Safety of the tau-directed monoclonal antibody BIIB092 in progressive supranuclear palsy: a randomised, placebo-controlled, multiple ascending dose phase 1b trial

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Summary

Background Progressive supranuclear palsy is a rare neurodegenerative disease associated with dysfunctional tau protein. BIIB092 is a humanised monoclonal antibody that binds to N-terminal tau and is thus being assessed as a potential novel treatment for progressive supranuclear palsy. We aimed to investigate the safety and tolerability of BIIB092 in individuals with progressive supranuclear palsy.

Methods This 12-week, double-blind, randomised, placebo-controlled, multiple ascending dose, phase 1b trial was done at 13 outpatient sites in the USA. Participants aged 41–86 years with probable or possible progressive supranuclear palsy with a score of 20 or greater on the Mini-Mental State Examination (MMSE) were enrolled. Three BIIB092 dose escalation cohorts (150 mg, 700 mg, or 2100 mg; eight participants per cohort) were tested sequentially. For each dose cohort, the first two participants were randomly assigned by a computer-generated scheme to receive either BIIB092 or placebo intravenously every 4 weeks for 57 days. After 2 days, the six remaining participants in each cohort were randomly assigned (5:1) to receive BIIB092 or placebo for 57 days. An additional expansion panel of 24 patients was randomly assigned (3:1) to receive 2100 mg or placebo every 4 weeks for 57 days. All participants were followed up to day 85. The primary outcome was safety, which was analysed in the treated population (all enrolled participants who received at least one dose of the study drug). This trial is registered with ClinicalTrials.gov, NCT02460094.

Findings Between Oct 2, 2015, and Oct 19, 2016, 48 participants were enrolled and randomly assigned to the BIIB092 (n=36) and placebo (n=12) groups. No apparent demographic differences were observed between the two groups at baseline. All 48 participants completed the treatment phase of the study. Adverse events were generally mild to moderate in severity; the most common in the placebo and BIIB092 groups were falls (in two [17%] of 12 patients and in ten [28%] of 36 patients), urinary tract infections (in one [8%] of 12 and in six [17%] of 36), contusions (in one [8%] of 12 and in five [14%] of 36), and headaches (in none and in five [14%] of 36). Four serious adverse events resulting in admission to hospital were reported in three participants who received BIIB092 2100 mg: two severe adverse events of urinary tract infection, one severe adverse event of change in mental status, and one moderate adverse event of aspiration pneumonia. None was considered to be related to the study drug, all were resolved, and no deaths were reported.

Interpretation Repeated administration of the anti-tau monoclonal antibody BIIB092, at doses of up to 2100 mg, appears to be well tolerated in participants with progressive supranuclear palsy. Results of this phase 1b trial have informed the design of the ongoing phase 2 PASSPORT (NCT03068468) study to examine the efficacy and safety of BIIB092.

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Introduction

Progressive supranuclear palsy is a neurodegenerative disease that causes impairments in physical function, including gait, postural stability (resulting in falls), speech, and swallowing, as well as in cognition and behaviour, such as apathy and frontal dementia.[1] Individuals with the classic form of the disease, progressive supranuclear palsy-Richardson syndrome, have progressive ocular motor impairments and frequent falls. Progressive supranuclear palsy imparts a substantial caregiver and economic burden; individuals with the neurodegenerative disease require a wide range of services, many of which are provided by unpaid caregivers (ie, family and friends).[2] Currently, no disease-modifying therapies for progressive supranuclear palsy exist.[1] Present therapeutic approaches, including levodopa, are palliative and generally provide only transient symptomatic benefit.[1] Inevitably, progressive supranuclear palsy is fatal, and death occurs a median of 7·3 years after symptom onset.[1,3]

The protein tau binds and stabilises neuronal microtubules and is thought to promote axonogenesis, regulate axonal transport and signalling of synaptic neurotransmitter

Research in context

Evidence before this study

We searched PubMed using the terms "progressive supranuclear palsy"[All Fields] AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND "clinical trial"[All Fields] for studies published between Jan 1, 1900, and Dec 31, 2013. We identified 22 reports, including case series, single-arm studies, pilot trials, and randomised clinical trials. None reported noteworthy disease modification with the agents tested. The exact composition of the pathogenic tau species in progressive supranuclear palsy is unknown. However, preclinical data support the hypothesis that tau pathology might spread via an extracellular transmissible tau species and that anti-tau monoclonal antibodies might block this spreading. In a previous phase 1 trial, single doses of BIIB092 (up to 4200 mg) were well tolerated and reduced unbound N-terminal tau by up to 97% in the CSF of healthy volunteers 28 days after administration.

Added value of this study

The results of our phase 1b study show that BIIB092 was able to cross the blood–brain barrier with a CSF concentration approximately 1% of that in plasma. BIIB092 is, to the best of our knowledge, the first agent to show engagement with and reduction of the target, unbound N-terminal tau, in the CSF of participants with progressive supranuclear palsy. BIIB092 was well tolerated in these participants.

