
Vishnu Sharma, OCP
Atul Bhattaram, OCP
Sabarinath Sreedharan, OCP
Hao Zhu, OCP
Ramana Uppoor, OCP
Mehul Mehta, OCP

PRE-DECISIONAL/DELIBERATIVE
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Internal Review of FDA-Biogen Interactions for Aducanumab BLA
Findings and Analysis
May 30, 2021

I. PURPOSE

The purpose of this review is to examine the interactions of CDER staff with Biogen, the sponsor of the biologics license application (BLA) for aducanumab, in preparation for and during the November 6, 2020 Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee (AC) meeting. The main objective of this review is to determine whether those interactions were consistent with current FDA policies and procedures and, if so, whether potential changes might nonetheless be considered in light of our findings pursuant to this internal review. Public Citizen has asserted that the Center's objectivity may have been compromised in its interactions with Biogen, and there have been some similar implicit critiques from certain AC members.

II. BACKGROUND

In a letter to Dr. Woodcock dated January 28, 2021, Public Citizen alleged that interactions and coordination between FDA and Biogen before and after the submission of Biogen's BLA for aducanumab were inappropriate.[1] Specifically, Public Citizen alleged that CDER staff improperly collaborated with Biogen in preparing for and conducting the AC Meeting on November 6, 2020, to discuss scientific and clinical issues related to aducanumab's efficacy and safety. According to Public Citizen, these interactions "dangerously compromised the independence and objectivity of senior staff and clinical reviewers."

Dr. Woodcock responded to Public Citizen in a letter dated February 11, 2021, in which she emphasized that FDA takes the allegations very seriously and will continue to consider the issues raised.[2] She also described relevant FDA principles and practices that highlight FDA's commitment to maintaining scientific integrity, to reviewing results without bias, and to basing regulatory decisions on the drug trial results and their implications for safety and effectiveness.

In addition to the Public Citizen allegations, several AC members commented that the AC briefing materials seemed to selectively identify lines of argument which would be supportive of approval, the sponsor's position, but did not seem to give equal weight to lines of argument that detracted from that conclusion.

[1] See Appendix 1 for a copy of Public Citizen's letter.
[2] See Appendix 2 for a copy of FDA's response to Public Citizen.

PRE-DECISIONAL/DELIBERATIVE
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In response to these concerns, Dr. Cavazzoni, Director of CDER,[3] requested the Office of Medical Policy to conduct an examination of FDA-Biogen interactions in preparation for and during the AC meeting in light of current policies.

Methodology

Our review is based on multiple sources. We reviewed the available minutes for relevant meetings for the Investigational New Drug Application (IND) and BLA for aducanumab. A timeline of the Type C meetings that occurred between June 2019 and June 2020 and a description of the issues that were raised in those meetings, as well as other relevant events, are provided at Appendix 3. We also reviewed the transcript and the final summary minutes from the PCNS Drugs Advisory Committee Meeting held on November 6, 2020. In addition, we reviewed FDA guidance documents and policies pertaining to communications between FDA and sponsors or applicants during the drug development process, FDA principles and practices to ensure the integrity of the scientific and regulatory processes and those relating to good review management, conduct of AC meetings, and scientific dispute resolution.

To further our understanding, we discussed the matter with staff in CDER's Office of New Drugs, Office of Neuroscience, including review staff in the Division of Neurology I, as well as staff in CDER's Office of Translational Sciences, Office of Biostatistics, Division of Biometrics I. We also spoke with staff in the Office of Oncologic Diseases to gain insight into that office's experience in piloting the use of a joint briefing document for an AC meeting.

III. FDA GUIDANCE AND POLICIES

FDA's timely interactive communication with sponsors during drug development is a core Agency activity to help achieve its mission to facilitate the conduct of efficient and effective drug development programs.[4] In the HHS Office of Inspector General's (OIG) report on "FDA's Review Process for New Drug Applications" (March 2003), OIG recognized FDA's strength of effectively working collaboratively with sponsors and providing valuable advice that can help speed up the drug development process.[5] FDA guidance documents and internal policies encourage FDA communication with sponsors as a way to ensure transparency and clarity throughout the review process, as well as provide practices and processes to ensure that those communications are appropriate.[6]

[3] The permanent appointment of Dr. Cavazzoni as Director of CDER was announced on April 12, 2021.
[4] PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022, available at https://www.fda.gov/media/99140/download.
[5] The report is available at https://oig.hhs.gov/oei/reports/oei-01-01-00590.pdf.
[6] See Appendix 4 for a table of policy documents reviewed.

