A PRELIMINARY ASSESSMENT OF LONGITUDINAL AMYLOID STATUS IN THE ONGOING OPEN-LABEL EXTENSION PHASE IN SUBJECTS TREATED WITH BAN2401 IN EARLY ALZHEIMER'S DISEASE

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Background

- BAN2401 is a humanized IgG1 monoclonal antibody that selectively binds soluble Aβ aggregates (oligomers and protofibrils) over monomers [1-5]
- A large, 18-month phase 2 proof of concept study (BAN2401-G000-201, NCT01767311) using Bayesian adaptive design with response adaptive randomization was completed in 856 patients with early Alzheimer's Disease (EAD) (mild cognitive impairment (MCI) due to Alzheimer's Disease (AD) or mild AD dementia)[6-7]
- Although the success threshold for the primary Bayesian analysis at 12 months was not met, results from pre-specified 18-month Bayesian and frequentist analyses indicated that BAN2401 treatment produced robust and dose dependent reduction in brain amyloid, with consistent reduction in clinical decline in subjects with EAD at the highest dose (10 mg/kg biweekly)
- We have previously shown that amyloid reduction over 18 months of BAN2401 treatment in the 10mg/kg biweekly arm persists at open label extension (OLE) Baseline following long-term withdrawal from BAN2401
- Here, we present preliminary data on the early time course of amyloid reduction with 10 mg/kg biweekly BAN2401 (ie, dose selected for BAN2401 phase 3 trial [ClarityAD]) in the OLE across Core treatment group for those subjects who participated in the OLE amyloid imaging substudy

Methods

- The BAN2401-G000-201 Core Study was a multinational, multicenter, double-blind, placebo-controlled, parallel-group, 18-month phase 2 study designed to establish proof of concept for BAN2401 in EAD subjects (mild cognitive impairment (MCI) due to AD and mild AD dementia subjects) with confirmed amyloid pathology
- The OLE was initiated following completion and data analysis of the Core Study to allow subjects to receive open-label BAN2401 10mg/kg biweekly for up to 24 months (2 years).
- Any subject who completed study treatment (Visit 42 [Week79] of the Core Study) and fulfilled the Extension Phase inclusion and exclusion criteria was eligible to participate
- Subjects who discontinued the Core Study were also eligible to participate in the OLE, provided they met 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
- Data are shown for subjects treated with placebo, 10 mg/kg monthly, and 10 mg/kg biweekly in the Core, as 10 mg/kg monthly and 10 mg/kg biweekly were identified as meaningful by the Bayesian algorithm in the Core study, and these dose arms represent most of the OLE participants
- Data for longitudinal PET standard uptake value ratio (SUVr) are shown only for subjects who participated in the imaging substudy in the OLE
- Results are shown for 2 Cohorts: Cohort 1 at 3-months and 12 months of treatment in OLE; Cohort 2 at 6-months and 12 months treatment in OLE
- Regression was used to predict amyloid PET SUVr change from OLE baseline over 12 months

Results

Baseline Characteristics and Longitudinal Amyloid PET SUVr

- There were 856 subjects randomized and dosed in the Core Study (Last Patient Out for Core Study was August 2018)
- A total of 59 sites dosed 180 subjects in the OLE, with the first OLE subject screened in December 2018
- 143 subjects have OLE baseline data across placebo, 10 mg/kg monthly, and 10 mg/kg biweekly treatment assignment in the Core study, and 77 of those have had longitudinal PET imaging in OLE
- OLE baseline characteristics and time off study drug between end of the Core and OLE Baseline (GAP period) are presented in Figure 1 and Table 1, respectively, for Placebo, 10 mg/kg monthly and 10 mg/kg biweekly Core treatment groups
- Observed longitudinal PET SUVr results for Cohort 1 (Baseline, 3months, and 12 months) and Cohort 2 (Baseline, 6 months, and 12 months) are summarized in Table 2. Note the differences in baseline SUVr between Cohort 1 and Cohort 2

Figure 1. Baseline Characteristics in OLE

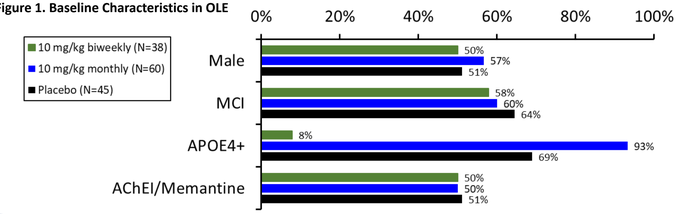


Table 1. Time Off Drug (months)

Treatment	Mean	Median	Min	Max
10 mg/kg biweekly	25.5	21.1	9.3	59.7
10 mg/kg monthly	26.7	24.4	9.2	51.1
Placebo	23.7	19.5	11.2	50.6