Implications of all the available evidence

In this study, BIIB092 showed favourable tolerability, pharmacokinetics, and pharmacodynamics (ie, reduction of unbound N-terminal tau in CSF) in participants with progressive supranuclear palsy, indicating target engagement after 12 weeks of treatment, and the results of this study confirm the findings of a phase 1 study done in healthy volunteers. These results have informed the design of the ongoing phase 2 PASSPORT study, which has a longer treatment period and has enrolled a larger group of participants with progressive supranuclear palsy. Results of studies such as PASSPORT will indicate whether or not BIIB092 is beneficial in slowing disease progression.

receptors, and protect neuronal DNA integrity.[4] Abnormal deposits of tau have been implicated in various neurodegenerative disorders, or tauopathies, including progressive supranuclear palsy.[4] Neuropathological examination of individuals with progressive supranuclear palsy reveals abnormal aggregates of four microtubule-binding domain-repeat (4R) tau isoforms, including neurofibrillary tangles and neuropil threads in both neurons and glia, tufted astrocytes, and oligodendroglial coiled bodies.[1,5] The amount and regional distribution of tau pathology in progressive supranuclear palsy is heterogeneous, which might account for the variable phenotypes.[6] Although tau is primarily an intracellular protein, both full-length tau and fragments of tau are found in the extracellular space, as evidenced by studies involving P301S tau transgenic mice, human brain tissue samples, and human induced pluripotent stem cell-derived neurons.[7,8] Several reports suggest that human CSF contains predominantly N-terminal or mid-domain tau fragments,[7,9,10] although recent reports with ultrasensitive immunoassays show that full-length tau (including the microtubule binding domain) is present in human CSF and plasma.[11] N-terminal tau fragments are particularly abundant in CSF and have longer half-lives than full-length tau.[7,12]

In tauopathies such as progressive supranuclear palsy, extracellular tau is hypothesised to be released from neurons, where it can have a variety of effects on nearby neurons and glia, including seeding neuropathological changes.[12,13] This might lead to the release of additional tau or tau fragments, thereby further spreading tau pathology from neuron to neuron.[12,13] This hypothesis is supported by studies showing that tau transgenic (ALZ17 or P301S) mice, when injected with recombinant 4R tau or brain homogenates from progressive supranuclear palsy or other 4R tauopathies, develop accelerated tau pathology that can spread along distinct neuronal connections to distant regions of the brain.[14,15] Moreover, antibodies recognising an N-terminal epitope of tau have been shown to inhibit development of tau seeding activity, reduce microglial activation, and improve cognitive deficits in P301S transgenic mice, suggesting that removal of N-terminal-containing tau particles might reduce transmission or pathological accumulation of tau within neurons.[16] The transmissible species of tau has not been unequivocally defined and might differ between tauopathies.[17,18]

No preclinical models exist that are specifically designed to recapitulate the pathology of progressive supranuclear palsy.[1] Most models used for anti-tau drug development rely on the expression of pathogenic mutations from human tau (*MAPT*) mutation carriers that lead to a range of phenotypes in humans, most commonly behavioural variant frontotemporal dementia, but occasionally also progressive supranuclear palsy. A major question for anti-tau therapeutic development is how well findings from preclinical models such as transgenic mice will translate into individuals with tauopathy, since the transmissible species identified in human brain specimens cannot be generated de novo in preclinical models without injection of human tissue. Pathogenic tau species generated from human *MAPT* mutations in mice might have different seeding properties to those found in the human brain.[19] Because the only readily accessible forms of tau in living humans are in CSF, whereas preclinical data suggest that transmission might occur transynaptically in the brain parenchyma, identification

of the transmissible species of tau in humans has been challenging. However, some evidence suggests that such species are present in the CSF of individuals with Alzheimer's disease.[20] A previous study[21] showed that an anti-tau monoclonal antibody can block tau aggregation in a cell culture assay that is induced by tau seeds from progressive supranuclear palsy brain homogenates. Although the exact composition of these tau seeds is not clear, much of the tau that is secreted by human neurons contains the N-terminal domain,[7] suggesting that N-terminal tau epitopes could be appropriate targets for anti-tau therapeutic agents.

BIIB092 (formerly BMS-986168/IPN007) is a humanised monoclonal antibody (immunoglobulin G4P) derived from a murine immunoglobulin G1 monoclonal antibody, IPN002, that was shown to bind to tau at the N terminus with high affinity.[12] BIIB092 was discovered because of its ability to bind to and neutralise the effects of N-terminal tau fragments that are secreted from neurons derived from human induced pluripotent stem cells and thus lead to potent electrophysiological changes in neighbouring cells.[12] In a previous phase 1 trial,[22] single doses of BIIB092 (up to 4200 mg) reduced unbound N-terminal tau (a measurement of N-terminal tau in the presence of BIIB092) by up to 97% in the CSF of healthy volunteers 28 days after administration and were well tolerated, showing no safety signals that would preclude continued investigation of BIIB092 as a potential treatment for human tauopathies, including progressive supranuclear palsy. Therefore, we aimed to investigate the safety and tolerability of BIIB092 in participants with progressive supranuclear palsy and to ascertain the effects of BIIB092 on N-terminal tau in CSF.

Methods

Study design and participants

In this randomised, double-blind, placebo-controlled, multiple ascending dose, phase 1b trial, investigators enrolled participants at 13 outpatient sites in the USA. Study visits occurred from Oct 2, 2015, to Oct 19, 2016. Eligible participants were aged 41–86 years with a bodyweight of 43–118 kg, a score of 20 or greater on the Mini-Mental State Examination (MMSE), and a diagnosis of probable or possible progressive supranuclear palsy with symptoms present for less than 5 years. Diagnosis was based on modified National Institute of Neurological Disorders and Stroke and the Society for Progressive Supranuclear Palsy (NINDS-SPSP) criteria,[23] including a 12-month history of postural instability or falls during the first 3 years that symptoms were present; decreased downward saccade velocity or supranuclear ophthalmoplegia; and an akinetic-rigid syndrome with prominent axial rigidity. Participants also had to be able to tolerate MRI scans and lumbar punctures, ambulate independently or with assistance, have a reliable caregiver present at all study visits, and live outside a skilled nursing facility or dementia care facility. Levodopa or carbidopa and other anti-parkinsonian medications and coenzyme Q10 were permitted if the dose was stable for 90 days or longer. Participants were excluded if they had any other noteworthy neurological or psychiatric disorders, or MRI scans indicative of substantial abnormality.

