A randomized, single ascending dose study of intravenous BIIB092 in healthy participants

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Abstract

Introduction: Extracellular tau is hypothesized to mediate the onset and progression of tauopathies, including Alzheimer’s disease, progressive supranuclear palsy, and a subset of frontotemporal lobar degenerations. A putative strategy for treating these disorders is to reduce extracellular tau levels using tau-directed immunotherapy. The results of the first-in-human study of BIIB092 (formerly BMS-986168/IPN007), a humanized monoclonal antibody that binds to N-terminal tau, are reported here. This randomized, double-blind, single ascending dose study evaluated the safety, tolerability, pharmacokinetics, pharmacodynamics, and immunogenicity profile of BIIB092 after a single intravenous infusion in healthy participants.

Methods: Sixty-five participants were randomized to receive a single intravenous infusion of placebo or BIIB092 at doses of 21, 70, 210, 700, 2100, or 4200 mg (or 700 or 2100 mg for Japanese participants). Serial blood and cerebrospinal fluid samples were obtained for assessment of pharmacokinetic parameters and unbound N-terminal tau suppression.

Results: There were no deaths, serious adverse events (AEs), severe AEs, or discontinuations due to an AE. The majority of AEs were mild. Serum BIIB092 concentrations increased in a dose-proportional manner and suppressed unbound cerebrospinal fluid N-terminal tau by 67\%–97\% at 28 days after dose, with doses of \geq 210 mg producing persistent unbound N-terminal tau suppression over 12 weeks. Levels of cerebrospinal fluid N-terminal tau suppression were similar for Japanese and non-Japanese participants.

Discussion: BIIB092 was generally safe and well tolerated after a single dose of up to 4200 mg, and up to 2100 mg in Japanese participants. BIIB092 exhibited a dose-dependent increase in the extent and duration of unbound N-terminal tau suppression.

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Keywords: Alzheimer’s disease; Phase 1; Progressive supranuclear palsy; Tau; Tauopathy

1. Introduction

Tau is a microtubule-associated protein present in the central nervous system that is hypothesized to mediate a diverse array of processes, including stabilization of the axonal cytoskeleton and neurite growth, synaptic plasticity, cellular signaling, neurogenesis, and regulation of genomic stability \cite{1,2,3}. Tau phosphorylation, aggregation, and neurofibrillary tangle formation are the hallmarks of a
spectrum of neurodegenerative disorders, including Alzheimer’s disease (AD), progressive supranuclear palsy (PSP), and frontotemporal lobar degenerations with tau pathology [4]. These disorders have distinct but overlapping clinical presentations and exhibit specific cellular and neuroanatomical patterns of tau accumulation. Tau filaments can be composed of three or four microtubule-binding repeat isoforms of tau (3R or 4R tau), have different morphological and biochemical features, and may potentially adopt disease-specific molecular conformations. Also, studies of cerebrospinal fluid (CSF) from patients with different tauopathies have shown divergent tau analyte concentration profiles [5–7], despite the presence of severe tau pathology in all of these disorders. For example, CSF phosphorylated tau (p-tau) levels are consistently elevated in AD [7], whereas CSF p-tau levels have been shown to be decreased in PSP but correlated with disease severity and rate of disease progression [8]. Despite clinical and scientific advances in the study of tauopathies, treatment options for patients with these disorders remain symptomatic and have only limited effectiveness [9–11]. Ongoing research efforts are focused on identifying tau-directed therapies that will prevent the formation and spreading of tau pathology and stop progressive neurodegeneration [12].

Although tau is primarily an intracellular protein that is found in neuronal and glial cells, a small amount of tau is secreted into the extracellular space [13–15]. Although the precise molecular species of extracellular tau are unclear, recent evidence suggests that N-terminal fragments of tau lacking the microtubule-binding repeat domains and C-terminal region of full-length tau [13,16–18] are likely to be present in the interstitial fluid. It is not clear whether these N-terminal species have any normal physiological functions. However, these fragments appear to play a role in the pathophysiology of tauopathies via two potential mechanisms [13,19–21]: first, by inducing neuronal hyperexcitability and directly causing neuronal dysfunction and, second, by facilitating the transcellular spread of tau pathology.

