LECANEMAB (BAN2401) INFUSION REACTIONS AND IMMUNOGENICITY: RESULTS FROM RANDOMIZED PHASE 2 STUDY AND AN OPEN-LABEL EXTENSION

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Introduction

- Lecanemab is a humanized IgG1 monoclonal antibody that preferentially targets soluble aggregated Aβ species (protofibrils) with activity at insoluble fibrils[1-5]
- Treatment with 10 mg/kg lecanemab has been shown to reduce amyloid positron emission tomography (PET) standard uptake value ratio (SUVr) and slow clinical decline in an 18-month, phase 2 proof-of-concept study (Study 201 Core) in early Alzheimer's disease with an open-label extension (OLE)[6-7]
- The present analysis aimed to review infusion-related reactions from Study 201 and the results of immunogenicity assessments from the completed lecanemab clinical trial

Methods

Study Design

- The Study 201 design has been previously published[6-7]
- Briefly, Study 201 was a multicenter, double-blind, placebo-controlled, phase 2 study conducted in 856 subjects with early Alzheimer's disease with an OLE
- Subjects were randomized to 5 lecanemab regimens: 2.5 mg/kg biweekly, 5 mg/kg monthly, 5 mg/kg biweekly, 10 mg/kg monthly and 10 mg/kg biweekly, or placebo
- In the OLE, subjects received the 10 mg/kg biweekly lecanemab dose

Inclusion/Exclusion Criteria

- Participants were required to have either mild cognitive impairment due to AD or mild AD dementia
- All subjects were confirmed amyloid positive via amyloid PET or cerebrospinal fluid (CSF) Aβ1-42 for eligibility
- Key inclusion criteria included objective impairment in episodic memory (Wechsler Memory Scale-IV Logical Memory II [WMS-IV LMII]), Mini Mental State Examination (MMSE) score equal to or greater than 22-28 at screening and baseline, and naïve to or on stable dose (12 weeks) of approved AD medications
- Subjects who participated in the Core study were eligible for the OLE as long as they met the inclusion/exclusion criteria of the OLE
- There was a gap period between the end of the Study 201 Core and OLE baseline when no treatment was provided. The gap period lasted for 9-59 months for all subjects who entered the OLE

Assessments

- Key efficacy assessments included: Clinical change on the Alzheimer's Disease Composite Score (ADCOMS), Clinical Dementia Rating-Sum-of-Boxes (CDR-SB), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog14), and biomarkers
- Key safety assessments included monitoring for adverse events coded using MedDRA version 24.0
- Infusion-related reactions were summarized by treatment group using descriptive statistics
- Analysis of anti-drug antibodies (ADA) and its impact on pharmacokinetics, pharmacodynamics, efficacy, and safety during Study 201 were undertaken
- All ADA and neutralizing antibody (NAb) assays were developed and validated in accordance with FDA guidance and were performed using a tiered approach

Results

Subjects

- In Study 201 Core, 856 subjects were randomized across 6 treatment groups
- In the OLE, 180 subjects were treated with 10 mg/kg lecanemab biweekly
- In the Core, 483 subjects were exposed to lecanemab for at least 6 months, and 363 subjects exposed for 18 months
- In the ongoing OLE phase, 165 subjects have been exposed to lecanemab for at least 6 months, with 77 subjects receiving lecanemab for at least 24 months by the cutoff date

Infusion-Related Reactions

- Infusion-related reactions were the most common adverse event associated with 10 mg/kg lecanemab biweekly treatment, with 19.9% (32/161) of subjects compared to 3.3% (8/245) of placebo subjects
- All events were mild/moderate in severity, most occurred with the first infusion, and resulted in a low rate of discontinuations (10 mg/kg lecanemab biweekly: 2.5%; placebo: 0.8%)
- Over 70% of subjects who initially experienced infusion-related reactions had no further reactions with preventative medications; Prophylactic treatment with antihistamines, corticosteroids, or anti-inflammatory drugs prior to future infusions may be considered
- In Study 201 OLE, infusion-related reactions were reported in 20.6% subjects
- Most infusion related reactions (>90%) were grade 1 or 2 (mild/moderate)