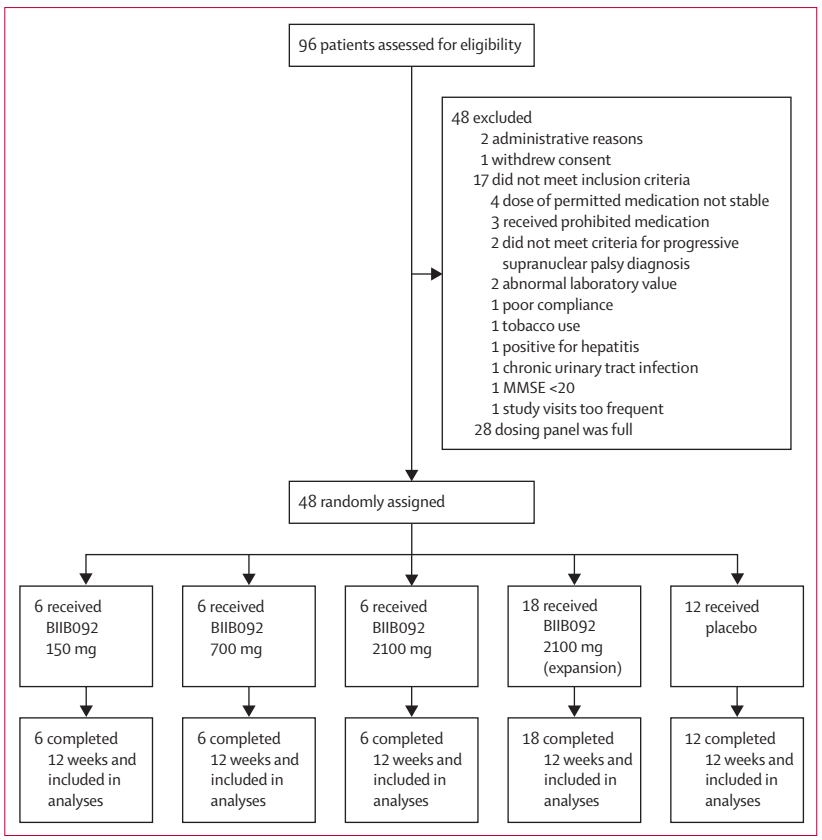

Figure 1: **Trial profile**
MMSE=Mini-Mental State Examination.

This study was done in accordance with the Declaration of Helsinki and Good Clinical Practice. The protocol was approved by the institutional review board or ethics committee at each study site, and all participants or their legally acceptable representatives gave written informed consent. The protocol can be requested from the Biogen Data Request Portal.

To **request the study protocol, use the Biogen Data Request Portal** at http://www.biogenclinicaldatarequest.com

See **Online** for appendix

Randomisation and masking

Three BIIB092 dose escalation cohorts (150 mg, 700 mg, or 2100 mg; eight participants per cohort) were tested sequentially (appendix). For each dose cohort, the first two participants (sentinel group) were randomly assigned to receive either BIIB092 or placebo. After 2 days, the six remaining participants in each cohort were randomly assigned (5:1) to receive BIIB092 or placebo; randomisation was done according to a computer-generated scheme prepared by a randomisation coordinator. Randomisation numbers were assigned before dosing. All participants and study personnel were masked to treatment assignment, except for unmasked pharmacists who prepared