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In particular, FDA guidance recommends that FDA review staff play active roles during drug development by providing advice and feedback to sponsors on both specific trials and overall development programs.[7] Applicant and sponsor involvement is "important to good review management and helps to ensure transparency and clarity."[8] To that end, FDA guidance sets out avenues through which important issues can be discussed by FDA and sponsors or applicants.[9] The *CDER 21st Century Review Process – Desk Reference Guide* describes the review activities and processes required for new drug applications and biologics license applications, including the types of communications that take place during the review process and best practices for AC meetings.[10]

In addition to communications with sponsors or applicants, during the review process "[t]imely and frequent review team collaboration is critical to good review management." FDA guidance makes it clear that the review team should communicate with supervisory personnel "early and often to ensure alignment on the approach to review and to maintain awareness of issues identified during the review cycle."[11] In the event that scientific or regulatory issues arise that would benefit from further discussion with upper management and review peers, a CDER Regulatory Briefing may be held or discussion at a CDER Medical Policy and Program Review Council (MPPRC) meeting may be requested.[12]

Furthermore, FDA has issued numerous guidance documents and policies that provide FDA staff with principles and practices to ensure the integrity of the scientific and regulatory processes, focusing on public health considerations and ensuring independence and scientific excellence as cornerstones of FDA's work. FDA's Staff Manual Guide (SMG) 9001.1, *Scientific Integrity at FDA*, provides key principles of scientific integrity at FDA, including the requirement of a fair and transparent approach to resolving internal scientific disputes.[13] Similarly, FDA's SMG 9010.1, *Scientific Dispute Resolution at FDA*, sets forth mandatory elements to be included in all scientific dispute resolution processes and clarifies that "disputes should be resolved whenever possible at the working level within the organization, and after full and frank discussion

[7] Guidance for Industry and Review Staff – *Best Practices for Communications Between IND Sponsors and FDA During Drug Development*, available at https://www.fda.gov/media/94850/download.
[8] Draft Guidance for Industry and Review Staff – *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications*, available at https://www.fda.gov/media/72259/download.
[9] Guidance for Industry – *Formal Meetings Between the FDA and Sponsors or Applicants,* available at https://www.fda.gov/media/72253/download.
[10] *CDER 21st Century Review Process – Desk Reference Guide,* available at https://www.fda.gov/media/78941/download; MAPP 4180.4, *NDAs/BLAs: Using the 21st Century Review Process Desk Reference Guide*, available at https://www.fda.gov/media/80084/download.
[11] Draft Guidance for Industry and Review Staff – *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications*, available at https://www.fda.gov/media/72259/download.
[12] See *Charter of the Medical Policy and Program Review Council (OND Program Review Council)*, http://inside.fda.gov:9003/downloads/CDER/OfficeofMedicalPolicy/ImmediateOffice/UCM640745.pdf.
[13] The SMG is available at https://www.fda.gov/media/82932/download.

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involving interested parties."[14] Importantly, CDER's MAPP (4151.8), *Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions*, explains CDER's policy on participation of various disciplines and organizational components in the decision-making process and the resolution of disputes. If one of the disciplines cannot align with a pending interdisciplinary decision, the decision should be escalated up the management chain; if alignment cannot be achieved within an office, the decision should be raised to the Center Director or his or her designee.[15] This MAPP specifically recognizes that there will be a signatory authority but that, regardless of where the signatory authority resides, decisions are made only after all appropriate expertise is brought to bear. In addition, the MAPP notes the following: **If one of the disciplines or organizational components cannot align with a pending interdisciplinary decision because the proposed action is believed to be counter to law, regulation, interpretation of data, or existing precedent without adequate justification for deviation, or will result in a significant adverse impact on public health and safety, the decision should be escalated**. (bold in original)

IV. FINDINGS

A. The collaboration between FDA and Biogen in preparation for and during the AC meeting was typical in that CDER staff were proactive and engaged in order to fully understand the data. The extent of the collaboration exceeded the norm in some respects, but given the public health implications – potentially the first disease modifying drug for Alzheimer's disease – and the unusual evidence package (one positive and one negative study, which were identically designed and both stopped prematurely for futility), the increased interactions and guidance from FDA were consistent with the Agency's public health mission.

