PHARMACEUTICAL COMPOSITIONS CONTAINING ANTI-BETA AMYLOID ANTIBODIES

Cross-Reference to Related Application

This application claims the benefit of priority of U.S. Provisional Application No. 62/548,583, filed August 22, 2017, the content of which is incorporated by reference herein in its entirety.

Field

The present application relates generally to pharmaceutical compositions comprising anti-beta amyloid (Aβ) antibodies and uses thereof.

Background

Aβ is a peptide generated from the metabolism of amyloid precursor protein (APP). Several Aβ peptide alloforms exist (*e.g.*, Aβ40 and Aβ42). These monomeric peptides have a variable tendency to aggregate into higher order dimers and oligomers. Through a process of fibrillogenesis, soluble oligomers may transition into insoluble deposits having a β pleated sheet structure. These deposits are also referred to as amyloid plaques and are composed of predominantly fibrillar amyloid (Hampel et al., *Exp Neurol.*, 223(2):334-46 (2010); Gregory and Halliday, *Neurotox Res.*, 7(1-2):29-41 (2005)). Both soluble and fibrillar forms of Aβ appear to contribute to disease process in disorders characterized by deposition of Aβ such as Alzheimer's disease (AD) (Meyer-Luehmann, *J Neurosci.*, 29(40):12636-40 (2009); Hock, *Dialogues Clin Neurosci.*, 5(1):27-33 (2003); Selkoe, *Cold Spring Harb Perspect Biol.*, 3(7). pii: a004457 (2011)).

AD patients having high serum titers of anti-Aβ antibodies that recognize amyloid plaques have slower rates of cognitive decline and disability as compared to patients that do not have anti-Aβ antibodies. Moreover, patients who develop high titers of anti-Aβ antibodies show reduced numbers of brain Aβ plaques and improved cognitive performance assessed after long-term follow up. These clinical data suggest that AD patients treated with anti-Aβ antibodies in a passive immunotherapy paradigm are likely to show reduced cognitive impairment, a lower density of brain Aβ deposits, and reduced rates of cognitive deterioration.

The anti-Aβ antibody, BIIB037, is a fully human antibody comprising a glycosylated human IgG1 heavy chain and a human kappa light chain. Recombinantly expressed BIIB037 binds with high apparent affinity to high molecular weight aggregates, presumably fibrils, of human Aβ. By immunohistochemistry, BIIB037 shows high affinity binding to Aβ plaques

in human AD brain and in brain tissues derived from human APP-expressing transgenic mice. The affinity and specificity of BIIB037 for high molecular weight aggregates of human Aβ was confirmed by immunoprecipitation, immunoblotting, and immunohistochemistry. In Tg2576 AD transgenic mice, BIIB037 treatment results in measurable drug levels in brain as assessed by ELISA. Following administration of BIIB037 in Tg2576 mice, immunoreactivity for BIIB037 was observed in association with brain parenchymal and vascular amyloid deposits, suggesting that BIIB037 enters brain parenchyma and binds to its target. It is believed that systemically administered anti-Aβ antibodies such as BIIB037 enter the brain, bind to deposits
of Aβ, and trigger their clearance from the brain by Fc receptor dependent mechanisms. Antibody-mediated removal of Aβ from the brain is hypothesized to decrease Aβ burden, thereby preventing neuronal dysfunction, slowing the progression of pathology and reducing the rate of cognitive decline in AD.

Summary

This disclosure relates, in part, to pharmaceutical compositions containing anti-Aβ antibody or Aβ-binding fragments thereof and their use in the treatment of abnormal accumulation or deposition of Aβ in the central nervous system, mild cognitive impairment, and Aβ-associated disorders such as Alzheimer's disease.

In one aspect, the disclosure features a pharmaceutical composition comprising an anti-Aβ antibody or Aβ-binding fragment thereof and arginine hydrochloride (Arg.HCl).

In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof comprises an immunoglobulin heavy chain variable domain (VH) and an immunoglobulin light chain variable domain (VL), the VH and VL comprising the CDRs of BIIB037. In some instances, the six CDRs of BIIB037 comprise or consist of the amino acid sequences set forth in SEQ ID NO:1; SEQ ID NO:2; SEQ ID NO:3; SEQ ID NO:4; SEQ ID NO:5; and SEQ ID NO:6.

In some embodiments, the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 50 mg/ml to 250 mg/ml. In other embodiments, the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 75 mg/ml to 165 mg/ml. In certain embodiments, the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 150 mg/ml. In certain embodiments, the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 100 mg/ml.

In some embodiments, the composition comprises Arg.HCl at a concentration of 50 mM to 250 mM. In other embodiments, the composition comprises Arg.HCl at a concentration of 75 mM to 175 mM. In certain embodiments, the composition comprises Arg.HCl at a concentration of 150 mM.

In some embodiments, the composition further comprises Polysorbate-80 (PS80). In some embodiments, the composition comprises PS80 at a concentration of 0.01% to 0.1%. In other embodiments, the composition comprises PS80 at a concentration of 0.03% to 0.08%. In certain embodiments, the composition comprises PS80 at a concentration of 0.05%.

In some embodiments, the composition further comprises a buffer selected from the group consisting of histidine, acetate, succinate, and citrate. In certain instances, the buffer is histidine. In certain instances, the buffer is acetate. In certain instances, the buffer is succinate. In certain instances, the buffer is citrate. In certain embodiments, the composition comprises histidine, acetate, succinate, or citrate at a concentration of 10 mM to 30 mM. In certain embodiments, the composition comprises histidine, acetate, succinate, or citrate at a concentration of 20 mM. In certain embodiments, the composition comprises histidine at a concentration of 10 mM to 30 mM. In certain embodiments, the composition comprises histidine at a concentration of 20 mM.

In some embodiments, the composition further comprises methionine. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 150 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 125 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 100 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 75 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 50 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 20 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 15 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 50 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 75 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 100 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 125 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 150 mM. In certain embodiments, the composition comprises methionine at a concentration of 10 mM. In certain embodiments, the composition comprises methionine at a concentration of 50 mM. In certain embodiments, the

composition comprises methionine at a concentration of 75 mM. In certain embodiments, the composition comprises methionine at a concentration of 100 mM. In certain embodiments, the composition comprises methionine at a concentration of 125 mM. In certain embodiments, the composition comprises methionine at a concentration of 150 mM.

In some embodiments, the composition further comprises sucrose. In some embodiments, the composition comprises sucrose at a concentration of 0.01% to 5%. In other embodiments, the composition comprises sucrose at a concentration of 1% to 4%. In certain embodiments, the composition comprises sucrose at a concentration of 3%.

In some embodiments, the composition has a pH of 5.2 to 6.2. In certain embodiments, the composition has a pH of 5.2 to 6.0. In certain embodiments, the composition has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5.

In certain embodiments, the pharmaceutical composition comprises the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 50 mg/ml to 250 mg/ml; Arg.HCl at a concentration of 50 mM to 200 mM; methionine at a concentration of 0 mM to 20 mM; histidine at a concentration of 10 mM to 30 mM; PS80 at a concentration of 0.01% to 0.1%; and sucrose at a concentration of 0 to 3%. In some cases, this composition has a pH of 5.2 to 6.2. In some cases, this composition has a pH of 5.2 to 6.0. In certain embodiments, the composition has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5.

In certain embodiments, the pharmaceutical composition comprises the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 150 mg/ml; Arg.HCl at a concentration of 150 mM; methionine at a concentration of 10 mM; histidine at a concentration of 20 mM; and PS80 at a concentration of 0.05%. In some cases, this composition has a pH of 5.2 to 6.2. In some cases, this composition has a pH of 5.2 to 6.0. In certain embodiments, the composition has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5.

In certain embodiments, the pharmaceutical composition comprises the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 100 mg/ml; Arg.HCl at a concentration of 150 mM; methionine at a concentration of 10 mM; histidine at a concentration of 20 mM; and PS80 at a concentration of 0.05%. In some cases, this composition has a pH of 5.2 to 6.2. In some cases, this composition has a pH of 5.2 to 6.0. In certain embodiments, the composition has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5.

In some embodiments, the VH comprises or consists of a sequence at least 80% identical to SEQ ID NO:7 and the VL comprises or consists of a sequence at least 80% identical to SEQ ID NO:8. In some embodiments, the VH comprises or consists of a sequence at least 90% identical to SEQ ID NO:7 and the VL comprises or consists of a sequence at least 90% identical to SEQ ID NO:8. In some embodiments, the VH comprises or consists of the sequence of SEQ ID NO:7 and the VL comprises or consists of the sequence of SEQ ID NO:8.

In some embodiments, the anti-Aβ antibody comprises an immunoglobulin heavy chain and an immunoglobulin light chain. In certain instances, the heavy chain comprises or consists of a sequence at least 80% identical to SEQ ID NO:9 and the light chain comprises or consists of a sequence at least 80% identical to SEQ ID NO:10. In other instances, the heavy chain comprises or consists of a sequence at least 90% identical to SEQ ID NO:9 and the light chain comprises or consists of a sequence at least 90% identical to SEQ ID NO:10. In yet other instances, the heavy chain comprises or consists of the sequence of SEQ ID NO:9 and the light chain comprises or consists of the sequence of SEQ ID NO:10.

In another aspect, the disclosure features a method of treating abnormal accumulation or deposition of Aβ in the central nervous system in a human subject in need thereof. The method comprises administering to the human subject a pharmaceutical composition described herein.

In another aspect, the disclosure features a method of treating mild cognitive impairment in a human subject in need thereof. The method comprises administering to the human subject a pharmaceutical composition described herein.

In another aspect, the disclosure features a method of treating Alzheimer's disease in a human subject in need thereof. The method comprises administering to the human subject a pharmaceutical composition described herein.

In some embodiments, of these aspects, the pharmaceutical composition is administered subcutaneously to the human subject. In some embodiments, of these aspects, the pharmaceutical composition is administered intravenously to the human subject.

In another aspect, the disclosure provides a pharmaceutical composition comprising an anti-Aβ antibody or Aβ-binding fragment thereof, a thiol-containing antioxidant, and arginine hydrochloride (Arg.HCl).

In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof comprises an immunoglobulin heavy chain variable domain (VH) and an immunoglobulin light chain variable domain (VL), the VH and VL comprising the CDRs of BIIB037. In some

instances, the six CDRs of BIIB037 comprise or consist of the amino acid sequences set forth in SEQ ID NO:1; SEQ ID NO:2; SEQ ID NO:3; SEQ ID NO:4; SEQ ID NO:5; and SEQ ID NO:6.

In some embodiments, the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 50 mg/ml to 250 mg/ml. In other embodiments, the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 75 mg/ml to 165 mg/ml. In certain embodiments, the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 150 mg/ml. In certain embodiments, the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 100 mg/ml.