	Placebo (n=12)	BIIB092 (n=36)		
		150 mg (n=6)	700 mg (n=6)	2100 mg; combined* (n=24)
Age, years	68·6 (6·0)	68·8 (6·6)	64·2 (6·4)	67·3 (4·7)
Sex				
Women	5 (42%)	3 (50%)	5 (83%)	13 (54%)
Men	7 (58%)	3 (50%)	1 (17%)	11 (46%)
Race				
White	10 (83%)	6 (100%)	6 (100%)	21 (88%)
Asian	0	0	0	1 (4%)
Other	2 (17%)	0	0	2 (8%)
Concomitant anti-parkinsonian medications†	6 (50%)	5 (83%)	4 (67%)	16 (67%)
Carbidopa-levodopa	3 (25%)	1 (17%)	2 (33%)	12 (50%)
Amantadine	0	4 (67%)	1 (17%)	3 (13%)
Rasagiline	0	0	0	5 (21%)
PSPRS score	33·4 (8·3)	32·3 (16·2)	33·0 (9·4)	38·3 (14·5)
MMSE	27·3 (2·0)	27·5 (2·3)	28·3 (2·0)	27·3 (2·3)
SEADL, %	70·0% (21·7)	63·3% (18·6)	60·0% (32·9)	57·5% (24·4)
CGI-S	3·3 (0·5)	3·3 (0·8)	3·8 (0·8)	3·6 (1·0)
CSF analytes, pg/mL				
Unbound N-terminal tau‡	248·16 (200·76)	233·26 (126·13)	191·04 (138·55)	237·23 (99·14)
Mid-domain tau§	394·3 (141·7)	404·5 (134·1)	365·3 (170·1)	437·9 (198·0)
ptau181§	51·50 (30·48)	43·61 (16·12)	40·14 (18·91)	52·77 (15·38)
β-amyloid 40§	4386·4 (1617·7)	4273·3 (2218·4)	4315·0 (1528·7)	5126·5 (1887·4)
β-amyloid 42§	337·5 (176·7)	330·0 (233·1)	362·7 (151·2)	374·0 (169·6)
Neurofilament light chain§	2073·1 (610·9)	2723·2 (974·1)	2421·2 (580·8)	3032·2 (2261·3)
Serum neurofilament light chain, pg/mL¶	37·85 (29·05)	42·68 (17·41)	30·86 (6·92)	44·94 (26·77)
Verbal fluency				
Correct F-words	6·3 (4·0)	6·2 (3·1)	6·8 (2·1)	6·1 (3·4)
Correct L-words	5·8 (3·2)	7·2 (2·5)	7·3 (5·0)	6·0 (3·4)
MRI, $\times 10^3$ mm^3‖				
Whole brain volume	1113·3 (109·2)	1141·7 (92·6)	1052·8 (101·6)	1066·3 (102·4)
Ventricular volume	33·4 (12·9)	21·6 (6·9)	23·1 (9·4)	23·2 (9·0)
Midbrain volume	7·0 (1·6)	7·0 (1·0)	6·4 (1·7)	6·6 (0·9)
Superior cerebellar peduncle volume	0·70 (0·19)	0·70 (0·16)	0·59 (0·17)	0·64 (0·19)
Pons volume	15·4 (2·6)	14·9 (1·5)	13·3 (2·6)	14·3 (2·1)
Midbrain-to-pons volume ratio	0·45 (0·04)	0·47 (0·05)	0·48 (0·03)	0·47 (0·04)

Data are n (%) or mean (SD). PSPRS=Progressive Supranuclear Palsy Rating Scale. MMSE=Mini-Mental State Examination. SEADL=Schwab and England Activities of Daily Living. CGI-S=Clinical Global Impression of Severity. ptau181=phosphorylated tau at epitope 181. *Data for participants receiving 2100 mg in the third dose cohort or expansion cohort were combined. †Includes dopaminergic agents: carbidopa, levodopa, pramipexole, benserazide, and rotigotine. ‡Analysed in ten participants in the placebo group and 19 in the BIIB092 2100 mg group. §Analysed in 11 participants in the placebo group and 23 in the BIIB092 2100 mg group. ¶Analysed in four participants in the BIIB092 700 mg group and 21 in the BIIB092 2100 mg group. ‖Analysed in ten participants in the placebo group.

Table 1: **Demographic and baseline disease characteristics**

the study drug and provided the masked study drug to masked personnel. The randomisation schedules were maintained in a secure location with access limited to authorised personnel. The study drug was administered intravenously every 4 weeks for 57 days. Dose escalation to the next panel did not occur until safety data through day 43, and clinical laboratory results through day 29, were reviewed for at least six participants from each dose cohort and deemed acceptable by a safety monitoring committee. Serum and CSF pharmacokinetic BIIB092 data and CSF unbound N-terminal tau data that were available were also reviewed to inform the doses selected for succeeding cohorts and an expansion panel. Administered doses were determined by the safety monitoring committee on the basis of safety, pharmacokinetic, and pharmacodynamic data obtained from the earlier dose cohorts. After the first three panels were filled, an additional 24 participants were randomly assigned to either BIIB092 2100 mg or placebo in a ratio of 3:1 in an expansion panel. After 85 days, participants who completed the study and continued to meet eligibility criteria were invited to enrol in an open-label extension study (NCT02658916).

Procedures

At screening and on days 1, 2, 15, 29, 43, 57, and 85, and at follow-up (in any participant not enrolling in the extension study), blood and urine samples were obtained for clinical laboratory assessments. Participants were closely monitored for adverse events throughout the study by study site staff who were masked to study treatment assignment. Serum samples were collected for pharmacokinetic and immunogenicity analyses on days 1, 15, 57, and 85, and at follow-up (in any participant not enrolling in the extension study), and for pharmacokinetic analysis only on days 2, 29, and 43. Serum and CSF (via lumbar puncture) samples were collected for pharmacokinetic, pharmacodynamic, and biomarker analysis during screening and on days 29 and 85. Physical and neurological examinations, vital signs measurements, 12-lead electrocardiograms (ECGs), physical measurements, volumetric MRI (acquired according to the Alzheimer's Disease Neuroimaging Initiative protocol), and assessments on the Progressive Supranuclear Palsy Rating Scale (PSPRS),[3] Schwab and England Activities of Daily Living (SEADL) scale, Clinical Global Impression of Severity and Change (CGI-S, CGI-C), and verbal fluency (number of words beginning with the letters F and L that can be named in 1 min) were done at selected timepoints throughout the study period.

BIIB092 in serum and CSF was quantified at QPS (Newark, DE, USA) by use of a validated chemiluminescent immunoassay. Anti-BIIB092 antibodies in serum were quantified by use of a validated bridging electrochemiluminescence immunoassay Meso Scale Discovery platform. CSF samples were analysed for N-terminal tau (Meso Scale Diagnostics LLC, Gaithersburg, MD, USA), mid-domain tau, and phosphorylated tau at epitope 181 (ptau181; QPS, Newark, DE, USA), with validated fit-for-purpose immunoassays (appendix). Details about the

performance of these assays are provided in the appendix. β-amyloid 40 and β-amyloid 42 were quantified (QPS, Newark, DE, USA) with validated fit-for-purpose assays.