A review of FDA guidance documents and policies and discussions with CDER staff underscored that FDA's interactions with sponsors are critically important to the development of therapeutic products. According to CDER staff involved with the review of the aducanumab BLA, the collaboration between FDA and Biogen was typical in some respects and unusual in others. The Director of the Office of Neuroscience felt that they were following CDER policy, including statements to review staff by the now Acting FDA Commissioner, Dr. Woodcock, during her tenure as CDER Director, to be proactive and engage with sponsors in the interest of fully understanding the data. Both the clinical team in the Office of Neuroscience and the statistical reviewer in CDER's Office of Translational Sciences, Office of Biostatistics, Division of Biometrics I (hereinafter referred to as the

[14] The SMG is available at https://www.fda.gov/media/79659/download; see also CDER MAPP (4151.1), *Scientific / Regulatory Dispute Resolution for Individuals Within a Management Chain*, available at https://www.fda.gov/media/71608/download.
[15] The MAPP is available at https://www.fda.gov/media/79353/download.

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Division of Biometrics I), described the meetings with the sponsor as collaborative and supported by leadership.

However, both the clinical reviewer from the Office of Neuroscience, Division of Neurology I, and the statistical reviewer from the Division of Biometrics I, acknowledged that the circumstances surrounding the review of the BLA, as well as the amount of time and effort spent on the review and extent of the collaboration, were atypical. For example, in order to try to understand why the results of the two identically designed studies at issue were so different, the clinical reviewer in the Office of Neuroscience reported meeting regularly with the sponsor between Type C meetings, which is not typical of other development programs. According to the Director of the Office of Neuroscience, when there is one study in which the drug appears to work and another study in which it does not, reviewers should try to understand the data to ensure they are making the right decision on next steps. Note that between the documented Type C meetings there were working meetings between the sponsor and FDA that were recorded by the sponsor and records documenting the meetings were shared with the clinical team in the Office of Neuroscience, Division of Neurology I; however, documentation from those meetings was not consistently maintained in FDA's document archival system.

At the Type C meeting that occurred on June 14, 2019 (the first after Biogen's futility declaration on March 21, 2019), Study 302 was described by the clinical team in the Office of Neuroscience as exceptionally persuasive on several of the instruments used to evaluate efficacy if not confounded by early termination. Given the Office of Neuroscience Director's assessment that this study might be not only positive but "a home run," the decision to work proactively with the sponsor, especially given the public health implications (taking into account the large unmet medical need), is consistent with FDA policy. The Office of Neuroscience felt that the extent of the collaboration was warranted to understand how Study 302 could have such an apparently positive outcome and an identically designed study (Study 301) was negative. In this initial meeting, the Office of Neuroscience laid out the potential options that would guide the exploratory analyses, *including the possibility that the drug was ineffective or that another study would need to be conducted*, demonstrating that the team had not reached any conclusions prior to conducting their analyses:

1 – Adequate evidence exists to conclude that aducanumab is ineffective

2 – Study 302 establishes effectiveness; Study 301 provides supportive data; standard (full) approval

3 – Study 302 establishes effectiveness; Study 301 does not provide supportive data but is understood well enough to be dismissible; standard (full) approval

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4 – Accelerated approval based on a persuasive effect on amyloid reduction, accompanied by a reasonable likelihood of clinical benefit based on the available clinical results

5 – Conduct an additional clinical study based on the suggestion of effectiveness seen thus far in the clinical development program that, after further detailed exploration and consideration, proves inadequate to independently establish effectiveness.

Given the Division of Neurology I's initial assessment that Study 302 may be exceptionally persuasive and there is an unmet medical need, the decision to engage in analysis to determine which of the five potential conclusions (options) for the application was supported by the data was reasonable and consistent with FDA policy.[16]

B. The scientific dispute between the Office of Neuroscience and the statistics team in the Division of Biometrics I was not addressed early enough in the process, making it difficult to engage up the management chain in advance of the Advisory Committee meeting.