In some embodiments, the thiol-containing antioxidant in the composition is selected from the group consisting of GSH, GSSG, the combination of GSH and GSSG, cystine, cysteine, and the combination of cysteine and cystine. In certain instances, the thiol-containing antioxidant is GSH. In certain instances, the thiol-containing antioxidant is GSSG. In certain instances, the thiol-containing antioxidant is GSH and GSSG. In certain embodiments, the thiol-containing antioxidant is at a concentration of 0.02 mM to 4 mM. In certain embodiments, the thiol-containing antioxidant is at a concentration of 0.02 mM to 2 mM. In certain embodiments, the thiol-containing antioxidant is at a concentration of 0.2 mM. In certain embodiments, the thiol-containing antioxidant is at a concentration of 0.4 mM. In certain embodiments, the thiol-containing antioxidant is at a concentration of 1 mM. In certain embodiments, the thiol-containing antioxidant is at a concentration of 2 mM. In certain embodiments, the thiol-containing antioxidant is at a concentration of 4 mM. In certain instances, the thiol-containing antioxidant in the composition is GSH at a concentration of 0.4 mM and GSSG at a concentration of 0.2 mM. In certain instances, the thiol-containing antioxidant in the composition is GSH at a concentration of 4 mM and GSSG at a concentration of 2 mM. In certain instances, the thiol-containing antioxidant in the composition is GSH at a concentration of 2 mM and GSSG at a concentration of 1 mM. In certain instances, the thiol-containing antioxidant in the composition is cysteine at a concentration of 0.4 mM and cystine at a concentration of 0.2 mM.

In some embodiments, the composition comprises Arg.HCl at a concentration of 50 mM to 250 mM. In other embodiments, the composition comprises Arg.HCl at a concentration of 75 mM to 175 mM. In certain embodiments, the composition comprises Arg.HCl at a concentration of 150 mM.

In some embodiments, the composition further comprises Polysorbate-80 (PS80). In some embodiments, the composition comprises PS80 at a concentration of 0.01% to 0.1%. In other embodiments, the composition comprises PS80 at a concentration of 0.03% to 0.08%. In certain embodiments, the composition comprises PS80 at a concentration of 0.05%.

In some embodiments, the composition further comprises a buffer selected from the group consisting of histidine, acetate, succinate, and citrate. In certain instances, the buffer is histidine. In certain instances, the buffer is acetate. In certain instances, the buffer is succinate. In certain instances, the buffer is citrate. In certain embodiments, the composition comprises histidine, acetate, succinate, or citrate at a concentration of 10 mM to 30 mM. In certain embodiments, the composition comprises histidine, acetate, succinate, or citrate at a concentration of 20 mM. In certain embodiments, the composition comprises histidine at a concentration of 10 mM to 30 mM. In certain embodiments, the composition comprises histidine at a concentration of 20 mM.

In some embodiments, the composition further comprises sucrose. In some embodiments, the composition comprises sucrose at a concentration of 0.01% to 5%. In other embodiments, the composition comprises sucrose at a concentration of 1% to 4%. In certain embodiments, the composition comprises sucrose at a concentration of 3%.

In some embodiments, the composition further comprises methionine. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 150 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 125 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 100 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 75 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 50 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 20 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 15 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 50 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 75 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 100 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 125 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 150 mM. In certain embodiments, the composition comprises methionine at a concentration of 10 mM. In certain embodiments, the composition comprises methionine at a concentration of 50 mM. In certain embodiments, the

composition comprises methionine at a concentration of 75 mM. In certain embodiments, the composition comprises methionine at a concentration of 100 mM. In certain embodiments, the composition comprises methionine at a concentration of 125 mM. In certain embodiments, the composition comprises methionine at a concentration of 150 mM. In some embodiments, the composition has a pH of 5.2 to 6.2. In certain embodiments, the composition has a pH of 5.2 to 6.0. In certain embodiments, the composition has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5.

In certain embodiments, the pharmaceutical composition comprises the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 50 mg/ml to 250 mg/ml; a thiol-containing antioxidant at a concentration of 0.02 mM to 4 mM; Arg.HCl at a concentration of 50 mM to 200 mM; histidine at a concentration of 10 mM to 30 mM; PS80 at a concentration of 0.01% to 0.1%; and sucrose at a concentration of 0 to 3%. In some cases, this composition has a pH of 5.2 to 6.2. In some cases, this composition has a pH of 5.2 to 6.0. In certain embodiments, the composition has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5. In some instances, the thiol-containing antioxidant is selected from the group consisting of GSH, GSSG, the combination of GSH and GSSG, cystine, cysteine, and the combination of cysteine and cystine. In some instances, the thiol-containing antioxidant is GSH. In some instances, the thiol-containing antioxidant is GSSG. In some instances, the thiol-containing antioxidant is the combination of GSH and GSSG.

In certain embodiments, the pharmaceutical composition comprises the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 150 mg/ml; Arg.HCl at a concentration of 150 mM; a thiol-containing antioxidant at a concentration of 0.02 mM to 4 mM; histidine at a concentration of 20 mM; and PS80 at a concentration of 0.05%. In some cases, this composition has a pH of 5.2 to 6.2. In some cases, this composition has a pH of 5.2 to 6.0. In certain embodiments, the composition has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5. In some instances, the thiol-containing antioxidant is selected from the group consisting of GSH, GSSG, the combination of GSH and GSSG, cystine, cysteine, and the combination of cysteine and cystine. In some instances, the thiol-containing antioxidant is GSH. In some instances, the thiol-containing antioxidant is GSSG. In some instances, the thiol-containing antioxidant is the combination of GSH and GSSG.

In certain embodiments, the pharmaceutical composition comprises the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 100 mg/ml; Arg.HCl at a

concentration of 150 mM; a thiol-containing antioxidant at a concentration of 0.02 mM to 4 mM; histidine at a concentration of 20 mM; and PS80 at a concentration of 0.05%. In some cases, this composition has a pH of 5.2 to 6.2. In some cases, this composition has a pH of 5.2 to 6.0. In certain embodiments, the composition has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5. In some instances, the thiol-containing antioxidant is selected from the group consisting of GSH, GSSG, the combination of GSH and GSSG, cystine, cysteine, and the combination of cysteine and cystine. In some instances, the thiol-containing antioxidant is GSH. In some instances, the thiol-containing antioxidant is GSSG. In some instances, the thiol-containing antioxidant is the combination of GSH and GSSG.

In some embodiments, the VH comprises or consists of a sequence at least 80% identical to SEQ ID NO:7 and the VL comprises or consists of a sequence at least 80% identical to SEQ ID NO:8. In some embodiments, the VH comprises or consists of a sequence at least 90% identical to SEQ ID NO:7 and the VL comprises or consists of a sequence at least 90% identical to SEQ ID NO:8. In some embodiments, the VH comprises or consists of the sequence of SEQ ID NO:7 and the VL comprises or consists of the sequence of SEQ ID NO:8.

In some embodiments, the anti-Aβ antibody comprises an immunoglobulin heavy chain and an immunoglobulin light chain. In certain instances, the heavy chain comprises or consists of a sequence at least 80% identical to SEQ ID NO:9 and the light chain comprises or consists of a sequence at least 80% identical to SEQ ID NO:10. In other instances, the heavy chain comprises or consists of a sequence at least 90% identical to SEQ ID NO:9 and the light chain comprises or consists of a sequence at least 90% identical to SEQ ID NO:10. In yet other instances, the heavy chain comprises or consists of the sequence of SEQ ID NO:9 and the light chain comprises or consists of the sequence of SEQ ID NO:10.

In another aspect, the disclosure provides a pharmaceutical composition comprising an anti-Aβ antibody or Aβ-binding fragment thereof, a thiol-containing antioxidant, methionine, and arginine hydrochloride (Arg.HCl).

In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof comprises an immunoglobulin heavy chain variable domain (VH) and an immunoglobulin light chain variable domain (VL), the VH and VL comprising the CDRs of BIIB037. In some instances, the six CDRs of BIIB037 comprise or consist of the amino acid sequences set forth in SEQ ID NO:1; SEQ ID NO:2; SEQ ID NO:3; SEQ ID NO:4; SEQ ID NO:5; and SEQ ID NO:6.

In some embodiments, the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 50 mg/ml to 250 mg/ml. In other embodiments, the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 75 mg/ml to 165 mg/ml. In certain embodiments, the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 150 mg/ml. In certain embodiments, the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 100 mg/ml.

In some embodiments, the thiol-containing antioxidant in the composition is selected from the group consisting of GSH, GSSG, the combination of GSH and GSSG, cystine, cysteine, and the combination of cysteine and cystine. In certain instances, the thiol-containing antioxidant is GSH. In certain instances, the thiol-containing antioxidant is GSSG. In certain instances, the thiol-containing antioxidant is GSH and GSSG. In certain embodiments, the thiol-containing antioxidant is at a concentration of 0.02 mM to 4 mM. In certain embodiments, the thiol-containing antioxidant is at a concentration of 0.02 mM to 2 mM. In certain embodiments, the thiol-containing antioxidant is at a concentration of 0.2 mM. In certain embodiments, the thiol-containing antioxidant is at a concentration of 0.4 mM. In certain embodiments, the thiol-containing antioxidant is at a concentration of 1 mM. In certain embodiments, the thiol-containing antioxidant is at a concentration of 2 mM. In certain embodiments, the thiol-containing antioxidant is at a concentration of 4 mM. In certain instances, the thiol-containing antioxidant in the composition is GSH at a concentration of 0.4 mM and GSSG at a concentration of 0.2 mM. In certain instances, the thiol-containing antioxidant in the composition is GSH at a concentration of 4 mM and GSSG at a concentration of 2 mM. In certain instances, the thiol-containing antioxidant in the composition is GSH at a concentration of 2 mM and GSSG at a concentration of 1 mM. In certain instances, the thiol-containing antioxidant in the composition is cysteine at a concentration of 0.4 mM and cystine at a concentration of 0.2 mM.

In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 150 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 125 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 100 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 75 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 50 mM. In some embodiments, the composition comprises methionine at a concentration of 0.01 mM to 20 mM. In other embodiments, the composition comprises methionine at a

concentration of 5 mM to 15 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 50 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 75 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 100 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 125 mM. In other embodiments, the composition comprises methionine at a concentration of 5 mM to 150 mM. In certain embodiments, the composition comprises methionine at a concentration of 10 mM. In certain embodiments, the composition comprises methionine at a concentration of 50 mM. In certain embodiments, the composition comprises methionine at a concentration of 75 mM. In certain embodiments, the composition comprises methionine at a concentration of 100 mM. In certain embodiments, the composition comprises methionine at a concentration of 125 mM. In certain embodiments, the composition comprises methionine at a concentration of 150 mM.