Outcomes

The primary outcome was safety, defined as the frequency of adverse events, serious adverse events, adverse events leading to discontinuation, and death, and measured by marked abnormalities in clinical laboratory tests, vital signs measurements, ECGs, and physical and neurological examinations. Secondary outcomes were BIIB092 pharmacokinetics, including maximum serum concentration (C_{max}), trough serum concentration (C_{trough}), serum concentration at 4 weeks, time to maximum serum concentration (T_{max}), area under the curve in one dosing interval ($AUC_{[tau]}$), and CSF to serum BIIB092 concentration ratios; immunogenicity (presence of antibodies to BIIB092 in serum); and pharmacodynamics, as assessed by changes from baseline in unbound N-terminal tau concentrations in CSF at days 29 and 85. Exploratory clinical outcomes included, but were not limited to, PSPRS, SEADL, CGI-S, CGI-C, and verbal fluency at day 85. Exploratory biomarker outcomes included CSF concentrations of mid-domain tau, ptau181, β-amyloid 40, and β-amyloid 42; CSF and serum concentrations of neurofilament light chain; and change in brain volume as measured by MRI (ventricles, whole brain, midbrain, superior cerebellar peduncle, and pons) at day 85.

Statistical analysis

Safety was analysed in the treated population (all enrolled participants who received at least one dose of the study drug). Pharmacokinetics were assessed in the evaluable pharmacokinetics population (all participants who received at least one dose of BIIB092 and had adequate pharmacokinetics profiles [serum concentrations above the lower limit of quantification; LLOQ]). Pharmacodynamics was assessed in the pharmacodynamics population (all participants who received at least one dose of study medication and had any evaluable data). Although the sample size was not based on statistical power considerations, administration of BIIB092 to six participants in each of the first three cohorts provided an 80% probability of observing at least one occurrence of any adverse event that would have occurred with a frequency of 24% in a population of patients with progressive supranuclear palsy. Additionally, administration of BIIB092 to 18 participants in the expansion cohort provided an 80% probability of observing at least one occurrence of any adverse event that would have occurred with a frequency of 9% in a population of patients with progressive supranuclear palsy.

All analyses were done with SAS, version 9.3. For all analyses, data for participants receiving 2100 mg in the third or expansion cohorts were combined. Individual pharmacokinetic parameter values were derived by non-compartmental methods with Phoenix 11-12WinNonlin, version 6.2.1 or higher. Medians and ranges were calculated for T_{max}, geometric means and coefficients of variation were calculated for BIIB092 C_{max} and $AUC_{[tau]}$ and percentage of baseline CSF N-terminal tau; and means and SD were calculated for other pharmacokinetic, pharmacodynamic, and exploratory endpoints. For serum and CSF BIIB092 concentration–time data, concentrations that were less than the LLOQ were treated as missing. Pre-dose concentrations less than the LLOQ and concentrations obtained before the

	Placebo (n=12)	BIIB092 (n=36)			
		150 mg (n=6)	700 mg (n=6)	2100 mg; combined* (n=24)	All (n=36)
Any adverse event	9 (75%)	4 (67%)	4 (67%)	19 (79%)	27 (75%)
Mild	8 (67%)	3 (50%)	2 (33%)	11 (46%)	16 (44%)
Moderate	1 (8%)	1 (17%)	2 (33%)	6 (25%)	9 (25%)
Severe	0	0	0	2 (8%)	2 (6%)
Very severe	0	0	0	0	0
Any serious adverse event	0	0	0	3 (13%)†	3 (8%)†
Frequent adverse events‡					
Fall	2 (17%)	1 (17%)	2 (33%)	7 (29%)	10 (28%)
Urinary tract infection	1 (8%)	1 (17%)	1 (17%)	4 (17%)	6 (17%)
Contusions§	1 (8%)	0	0	5 (21%)	5 (14%)
Headaches	0	0	3 (50%)	2 (8%)	5 (14%)

Data are number of patients having an adverse event. Mild=awareness of event but easily tolerated. Moderate=discomfort enough to cause some interference with usual activity. Severe=inability to carry out usual activity. Very severe=debilitating, significantly incapacitates participant despite symptomatic therapy. *Data for participants receiving 2100 mg in the third dose cohort or expansion cohort were combined. †One participant had serious adverse events of urinary tract infection and mental status changes (both considered severe); one participant had a serious adverse event of a severe urinary tract infection, and one patient had moderate aspiration pneumonia. ‡Reported in 10% or more of all participants receiving BIIB092. §Generally soft tissue haematomas associated with falls.

Table 2: **Frequency of adverse events**

	Geometric mean C_{max}, μg/mL (CV)	Geometric mean $AUC_{[tau]}$, h·μg/mL (CV)	Median T_{max}, h (range)
150 mg			
Day 1 (n=5)	64 (28%)	16 065 (17%)	1·50 (0·93–5·08)
Day 57 (n=6)	84 (29%)	21 466 (16%)	1·45 (0·97–3·00)
700 mg			
Day 1 (n=6)	280 (24%)	59 085 (26%)	1·30 (0·933–1·82)
Day 57 (n=6)	369 (22%)	127 494 (31%)*	2·23 (0·82–3·02)
2100 mg; combined†			
Day 1 (n=24)	672 (27%)	156 366 (22%)	2·00 (0·83–5·00)
Day 57 (n=23)	913 (28%)	299 954 (23%)‡	1·50 (0·97–5·00)

C_{max}=maximum serum concentration. CV=coefficient of variation. $AUC_{[tau]}$=exposure (area under the curve in one dosing interval). T_{max}=time to maximum serum concentration. *n=5. †Data for participants receiving 2100 mg in the third dose cohort or expansion cohort were combined. ‡n=21.