Both the clinical team in the Office of Neuroscience and the statistics team in the Division of Biometrics I were present and contributing at the early meetings held with the sponsor. When the meetings between the clinical team in the Office of Neuroscience and the sponsor shifted to the exploratory analysis phase, starting around October 2019, for reasons discussed below, the statistics team in the Division of Biometrics I was not as involved with the exploratory analyses, although the statistics team was present for all Type C meetings that were held.

To provide more detail, the first analysis (Wave 1) determined whether the declaration of futility and the stopping of both trials rendered the data noninterpretable. This was done in collaboration with the Office of Biostatistics. The next part of the analysis (Wave 2 and 2+) was to understand Study 301 and whether it detracted from the finding in Study 302, and in particular, whether there were patients in Study 301 that seemed to have the same outcomes as 302. Much of this was conducted focusing on the PK/PD analyses of both trials. The clinical reviewer in the Division of Neurology I stated that the statistics team in the Division of Biometrics I was not engaged in, and possibly not comfortable with, the Wave 2 and 2+ exploratory analyses, and some comments made during Type C meetings seem to reflect the statistician's reservations about post-hoc analyses, especially those that did not maintain randomization. The statistical reviewer in the Division of Biometrics I stated that once the focus turned to the PK/PD analyses, the Division of Neurology I communicated that the

[16] See, e.g., FDA's SMG 9001.1, *Scientific Integrity at FDA*, available at https://www.fda.gov/media/82932/download; *Guidance for Industry and Review Staff – Best Practices for Communication Between IND Sponsors and FDA During Drug Development*, available at https://www.fda.gov/media/94850/download.

statistical team were no longer needed and they were not invited to the working group meetings for the Wave 2 analyses. The statistical reviewer also noted that the primary clinical reviewer in the Division of Neurology I was previously a clinical pharmacology reviewer and so additional input from the Division of Biometrics I was not necessary. However, some of Wave 2 went beyond PK/PD analyses. For example, according to the primary statistical reviewer in Division of Biometrics I, although he suggested propensity score matching as a potential exploratory approach, they were not consulted on the final details of the propensity score matching model used in the integrated summary of efficacy. Therefore, the Division of Biometrics I was not very engaged in such exploratory analyses that were undertaken for Study 301 between October 2019 and the filing of the BLA in July 2020.

By the October 2019 Type C meeting, the Division of Neurology I expressed that Wave 1 and Wave 2 had been completed. FDA communicated to the sponsor that the evidence reviewed at that stage indicated that the above options 2 or 3 (both supporting full approval), or a hybrid of options 2 and 3, were the most appropriate path forward. Therefore, a year before the submission of materials to an AC, the Division of Biometrics I understood the direction the Office of Neuroscience was leaning towards possible approval. Of note, in September 2019, the statistical reviewer in the Division of Biometrics I had presented at an internal Office of Biostatistics Rounds on this application with the conclusion that substantial evidence of effectiveness was not met. Leadership from the Office of Biostatistics participated in these rounds but the clinical team from the Division of Neurology I that was reviewing the application did not. There is no evidence that there was a discussion in October 2019 between the Office of Neuroscience and the Division of Biometrics I regarding these diverging assessments. However, as noted below, the Division of Biometrics conveyed their reservations regarding the evidence to the Division of Neurology 1 and the applicant in Type C meetings.

The BLA was filed on July 7, 2020 and, at the filing meeting on July 22nd, it was determined that it would not only be a priority review but expedited with the goal of a decision by December 2020. A decision that the application would go to an AC was communicated in the pre-BLA meeting.[17] This meant that an AC meeting needed to be scheduled by October. The respective disciplines began their reviews.

The clinical team in the Office of Neuroscience expected the focus of the review from a statistical reviewer to be on the effectiveness of Study 302, because the statistics team in the

[17] FDA's written responses from the pre-BLA meeting stated: "The final determination regarding the need for an Advisory Committee meeting will be determined during review of your complete marketing application. At this time, it is reasonable to plan for the occurrence of an Advisory Committee meeting during the conduct of the review of the application."

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Division of Biometrics I considered Study 301 a negative study. The statistics team in the Division of Biometrics I noted that the Office of Neuroscience Director told them during the filing meeting that their review should focus on Study 302 and that they did not have to review Study 301. The clinical reviewer in the Division of Neurology I stated that the statistical review was not a traditional review because it did not focus primarily on Study 302. The Division of Biometrics I Director felt that it was their role to review the totality of the evidence, not just Study 302. Although explanation for the limited interactions between the clinical and statistical teams between filing and mid-cycle cannot be fully explained from the available information, their difference in expectation regarding the focus of their reviews may have contributed.