In some embodiments, the composition comprises Arg.HCl at a concentration of 50 mM to 250 mM. In other embodiments, the composition comprises Arg.HCl at a concentration of 75 mM to 175 mM. In certain embodiments, the composition comprises Arg.HCl at a concentration of 150 mM.

In some embodiments, the composition further comprises Polysorbate-80 (PS80). In some embodiments, the composition comprises PS80 at a concentration of 0.01% to 0.1%. In other embodiments, the composition comprises PS80 at a concentration of 0.03% to 0.08%. In certain embodiments, the composition comprises PS80 at a concentration of 0.05%.

In some embodiments, the composition further comprises a buffer selected from the group consisting of histidine, acetate, succinate, and citrate. In certain instances, the buffer is histidine. In certain instances, the buffer is acetate. In certain instances, the buffer is succinate. In certain instances, the buffer is citrate. In certain embodiments, the composition comprises histidine, acetate, succinate, or citrate at a concentration of 10 mM to 30 mM. In certain embodiments, the composition comprises histidine, acetate, succinate, or citrate at a concentration of 20 mM. In certain embodiments, the composition comprises histidine at a concentration of 10 mM to 30 mM. In certain embodiments, the composition comprises histidine at a concentration of 20 mM.

In some embodiments, the composition further comprises sucrose. In some embodiments, the composition comprises sucrose at a concentration of 0.01% to 5%. In other embodiments, the composition comprises sucrose at a concentration of 1% to 4%. In certain embodiments, the composition comprises sucrose at a concentration of 3%.

In some embodiments, the composition has a pH of 5.2 to 6.2. In certain embodiments, the composition has a pH of 5.2 to 6.0. In certain embodiments, the composition has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5.

In certain embodiments, the pharmaceutical composition comprises the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 50 mg/ml to 250 mg/ml; a thiol-containing antioxidant at a concentration of 0.02 mM to 4 mM; methionine at a concentration of 5 mM to 150 mM; Arg.HCl at a concentration of 50 mM to 200 mM; histidine at a concentration of 10 mM to 30 mM; PS80 at a concentration of 0.01% to 0.1%; and sucrose at a concentration of 0 to 3%. In some cases, this composition has a pH of 5.2 to 6.2. In some cases, this composition has a pH of 5.2 to 6.0. In certain embodiments, the composition has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5. In some instances, the thiol-containing antioxidant is selected from the group consisting of GSH, GSSG, the combination of GSH and GSSG, cystine, cysteine, and the combination of cysteine and cystine. In some instances, the thiol-containing antioxidant is GSH. In some instances, the thiol-containing antioxidant is GSSG. In some instances, the thiol-containing antioxidant is the combination of GSH and GSSG.

In certain embodiments, the pharmaceutical composition comprises the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 150 mg/ml; Arg.HCl at a concentration of 150 mM; a thiol-containing antioxidant at a concentration of 0.02 mM to 4 mM; methionine at a concentration of 10 mM; histidine at a concentration of 20 mM; and PS80 at a concentration of 0.05%. In some cases, this composition has a pH of 5.2 to 6.2. In some cases, this composition has a pH of 5.2 to 6.0. In certain embodiments, the composition has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5. In some instances, the thiol-containing antioxidant is selected from the group consisting of GSH, GSSG, the combination of GSH and GSSG, cystine, cysteine, and the combination of cysteine and cystine. In some instances, the thiol-containing antioxidant is GSH. In some instances, the thiol-containing antioxidant is GSSG. In some instances, the thiol-containing antioxidant is the combination of GSH and GSSG.

In certain embodiments, the pharmaceutical composition comprises the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 150 mg/ml; Arg.HCl at a concentration of 150 mM; a thiol-containing antioxidant at a concentration of 0.02 mM to 4 mM; methionine at a concentration of 150 mM; histidine at a concentration of 20 mM; and PS80 at a concentration of 0.05%. In some cases, this composition has a pH of 5.2 to 6.2. In some cases, this composition has a pH of 5.2 to 6.0. In certain embodiments, the composition

has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5. In some instances, the thiol-containing antioxidant is selected from the group consisting of GSH, GSSG, the combination of GSH and GSSG, cystine, cysteine, and the combination of cysteine and cystine. In some instances, the thiol-containing antioxidant is GSH. In some instances, the thiol-containing antioxidant is GSSG. In some instances, the thiol-containing antioxidant is the combination of GSH and GSSG.

In certain embodiments, the pharmaceutical composition comprises the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 100 mg/ml; Arg.HCl at a concentration of 150 mM; a thiol-containing antioxidant at a concentration of 0.02 mM to 4 mM; methionine at a concentration of 10 mM; histidine at a concentration of 20 mM; and PS80 at a concentration of 0.05%. In some cases, this composition has a pH of 5.2 to 6.2. In some cases, this composition has a pH of 5.2 to 6.0. In certain embodiments, the composition has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5. In some instances, the thiol-containing antioxidant is selected from the group consisting of GSH, GSSG, the combination of GSH and GSSG, cystine, cysteine, and the combination of cysteine and cystine. In some instances, the thiol-containing antioxidant is GSH. In some instances, the thiol-containing antioxidant is GSSG. In some instances, the thiol-containing antioxidant is the combination of GSH and GSSG.

In certain embodiments, the pharmaceutical composition comprises the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 100 mg/ml; Arg.HCl at a concentration of 150 mM; a thiol-containing antioxidant at a concentration of 0.02 mM to 4 mM; methionine at a concentration of 150 mM; histidine at a concentration of 20 mM; and PS80 at a concentration of 0.05%. In some cases, this composition has a pH of 5.2 to 6.2. In some cases, this composition has a pH of 5.2 to 6.0. In certain embodiments, the composition has a pH of 5.3 to 5.7. In other embodiments, the composition has a pH of 5.5. In some instances, the thiol-containing antioxidant is selected from the group consisting of GSH, GSSG, the combination of GSH and GSSG, cystine, cysteine, and the combination of cysteine and cystine. In some instances, the thiol-containing antioxidant is GSH. In some instances, the thiol-containing antioxidant is GSSG. In some instances, the thiol-containing antioxidant is the combination of GSH and GSSG.

In some embodiments, the VH comprises or consists of a sequence at least 80% identical to SEQ ID NO:7 and the VL comprises or consists of a sequence at least 80% identical to SEQ ID NO:8. In some embodiments, the VH comprises or consists of a sequence at least 90% identical to SEQ ID NO:7 and the VL comprises or consists of a

sequence at least 90% identical to SEQ ID NO:8. In some embodiments, the VH comprises or consists of the sequence of SEQ ID NO:7 and the VL comprises or consists of the sequence of SEQ ID NO:8.

In some embodiments, the anti-Aβ antibody comprises an immunoglobulin heavy chain and an immunoglobulin light chain. In certain instances, the heavy chain comprises or consists of a sequence at least 80% identical to SEQ ID NO:9 and the light chain comprises or consists of a sequence at least 80% identical to SEQ ID NO:10. In other instances, the heavy chain comprises or consists of a sequence at least 90% identical to SEQ ID NO:9 and the light chain comprises or consists of a sequence at least 90% identical to SEQ ID NO:10. In yet other instances, the heavy chain comprises or consists of the sequence of SEQ ID NO:9 and the light chain comprises or consists of the sequence of SEQ ID NO:10.

In another aspect, the disclosure features a method of treating abnormal accumulation or deposition of Aβ in the central nervous system in a human subject in need thereof. The method comprises administering to the human subject a pharmaceutical composition described herein.

In another aspect, the disclosure features a method of treating mild cognitive impairment in a human subject in need thereof. The method comprises administering to the human subject a pharmaceutical composition described herein.

In another aspect, the disclosure features a method of treating Alzheimer's disease in a human subject in need thereof. The method comprises administering to the human subject a pharmaceutical composition described herein.

In some embodiments, of these aspects, the pharmaceutical composition is administered subcutaneously to the human subject. In some embodiments, of these aspects, the pharmaceutical composition is administered intravenously to the human subject.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the exemplary methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present application, including definitions, will control. The materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the invention will be apparent from the following detailed description and from the claims.

Brief Description of the Drawings

FIG. 1 is a bar graph depicting the %HMW for the indicated formulations stored at 40°C over 4 weeks.

FIG. 2 is a graph showing the %HMW for the indicated formulations stored at 40°C for 6 weeks.

FIG. 3 is a graph showing the %HMW trends at varying pH when stored at 25°C + 60% relative humidity.

FIG. 4 is a graph showing the %HMW trends for varying excipients when stored at 25°C + 60% relative humidity.

FIG. 5 is a bar graph showing the viscosity at 20°C for formulations.

FIG. 6 is a bar graph depicting the %HMW results for polysorbate-80 formulations after 72 hours at room temperature.

FIG. 7 is a graph showing the effect of the combination of GSH and GSSG on the stability of Aducanumab formulations at 25°C and 60% relative humidity.

FIG. 8 is a graph showing the effect of the combination of Cysteine and Cystine on the stability of Aducanumab formulations at 25°C and 60% relative humidity.

FIG. 9 is a graph showing that the reduced form of a thiol-containing excipient has the same impact on stability at 25°C and 60% relative humidity as the redox pair.

FIG. 10 is a graph illustrating that methionine provides limited benefit when combined with GSH on the stability of Aducanumab formulations at 25°C and 60% relative humidity.

FIG. 11 is a pair of graphs showing the effect of different antibody concentrations and GSH on stability at 25°C and 60% relative humidity.

FIG. 12 is a pair of graphs showing that even low concentrations of GSH can improve HMW stability.

FIG. 13 is a graph showing that GSH at 4 mM has the same impact on HMW reduction as GSH from 0.5 mM to 2 mM.

FIG. 14 is a pair of graphs showing the effect of increasing methionine on HMW levels at 25^0C (top) and 40^0C (bottom).

Detailed Description

This application provides pharmaceutical compositions containing anti-Aβ antibodies and Aβ-binding fragments thereof and their use in the treatment of abnormal accumulation or deposition of Aβ in the central nervous system, mild cognitive impairment, and Aβ-associated disorders (*e.g.*, Alzheimer's disease).

Amyloid beta (Aβ or Abeta)

The Aβ peptide is an important risk factor and has a central role in the onset and progression of Alzheimer's disease. Aβ is produced in normal individuals, but under some circumstances, this molecule aggregates leading to disease progression.

Aβ denotes peptides of 36 to 43 amino acids that are involved in forming amyloid plaques found in the brains of patients with Alzheimer's disease. Similar plaques appear in some variants of Lewy body dementia and in inclusion body myositis. Aβ also forms the aggregates that coat cerebral blood vessels in cerebral amyloid angiopathy.