Table 3: **BIIB092 serum pharmacokinetics at days 1 and 57 (pharmacokinetics set)**

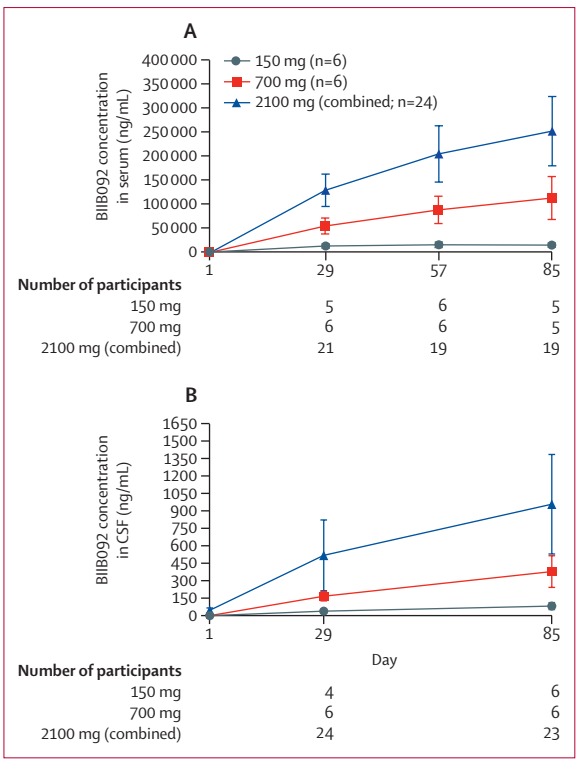

Figure 2: **Exposure of BIIB092 in (A) serum and (B) CSF**
Data are mean concentration (SD). Data for participants receiving 2100 mg in the third dose or expansion cohorts were combined. Low variability for the 150 mg and 700 mg groups cause the error bars to not be visible at some timepoints.

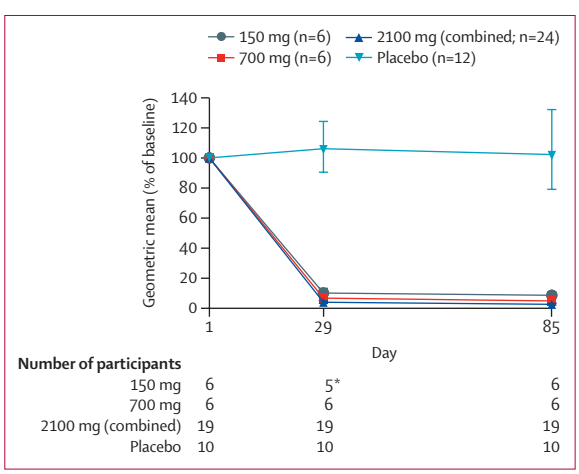

Figure 3: **Change (95% CI) in unbound N-terminal tau in CSF**
Data for participants receiving 2100 mg in the third dose cohort or expansion cohort were combined. *A CSF sample was not collected at day 29 for one participant in the 150 mg group. Error bars are 95% CIs.

first quantifiable concentration that were less than the LLOQ were set to zero. For serum C_{trough}, CSF unbound N-terminal tau, and exploratory biomarkers below the LLOQ, the values were imputed as 0·5×LLOQ.

This trial is registered with ClinicalTrials.gov, number NCT02460094.

Role of the funding source

This study was sponsored by Bristol-Myers Squibb (Lawrenceville, NJ, USA). Biogen (Cambridge, MA, USA) provided funding for medical writing support in the development of this paper. Employees of Bristol-Myers Squibb and Biogen (IQ, MA, GST, CB, TO, KKM, DLG, JO'G, SBH, and TD) contributed to the study design, data analysis, data interpretation, and writing of the report. The corresponding author (TD) had full access to all the data from the study and had final responsibility for the contents of the report and for the decision to submit for publication.

Results

96 individuals were screened (figure 1) and 48 were randomly assigned to the placebo (n=12) or BIIB092 groups (n=36). All participants completed the treatment phase of the study (day 85), and 47 continued in the open-label extension. Table 1 shows participant demographics and baseline disease characteristics; 31 (65%) participants took concomitant anti-parkinsonian medications during the study, including carbidopa-levodopa (18 [38%]), amantadine (eight [17%]), or rasagiline (five [10%]).

Table 2 summarises the frequency of adverse events. By day 85, 27 (75%) participants who received BIIB092 and nine (75%) participants who received placebo reported one or more adverse events (table 2). Falls, urinary tract infections, contusions (generally soft tissue haematomas associated with falls), and headaches were reported in 10% or more of all participants who were treated with BIIB092. Moderate adverse events were reported in nine (25%) BIIB092-treated participants and one (8%) placebo-treated participant; severe adverse events were reported in two (6%) BIIB092-treated participants and no placebo-treated participants. Four serious adverse events resulting in admission to hospital were reported in three participants who received BIIB092 2100 mg, and included urinary tract infection (in two participants; both adverse events considered severe), changes in mental status (in one participant; considered severe), and aspiration pneumonia (in one participant; considered moderate). None of these serious adverse events was considered to be related to the study drug by the investigator, and all were resolved. No adverse events led to study drug discontinuation, and no deaths were reported. No clinically relevant findings in vital signs, ECGs, clinical laboratory results, or MRI safety assessments were observed in either treatment group.