There are different perspectives on when it became apparent that the Office of Neuroscience and the statistics team in the Division of Biometrics I had very different views on whether there was substantial evidence of effectiveness to support the approval of aducanumab. The statistics team in the Division of Biometrics I noted that they had expressed reservations multiple times regarding the analysis of Studies 301 and 103, but it appeared that the clinical team in the Division of Neurology I considered those reservations understandable because the statistics team was not comfortable with exploratory analyses of the type that needed to be done to understand Study 301: subgroup analyses of a failed study that included some comparisons that did not follow randomization. Perhaps because the Office of Neuroscience expected the statistical review to focus on study 302, and there was alignment that Study 302 was interpretable and a positive study, the Office of Neuroscience and the Division of Biometrics did not engage earlier on their different assessments regarding substantial evidence.

Per the clinical reviewer in the Division of Neurology I, by the mid-cycle, around mid-September 2020, the divergence between the clinical team in the Office of Neuroscience and the statistics team in the Division of Biometrics I became more apparent in their meetings. However, the Office of Neuroscience did not understand the degree to which there was disagreement until approximately 10 days before the due date for the AC briefing package, when the statistical reviewer in the Division of Biometrics I provided an independent review to be included in the AC briefing package. According to the Division of Biometrics I, they had raised the issues included in the review during Type C meetings.[18] The Office of Neuroscience Director states that upon seeing the statistical review, he reached out to the Division of Biometrics I leadership to discuss the statistical review, which the Office of

[18] See Appendix 3 for a timeline of the Type C meetings, including a description of the issues that were raised in those meetings, and other relevant events.

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Neuroscience did not consider completely accurate.[19] According to the Office of Neuroscience Director, the Division of Biometrics I leadership insisted it was important to include a separate statistical review in the AC meeting joint review and, given the differences in scientific assessments, alignment prior to the AC meeting was not feasible. The Director of the Division of Biometrics I does not recall meeting with the Office of Neuroscience to discuss the statistical review.

In addition, on October 23rd, after the materials were filed to the AC but before the AC meeting had occurred, there was another Office of Biostatistics Rounds attended by leadership of the Office of Biostatistics including (per the Director of the Division of Biometrics I) the Office of Biostatistics Director, at which the statistical reviewer again presented his opinion that substantial evidence was lacking. At this meeting, the clinical reviewer in the Division of Neurology I also presented their assessment of why the application was approvable.

As previously noted in this report, FDA has many guidance documents and policies that provide staff with principles and practices to ensure the integrity of the scientific and regulatory processes, including the resolution of internal scientific disputes. FDA policy encourages resolution of disputes whenever possible at the working level within the organization, after full and frank discussions involving all interested parties.[20] If a dispute cannot be resolved within an office, the issue should be escalated up the management chain, including to the Center Director.[21]

While the extent of the disagreement may not have been known until a month before the AC meeting, the escalation that occurred seemed to have stopped at the Office Director level in the Office of Neuroscience and the Division Director level in the Office of Biostatistics. At about the time the materials were due to the Advisory Committee, the Office Director of the Office of New Drugs first became aware of the interdisciplinary dispute. It is not clear whether the closeness of the impending AC meeting led to a decision to not escalate the dispute up the management chain. Both the clinical and statistical reviewers acknowledged that to delay the AC meeting to seek alignment would have been very difficult if the commitment to complete the review by December was to be met.

[19] For example, the Office of Neuroscience felt their analysis had addressed the issue raised regarding potential unblinding due to amyloid-related imaging abnormalities (ARIA) [an adverse event of special interest] and impact on outcomes in Study 302.
[20] FDA SMG 9010.1, *Scientific Dispute Resolution at FDA*, available at https://www.fda.gov/media/79659/download.
[21] CDER MAPP (4151.8), *Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions*, available at https://www.fda.gov/media/79353/download.

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C. The preparation of a joint FDA-sponsor Advisory Committee briefing document in this case, where two disciplines within CDER were not aligned, may have contributed to the impression expressed by Public Citizen that FDA's objectivity may have been compromised.