The tau propagation hypothesis proposes that pathological forms of extracellular tau spread from cell to cell and region to region along anatomically connected networks in the brain [22]. The tau protein is known to misfold and recruit native tau monomers to form soluble tau aggregates [22,23]. It is believed that pathological tau “seeds” comprising soluble tau aggregates are released into the extracellular space and are subsequently internalized by neighboring cells [22,23]. These tau seeds then induce template-directed tau misfolding and aggregation in neighboring cells, promoting the spread of tau pathology across neural networks [22,23]. Accumulating evidence that supports the propagation hypothesis has generated significant interest in extracellular tau as a therapeutic target for tauopathies [24]. One promising approach is to use tau-directed immunotherapy to reduce extracellular tau in the brain interstitial fluid [13,19,25]. Indeed, administration of anti-tau antibodies appears to reduce the propagation of tau pathology and improve cognitive and behavioral phenotypes in transgenic mouse models of tauopathy [12,13,19,25].

BIIB092 (formerly BMS-986168/IPN007) is a humanized immunoglobulin G4 monoclonal antibody directed against tau (Ahlijanian M, Malone H, Kukral D, et al. Manuscript in preparation). It binds with high affinity to human and nonhuman primate forms of tau. Specifically, BIIB092 exhibits high affinity to the N-terminal region of tau, implying that BIIB092 will associate with tau species with an intact amino terminal (Ahlijanian M, Malone H, Kukral D, et al. Manuscript in preparation) [13]. BIIB092 was engineered from a mouse monoclonal antibody, IPN002, and both antibodies recognize a linear, nonphosphorylated epitope included in the amino terminus (N-terminus) of tau, corresponding to amino acid residues 15-24 of ON4R tau [13] (Ahlijanian M, Malone H, Kukral D, et al. Manuscript in preparation). Both the human and murine antibodies carry the same epitope-recognition domain. In transgenic mouse models of tauopathy, weekly doses of IPN002 (the murine analog of BIIB092) reduced levels of N-terminal tau in the interstitial fluid and CSF as well as levels of amyloid β in the cerebral cortex [13]. Intriguingly, treatment with IPN002 also improved histopathological, biochemical, and functional measures (Ahlijanian M, Malone H, Kukral D, et al. Manuscript in preparation) in tau transgenic mice displaying age-related tau hyperphosphorylation, aggregation, neurofibrillary tangle formation, and motor deficits [26]. In cynomolgous monkeys, single intravenous (IV) infusions of BIIB092 at 20 mg/kg similarly reduced N-terminal tau in CSF by >90% (Ahlijanian M, Malone H, Kukral D, et al. Manuscript in preparation). This promising preclinical profile supports the investigation of BIIB092 in healthy participants, as well as in patients with tauopathies such as PSP and AD (ClinicalTrials.gov identifiers NCT02460094, NCT03068468, NCT03352557).

The primary objective of this phase 1 study was to evaluate the safety and tolerability of single ascending dose IV infusions of BIIB092 in healthy participants. Secondary objectives included the evaluation of pharmacokinetic (PK) parameters, pharmacodynamic (PD) effects of BIIB092 on CSF concentrations of unbound N-terminal tau, and immunogenicity of BIIB092 in these participants.

2. Methods

2.1. Study design and population

This study (NCT02294851) was conducted in compliance with the Declaration of Helsinki and Good
Clinical Practice guidelines. The study protocol and amendments received appropriate approval by an institutional review board/independent ethics committee before initiation of the study. Written informed consent was obtained from each participant before study participation, including informed consent for any screening procedures conducted to establish participant eligibility in the study.

This phase 1 trial was a randomized, double-blind, placebo-controlled, single ascending dose study conducted from December 31, 2014, to April 30, 2016. Healthy male and female participants, aged 21–65 years, with a body mass index of 18.5–30.0 kg/m² (18.0–25.0 kg/m² for Japanese participants), were eligible to participate.