30 (83%) of 36 participants who were assigned to BIIB092 were negative for anti-BIIB092 antibodies at baseline (appendix). Five participants who tested negative at baseline were positive for anti-BIIB092 antibodies after baseline; however, no dose-related trends in immunogenicity were seen after administration of BIIB092.

BIIB092 concentrations increased in a dose-dependent manner in serum and CSF (table 3, figure 2A, 2B; appendix). Maximum serum concentrations of BIIB092

were achieved at the end of infusion with T_{max} values generally similar between treatment groups (table 3). A modest accumulation in serum and CSF consistent with the half-life of BIIB092 seen in healthy volunteers (21·5–27·6 days[22]) was observed following administration of BIIB092 every 4 weeks (figure 2A, 2B, table 3); BIIB092 geometric mean $AUC_{[tau]}$ in serum increased from day 1 to day 57 by approximately 1·3 times to 2·2 times (table 3). At day 85, the CSF-to-serum ratio of BIIB092 was approximately 0·3–0·5% across all doses tested and was generally similar between days 29 and 85 (appendix).

After administration of BIIB092, the CSF concentration of unbound N-terminal tau was reduced from baseline by approximately 90–96% across all doses of BIIB092 at day 29, whereas the level of unbound N-terminal tau in the placebo group remained similar to that observed at baseline (figure 3). A post-hoc analysis of $AUC_{[tau]}$ of BIIB092 at day 1 versus percentage change in unbound CSF N-terminal tau at day 29 showed a clear separation by treatment group (appendix). Reduction of unbound N-terminal tau in CSF was sustained with BIIB092, as evidenced by a mean reduction of approximately 91–97% at day 85 across all doses of BIIB092 (figure 3).

We found no dose-related or treatment-related trends in the exploratory endpoints of PSPRS, CGI-S, CGI-C, SEADL, or in brain volume on MRI (appendix). Similarly, we found no dose-related or treatment-related trends in exploratory biomarkers, including mid-domain tau, ptau181, β-amyloid 40, β-amyloid 42 in CSF, and neurofilament light chain in CSF and serum (appendix).

Discussion

In this phase 1b study, multiple administrations of BIIB092 were well tolerated at doses up to 2100 mg in participants with progressive supranuclear palsy. No deaths, serious treatment-related adverse events, or discontinuations due to an adverse event were reported. Most adverse events were mild or moderate, with no treatment-related or dose-related trends in frequency or severity. We also found that concentrations of BIIB092 in CSF increased with higher doses. Based on the approximately two-fold accumulation of BIIB092 on day 57 compared with day 1, the effective half-life was estimated to be approximately 28 days,[24] which is consistent with the half-life seen in healthy volunteers.[22] Substantial (>90%) reductions in CSF unbound N-terminal tau concentrations were observed with all BIIB092 doses, whereas unbound N-terminal tau concentrations remained unchanged in the placebo group. The extent of reduction of CSF unbound N-terminal tau observed in this study shows target engagement by BIIB092 in the CSF of participants with progressive supranuclear palsy.

To our knowledge, this is the first study to show target engagement in CSF of an anti-tau therapy in participants with progressive supranuclear palsy. Tau dysfunction has been implicated in the pathogenesis of various primary and secondary tauopathies,[4] with particularly strong clinicopathological and genetic links to progressive supranuclear palsy.[1] Several anti-tau therapeutic approaches have been or are being investigated, including agents that target post-translational modification such as kinase inhibitors, which prevent phosphorylation; inhibitors of acetylation and deglycosylation; compounds that block tau aggregation; microtubule stabilisers; and active and passive immunotherapy.[25] Although progressive supranuclear palsy is a rare disease, three multicentre clinical trials that were larger than the current study and various smaller trials in progressive supranuclear palsy have been completed over the past decade with no evidence of efficacy.[26–28] The first was the Neuroprotection and Natural History in Parkinson Plus Syndromes (NNIPPS) study,[26] which randomly assigned 363 participants with progressive supranuclear palsy to placebo versus riluzole, a glutamatergic signalling modulator hypothesised to diminish tau pathology. Another phase 2/3 trial[27] randomly assigned 313 participants with progressive supranuclear palsy to placebo versus davunetide, a peptide thought to promote microtubule stability and reduce tau phosphorylation. The third trial[28] randomly assigned 146 participants to placebo versus tideglusib, a glycogen synthase kinase-3β inhibitor, for 1 year with no benefits demonstrated in clinical outcomes, although progression of brain atrophy was reported to be lower with tideglusib than with placebo in a subset of participants.[29] These studies were of longer duration than the present study and were done in participants who appeared to have similar PSPRS scores. The NNIPPS and davunetide trials also enrolled participants with lower mean SEADL scores than in the current study (approximately 50% *vs* 62%).[26,27] The effect of these agents on N-terminal tau concentrations or other specific fragments of tau in CSF has not been reported; only the davunetide study investigated ptau181 and total tau and found no change. The evidence of target engagement in this study addresses a major concern of previous studies, which did not include pharmacokinetic and pharmacodynamic data, showing that adequate doses of BIIB092 reached the CSF and engaged the intended targets.