While FDA's guidance on Advisory Committee briefing documents, *Advisory Committee Meetings – Preparation and Public Availability of Information Given to Advisory Committee Members*,[22] contemplates that there be separate briefing documents from FDA and the sponsor, there is no legal requirement for separate documents and FDA may depart from the guidance, provided staff document the rationale and get supervisory concurrence. In 2019, the Office of Oncologic Diseases rolled out a pilot program that introduced the use of the combined FDA-sponsor AC briefing document to cut down on the duplication of facts and to streamline the information provided to the AC. Before initiating the pilot program, the Office of Oncologic Diseases communicated the rollout to their AC and asked for feedback on the use of the joint briefing document. They have since received positive feedback on the pilot program and frequently use joint briefing documents for their ACs. However, staff within the Office of Oncologic Diseases recognize that the joint briefing document would not be ideal in cases in which there is an internal disagreement between review disciplines.

In the case of the aducanumab AC meeting, the Office of Neuroscience made the decision to prepare a joint FDA-sponsor briefing document, in part, to avoid duplication of materials and information provided to the AC. The statistics team in the Division of Biometrics I, however, noted that they had not expected the use of a joint document as this was not discussed at the mid-cycle meeting and they first learned of this approach when they received the document for comment. Per the statistical reviewer in the Division of Biometrics I, the statistics team was not involved in writing any sections of the joint document prior to receiving it for comment and the joint document was received two or three days before comments were needed. A meeting between the Division of Neurology I and the Division of Biometrics I was then held to discuss the comments. Per the Division of Neurology I, several changes were made to the joint document in response to the Division of Biometrics I comments on the joint document.

The briefing document, however, does not appear to give equal weight to the Division of Neurology I and Division of Biometrics I perspectives, in part likely due to the difficulty of summarizing an FDA position in the joint document that reflects such divergent views. The joint part of the document arguably lays out a more favorable perspective for approval upfront. One of the difficulties in judging the document, in retrospect, is that the Office of Neuroscience concluded that their analyses had already adequately addressed some the statistician's critiques, and this was reflected in the joint review. According to the statistical

[22] The guidance is available at https://www.fda.gov/media/75436/download.

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reviewer in the Division of Biometrics I, the statistics team prepared their own presentation for the AC meeting and there were no practice sessions with the Division of Neurology I. The statistical and the clinical reviewers' presentations for the AC were prerecorded.

The inclusion of the Division of Biometrics I's review as the final appendix, starting at page 246 of 300+ page briefing document, and only labeled in the table of contents as Appendix 2 (which was consistent with the clinical review being labeled as Appendix 1), may have been perceived by outside stakeholders as giving that review less weight, particularly given the stark disagreement between the disciplines. In addition, given these very divergent positions, the opening presentation by the Office of Neuroscience Director, which made a strong case for approval, may have been perceived by outside stakeholders as not adequately addressing the points made in the statistical review. The Office of Neuroscience may have miscalculated that their analysis would adequately address for the AC members the issues raised by their statistical colleagues. Of note, in discussions with the Office of Oncologic Diseases regarding applications going to an AC in which there was internal disagreement within the review team (admittedly rare), they stressed the need to be very objective in their presentation to an AC and noted that they would hesitate to use the joint briefing document in that situation.

V. CONCLUSION

It is clear that CDER staff spent significant time and effort on the review of the BLA for aducanumab in order to thoroughly understand the development program and to be able to come to a decision that is in the best interest of public health and the patients who so desperately need a safe and effective treatment for Alzheimer's disease. FDA has often used incremental resources and efforts to further the development of safe and effective treatments for diseases such as Alzheimer's that have unmet medical needs. There is no evidence that these interactions with the sponsor in advance of filing were anything but appropriate in this situation.

The following observations are intended to support recommendations that could be used to move forward and enhance processes that could prospectively prevent the situation that prompted this review in the future.