Eight healthy participants were assigned to each of the six sequential dose groups (groups 1–6: 21, 70, 210, 700, 2100, and 4200 mg; Fig. 1). For each dose group, the first two participants were randomized in a 1:1 ratio to receive an IV infusion of BIIB092 or placebo (0.9% sodium chloride), and the remaining six participants were randomized in a 5:1 ratio to receive BIIB092 or placebo. Japanese participants were assigned to two separate sequential dose groups (groups 7–8) and randomized in a 3:1 ratio to receive BIIB092 700 mg and 2100 mg or placebo. Participants were admitted to the clinical facility on day −2 and remained at the clinical site through day 3. Participants returned for outpatient visits on days 8, 15, 29, 43, 57, and 85. A follow-up telephone call was made by the site on day 92 to assess the status of all participants who underwent the day 85 lumbar puncture (LP) procedure.

Each participant in groups 1–6 underwent four LPs. The first three LPs took place on fixed study days (days −2 [baseline], 3, 15, 29, or 85), depending on the group; the timing of the last LP was randomized to days 29, 57,
or 85, also depending on the group (Supplementary Table 1). Japanese participants (groups 7–8) had LPs on days −2 and 29.

2.2. Safety assessments and PK/PD evaluations

2.2.1. Safety assessments

Participants were closely monitored throughout the study for nonserious and serious adverse events (AEs) and were discharged from the study only when the investigator had determined that the AEs had completely resolved or did not require continued monitoring. Clinical laboratory tests, vital sign measurements, electrocardiogram measurements, and physical examinations were conducted at specified intervals throughout the study.

2.2.2. PK/PD evaluations

The serum sampling schedule for PK assessments is shown in Supplementary Table 2. Serum and CSF samples were analyzed for BIIB092 using validated chemiluminescent immunoassays (QPS, Newark, DE) for human serum and CSF. The assay uses recombinant human tau as the capture reagent and a mouse anti-human IgG4 Fc antibody conjugated to horseradish peroxidase for detection. The validated range for this method in human serum is from 0.15 to 10.00 μg/mL and in human CSF from 5.00 to 625 ng/mL. PK parameters were derived from serum concentration versus time data and included maximum serum concentration (C_max), time to reach C_max (T_max), area under the curve (AUC) from time 0 to time of last quantifiable concentration (AUC_0-T), AUC from time 0 to infinity (AUC_0-inf), terminal half-life (t_1/2), total body clearance (CL), volume of distribution at steady state (Vss), and volume of distribution based on terminal phase (Vz).

CSF samples were analyzed for N-terminal tau (Meso Scale Diagnostics LLC, Gaithersburg, MD), mid-domain tau, Aβ40, and Aβ42 (QPS, Newark, DE) using validated fit-for-purpose assays. For N-terminal tau and mid-domain tau, the following capture and readout antibody combinations were used: Tau12 (N-terminal tau capture), HT7 and BT2 (N-terminal tau readout), Tau5 (mid-domain tau capture), and HT7 and BT2 (mid-domain tau readout) [6]. Blood samples also were analyzed for anti-BIIB092 antibodies using a validated bridging electrochemiluminescence immunoassay on the Meso Scale Discovery platform. Exploratory variables were analyzed using serum and CSF samples. A whole blood sample was collected on day 1 for DNA H1 and H2 haplotype sequencing analysis.

2.3. Statistical considerations

2.3.1. Sample size and power

The sample size was not based on statistical power considerations, but administration of BIIB092 to six participants per group provided an 80% probability of observing one or more occurrence of any AE that would occur with 24% incidence in the population from which the sample was drawn.