Immunogenicity

- In Study 201 Core:
  - The incidence of treatment emergent positive ADA in lecanemab 10 mg/kg biweekly was 40.9% with low titers (Q1, Q3 of maximum ADA titers were 5, and 125) and tended to decrease with longer duration of dosing (Figure 1 and Figure 2)
  - Treatment-boosted ADA were low
  - The ADA positivity onset was similar across early (on or before week 13 of treatment), middle (after week 13 to week 53), and late (after week 53)
- Relative to monthly dosing, biweekly dosing and higher doses of lecanemab resulted in lower rates of ADA positivity with the lowest rates seen with lecanemab 10 mg/kg biweekly (Figure 3)
- The pattern of development of transient ADA response was not time dependent, with approximately half of responses developing at Week 13 and the remainder developing by Week 53 (Figure 4)
  - Few subjects had persistent ADA by Week 90 (11 weeks after last dose) with low titer
- The incidences of ADA in the 201 OLE phase were considerably lower (6.1%) than the incidences of ADA in Study 201 Core
- The incidence of treatment emergent NAb positive was 25.4%, with low titers (≤5) in Study 201 Core
- The development of NAb was persistent up to 27 weeks (with late onset).
- In the OLE, no subjects developed treatment-induced/-boosted NAb
- Lecanemab ADA demonstrated no meaningful impact of ADA on pharmacokinetics (PK), pharmacodynamics (PD), efficacy, and safety

Figure 1. ADA Positive Titers Across Lecanemab Dosing Regimens in Study 201 Core

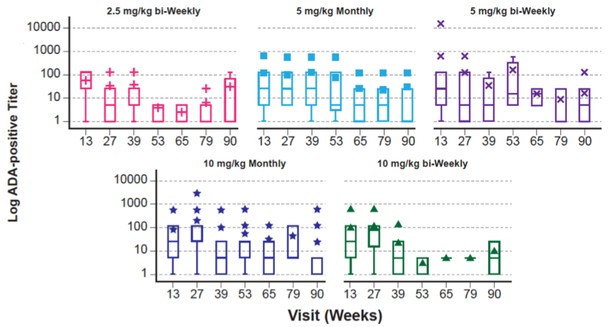


Figure 2. Cumulative Percentage of Maximum Titer Values Across Lecanemab Regimens in Study 201 Core

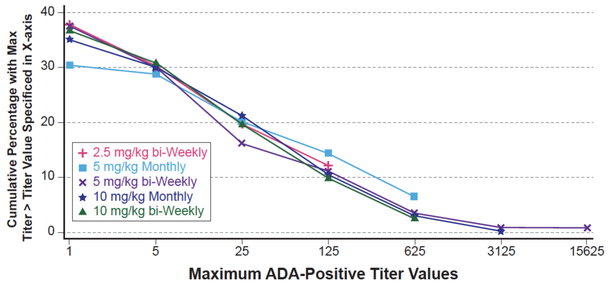


Figure 3. Time to First ADA Positive Across Lecanemab Dosing Regimens in Study 201 Core

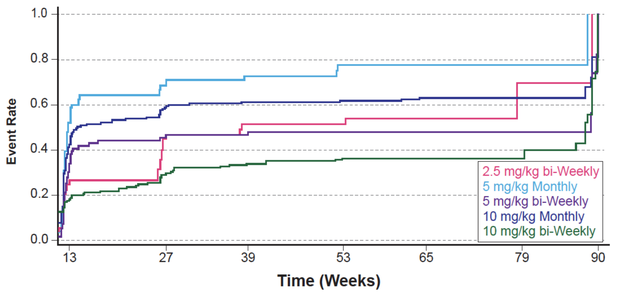
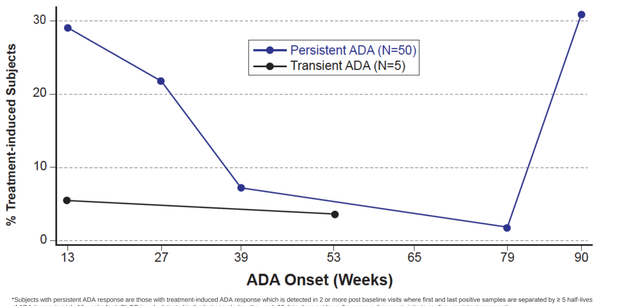


Figure 4. Persistent ADA and Transient ADA Over Onset Time for Lecanemab 10 mg/kg biweekly in Study 201 Core*



*Subjects with persistent ADA response are those with treatment-induced ADA response which is detected in 2 or more post baseline visits where first and last positive samples are separated by ≥ 5 half-lives of ADA (approximately 16 weeks for IgG) OR is only detected in the last sample (eg, the week 90 data does not have 2 or more subsequent visits to confirm persistent response).

Conclusions

- Infusion-related reactions were the most common adverse event associated with lecanemab 10 mg/kg biweekly
  - The mild/moderate of infusion-related reaction severity, low rates of discontinuation due to infusion-related reactions, and response to preventative medication support that infusion-related reaction is an ADR that can be managed
  - Data from the OLE was consistent with the Core study
- Lecanemab is a low-risk molecule for immunogenicity based on the ADA profile (with low titers) and minimal impact of ADA on PK, PD, efficacy, and safety

References

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