FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) Meeting
November 6, 2020

QUESTIONS

Sponsors of marketing applications are required to establish a drug's effectiveness by providing substantial evidence of effectiveness. Adequate and well-controlled clinical investigations provide the primary basis for determining whether there is substantial evidence to support the claims of effectiveness. The substantial evidence requirement for effectiveness is generally met by the provision of evidence from two adequate and well-controlled trials. Substantial evidence may also be provided by one adequate and well-controlled large multicenter trial whose strength of evidence on mortality, severe or irreversible morbidity, or prevention of a disease with potentially serious outcome is not meaningfully different from that provided by two smaller adequate and well-controlled trials. Such a study would typically demonstrate consistent and clinically meaningful effects on distinct prospectively specified endpoints. Moreover, an effect on a meaningful, objective endpoint, such as certain imaging endpoints or other biomarkers, may complement a clinical endpoint. In these cases, the internal consistency across endpoints not only reduces the possibility of a chance finding but also may further support the clinical utility of the results.

1. **DISCUSSION**: The primary evidence of effectiveness presented in support of aducanumab for the treatment of Alzheimer's disease is provided by Study 302. Discuss the evidence of effectiveness provided by Study 302, viewed independently and without regard for Study 301, with particular consideration of the size of the study, design of the study, analysis of the results to assess the effects of the drug, and consistency of results among various subgroups in the study.

2. **VOTE**: Does Study 302, viewed independently and without regard for Study 301, provide strong evidence that supports the effectiveness of aducanumab for the treatment of Alzheimer's disease? YES/NO/UNCERTAIN

3. **DISCUSSION**: The primary evidence of effectiveness presented in support of aducanumab for the treatment of Alzheimer's disease is provided by Study 302. Study 103 is presented as supportive evidence of aducanumab's effectiveness. Discuss the evidence of effectiveness provided by Study 103.

4. **VOTE**: Does Study 103 provide supportive evidence of the effectiveness of aducanumab for the treatment of Alzheimer's disease? YES/NO/UNCERTAIN

QUESTIONS (cont.)

5. **DISCUSSION**: The application presents evidence in support of effects on the pathological hallmarks of Alzheimer's disease, including effects on amyloid beta, tau, and downstream markers of neurodegeneration, using multiple assessment modalities. Discuss the impact of these results.

6. **VOTE**: Has the Applicant presented strong evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology? YES/NO/UNCERTAIN

7. **DISCUSSION**: Study 301 was a negative study. Post hoc exploratory analyses were conducted in order to achieve maximum understanding of the partially discordant results of Study 301 and Study 302, and to determine if this understanding precludes independent consideration of Study 302. Additional contribution to the understanding of aducanumab's pharmacological activity and clinical effects is provided by the results of Study 103. In light of the exploratory analyses that were conducted and the results of Study 103, discuss the impact of the results of Study 301 on the consideration of the results of Study 302.

8. **VOTE**: In light of the understanding provided by the exploratory analyses of Study 301 and Study 302, along with the results of Study 103 and evidence of a pharmacodynamic effect on Alzheimer's disease pathophysiology, is it reasonable to consider Study 302 as primary evidence of effectiveness of aducanumab for the treatment of Alzheimer's disease? YES/NO/UNCERTAIN