2.3.2. Statistical analyses

SAS, version 9.3 (SAS Institute, Cary, NC), was used for statistical analyses, tabulations, and graphical presentations. Medians and ranges were calculated for T_max, and geometric means and coefficients of variation were calculated for C_max, AUC_0-T, AUC_0-inf, CL, Vss, and Vz. Means and standard deviations were presented for all other PK parameters. Dose proportionality was assessed using the power model described by Gough et al. [27]. Analysis of variance was used to compare the treatment effect of BIIB092 between Japanese and non-Japanese participants. Linear fixed-effect models were used to generate point estimates, with race as a fixed effect on the log-transformed data. Analysis of covariance was performed to compare the treatment effect of BIIB092 between Japanese and non-Japanese participants at each dose level.

Mean and geometric mean percentage of baseline CSF N-terminal tau versus study day were plotted by group. The baseline was defined as the predose value measured during screening no later than day −2. CSF measures of mid-domain tau, Aβ40, and Aβ42 were analyzed in an exploratory manner. The relationship between CSF BIIB092 concentrations and these variables were explored graphically.

3. Results

3.1. Baseline demographic characteristics

The study duration per participant was ~113 days. Of the 226 participants enrolled in this study, 65 were randomized to receive study drug (Supplementary Fig. 1). Three patients were lost to follow-up (one participant who received BIIB092 70 mg, one participant who received BIIB092 700 mg, and one participant who received placebo). An additional Japanese participant who received placebo withdrew consent. Baseline characteristics were generally well balanced among the groups. The summary of baseline characteristics is presented in Supplementary Table 3.

3.2. Safety and tolerability

There were no deaths, serious AEs, severe AEs, or discontinuations because of an AE reported in this study. A total of 16 (32.7%) participants given BIIB092 reported AEs compared with eight (50.0%) participants who received placebo. A summary of AEs is presented in Table 1. The incidence of AEs was similar between non-Japanese and Japanese participants. No dose-related trend in the incidence of AEs was observed with increasing doses of BIIB092. The majority of AEs were mild in intensity. Overall, the most
### Table 1