The Aβ peptides are formed by cleavage of the amyloid precursor protein (APP) by the enzymes beta secretase and gamma secretase. Aβ molecules can aggregate to form flexible soluble oligomers which may exist in several forms. Several Aβ peptide alloforms exist, Aβ40 and Aβ42. The amino acid sequence of human Amyloid β Peptide (1-40) is provided below:

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVV (SEQ ID NO:11)

The amino acid sequence of human Amyloid β Peptide (1-42) is provided below:

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA (SEQ ID NO:12)

Soluble oligomeric forms of the Aβ peptide are thought to be causative agents in the development of Alzheimer's disease.

Anti-Aβ Antibodies

In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof used in the compositions and methods described herein comprises the three heavy chain variable domain complementarity determining regions (CDRs) of an antibody referred to as "BIIB037" or as aducanumab. In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof comprises the three light chain variable domain CDRs of BIIB037. In still other embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof comprises the three

heavy chain variable domain CDRs and the three light chain variable domain CDRs of BIIB037.

BIIB037 is a fully human antibody comprising a glycosylated human IgG1 heavy chain and a human kappa light chain. BIIB037 consists of the mature heavy chain amino acid sequence depicted in SEQ ID NO:9 and the mature light chain amino acid sequence depicted in SEQ ID NO:10.

The VH and VL of BIIB037 have amino acid sequences that are identical to the amino acid sequence of the VH and VL of antibody NI-101.12F6A described in US Patent No. 8,906,367 (*see*, Tables 2-4; incorporated by reference in its entirety herein). Specifically, antibody BIIB037 has an antigen binding domain comprising VH and VL variable regions depicted in **Table 1** (VH) and **Table 2** (VL), corresponding complementarity determining regions (CDRs) depicted in **Table 3**, and heavy and light chains depicted in **Table 4** (H) and **Table 5** (L).

Table 1: Amino acid sequences of the V_H region of anti-Aβ antibody BIIB037 (VH CDRs (Kabat definition) underlined).

Variable heavy chain sequence
QVQLVESGGG VVQPGRSLRL SCAASGFAFS SYGMHWVRQA PGKGLEWVAV IWFDGTKKYY TDSVKGRFTI SRDNSKNTLY LQMNTLRAED TAVYYCARDR GIGARRGPYY MDVWGKGTTV TVSS **(SEQ ID NO:7)**

Table 2: Amino acid sequences of the V_L region of anti-Aβ antibody BIIB037 (VL CDRs (Kabat definition) underlined).

Variable light chain sequence (kappa or lambda)
DIQMTQSPSS LSASVGDRVT ITCRASQSIS SYLNWYQQKP GKAPKLLIYA ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ SYSTPLTFGG GTKVEIKR **(SEQ ID NO:8)**

Table 3: Denomination of CDR protein sequences in Kabat Nomenclature of V_H and V_L regions of anti-Aβ antibody BIIB037.

CDR	**Variable heavy chain**	**Variable light chain**
CDR1	SYGMH **(SEQ ID NO:1)**	RASQSISSYLN **(SEQ ID NO:4)**
CDR2	VIWFDGTKKYYTDSVKG	AASSLQS

	(SEQ ID NO:2)	(SEQ ID NO:5)
CDR3	DRGIGARRGPYYMDV (SEQ ID NO:3)	QQSYSTPLT (SEQ ID NO:6)

The amino acid sequence of the mature heavy chain of BIIB037 is provided in **Table 4** below.

Table 4: Amino acid sequences of the heavy chain of anti-Aβ antibody BIIB037 (heavy chain CDRs (Kabat definition) underlined).

Heavy chain sequence
QVQLVESGGG VVQPGRSLRL SCAASGFAFS SYGMHWVRQA PGKGLEWVAV IWFDGTKKYY TDSVKGRFTI SRDNSKNTLY LQMNTLRAED TAVYYCARDR GIGARRGPYY MDVWGKGTTV TVSSASTKGP SVFPLAPSSK STSGGTAALG CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSSL GTQTYICNVN HKPSNTKVDK RVEPKSCDKT HTCPPCPAPE LLGGPSVFLF PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQP REPQVYTLPP SREEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL SPG (**SEQ ID NO:9**)

The amino acid sequence of the mature light chain of BIIB037 is provided in **Table 5** below.

Table 5: Amino acid sequences of the light chain of anti-Aβ antibody BIIB037 (light chain CDRs (Kabat definition) underlined).

Light chain sequence
DIQMTQSPSS LSASVGDRVT ITCRASQSIS SYLNWYQQKP GKAPKLLIYA ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ SYSTPLTFGG GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC(**SEQ ID NO:10**)

In some aspects, the anti-Aβ antibody or Aβ-binding fragment thereof comprises of a VH CDR1 comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:1, a VH CDR2 comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:2; and a VH CDR3 comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:3. In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof

comprises a VL CDR1 comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:4, a VL CDR2 comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:5; and a VL CDR3 comprising or consisting of the amino acid sequence set forth in SEQ ID NO.:6.

In certain aspects, the anti-Aβ antibody or Aβ-binding fragment thereof comprises the CDRs comprising or consisting of the amino acid sequences set forth in SEQ ID NOs.:1 to 6.

In certain embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof comprises a VH comprising or consisting of the amino acid sequence set forth in SEQ ID NO:7. In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof selectively binds to a peptide comprising or consisting of amino acids 1-16 of human Aβ and comprises a VH domain that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of the VH domain of BIIB037 (SEQ ID NO:7), or differs at least at 1 to 5 amino acid residues, but at fewer than 40, 30, 20, 15, or 10, residues, from SEQ ID NO:7. In some embodiments, these anti-Aβ antibody or Aβ-binding fragments thereof selectively binds to a peptide comprising or consisting of amino acids 3-6 of human Aβ.

In certain embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof comprises a VL comprising or consisting of the amino acid sequence set forth in SEQ ID NO:8. In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof selectively binds to a peptide comprising or consisting of amino acids 1-16 of human Aβ and comprises a VL domain that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of the VL domain of BIIB037 (SEQ ID NO:8), or differs at least at 1 to 5 amino acid residues, but at fewer than 40, 30, 20, 15, or 10, residues, from SEQ ID NO:8. In some embodiments, these anti-Aβ antibody or Aβ-binding fragments thereof selectively binds to a peptide comprising or consisting of amino acids 3-6 of human Aβ.

In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof comprises a VH having the amino acid sequence set forth in SEQ ID NO:7 and a VL having the amino acid sequence set forth in SEQ ID NO:8. In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof selectively binds to a peptide comprising or consisting of amino acids 1-16 of human Aβ and comprises (i) a VH domain that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of the VH domain of BIIB037 (SEQ ID NO:7), and (ii) a VL domain that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%,

97%, 98%, 99% or more identical to the amino acid sequence of the VL domain of BIIB037 (SEQ ID NO:8); or differs at least at 1 to 5 amino acid residues, but at fewer than 40, 30, 20, 15, or 10, residues, from SEQ ID NO:7 and/or SEQ ID NO:8. In some embodiments, these anti-Aβ antibody or Aβ-binding fragments thereof selectively binds to a peptide comprising or consisting of amino acids 3-6 of human Aβ.

In certain embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof comprises a heavy chain (HC) having the amino acid sequence set forth in SEQ ID NO:9. In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof selectively binds to a peptide comprising or consisting of amino acids 1-16 of human Aβ and comprises a HC that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO:9, or differs at least at 1 to 5 amino acid residues, but at fewer than 40, 30, 20, 15, or 10, residues, from SEQ ID NO:9. In some embodiments, these anti-Aβ antibody or Aβ-binding fragments thereof selectively binds to a peptide comprising or consisting of amino acids 3-6 of human Aβ.

In certain embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof comprises a light chain (LC) having the amino acid sequence set forth in SEQ ID NO:10. In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof selectively binds to a peptide comprising or consisting of amino acids 1-16 of human Aβ and comprises a LC that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO:10, or differs at least at 1 to 5 amino acid residues, but at fewer than 40, 30, 20, 15, or 10, residues, from SEQ ID NO:10. In some embodiments, these anti-Aβ antibody or Aβ-binding fragments thereof selectively binds to a peptide comprising or consisting of amino acids 3-6 of human Aβ.

In certain embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof comprises a HC having the amino acid sequence set forth in SEQ ID NO:9 and a LC having the amino acid sequence set forth in SEQ ID NO:10. In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof selectively binds to a peptide comprising or consisting of amino acids 1-16 of human Aβ and comprises (i) a HC that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO:9, or differs at least at 1 to 5 amino acid residues, but at fewer than 40, 30, 20, 15, or 10, residues, from SEQ ID NO:9; and (ii) a LC that is at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO:10, or differs at least at 1 to 5 amino acid residues, but at fewer than 40, 30, 20, 15, or 10, residues, from SEQ ID NO:10.

In some embodiments, these anti-Aβ antibody or Aβ-binding fragments thereof selectively binds to a peptide comprising or consisting of amino acids 3-6 of human Aβ.

In certain embodiments, the anti-Aβ antibody is an IgG antibody. In specific embodiments, the anti-Aβ antibody has heavy chain constant region chosen from, e.g., IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgD, and IgE. In one embodiment, the anti-Aβ antibody is of the human IgG1 isotype. In another embodiment, the anti-Aβ antibody is of the human IgG2 isotype. In yet another embodiment, the anti-Aβ antibody is of the human IgG3 isotype. In yet another embodiment, the anti-Aβ antibody is of the human IgG4 isotype. In further embodiments, the antibody has a light chain constant region chosen from, e.g., a human kappa or human lambda light chain. In a certain embodiment, the anti-Aβ antibody is a human IgG1/human kappa antibody. In some cases, the heavy chain constant region is human or a modified form of a human constant region. In certain instances the human constant region may include at least 1 and up to 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 substitutions. In a particular embodiment, the modified human Fc region is a modified human IgG1 Fc region. In some cases, the constant region of an anti-Aβ antibody is modified by mutation of one or more amino acid residues to impart a desired functional property (e.g., altered effector function or half-life, reduced glycosylation). For example, the N-linked glycosylation site may be substituted to prevent or reduce N-linked glycosylation of Fc region (e.g., human IgG1 Fc region).

In some embodiments, the anti-Aβ antibody is a full-length (whole) antibody or substantially full-length. The protein can include at least one, and preferably two, complete heavy chains, and at least one, and preferably two, complete light chains. In some embodiments, the anti-Aβ antibody is a Aβ-binding fragment. In some instances, the Aβ-binding fragment is a Fab, a Fab', an F(ab')2, a Facb, an Fv, a single chain Fv (scFv), a sc(Fv)2, or a diabody.

