A PRELIMINARY ACCOUNT OF ARIA-E IN THE ONGOING OPEN LABEL EXTENSION PHASE OF BAN2401-G000-201 IN SUBJECTS WITH EARLY ALZHEIMER'S DISEASE

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Background

- Amyloid related imaging abnormalities – edema/effusion (ARIA-E) are a common finding among anti-amyloid antibodies
- BAN2401, a humanized IgG1 monoclonal antibody that selectively binds soluble Aβ aggregates (oligomers and protofibrils) over monomers, had an ARIA-E incidence of 9.9% at the top dose of 10 mg/kg biweekly in the 18-month Phase 2b study BAN2401-G000-201 in 856 subjects with early Alzheimer's Disease (EAD) (mild cognitive impairment (MCI) due to AD and mild AD dementia subjects)
- All subjects with ARIA-E were immediately discontinued per protocol, regardless of radiologic severity or whether symptoms were noted
- Here, we assess preliminary ARIA-E rates for 10 mg/kg biweekly BAN2401 (ie, dose selected for BAN2401 phase 3 trial [ClarityAD]) in the ongoing open label extension (OLE), while exploring the ability to dose through ARIA-E depending on severity and whether symptoms were observed (data are current as of May 2020)

Methods

- The BAN2401-G000-201 Core Study was a multinational, multicenter, double-blind, placebo-controlled, parallel-group, 18-month phase 2 dose finding and proof of concept study in amyloid positive subjects with EAD
- The OLE was initiated following completion and data analysis of the Core Study to allow all participating subjects to receive open-label BAN2401 10mg/kg biweekly for up to 24 months (2 years)
- All subjects were off BAN2401 for variable periods of time prior to entering the OLE
- Any subject who completed study treatment (Visit 42 [Week79] of the Core Study) and fulfilled the Extension Phase inclusion and exclusion criteria had the option to participate
- Subjects who discontinued the Core Study were also eligible to participate in the OLE, provided they meet the inclusion and exclusion criteria for the OLE
- A total of 180 subjects have been dosed on the OLE to date; All subjects receive 10 mg/kg biweekly
- Magnetic resonance imaging (MRI) is conducted to monitor for ARIA-E at 9 weeks, 3 months, 6 months, and 12 months over the first 12 months of BAN201 treatment in the OLE
- Subjects in the US (the vast majority) who experienced mild or moderate radiologic ARIA-E and are asymptomatic continued dosing per protocol in US
- Dosing is temporarily interrupted in cases of severe (moderate or severe in Japan) and/or symptomatic ARIA-E and can be resumed up to 2 times upon resolution

Results

- Core treatments and ApoE4 status of subjects in OLE are summarized in Table 1
- 13 of 180 subjects treated with 10 mg/kg biweekly in OLE have had ARIA-E to date
  - 12 subjects with ARIA-E were APOE4 positive
  - 3 ARIA-E cases were symptomatic
  - 2 subjects had ARIA-E in the Core Study [1 experienced recurring ARIA-E in OLE]
- Most OLE ARIA-E cases occurred early in treatment (Figure 1)
  - Week 9: N = 6; 3 month: N = 5; 6 month: N = 2
- 1 ARIA-H (macrohemorrhage)
  - APOE4 negative, symptomatic
- 2 Discontinuations:
  - asymptomatic moderate ARIA-E (disease progression and travel difficulties)
  - severe symptomatic ARIA-E (withdrawal of informed consent)
- 8 ARIA-E cases with study drug interruption
  - 6 cases resolved within 3-4 months; 1 ongoing case with interruption
  - 1 symptomatic case dose interrupted for 3 doses and then WD consent
- 5 ARIA-E cases dosed through
  - 4 moderate (1 resolved and recurred as mild); 1 mild
- 2 cases of recurring ARIA-E in OLE both asymptomatic
  - 1) 1st and 2nd ARIA-E dosed through and resolved
  - 2) 1st ARIA-E required interruption (3 doses) with resumption of 2 doses prior to 2nd ARIA-E (also had ARIA-E in Core)
- 7 ARIA-E cases had concomitant ARIA-H or superficial siderosis, all are asymptomatic
- Doses administered in 13 cases of ARIA-E and macrohemorrhage are summarized in Table 2
- Timing and severity of ARIA-E cases are summarized in Figure 2 and Figure 3

Table 1. Core Treatment Assignments in OLE and ApoE4 Status

	ApoE4		
	Negative	Positive	Total
Placebo	14	31	45
2.5 mg/kg Biweekly	1	2	3
5 mg/kg Monthly	1	7	8
5 mg/kg Biweekly	0	26	26
10 mg/kg Monthly	4	56	60
10 mg/kg Biweekly	35	3	38
Total	55	125	180