**Adverse event summary: overall and drug-related adverse events**

| System Organ Class | Preferred Term, n (%) | PBO (n = 16) | 21 mg (n = 6) | 70 mg (n = 6) | 210 mg (n = 7) | 700 mg (Japanese) (n = 6) | 2100 mg (Japanese) (n = 6) | 4200 mg (n = 6) | ANY BIIB092 (n = 49) |
|--------------------|-----------------------|--------------|---------------|---------------|----------------|--------------------------|--------------------------|-----------------|---------------------|
| **Total number of participants with an event** | | 8 (50.0) | 2 (33.3) | 2 (33.3) | 3 (42.9) | 2 (33.3) | 2 (33.3) | 3 (50.0) | 16 (32.7) |
| **Injury, poisoning, and procedural complications** | | 2 (12.5) | 1 (16.7) | 0 | 1 (16.7) | 1 (14.3) | 0 | 1 (16.7) | 2 (33.3) | 0 | 6 (12.2) |
| Post-lumbar puncture syndrome | | 1 (6.3) | 0 | 0 | 1 (16.7) | 1 (14.3) | 0 | 0 | 1 (16.7) | 0 | 3 (6.1) |
| Procedural pain | | 1 (6.3) | 1 (16.7) | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 2 (4.1) |
| Infusion-related reaction | | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 1 (2.0) |
| Nervous system disorders | | 0 | 1 (16.7) | 0 | 0 | 3 (42.9) | 0 | 1 (16.7) | 2 (33.3) | 0 | 7 (14.3) |
| Headache | | 0 | 1 (16.7) | 0 | 0 | 3 (42.9) | 0 | 1 (16.7) | 2 (33.3) | 0 | 7 (14.3) |
| Dizziness | | 0 | 0 | 0 | 0 | 1 (14.3) | 0 | 0 | 0 | 1 (2.0) |
| Gastrointestinal disorders | | 1 (6.3) | 2 (33.3) | 0 | 0 | 1 (14.3) | 1 (16.7) | 0 | 1 (16.7) | 0 | 5 (10.2) |
| Nausea | | 1 (6.3) | 1 (16.7) | 0 | 0 | 1 (14.3) | 0 | 0 | 0 | 0 | 2 (4.1) |
| Toothache | | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 2 (4.1) |
| Abdominal discomfort | | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (2.0) |
| Ercuation | | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.0) |
| Feces soft | | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 1 (2.0) |
| Vomiting | | 1 (6.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Infections and infestations | | 2 (12.5) | 1 (16.7) | 0 | 1 (16.7) | 0 | 1 (16.7) | 0 | 1 (16.7) | 0 | 4 (8.2) |
| Upper respiratory tract infection | | 1 (6.3) | 1 (16.7) | 0 | 1 (16.7) | 0 | 1 (16.7) | 0 | 1 (16.7) | 0 | 4 (8.2) |
| Otitis media | | 1 (6.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | 1 (6.3) | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 1 (2.0) |
| Back pain | | 1 (6.3) | 0 | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 1 (2.0) |
| Respiratory, thoracic, and mediastinal disorders | | 0 | 0 | 2 (33.3) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (4.1) |
| Rhinorhrea | | 0 | 0 | 2 (33.3) | 0 | 0 | 0 | 0 | 0 | 0 | 2 (4.1) |
| Skin and subcutaneous tissue disorders | | 2 (12.5) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dermatitis contact | | 1 (6.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ecchymosis | | 1 (6.3) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Adverse events related to study drug** | | 0 | 1 (16.7) | 0 | 0 | 2 (28.6) | 0 | 0 | 1 (16.7) | 0 | 4 (8.2) |
| Gastrointestinal disorders | | 0 | 1 (16.7) | 0 | 0 | 1 (14.3) | 0 | 0 | 0 | 0 | 2 (4.1) |
| Nausea | | 0 | 1 (16.7) | 0 | 0 | 1 (14.3) | 0 | 0 | 0 | 0 | 2 (4.1) |
| Ercuation | | 0 | 1 (16.7) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (2.0) |
| Nervous system disorders | | 0 | 0 | 0 | 0 | 2 (28.6) | 0 | 0 | 0 | 0 | 2 (4.1) |
| Headache | | 0 | 0 | 0 | 0 | 2 (28.6) | 0 | 0 | 0 | 0 | 2 (4.1) |
| Injury, poisoning, and procedural complications | | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 1 (2.0) |
| Infusion-related reaction | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 | 1 (2.0) |
| Vascular disorders | | 0 | 0 | 0 | 0 | 1 (14.3) | 0 | 0 | 0 | 0 | 1 (2.0) |

Abbreviations: ANY BIIB092, any dose of BIIB092; PBO, placebo.
common AE was headache (n = 7; 14.3%), followed by upper respiratory tract infection (n = 4; 8.2%).

There were no significant differences between mean baseline and postdose clinical laboratory, electrocardiogram, and vital sign parameters across dose groups. No laboratory abnormalities were reported as AEs.

3.3. PK results

BIIB092 serum concentrations generally increased in a dose-proportional manner from 21 to 4200 mg (Fig. 2A and B). The slope estimate for $C_{\text{max}}$ and AUC$_{0-T}$ for BIIB092 doses of 21–4200 mg (in non-Japanese participants) approximated to 1, with the lower bounds of the 90% confidence intervals slightly greater than 1, supporting dose proportionality (Supplementary Fig. 2A and B). Exposure (C$_{\text{max}}$, AUC$_{0-T}$, AUC$_{0-t}$) was 22%–41% higher in Japanese versus non-Japanese participants administered a 700- or 2100-mg dose of BIIB092. CL, Vss, and Vz appeared to be similar across all dose levels but were 25%–29%, 18%–27%, and 24%–28% lower, respectively, in Japanese participants compared with non-Japanese participants. The $t_{1/2}$ appeared to be dose independent, with similar median $T_{\text{max}}$ (1.49–2.50 hours) and mean $t_{1/2}$ (515–663 hours) across all dose groups. CSF concentrations of BIIB092 also increased in a dose-proportional manner from 70 to 4200 mg (Fig. 2C and D). The serum PK parameters and corresponding statistical analysis for Japanese versus non-Japanese participants are summarized in Supplementary Tables 4 and 5.