Antibodies, such as BIIB037, or Aβ-binding fragments thereof can be made, for example, by preparing and expressing synthetic genes that encode the recited amino acid sequences or by mutating human germline genes to provide a gene that encodes the recited amino acid sequences. Moreover, this antibody and other anti-Aβ antibodies can be produced, *e.g.,* using one or more of the following methods.

Methods of Producing Antibodies

Anti-Aβ antibodies or Aβ-binding fragments may be produced in bacterial or eukaryotic cells. Some antibodies, *e.g.,* Fab's, can be produced in bacterial cells, *e.g., E. coli*

cells. Antibodies can also be produced in eukaryotic cells such as transformed cell lines (*e.g.*, CHO, 293E, COS). In addition, antibodies (*e.g.*, scFv's) can be expressed in a yeast cell such as *Pichia* (*see, e.g.,* Powers et al., *J Immunol Methods*. 251:123-35 (2001)), *Hanseula,* or *Saccharomyces*. To produce the antibody of interest, a polynucleotide encoding the antibody is constructed, introduced into an expression vector, and then expressed in suitable host cells. Polynucleotides encoding an anti-Aβ antibody comprising the VH and/or VL, HC and/or LC of the Aβ antibodies described herein would be readily envisioned by the ordinarily skilled artisan. Standard molecular biology techniques are used to prepare the recombinant expression vector, transfect the host cells, select for transformants, culture the host cells and recover the antibody.

If the anti-Aβ antibodies or Aβ-binding fragments is to be expressed in bacterial cells (*e.g., E. coli*), the expression vector should have characteristics that permit amplification of the vector in the bacterial cells. Additionally, when *E. coli* such as JM109, DH5α, HB101, or XL1-Blue is used as a host, the vector must have a promoter, for example, a lacZ promoter (Ward et al., 341:544-546 (1989), araB promoter (Better et al., *Science*, 240:1041-1043 (1988)), or T7 promoter that can allow efficient expression in *E. coli*. Examples of such vectors include, for example, M13-series vectors, pUC-series vectors, pBR322, pBluescript, pCR-Script, pGEX-5X-1 (Pharmacia), "QIAexpress system" (QIAGEN), pEGFP, and pET (when this expression vector is used, the host is preferably BL21 expressing T7 RNA polymerase). The expression vector may contain a signal sequence for antibody secretion. For production into the periplasm of *E. coli*, the *pelB* signal sequence (Lei et al., *J. Bacteriol.*, 169:4379 (1987)) may be used as the signal sequence for antibody secretion. For bacterial expression, calcium chloride methods or electroporation methods may be used to introduce the expression vector into the bacterial cell.

If the antibody is to be expressed in animal cells such as CHO, COS, and NIH3T3 cells, the expression vector includes a promoter necessary for expression in these cells, for example, an SV40 promoter (Mulligan *et al., Nature*, 277:108 (1979)), MMLV-LTR promoter, EF1α promoter (Mizushima *et al.*, *Nucleic Acids Res.*, 18:5322 (1990)), or CMV promoter. In addition to the nucleic acid sequence encoding the immunoglobulin or domain thereof, the recombinant expression vectors may carry additional sequences, such as sequences that regulate replication of the vector in host cells (e.g., origins of replication) and selectable marker genes. The selectable marker gene facilitates selection of host cells into which the vector has been introduced (see e.g., U.S. Pat. Nos. 4,399,216, 4,634,665 and 5,179,017). For example, typically the selectable marker gene confers resistance to drugs,

such as G418, hygromycin, or methotrexate, on a host cell into which the vector has been introduced. Examples of vectors with selectable markers include pMAM, pDR2, pBK-RSV, pBK-CMV, pOPRSV, and pOP13.

In one embodiment, antibodies are produced in mammalian cells. Exemplary mammalian host cells for expressing an antibody include Chinese Hamster Ovary (CHO cells) (including *dhfr*$^-$ CHO cells, described in Urlaub and Chasin (1980) *Proc. Natl. Acad. Sci. USA* 77:4216-4220, used with a DHFR selectable marker, e.g., as described in Kaufman and Sharp (1982) *Mol. Biol.* 159:601-621), human embryonic kidney 293 cells (e.g., 293, 293E, 293T), COS cells, NIH3T3 cells, lymphocytic cell lines, e.g., NS0 myeloma cells and SP2 cells, and a cell from a transgenic animal, e.g., a transgenic mammal. For example, the cell is a mammary epithelial cell.

In an exemplary system for antibody expression, a recombinant expression vector encoding both the antibody heavy chain and the antibody light chain of an anti-Aβ antibody (*e.g.,* BIIB037) is introduced into *dhfr*$^-$ CHO cells by calcium phosphate-mediated transfection. Within the recombinant expression vector, the antibody heavy and light chain genes are each operatively linked to enhancer/promoter regulatory elements (e.g., derived from SV40, CMV, adenovirus and the like, such as a CMV enhancer/AdMLP promoter regulatory element or an SV40 enhancer/AdMLP promoter regulatory element) to drive high levels of transcription of the genes. The recombinant expression vector also carries a *DHFR* gene, which allows for selection of CHO cells that have been transfected with the vector using methotrexate selection/amplification. The selected transformant host cells are cultured to allow for expression of the antibody heavy and light chains and the antibody is recovered from the culture medium.

Antibodies can also be produced by a transgenic animal. For example, U.S. Pat. No. 5,849,992 describes a method of expressing an antibody in the mammary gland of a transgenic mammal. A transgene is constructed that includes a milk-specific promoter and nucleic acids encoding the antibody of interest and a signal sequence for secretion. The milk produced by females of such transgenic mammals includes, secreted-therein, the antibody of interest. The antibody can be purified from the milk, or for some applications, used directly. Animals are also provided comprising one or more of the nucleic acids described herein.

The antibodies of the present disclosure can be isolated from inside or outside (such as medium) of the host cell and purified as substantially pure and homogenous antibodies. Methods for isolation and purification commonly used for antibody purification may be used for the isolation and purification of antibodies, and are not limited to any particular method.

Antibodies may be isolated and purified by appropriately selecting and combining, for example, column chromatography, filtration, ultrafiltration, salting out, solvent precipitation, solvent extraction, distillation, immunoprecipitation, SDS-polyacrylamide gel electrophoresis, isoelectric focusing, dialysis, and recrystallization. Chromatography includes, for example, affinity chromatography, ion exchange chromatography, hydrophobic chromatography, gel filtration, reverse-phase chromatography, and adsorption chromatography (Strategies for Protein Purification and Characterization: A Laboratory Course Manual. Ed Daniel R. Marshak et al., Cold Spring Harbor Laboratory Press, 1996). Chromatography can be carried out using liquid phase chromatography such as HPLC and FPLC. Columns used for affinity chromatography include protein A column and protein G column. Examples of columns using protein A column include Hyper D, POROS, and Sepharose FF (GE Healthcare Biosciences). The present disclosure also includes antibodies that are highly purified using these purification methods.

Anti-Aβ Antibody Compositions

This disclosure also provides compositions (*e.g.,* pharmaceutical compositions) comprising the anti-Aβ antibodies or Aβ-binding fragments thereof described herein. For example, the anti-Aβ antibody compositions comprises an anti-Aβ antibody or Aβ-binding fragment thereof comprising an immunoglobulin heavy chain variable domain (VH) and an immunoglobulin light chain variable domain (VL), wherein the VH comprises the H-CDRs and the VL comprises the L-CDRs of BIIB037. In certain instances, the heavy chain CDRs (H-CDRs) comprise or consist of the amino acid sequences set forth in SEQ ID NO:1, SEQ ID NO:2, and SEQ ID NO:3; and the light chain CDRs (L-CDRs) comprise or consist of the amino acid sequences set forth in SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6. In some embodiments, the anti-Aβ antibody compositions comprises an anti-Aβ antibody or Aβ-binding fragment thereof comprising (i) a VH comprising or consisting of an amino acid sequence that is at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO:7; and (ii) a VL comprising or consisting of an amino acid sequence that is at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO:8. In certain embodiments, the anti-Aβ antibody compositions comprises an anti-Aβ antibody comprising (i) a heavy chain comprising or consisting of an amino acid sequence that is at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO:9; and (ii) a light chain

comprising or consisting of an amino acid sequence that is at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence set forth in SEQ ID NO:10. In some embodiments, the anti-Aβ antibodies selectively bind to a peptide comprising or consisting of amino acids 1-16 of human Aβ. In some embodiments, the anti-Aβ antibodies selectively bind to a peptide comprising or consisting of amino acids 3-6 of human Aβ.

In certain embodiments, these compositions are high concentration anti-Aβ antibody compositions. By "high concentration anti-Aβ antibody composition" is meant a composition comprising anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of greater than 50 mg/ml and less than 300 mg/ml. In certain instances, the anti-Aβ antibody composition comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 50 mg/ml to 250 mg/ml. In certain instances, the anti-Aβ antibody composition comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 50 mg/ml to 225 mg/ml. In other instances, the anti-Aβ antibody composition comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 75 mg/ml to 225 mg/ml. In other instances, the anti-Aβ antibody composition comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 75 mg/ml to 165 mg/ml. In other instances, the anti-Aβ antibody composition comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 100 mg/ml to 225 mg/ml. In yet other instances, the anti-Aβ antibody composition comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 125 mg/ml to 225 mg/ml. In other instances, the anti-Aβ antibody composition comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 125 mg/ml to 175 mg/ml. In certain instances, the anti-Aβ antibody composition comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 240 mg/ml. In certain instances, the anti-Aβ antibody composition comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 225 mg/ml. In certain instances, the anti-Aβ antibody composition comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 200 mg/ml. In certain instances, the anti-Aβ antibody composition comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 175 mg/ml. In certain instances, the anti-Aβ antibody composition comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 150 mg/ml. In other instances, the anti-Aβ antibody composition comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 125 mg/ml. In some instances, the anti-Aβantibody composition

comprises anti-Aβ antibodies or Aβ-binding fragments thereof at a concentration of 100 mg/ml.

A composition (e.g., a pharmaceutical composition) comprising an anti-Aβ antibody or Aβ-binding fragment thereof described herein may be in any one of a variety of forms. These include, for example, liquid solutions (e.g., injectable and infusible solutions), dispersions, or suspensions. The preferred form can depend on the intended mode of administration and therapeutic application. In certain embodiments, a pharmaceutical composition described herein is in the form of a sterile injectable or infusible solution.

Sterile injectable solutions can be prepared by incorporating an antibody described herein in the required amount with one or a combination of ingredients, followed by filtered sterilization. Generally, dispersions are prepared by incorporating an antibody described herein into a sterile vehicle that contains a basic dispersion medium and the required other ingredients. In the case of sterile powders for the preparation of sterile injectable solutions, an exemplary method of preparation is vacuum drying and freeze drying that yields a powder of an antibody described herein plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants.