Figure 1. Observed ARIA-E Events in OLE

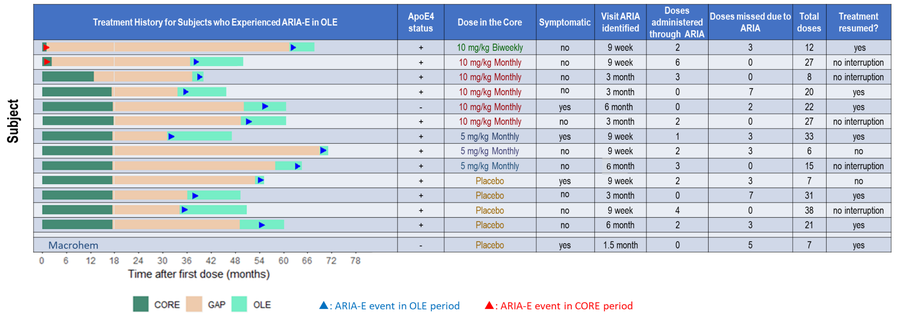


Table 2. Number of Doses Administered in 13 subjects with ARIA-E and 1 subject with Macrohemorrhage

	Number of doses given prior to ARIA in OLE	Number of doses administered through ARIA*	Number of doses interrupted due to ARIA*	Total number of doses administered to date
Mean	7	2	2	20
Range	3-14	0-6	0-5	6-38

*** When applicable**

Figure 2. Histograms for Time from OLE Treatment Initiation to 1st ARIA-E (n=13)

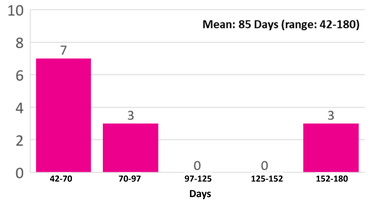
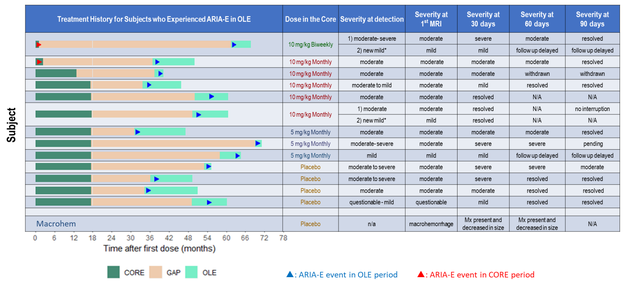


Figure 3. ARIA- E Radiologic Severity at 1st and Subsequent MRIs



*Recurring cases of ARIA within the OLE for the same subject. N/A = not applicable.

Figure 4. Kaplan-Meier Plots for ARIA Risk by Treatment in Core for Overall population

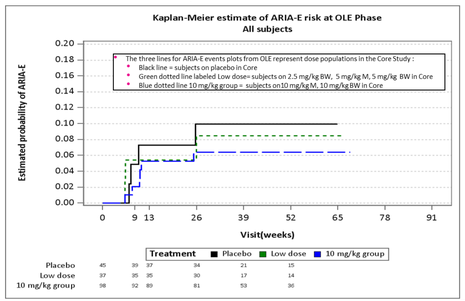
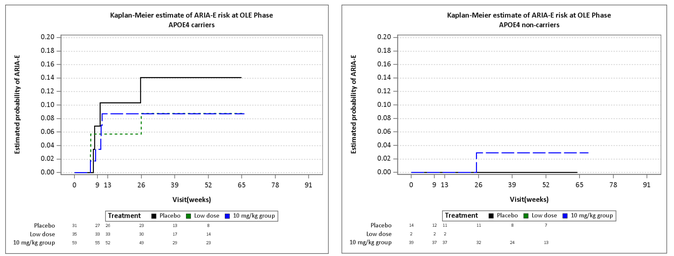


Figure 5. Kaplan-Meier Plots for ARIA Risk by Treatment in Core by APOE4 carrier status



Data are combined according to Core treatment based on relative Ns and ARIA incidence in Core

- Kaplan-Meier (KM) estimate of placebo converted subjects (black line) is 10.0% which aligns with the observed number of ARIA-E cases for these doses in the Core (9.9%) (Figure 4)
- For APOE carriers the KM estimate of placebo converted subjects is 14.1% (black line) which aligns with the observed number of ARIA-E cases for these doses in the Core (10.2% and 14.6% in 10 mg/kg monthly and biweekly, respectively) (Figure 5)
- Comparisons could not be made fo APOE4 non carriers due to small number of subjects who were APOE non carriers (Figure 5)

Summary and Conclusions

- ARIA-E incidence rates are similar in OLE compared to those in the Core
  - In the OLE, 13/180 (7.2%) dosed subjects have had ARIA-E to date
    - Of note, 4/45 (8.9%) subjects treated with placebo in Core had ARIA-E in the OLE (all ARIA-E cases were in ApoE4 positives: 4/31 [13% incidence in APOE+])
- ARIA-E occurred early in OLE treatment
- Most cases were asymptomatic and few recurrences were observed
  - 3 cases of symptomatic ARIA-E and 1 case of symptomatic ARIA-H (macrohemorrhage)
  - 2 ARIA cases have recurred from Core to OLE, and
  - 2 cases have recurred within OLE
- Mild and moderate ARIA-E cases can be successfully dosed through without interruption under some circumstances
- Further research is needed to explore impact of the following:
  - Influence of amyloid load at OLE baseline on likelihood to develop ARIA-E
  - Influence of rate of amyloid load decrease on likelihood to develop ARIA-E
  - Factors that influence ability to dose through mild or moderate ARIA-E

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