3.4. PD results

Maximum decreases in CSF unbound N-terminal tau were evident at the first postdose assessment in non-Japanese participants (day 3). Single ascending doses of BIIB092 21–4200 mg decreased CSF unbound N-terminal tau levels substantially versus the predose assessment (day −2), and maximal reductions in unbound CSF N-terminal tau were seen at this time point for the majority of the doses (Fig. 3A and B). At 28 days after dose, BIIB092 doses of 70–4200 mg suppressed CSF unbound N-terminal tau by 67%–97%, with a dose-related effect on the extent and duration of unbound N-terminal tau suppression. Similar CSF unbound N-terminal tau reductions were observed in Japanese and non-Japanese participants on day 29 after administration of single doses of BIIB092 700 mg or 2100 mg. In non-Japanese participants, robust CSF unbound N-terminal tau suppression was observed until the end of the study period (day 85) for single doses of BIIB092 $\geq$210 mg. There was a strong inverse correlation between CSF concentrations of BIIB092 and CSF levels of unbound N-terminal tau (Supplementary Fig. S3), in that substantial reductions in N-terminal tau (>80%) were observed with BIIB092 concentrations of $\geq$50 ng/mL. No changes in the levels of mid-domain tau, Aβ40, or Aβ42 were observed after BIIB092 administration.

3.5. Immunogenicity

A total of four participants, comprising one each from the 21, 210, 700 (Japanese), and 2100 mg (Japanese) dose groups, developed anti-BIIB092 antibodies relative to baseline (baseline antidrug antibody [ADA] negative). There was no apparent difference between ADA-positive (n = 4) and ADA-negative (n = 30) participants with respect to the change in N-terminal tau values after treatment relative to baseline. No dose-related trend in immunogenicity and no relationship between immunogenicity status and safety outcomes were observed.

4. Discussion

Tau-directed immunotherapy is a promising disease-modifying treatment strategy for tauopathies such as AD, PSP, and frontotemporal lobar degenerations with tau pathology (Ahlijanian M, Malone H, Kukral D, et al. Manuscript in preparation) [13,19,25,28]. This was one of the first studies examining the safety and pharmacological profile of a humanized anti-tau monoclonal antibody in human participants. Notably, this study included measures of N-terminal tau suppression in CSF, which have not yet been reported for other anti-tau monoclonal antibodies.

BIIB092 was well tolerated when administered as a single IV infusion at doses of up to 4200 mg in healthy participants. There were no deaths, serious AEs, or discontinuations because of an AE. The majority of AEs were mild, with no treatment- or dose-related trends in the frequency or severity of AEs. BIIB092 exhibited a predictable PK profile in healthy participants across all doses studied. Exposure of BIIB092 increased in a dose-proportional manner, with proportional increases in CSF concentrations of BIIB092. Exposure of BIIB092 was 22%–41% higher in Japanese than in non-Japanese participants administered a 700- or 2100-mg dose, which may be attributed to the difference in body weight between the two groups, based on an exploratory analysis. Mean body weight was ~20 kg lower in Japanese than in non-Japanese participants. After adjusting for individual body weight, the mean exposures were similar between the two populations, suggesting that the observed differences in BIIB092 exposures were because of this difference. The modestly higher exposure in Japanese participants is not considered to be a clinically meaningful difference because of the largely uneventful safety profile of BIIB092 and the lack of any exposure-related AEs observed in this study. Single doses of BIIB092 suppressed unbound CSF N-terminal tau levels rapidly, with higher doses resulting in a greater degree and longer duration of suppression. After administration of BIIB092 doses of $\geq$210 mg, unbound CSF N-terminal tau suppression ranged from 88% to 97% on day...
Fig. 2. Mean (A, B) serum and (C, D) cerebrospinal fluid concentrations of BIIB092 over time. Mean data are presented at nominal times normalized at the start time of infusion. The nominal infusion duration for the 21- to 2100-mg doses was 1 hour, and the nominal infusion duration for the 4200-mg dose was 2 hours. Lower limit of quantification (LLOQ) values were treated as missing for calculation of mean values.
Fig. 3. (A) Mean cerebrospinal fluid (CSF) N-terminal tau over time and (B) CSF N-terminal tau geometric mean percentage of baseline over time. Lower limit of quantification (LLOQ) values were treated as missing for calculation of mean values. Abbreviation: PBO, placebo.
29 and from 82% to 91% on day 85. Similar levels of unbound CSF N-terminal tau suppression were observed for Japanese participants on day 29, after administration of 700- and 2100-mg doses (93% and 94%, respectively).