The anti-Aβ antibody compositions (e.g., pharmaceutical compositions) may additionally comprise one or more excipients.

In one embodiment, the excipient lowers/reduces the aggregation and/or viscosity of the antibody in the composition compared to aggregation and/or viscosity of the antibody in the pharmaceutical composition without that excipient. In certain embodiments, such an excipient is arginine. In one instance, the excipient is L-arginine hydrochloride. Arginine (*e.g.*, L-arginine hydrochloride) can be included in the composition at a concentration of 40 mM to 260 mM, 50 mM to 250 mM, 50 mM to 200 mM, 50 mM to 150 mM, 50 mM to 125 mM, 50 mM to 100 mM, 75 mM to 250 mM, 75 mM to 200 mM, 75 mM to 150 mM, or 75 mM to 100 mM. In certain embodiments arginine (e.g., Arg.HCl) is present in the composition at a concentration of 50 mM to 250 mM. In other embodiments, arginine (e.g., Arg.HCl) is present in the composition at a concentration of 50 mM to 200 mM. In certain instances, arginine (*e.g.*, arginine hydrochloride) can be included in the composition at a concentration of 80 mM, 100 mM, 120 mM, 125 mM, 130 mM, 135 mM, 140 mM, 145 mM, 150 mM, 220 mM, or 260 mM. In a specific instance, arginine (*e.g.*, arginine hydrochloride) can be included in the composition at a concentration of 100 mM. In another specific

instance, arginine (e.g., arginine hydrochloride) can be included in the composition at a concentration of 150 mM.

Sometimes, solutions containing arginine develop visible particles after incubation at room temperature or higher temperatures (*e.g.*, 40^0C). Addition of sucrose can reduce or prevent the formation of visible particles. Furthermore, sucrose can lower the counts of sub visible particulates. In some embodiments, the anti-Aβ antibody composition comprises sucrose at a concentration of 0.05% to 5%, 0.05% to 4%, 0.05% to 3%, 1% to 5 %, 1% to 4%, 1% to 3%, 2% to 5%, 2% to 4%, or 2% to 3%. In certain embodiments, the anti-Aβ antibody composition comprises sucrose at a concentration of 0.5%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, or 5%. In a particular embodiment, the anti-Aβ antibody composition comprises sucrose at a concentration of 3%. In another particular embodiment, the anti-Aβ antibody composition comprises sucrose at a concentration of 1%.

In one embodiment, the anti-Aβ antibody compositions comprise methionine. In one instance, methionine is included in the composition at a concentration from 0.5 mM to 150 mM. In another instance, methionine is included in the composition at a concentration from 0.5 mM to 25 mM. In yet another instance, methionine is included in the composition at a concentration from 5 mM to 150 mM. In one instance, methionine is included in the composition at a concentration of 5 mM, 10 mM, 15 mM, 20 mM or 25 mM, 50 mM, 75 mM, 100 mM, 125 mM, or 150 mM. In a particular instance, methionine is included in the composition at a concentration of 10 mM. In another particular instance, methionine is included in the composition at a concentration of 150 mM.

Antibody product manufacturing is a complex process that can involve several steps such as, e.g., drug substance and bulk formulation, filtration, shipping, pooling, filling, lyophilization, inspections, packaging, and storage. During these steps, antibodies may be subjected to many different forms of stresses, e.g., agitation, temperature, light exposure, and oxidation. These types of stresses can lead to denaturation and aggregation of the antibody, which compromise the product quality and can even lead to loss of a production batch. Agitation is one of the common physical stresses that antibody therapeutics are subjected to during the course of the manufacturing process. Agitation occurs, e.g., during mixing, ultrafiltration/diafiltration, pumping, shipping, and filling. To protect the antibody composition against agitation-induced stress, the composition may include a polysorbate. In certain embodiments, the composition comprises polysorbate-80 at a concentration of 0.01% to 0.5%, 0.01% to 0.1%, 0.01% to 0.09%, 0.01% to 0.08%, 0.01% to 0.07%, 0.01% to 0.06%, 0.01% to 0.05%, 0.01% to 0.04%, or 0.01% to 0.03%. In certain embodiments, the

composition comprises polysorbate-80 at a concentration of 0.02% to 0.08%. In some embodiments, the composition comprises polysorbate-80 at a concentration of 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, or 0.1%. In a particular embodiment, the composition comprises polysorbate-80 at a concentration of 0.05%.

Any antibody composition benefits from a buffer that provides good buffering capacity. In certain embodiments, the antibody composition comprises histidine as the buffering agent. In certain embodiments, the composition comprises histidine at a concentration of 5 mM to 50 mM, 5 mM to 40 mM, 5 mM to 35 mM, 5 mM to 30 mM, 5 mM to 25 mM, 10 mM to 50 mM, 10 mM to 40 mM, 10 mM to 30 mM, 10 mM to 25 mM, 15 mM to 50 mM, 15 mM to 40 mM, 15 mM to 30 mM, or 15 mM to 25 mM. In certain embodiments, the composition comprises histidine at a concentration of 5 mM to 35 mM. In certain embodiments, the composition comprises histidine at a concentration of 10 mM to 30 mM. In some embodiments, the composition comprises histidine at a concentration of 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, or 35 mM. In a particular embodiment, the composition comprises histidine at a concentration of 20 mM. In certain embodiments, the antibody composition comprises acetate as the buffering agent. In certain embodiments, the composition comprises acetate at a concentration of 5 mM to 50 mM, 5 mM to 40 mM, 5 mM to 35 mM, 5 mM to 30 mM, 5 mM to 25 mM, 10 mM to 50 mM, 10 mM to 40 mM, 10 mM to 30 mM, 10 mM to 25 mM, 15 mM to 50 mM, 15 mM to 40 mM, 15 mM to 30 mM, or 15 mM to 25 mM. In certain embodiments, the composition comprises acetate at a concentration of 5 mM to 35 mM. In certain embodiments, the composition comprises acetate at a concentration of 10 mM to 30 mM. In some embodiments, the composition comprises acetate at a concentration of 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, or 35 mM. In a particular embodiment, the composition comprises acetate at a concentration of 20 mM. In certain embodiments, the antibody composition comprises succinate as the buffering agent. In certain embodiments, the composition comprises succinate at a concentration of 5 mM to 50 mM, 5 mM to 40 mM, 5 mM to 35 mM, 5 mM to 30 mM, 5 mM to 25 mM, 10 mM to 50 mM, 10 mM to 40 mM, 10 mM to 30 mM, 10 mM to 25 mM, 15 mM to 50 mM, 15 mM to 40 mM, 15 mM to 30 mM, or 15 mM to 25 mM. In certain embodiments, the composition comprises succinate at a concentration of 5 mM to 35 mM. In certain embodiments, the composition comprises succinate at a concentration of 10 mM to 30 mM. In some embodiments, the composition comprises succinate at a concentration of 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, or 35 mM. In a particular embodiment, the composition comprises succinate at a concentration of 20 mM. In certain embodiments, the antibody

composition comprises citrate as the buffering agent. In certain embodiments, the composition comprises citrate at a concentration of 5 mM to 50 mM, 5 mM to 40 mM, 5 mM to 35 mM, 5 mM to 30 mM, 5 mM to 25 mM, 10 mM to 50 mM, 10 mM to 40 mM, 10 mM to 30 mM, 10 mM to 25 mM, 15 mM to 50 mM, 15 mM to 40 mM, 15 mM to 30 mM, or 15 mM to 25 mM. In certain embodiments, the composition comprises citrate at a concentration of 5 mM to 35 mM. In certain embodiments, the composition comprises citrate at a concentration of 10 mM to 30 mM. In some embodiments, the composition comprises citrate at a concentration of 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, or 35 mM. In a particular embodiment, the composition comprises citrate at a concentration of 20 mM.

The pH of the antibody composition can be from 5.0 to 6.5. In certain cases, the pH of the antibody composition can be 5.2 to 6.2. In certain instances, the pH of the antibody composition is 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, or 6.5. In a particular embodiment, the pH of the antibody composition is 5.5.

In certain instances, the Aβ compositions comprise arginine (e.g., Arg. HCl). In other instances, the Aβ compositions comprise arginine (e.g., Arg. HCl) and methionine.

In certain embodiments, the Aβ compositions comprise L-arginine hydrochloride (e.g., 150 mM), methionine (e.g., 10 mM), histidine (e.g., 20 mM), and PS80 (e.g., 0.05%), and has a pH of 5.2 to 6.2. In some embodiments, the Aβ compositions comprise L-arginine hydrochloride (e.g., 150 mM), methionine (e.g., 10 mM, 150 mM), histidine (e.g., 20 mM), and PS80 (e.g., 0.05%), and has a pH of 5.5. In certain embodiments, the Aβ compositions comprise L-arginine hydrochloride (e.g., 150 mM), methionine (e.g., 10 mM, 150 mM), histidine (e.g., 20 mM), PS80 (e.g., 0.05%), and sucrose (up to 3%), and has a pH of 5.2 to 6.2. In some embodiments, the Aβ compositions comprise L-arginine hydrochloride, methionine, histidine, PS80, and sucrose, and has a pH of 5.5. In all of these embodiments, the anti-Aβ antibody is present at a concentration of 100 mg/ml to 165 mg/ml. In one instance, the anti-Aβ antibody is present at a concentration of 150 mg/ml. In one instance, the anti-Aβ antibody is present at a concentration of 100 mg/ml.

In some cases, the anti-Aβ composition comprises a thiol-containing antioxidant (e.g., reduced glutathione (GSH), oxidized glutathione (GSSG), GSH + GSSG, cysteine, cystine, cysteine + cystine) at a concentration of 0.02 mM to 4 mM (e.g., 0.02, 0.03, 0.05, 0.06, 0.08, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7. 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, or 4.0 mM). Such thiol-containing antioxidants can cleave unfavorable or misbridged disulfide bonds and promote the formation of favorable or properly bridged disulfide bonds. This would result in

the stabilization of the native confirmation of the antibody or fragment thereof and slow down aggregation rates. The antioxidant properties of these molecules may slow down oxidative processes that lead to aggregation. In some cases, the composition comprises GSH at a concentration of 0.4 mM. In some cases, the composition comprises GSSG at a concentration of 0.2 mM. In some cases, the composition comprises GSH at a concentration of 0.4 mM and GSSG at a concentration of 0.2 mM. In some cases, the composition comprises GSH at a concentration of 4 mM and GSSG at a concentration of 2 mM. In some cases, the composition comprises GSH at a concentration of 2 mM and GSSG at a concentration of 1 mM. In some cases, the composition comprises cysteine at a concentration of 0.4 mM. In some cases, the composition comprises cystine at a concentration of 0.2 mM. In some cases, the composition comprises cysteine at a concentration of 0.4 mM and cystine at a concentration of 0.2 mM.