This study also examined the effect of BIIB092 on several exploratory clinical and biomarker endpoints, including PSPRS, SEADL, CGI-S, CGI-C, CSF concentrations of neurofilament light chain, standard measures of total tau, ptau181, β-amyloid 40 and β-amyloid 42, and serum concentrations of neurofilament light chain. This study was of a short duration and not sufficiently powered for efficacy; accordingly, as expected, there was no evidence that BIIB092 had an effect on the exploratory clinical, biomarker, or MRI measurements. Based on data from the davunetide study,[27,30] neurofilament light chain concentrations were not expected to change over the short time period of this study.

This study had some important limitations. We found a reduction of unbound N-terminal tau fragment concentrations in CSF in response to BIIB092 treatment but

no changes in the concentration of standard mid-domain tau or ptau181 fragment concentrations commonly measured in Alzheimer's disease trials. Furthermore, it is unclear whether BIIB092 penetrated the brain parenchyma and interstitial fluid, where transmissible forms of tau would be likely to exert their pathological effects. Additional studies are needed to address these questions, and will require the development of novel biomarkers, such as new 4R tau-sensitive PET ligands, that can assess tau species in these CNS compartments.

These data suggest that the majority of N-terminal fragments that contained the BIIB092 epitope in CSF were bound by peripherally administered BIIB092. The absence of reduction of total tau or ptau181 concentrations by BIIB092 binding to these fragments suggests that at least some antibody-bound fragments remained present in the CSF. Even if they were present, preclinical data suggest that N-terminal monoclonal antibody binding is sufficient to block physiological effects and transmission of tau fragments.[12] Further work will be necessary to understand whether the N-terminal tau epitope target for BIIB092 is present in and necessary for the transmission of the tau species that are thought to be responsible for disease progression in patients with progressive supranuclear palsy.

An additional limitation of tau assays that use ELISA-based measurements might be that only a subset of all known tau protein fragments were assessed according to the binding specificity of the assay antibodies. Although N-terminal tau fragments are abundant in CSF in healthy individuals and those with Alzheimer's disease, they might be different from the fragments measured by the typical total tau and ptau assays.[9] Moreover, it is not known how the concentrations of these CSF tau fragments relate to full-length tau and C-terminal fragments that are present in neurons and the interstitial fluid, or the insoluble deposits of 4R tau that are the pathological hallmarks of progressive supranuclear palsy. Nor is it known which of these species are actually pathogenic in patients with progressive supranuclear palsy.

Modest reductions in N-terminal tau fragments and ptau181 in CSF have been observed in progressive supranuclear palsy, and the magnitude of ptau181 reduction inversely correlates with the rate of disease progression.[31] The physiological mechanisms responsible for subtle CSF N-terminal fragment and ptau181 reductions in progressive supranuclear palsy are unknown, but might reflect increasing sequestration of these fragments into insoluble aggregates; this has been suggested as a possible underlying mechanism for CSF ptau181 reductions in patients with symptomatic dominantly inherited Alzheimer's disease.[32] If true, this complicates interpretation of the concentrations of CSF tau fragments in BIIB092-treated participants with progressive supranuclear palsy, since binding of a monoclonal antibody might increase or reduce the clearance rate of fragments from the CSF. If the rate of clearance is reduced, measured tau fragment concentrations might increase, as has been shown for plasma tau concentrations after treatment of individuals with a different N-terminal monoclonal antibody.[33] Overall, new biomarkers and approaches that can assess a greater range of tau fragments in the different CNS compartments (including both fluid and insoluble phases) will be necessary to fully understand the biochemical effects of BIIB092 treatment, and these are not likely to be available until after the first progressive supranuclear palsy clinical efficacy study is completed.

In conclusion, we have shown that an anti-tau monoclonal antibody, BIIB092, administered every 4 weeks over a 12-week period, crosses the blood–brain barrier and engages its intended target, N-terminal tau, in the CSF of participants with progressive supranuclear palsy with an acceptable tolerability profile, confirming the findings of the earlier phase 1 study in healthy volunteers.[22] These data support ongoing clinical trials of anti-tau immunotherapy to slow the spread of tau and disease progression in patients with progressive supranuclear palsy and other tauopathies. The neuroprotective efficacy and clinical safety of BIIB092 is currently being assessed in a larger, 12-month, randomised, double-blind, phase 2 clinical trial in participants with progressive supranuclear palsy (PASSPORT; NCT03068468) that will provide additional insight into the safety profile of BIIB092.

Contributors

IQ, MA, GST, CB, TO, KKM, DLG, JO'G, SBH, and TD (employees or former employees of Bristol-Myers Squibb and Biogen) contributed to the study design, data analysis, data interpretation, and writing of the report. ALB and MGru contributed to the study design, data analysis, data interpretation, and writing of the report. All authors had full access to study data for interpretation and drafting of the report. Editorial and writing support was provided to authors and funded by Biogen. All decisions relating to the writing and contents of the manuscript were made jointly by the authors. The corresponding author (TD) had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

To request access to data, please visit http://www.biogenclinicaldatarequest.com. Following US and EU marketing approval of BIIB092 for progressive supranuclear palsy, the individual anonymised participant data collected during the trial, which supports the research proposal, will be available to qualified scientific researchers upon approval of the research proposal.

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