These findings in human participants are consistent with observations from single-dose administration studies in nonhuman primates. In cynomolgus monkeys, BIIB092 was infused at doses of 0.5–20 mg/kg (Ahlijanian M, Malone H, Kukral D, et al. Manuscript in preparation), which is a human-equivalent dose of 10–387 mg (based on standard methods for extrapolating equivalent dose [29]). Maximum suppression of CSF N-terminal tau in cynomolgus monkeys occurred 24–48 hours after infusion, achieving >90% suppression with the highest dose group (20 mg/kg) (Ahlijanian M, Malone H, Kukral D, et al. Manuscript in preparation). CSF N-terminal tau levels in cynomolgus monkeys returned to baseline levels 50 days after infusion in the lowest dose group (0.5 mg/kg), but suppression was maintained at 70% at 57 days after infusion in the highest dose group (20 mg/kg) (Ahlijanian M, Malone H, Kukral D, et al. Manuscript in preparation).

One of this study’s limitations is that evaluation of a single dose in a relatively small number of participants, who had a mean age of 44.1 years (standard deviation 12.77), makes it difficult to fully assess the safety, tolerability, and pharmacology of BIIB092 in humans, especially those that are elderly. Older subjects frequently have more comorbidities and higher rates of medication use than younger counterparts, and age-related biological changes may impact PK and PD effects. Moreover, the effects of BIIB092 on N-terminal tau suppression and other PD measures (e.g., neurofilament light chain) in patients with existing tau pathology remain unclear because this study was conducted in healthy participants. Furthermore, the similarity of N-terminal tau values between ADA-positive and ADA-negative participants should be interpreted with caution because a small number of participants (8%) were ADA-positive after treatment relative to baseline.

This phase 1 first-in-human study demonstrates that BIIB092 exhibits a predictable PK profile and is well tolerated when administered as single IV infusions up to 4200 mg in healthy participants and up to 2100 mg in healthy Japanese participants. Single doses of BIIB092 significantly suppressed CSF N-terminal tau by up to 97% at day 29, with a dose-related effect on the extent and duration of N-terminal tau suppression. There were no clinically meaningful differences for Japanese participants with regard to safety/tolerability, PK, or PD with BIIB092 doses of 700 and 2100 mg. These data in healthy human participants have facilitated dose selection for a phase 1 multiple ascending dose study in patients with PSP, and ongoing phase 2 studies in PSP and AD (ClinicalTrials.gov identifiers NCT02460094, NCT03068468, and NCT03352557, respectively). These PSP and AD clinical trials will help to test the tau propagation hypothesis and determine whether reducing N-terminal tau using tau-directed immunotherapy has potential as a disease-modifying treatment strategy for tauopathies.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trci.2018.10.007.

RESEARCH IN CONTEXT

1. Systematic review: The authors searched the literature using MEDLINE and meeting abstracts to identify research related to the hypothesis of extracellular tau propagation in tauopathies. Citations of previous work are included in the present study.

2. Interpretation: Our findings are the first-in-human data for BIIB092 and confirm its ability to suppress N-terminal tau in the cerebrospinal fluid. BIIB092 demonstrated dose dependency with respect to the extent and duration of cerebrospinal fluid N-terminal tau suppression. The pharmacokinetics of BIIB092 was linear and dose proportional in healthy participants.

3. Future directions: These data lay the foundation for future exploration of tau propagation and the use of tau-directed immunotherapy as a disease-modifying strategy in tauopathies, such as Alzheimer’s disease and progressive supranuclear palsy.