In certain embodiments, the Aβ compositions comprise arginine (e.g., Arg.HCl), a thiol-containing antioxidant, and methionine.

In certain embodiments, the Aβ compositions comprise L-arginine hydrochloride (e.g., 150 mM), methionine (e.g., 10 mM), histidine (e.g., 20 mM), a thiol-containing antioxidant such as GSH, GSSG, GSH and GSSG, cysteine, cystine, or cysteine and cystine (e.g., 0.02 mM to 4 mM), and PS80 (e.g., 0.05%), and has a pH of 5.2 to 6.2. In some embodiments, the Aβ compositions comprise L-arginine hydrochloride (e.g., 150 mM), methionine (e.g., 10 mM, 150 mM), histidine (e.g., 20 mM), a thiol-containing antioxidant such as GSH, GSSG, GSH and GSSG, cysteine, cystine, or cysteine and cystine (e.g., 0.02 mM to 4 mM), and PS80 (e.g., 0.05%), and has a pH of 5.5. In certain embodiments, the Aβ compositions comprise L-arginine hydrochloride (e.g., 150 mM), methionine (e.g., 10 mM, 150 mM), histidine (e.g., 20 mM), PS80 (e.g., 0.05%), a thiol-containing antioxidant such as GSH, GSSG, GSH and GSSG, cysteine, cystine, or cysteine and cystine (e.g., 0.02 mM to 4 mM), and sucrose (up to 3%), and has a pH of 5.2 to 6.2. In some embodiments, the Aβ compositions comprise L-arginine hydrochloride, methionine, histidine, PS80, a thiol-containing antioxidant such as GSH, GSSG, GSH and GSSG, cysteine, cystine, or cysteine and cystine, and sucrose, and has a pH of 5.5. In all of these embodiments, the anti-Aβ antibody is present at a concentration of 100 mg/ml to 165 mg/ml. In one instance, the anti-Aβ antibody is present at a concentration of 150 mg/ml. In one instance, the anti-Aβ antibody is present at a concentration of 100 mg/ml.

In certain embodiments, the composition (e.g., a pharmaceutical composition) comprises an anti-Aβ antibody or a Aβ-binding fragment thereof at a concentration of 50

mg/ml to 250 mg/ml, arginine (*e.g.*, L-arginine hydrochloride) at a concentration of 50 mM to 200 mM, methionine at a concentration of 1 mM to 150 mM (e.g., 1 mM to 20 mM); polysorbate-80 at a concentration of 0.01% to 0.1%, histidine at a concentration of 10 mM to 30 mM, and sucrose at a concentration of 0% to 3%. In some cases, the composition has a pH of 5.2 to 6.2. In other cases, the composition has a pH of 5.2 to 6.0. In certain embodiments, the anti-Aβ antibody or a Aβ-binding fragment thereof of the composition comprises a VH and a VL comprising the CDRs of BIIB037 (*e.g.*, SEQ ID NOs.: 1, 2, 3, 4, 5, and 6). In certain embodiments, the anti-Aβ antibody or a Aβ-binding fragment thereof of the composition comprises a VH and a VL comprising SEQ ID NOs: 7 and 8, respectively. In some embodiments, the anti-Aβ antibody or a Aβ-binding fragment thereof of the composition comprises a heavy chain and a light chain comprising SEQ ID NOs: 9 and 10, respectively. In one embodiment, the composition has a pH of 5.5 and comprises BIIB037 or a BIIB037-binding fragment thereof at a concentration of 150 mg/ml, L-arginine hydrochloride at a concentration of 150 mM, methionine at a concentration of 10 mM or 150,mM, polysorbate-80 at a concentration of 0.05%, and histidine at a concentration of 20 mM (16.2 mM L-histidine HCl monohydrate, 3.8 mM L-Histidine free base). In certain embodiments, the composition further comprises a thiol-containing antioxidant (e.g., GSH, GSSG, GSH + GSSG, cysteine, cystine, cysteine + cystine) at a concentration of 0.02 mM to 4 mM. In some embodiments, the composition further comprises sucrose at a concentration of 0.01% to 3%. In certain embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof of the composition comprises a VH and a VL comprising the CDRs of BIIB037 (e.g., SEQ ID NOs.: 1, 2, 3, 4, 5, and 6). In certain embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof of the composition comprises a VH and a VL comprising SEQ ID NOs: 7 and 8, respectively. In some embodiments, the anti-Aβ antibody or Aβ-binding fragment thereof of the composition comprises a heavy chain and a light chain comprising SEQ ID NOs: 9 and 10, respectively.

In one embodiment, the composition has a pH of 5.5 and comprises BIIB037 or a BIIB037-binding fragment thereof at a concentration of 150 mg/ml, L-arginine hydrochloride at a concentration of 150 mM, a thiol-containing antioxidant (e.g., GSH, GSSG, GSH + GSSG, cysteine, cystine, cysteine + cystine) at a concentration of 0.02 mM to 4 mM, polysorbate-80 at a concentration of 0.05%, and histidine at a concentration of 20 mM. In one embodiment, the thiol-containing antioxidant is GSH at a concentration of 0.4 mM. In one embodiment, the thiol-containing antioxidant is GSH at a concentration of 0.4 mM and GSSG at a concentration of 0.2 mM. In one embodiment, the thiol-containing antioxidant is

GSH at a concentration of 4 mM and GSSG at a concentration of 2 mM. In one embodiment, the thiol-containing antioxidant is GSH at a concentration of 2 mM and GSSG at a concentration of 1 mM. In another embodiment, the thiol-containing antioxidant is cysteine at a concentration of 0.4 mM. In another embodiment, the thiol-containing antioxidant is cysteine at a concentration of 0.4 mM and cystine at a concentration of 0.2 mM.

Methods of Treatment

BIIB037 recognizes aggregated forms of Aβ, including plaques. *In vitro* characterization studies have established that antibody BIIB037 recognizes a conformational epitope present in Aβ aggregates, the accumulation of which is believed to underlie the development and progression of Alzheimer's disease (AD). *In vivo* pharmacology studies indicate that a murine IgG2a chimeric version of the antibody (ch12F6A) with similar properties significantly reduces amyloid plaque burden in the brains of aged Tg2576 mice, a mouse model of AD. The reduction in parenchymal amyloid was not accompanied by a change in vascular amyloid, as has been reported for certain anti-Aβ antibodies.

The compositions disclosed herein are useful in treating abnormal accumulation or deposition of Aβ in the central nervous system of a human subject in need thereof. The compositions disclosed herein are also useful in treating mild cognitive impairment in a human subject in need thereof. As used herein, the terms "treat", "treating", or "treatment" generally mean obtaining a desired pharmacological and/or physiological effect.

In certain embodiments, the compositions disclosed herein are useful in treating AD in a human subject in need thereof. In other embodiments, the compositions disclosed herein are useful in preventing AD in a human subject in need thereof.

The compositions disclosed herein can be used to: (a) prevent AD from occurring in a subject who may be predisposed to AD, but has not yet been diagnosed as having it; (b) inhibiting AD, e.g. arresting its development; (c) relieving AD, e.g. causing regression of AD; or (d) prolonging survival as compared to expected survival if not receiving treatment.

A human subject in need thereof is administered a therapeutically effective amount or dose of the anti-Aβ antibody or Aβ-binding fragment thereof. A therapeutically effective amount refers to the amount of the antibody sufficient to ameliorate a symptom or condition associated with AD. Therapeutic efficacy and toxicity of the antibody can be determined by standard pharmaceutical procedures. Ideally, the antibody is employed in an amount

sufficient to restore normal behavior and/or cognitive properties in case of Alzheimer's disease, or at least delay or prevent the progression of AD in the patient.

In some embodiments, the composition comprising the anti-Aβ antibody or Aβ-binding fragment thereof is administered intravenously to the human subject. In certain embodiments, the composition comprising the anti-Aβ antibody or Aβ-binding fragment thereof is administered subcutaneously to the human subject.

The following are examples of the practice of the invention. They are not to be construed as limiting the scope of the invention in any way.

Examples

Example 1: pH and Buffer Screened for Optimal Formulation

The following formulations were prepared and screened to determine the optimal buffer and pH.

Table 6: pH and buffer screen formulations

Buffer	pH	Excipients	Protein Concentration
20mM Acetate	4.5	150mM L-Arginine HCl 0.05% Polysorbate-80	155 – 165 mg/mL
	5.0		
	5.5		
20mM Succinate	4.5		
	5.0		
	5.5		
	6.0		
20mM Histidine	5.5		
	6.0		
	6.5		
20mM Citrate	5.0		
	5.5		
	6.0		
	6.5		

Formulations were stored at 40°C + 75% relative humidity (RH) for 4 weeks (**Figure 1**).

Conclusions:

1) Histidine buffer showed the lowest change in percentage high molecular weight species (% HMW) compared to Acetate, Succinate, and Citrate buffers.

2) The trend was consistent across the pH range of 5.5 to 6.5.

Example 2: Arginine as an Optimal Excipient for Controlling HMW

The following formulations were prepared to determine the optimal stabilizing excipient(s). Most contain L-Arginine HCl, either alone or combined with another excipient. Two formulations did not contain Arginine and only contained a sugar (sucrose or trehalose).

Table 7: Excipient screen formulations

Excipient (all contain 20mM Histidine and 0.05% Polysorbate-80)	pH	Protein concentration
150 mM L-Arginine HCl	6.0	220 – 230 mg/mL
150 mM L-Arginine HCl	5.5	
100 mM L-Arginine HCl	5.5	
100 mM L-Arginine HCl + 3% Sucrose	5.5	
100 mM L-Arginine HCl + 3% Sucrose	6.0	
100 mM L-Arginine HCl + 50 mM NaCl	5.5	
75 mM L-Arginine HCl + 75 mM glutamate	5.5	
150 mM L-Arginine HCl + 10 mM Methionine	5.5	
150 mM L-Arginine HCl + 10 mM Methionine	6.0	
300 mM Sucrose	5.5	
300 mM Trehalose	5.5	
50 mM L-Arginine HCl + 4.5% Sucrose	5.5	

The formulations were stored at 40°C + 75% RH and tested for %HMW over 6 weeks (**Figure 2**).

Conclusions:

1) Formulations containing Arginine (solid lines) performed better than the formulations without Arginine (dashed lines).

2) The Arginine + Methionine combination (lowest two solid lines in the plot) performed better than Arginine alone and Arginine in combination with other excipients.

3) Formulations prepared at both pH 5.5 and 6.0 always performed better at pH 5.5.