First, further discussion of the roles of the respective disciplines may be warranted. This application was very unusual in that there was a positive study, for which the statistical review was relatively straightforward, and an identically designed negative study, which from a statistical perspective should be rejected as evidence of effectiveness. However, to comprehensively evaluate for the presence or absence of evidence of effectiveness, further exploratory analyses were critical. While OND's Office of Neuroscience has signatory authority for this original BLA, one question is where is the appropriate balance between focusing on each

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discipline's expertise and working as a unified cross-disciplinary team? The assessment by the Office of Neuroscience that the statistical involvement and interests should be largely limited to Study 302, and perhaps Study 103, rather than the exploratory analysis of Study 301, may have led to some compartmentalization of roles and a lack of acknowledgement that both the Office of Neuroscience and the Division of Biometrics I had equities in the decision regarding whether substantial evidence was met. Such compartmentalization, which likely reflects a reasonable assessment as to where the primary expertise lies for different analyses, may have nonetheless contributed to a lack of understanding and dialogue earlier in the review and speaks to a potential need for discussions regarding the appropriate roles of statistical, clinical pharmacology and clinical review teams in application decisions.

The decision to expedite the priority review, understandable perhaps given the Division of Neurology I team's year-long review of the data, may have also contributed to the loss of opportunity to both recognize the degree of disagreement and to use the internal processes for broader cross-discipline or management input prior to going to an AC.

A desire to take a more innovative approach, similar to the Office of Oncologic Diseases, extended to the introduction of the first joint review document for a Neurology AC. Again, while reasonable to consider this approach outside of Oncology, the tight deadline to prepare the document and the compressed timeline to understand and resolve the differences in opinion within the review teams may have hindered cross-discipline alignment prior to the AC meeting. Given the internal disagreement between the Division of Neurology I and the Division of Biometrics I, and the lack of a unified FDA perspective on the data, the use of the joint briefing document was not an appropriate approach in this instance. In addition, the joint document and use of appendices for the opposing statistical review contributed to perceptions about a lack of balance in the clinical team's presentation of the data.

Finally, although questions remain regarding when exactly the disagreement between the Division of Neurology I and the Division of Biometrics I came to light, it is not clear that all efforts were exhausted to resolve the disagreement prior to the AC meeting. More importantly (since resolution of the disagreement may not have been achievable), prior to the AC meeting, the issue could have been elevated to the higher levels of management within the relevant CDER Super Offices or the Center Director. However, the pressures of an upcoming AC meeting and commitment to a December decision may have precluded further action in accordance with CDER policy.

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VI. RECOMMENDATIONS

A. Engage CDER leadership on further discussions regarding whether this application represents an isolated issue or reflects a need for further education regarding CDER's Equal Voice and the importance of a team culture.

CDER has instituted a number of policies and procedures to optimize high quality decision-making, including several on the resolution of scientific and/or regulatory differences of opinion within a management chain. The EV initiative was developed to ensure that, regardless of where the signatory authority resides, decisions are made only after all appropriate expertise is brought to bear. EV notes that this is accomplished by an environment that requires open communication and exchange of ideas in a mutually respectful professional environment, and the full and open participation of all relevant disciplines and organizational components in the decision-making process.[23]

What is most notable in this case is the apparent lack of awareness, right up to the deadline for submission of the AC materials, of the degree to which there was lack of concurrence on the application. Regardless of whether the Office of Neuroscience was the ultimate decision-maker for an approval or a complete response, in over a year of collaborations with the sponsor and a number of Type C meetings, communication around this fundamental question seemed lacking until the need to communicate FDA's perspective for the AC. This timing largely precluded the ability to seek alignment through escalation beyond the Office of Neuroscience and the Division of Biometrics I, as would be expected in CDER MAPPs. Indeed, the EV MAPP acknowledges the importance of raising concerns in a timely manner, and that concerns raised late in the EV process, and/or close to the deadline, by any party, are difficult to incorporate in timely decision-making.

A key issue in this case may be the interpretation of relevant disciplines' role in the decision. While the EV MAPP acknowledges that the decision-maker may not have considered each discipline's perspective to carry equal importance when reaching a conclusion, EV gives all disciplines and organizational components the opportunity to voice their concerns. The MAPP contains an example to illustrate that point. If a decision to be made is central to regulation of pharmaceutical quality, then the quality staff have a key role in the decision-making process and may plan to raise the matter to higher level staff if the decision is in conflict with existing policy. On the other hand, if a quality issue arises that toxicology and clinical need to be aware of but does not impact quality policy then it is not crucial to policy

[23] MAPP 4151.8, *Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions*, available at https://www.fda.gov/media/79353/download.

in the quality area, and the quality discipline representatives simply need to ensure that their analysis has been considered in making the decision.