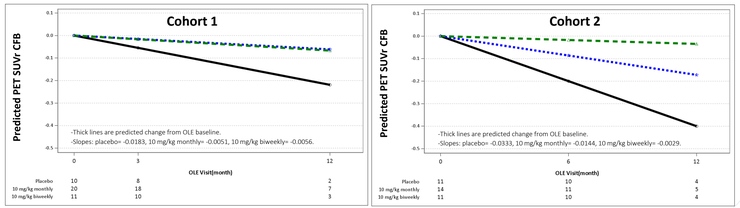
Table 2. Observed Longitudinal PET SUVr in OLE

	10 mg/kg biweekly (n)	10 mg/kg monthly (n)	Placebo (n)
Cohort 1			
OLE baseline	1.04±0.12 (11)	1.19±0.13 (20)	1.29±0.18 (10)
3 month	1.01±0.10 (10)	1.16±0.15 (18)	1.19±0.13 (8)
12 month	0.97±0.03 (3)	1.06±0.07 (7)	0.93±0.03 (2)
Cohort 2			
OLE baseline	1.12±0.13 (11)	1.24±0.18 (14)	1.45±0.17 (11)
6 month	1.09±0.13 (10)	1.15±0.17 (11)	1.18±0.14 (10)
12 month	1.12±0.11 (4)	1.11±0.14 (5)	1.06±0.12 (4)

n is the number of subjects who participated in OLE PET substudy. Data are expressed as mean±SD (N) for longitudinal amyloid PET results in cohorts 1 and Cohort 2

- Predicted change from OLE baseline in PET SUVr for cohort 1 and cohort 2 across Core treatment group is shown in Figure 2
- Spaghetti plots for observed subject-level longitudinal PET SUVr data are shown across Core treatment for Cohort 1 (Figure 3) and Cohort 2 (Figure 4). Bold lines are predicted change from OLE Baseline over 12 months of treatment in OLE

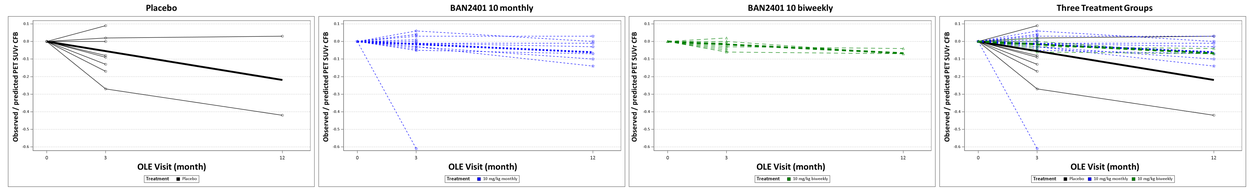
Figure 2. Predicted PET SUVR change from OLE baseline over 12 months of treatment in OLE



Results

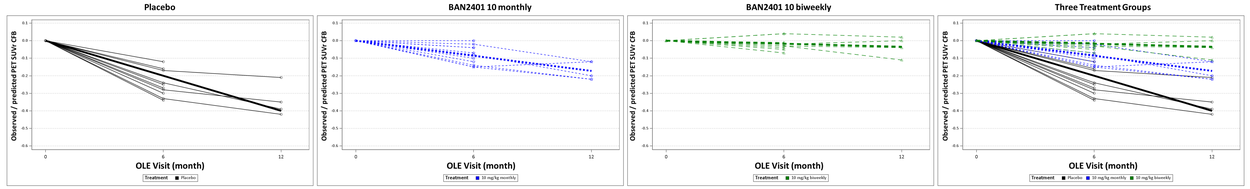
- Spaghetti plot of observed and predicted PET SUVR change from OLE baseline for cohorts 1 and 2 are shown in Figure 3 and Figure 4, respectively

Figure 3. Observed and predicted PET SUVR change from OLE baseline (Cohort 1))



Slopes: placebo= -0.0183, 10 mg/kg monthly= -0.0051, 10 mg/kg biweekly= -0.0056.
Predicted change in bold (re-draw of Figure 2)

Figure 4. Observed and predicted PET SUVR change from OLE baseline (Cohort 2))



Slopes: placebo= -0.0333, 10 mg/kg monthly= -0.0144, 10 mg/kg biweekly= -0.0029
Predicted change in bold (re-draw of Figure 2)

Conclusions

- In this preliminary analysis, 10 mg/kg-biweekly BAN2401-mediated amyloid reduction in the OLE was dependent on core treatment/SUVr at OLE baseline, with greatest change occurring in those subjects on placebo in the Core
- BAN2401 at 10 mg/kg biweekly in OLE produces time-dependent amyloid reduction in subjects who were treated with placebo in Core
  - Amyloid reduction for 10 mg/kg biweekly in the OLE was rapid in subjects treated with placebo in Core, with effects evident following 3 months of treatment in OLE
  - Amyloid reduction for 10 mg/kg biweekly in the OLE in subjects treated with placebo in Core appears to approach maximum levels at 12 months of treatment in OLE; this observation is supported by the little change in brain amyloid levels observed over 12 months for those subjects who had been treated with 10 mg/kg biweekly in the Core (ie, who had low levels of amyloid at OLE Baseline)
- Additional follow up is needed to further characterize the time course of amyloid reduction and to ascertain the maximum amyloid reduction that can be achieved under the present OLE conditions

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