A key question is whether the differing interpretation of the respective roles of the Division of Neurology I and the Division of Biometrics I in the decision around whether there was substantial evidence of effectiveness led to a siloed team and less opportunity for the type of exchange on the question of substantial evidence of effectiveness that eventually was aired in the AC briefing materials. The Office of Neuroscience considered that the statistical review should have primarily been focused on Study 302, which was to be used to support substantial evidence of effectiveness. Study 301 was a failed trial from a statistical perspective, and therefore, any analysis of those data was exploratory and focused on clinical and PK/PD parameters. The Division of Biometrics I considered their role more broadly and in addition to aligning on whether the early termination of the trials rendered the data uninterpretable, they considered their role to include input into the question of substantial evidence of effectiveness, taking into account the totality of evidence.

Ultimately, the Office of Neuroscience is the signatory body and the Division of Biometrics I acknowledged that the exploratory analysis done with respect to Study 301 was more about PK/PD and not their expertise. However, these reasonable work assignments based on discipline expertise may have also led to a lack of engagement on the fundamental questions around approvability, missing the opportunity to identify earlier that one discipline felt that the decision being contemplated was inconsistent with the regulatory standard of substantial evidence. However, this is a single case, and an unusual case at many levels. The question for CDER leadership is whether this is an isolated case, in which case sharing a root cause analysis with the team should be sufficient, or whether it is a sign of a more systemic issue for which new policies or training may be warranted. A conversation with CDER leadership regarding the need for any further internal guidance or education on roles, responsibilities, team culture and the need for proactive processes for raising issues may be warranted.

B. Recommend that Office Directors and Super Office Directors, as applicable, be briefed in a timeframe that would allow further escalation of any issues before an AC meeting.

It is not clear that the complexity of the application and potential for discordant views were adequately communicated to senior leadership within the respective offices. This was a highly unusual application that was proposed for full approval when identically designed, well-conducted pivotal trials were both stopped prematurely for futility, and where one was positive and the second was negative. Such an application is not only precedent setting for the Office but also for CDER and should have had more visibility at the OND and CDER leadership level. Consider establishing a routine practice for staff to brief their office

leadership regarding any potential controversial issues to be presented to an AC well in advance of the deadline for submission of AC materials. Instituting processes to ensure this occurs with adequate time to allow for broader discussion should be considered.

C. Recommend using a joint FDA-sponsor AC briefing document only when there is a unified FDA perspective on the data.

Consider limiting the use of a joint FDA-sponsor AC briefing document to situations in which there is no internal disagreement within FDA and establish that is the case before committing to joint briefing documents. In the event of internal disagreement (among disciplines or within a discipline), efforts should be made to resolve the disagreement internally (by the parties involved and their management) before the AC meeting, in accordance with relevant FDA and CDER policy and procedures.[24] For example, it was suggested by the Division of Biometrics I that if a joint clinical-statistical review was planned, this may have provided an opportunity to better align or at least provide a better summary of the differences.

There may, however, be scenarios in which differing views may be brought to the AC for a presentation of the facts, and the AC meeting should then be structured such that there is a focus on discussion of the different perspectives. The AC would then be tasked with evaluating the various perspectives and make a recommendation. The use of a joint briefing document may not be optimal for such a situation.

D. Recommend maintaining documentation of interactions between the sponsor and FDA outside of Type C meetings in FDA's document archival system.

FDA should be encouraged to provide necessary information to sponsors outside of Type C meetings when it is in both parties' interest; therefore, such informal interactions are not unusual. In this application, there were numerous interactions, outside of Type C meetings, that arguably were more structured and characterized as workstreams. Per the clinical reviewer in the Division of Neurology I, the sponsor kept records of those meetings and provided those records to FDA in emails documenting the meetings. Review of the Type C meetings did not reveal a clear record of the number and nature of interactions between the sponsor and FDA that occurred outside of Type C meetings. If there are frequent interactions that are organized around joint analyses of the data on an ongoing basis, it may be advisable to either have the Type C meeting minutes generally describe the number and

[24] See FDA SMG 9010.1, *Scientific Dispute Resolution at FDA*; CDER MAPP (4151.1), *Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain*; CDER MAPP (4151.8), *Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions*.

nature of the interactions since the last Type C meeting or maintain informal notes, even if just a bulleted email summary, that can be placed into DAARTS.