Example 3: Robustness of the Formulation for pH and Protein Concentration

Further formulation optimization was performed by preparing various formulations based around a central formulation (Table 8) and screening for various quality attributes.

Table 8: Optimization screen formulations (variations from the central formulation are highlighted in grey).

Formulation Variation	[Protein] mg/mL	pH	Buffer (20mM)	Arginine (mM)	Methionine (mM)	Sucrose (%)	PS-80 (%)
Center formulation	220	5.7	His	150	10		0.05
Center @ 165mg/mL	165	5.7	His	150	10		0.05
Center @ 280mg/mL	280	5.7	His	150	10		0.05
Center @ pH 5.2	220	5.2	His	150	10		0.05
Center @ pH 6.2	220	6.2	His	150	10		0.05
Center with 100mM Arginine	220	5.7	His	100	10		0.05
Center without Methionine	220	5.7	His	150	0		0.05
Center with 100mM Arginine + 3% Sucrose	220	5.7	His	100	0	3	0.05
Center with 20mM Citrate	220	5.7	Citrate	150	10		0.05

Figure 3 shows the %HMW trends at varying pH when stored at 25°C + 60% relative humidity. The rate of increase of %HMW over time is consistent across this pH range.

Figure 4 shows the %HMW trends for varying excipients when stored at 25°C + 60% relative humidity. The rate of increase of %HMW is consistent whether the stabilizing excipient is 150mM L-Arginine HCl + 10mM Methionine, 100mM L-Arginine HCl + 10mM Methionine, 150mM L-Arginine HCl without Methionine, or 100mM L-Arginine HCl + 3% Sucrose.

Example 4: Arginine Lowers Viscosity of the Formulations

The viscosity of each formulation was measured at ambient temperature (20°C). The protein concentration has a significant impact on viscosity, while other variations in the formulation recipe did not have impact. Viscosities < 50cP are optimal for manufacturing processes and route of administration options. The Arginine-based formulations provide consistently low viscosity (~20cP) at high protein concentration (~220mg/mL) (**Figure 5**).

Example 5: Robustness of Formulation to Polysorbate-80 Concentration

The following formulations were prepared to assess the optimal level of surfactant (Polysorabate-80) in the formulation.

Table 9: Surfactant screen formulations

Protein Concentration (mg/mL)	pH	Buffer	Excipients	% Polysorbate-80
160	5.7	20mM Histidine	150mM L-Arginine HCl + 10mM Methionine	0.00%
				0.005%
				0.01%
				0.03%
				0.05%
				0.075%
				0.10%

An agitation study was performed to determine the appropriate level of surfactant necessary to maintain product stability during physical stress. The formulations in Table 9 were dispensed into 3 mL glass vials and 1 mL glass staked-needle syringes, then agitated at 650rpm for 72 hours at room temperature. Unagitated controls were stored in glass vials for the same time and temperature.

%HMW results were consistent across all agitated formulations (**Figure 6**). The unagitated control vials show a gradual increase in HMW as the % polysorbate-80 drops from 0.05% to 0.00%. All results are within the variability (noise) of the method (±0.2%) and may not be real differences. Stability is comparable across a broad range of % Polysorbate-80.

Example 6: Thiol Group Containing Excipients Improve Aggregation Stability of Aducanumab Formulation

The addition of thiol group containing excipients to an Aducanumab formulation reduces aggregation as determined by the development of high molecular weight species during storage.

The control Aducanumab formulation has 165mg/mL Aducanumab, 20mM Histidine, 150 mM L-Arginine HCl, 10mM Methionine, 0.05% Polysorbate-80, pH 5.5. The control formulation was spiked with thiol group containing excipients: GSH and GSSG. The formulations were stored at 25°C at 60% relative humidity. As shown in **Figure 7**, the addition of GSH and GSSG reduces the development of HMW species during storage.

The same control formulation of Aducanumab was spiked with Cysteine and Cystine. These formulations were also stored at 25°C at 60% relative humidity. As was the case for GSH and GSGG, the addition of Cysteine and Cystine suppresses the development of HMW species during storage (**Figure 8**).

Example 7: Reduced Form of Thiol Group Containing Excipient is as Effective as Redox Pair in Controlling HMW

The addition of the reduced form of a thiol group containing excipient alone has the same impact as the addition of the redox pair.

A control Aducanumab formulation contains 165 mg/mL Aducanumab, 20 mM Histidine, 150 mM L-Arginine HCl, 10 mM Methionine, 0.05% Polysorbate-80, pH 5.5. This formulation was spiked with GSH + GSSG, GSH alone, or GSSG alone. The formulations were stored at 25°C at 60% relative humidity. As shown in **Figure 9**, the addition of GSH, GSSG, and GSH+ GSSG all reduced the formation of HMW species.

Example 8: Thiol Containing Excipients are Better than Methionine in controlling HMW

The addition of methionine does not increase the stability observed with GSH alone.

A control Aducanumab formulation has 165mg/mL Aducanumab, 20mM Histidine, 150mM L-Arginine HCl, pH 5.5. GSH or GSH + Methionine were added to the control formulation. These formulations were stored at 25°C at 60% relative humidity. The addition of methionine did not provide any additive benefit to the reduction in HMW species observed with GSH alone (**Figure 10**).

Example 9: Robustness for Thiol-Containing Excipient Formulation at Multiple Protein and GSH concentrations

Reduction in HMW species with the addition of GSH was observed at multiple concentrations of protein and multiple concentrations of GSH.

Aducanumab (165 or 200 mg/mL Aducanumab, 20 mM Histidine, 150 mM L-Arginine HCl, 10 mM Methionine, 0.05% Polysorbate-80, pH 5.5) was stored at 25°C at 60% relative humidity with various concentrations of GSH. As shown in **Figure 11**, GSH suppresses HMW species formation at concentrations from 0.2 mM to 1.0 mM, at protein concentrations up to 200 mg/ml.

Example 10: Thiol-Containing Excipient is Effective in Controlling HMW at Very Low Concentrations

Concentrations of a thiol-containing excipient as low as 0.02 mM improved the stability of Aducanumab at various concentrations.

Aducanumab (165 or 225 mg/mL Aducanumab, 20mM Histidine, 150mM L-Arginine HCl, 10mM Methionine, 0.05% Polysorbate-80, pH 5.5) was stored at 25ºC at 60% relative humidity with various concentrations of GSH. As shown in **Figure 12**, GSH suppresses HMW species formation at concentrations as low as 0.02 mM in formulations containing up to 225 mg/ml Aducanumab.

Example 11: Effect of Increasing Thiol-Containing Excipient on HMW

This experiment was performed to assess the impact of increasing the concentration of GSH on HMW reduction.

All tested formulations contained 210 mg/mL aducanumab, 20 mM histidine, 150 mM arginine, 10 mM methionine, and 0.05% polysorbate-80, and only differed by the GSH concentration. The GSH concentrations tested were 0 mM, 0.5 mM, 1 mM, 2 mM, and 4 mM. Samples were stored at 25°C, 60% relative humidity for up to 4.5 months.

The data showed that GSH at 4mM has same impact on HMW reduction as GSH from 0.5 mM to 2 mM (see, **Figure 13**).

Example 12: Effect of Increasing Methionine Concentrations on HMW

This experiment was performed to assess the impact of increasing the concentration of methionine on HMW reduction.

All tested formulations contained 165 mg/mL aducanumab, 20 mM histidine, 150 mM arginine, and 0.05% polysorbate-80, and only differed by the concentration of methionine or GSH as shown in **Figure 14**. Samples were stored at 25°C, 60% relative humidity (top) and 40°C, 75% relative humidity (bottom) for up to 3.5 months.

This experiment showed that that increasing the methionine concentration to 150 mM helped reduce HMW compared to 10 mM methionine.

Example 13: A 4-Week Tolerability and Toxicokinetic Study of BIIB037 when Administered by Intravenous and Subcutaneous Injection to Cynomolgus Monkeys

The objective of this study was to determine the tolerability of BIIB037 (150 mg/mL strength in 20 mM histidine buffer [16.2 mM L-histidine monohydrate, 3.8 mM L-histidine free base], 150 mM L-arginine hydrochloride (HCl), 10 mM methionine, and 0.05% polysorbate 80 pH 5.5) when given by intravenous (IV) or subcutaneous (SC) injection once a week for 4 weeks to 3 cynomolgus monkeys per group. In addition, the toxicokinetic characteristics of the test article were determined.

Both IV and SC administration of BIIB037 at 300 mg/kg/dose once a week for 4 weeks (Day 22 area under the concentration-time curve from time 0 to time t [AUC0-t]: 324,000 µg•h/mL and 243,000 µg•h/mL for IV and SC, respectively) resulted in no clinical observations, or adverse effects on body weight or food consumption. The SC injection site observations were limited to one SC injected animal following the third and fourth week administrations that consisted of non-adverse, very slight erythema and/or edema, accompanied by likely procedure-related mild focal neutrophilic and mononuclear cellular infiltration and hemorrhage (associated with the fourth injection site only). The absolute % bioavailability ranged from 56.7% to 75.1% for AUCτ on SD 1 and SD 22 indicating good absorption kinetics following aducanumab SC administration. The summary of mean TK parameters is presented in **Table 10**.

Table 10: Summary of Mean Toxicokinetic Parameters in the 4-Week IV and SC Male Cynomolgus Monkey Study

Dose	**300 mg/kg IV**	**300 mg/kg SC**
Number of Animals	**M (3)**	**M (3)**
Day 1		
C_{max} (µg/mL)	6,930	1,180
AUC_{τ} (µg*h/mL)	236,000	134,000
T_{max} (h)	0.083	12 or 24
Day 22		
C_{max} (µg/mL)	7,070	2,490
AUCτ (µg*h/mL)	324,000	243,000
T_{max}(h)	0.083 to 2	12 to 24
AUC_{τ} = AUC_{0-t} (TK parameter used in P037-16-01 study report) = area under the concentration-time curve from time 0 to last concentration; C_{max} = maximum observed concentration, occurring at T_{max}; SD = Study Day; T_{max} = time of maximum observed concentration		

Other Embodiments

While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

Claims

1. A pharmaceutical composition comprising an anti-beta amyloid (Aβ) antibody or Aβ-binding fragment thereof and arginine hydrochloride (Arg.HCl), wherein the anti-Aβ antibody or Aβ-binding fragment thereof comprises an immunoglobulin heavy chain variable domain (VH) and an immunoglobulin light chain variable domain (VL), the VH and VL, respectively, comprising:

(a) VH complementarity determining regions (CDRs), wherein

VH-CDR1 consists of the amino acid sequence set forth in SEQ ID NO:1;

VH-CDR2 consists of the amino acid sequence set forth in SEQ ID NO:2; and

VH-CDR3 consists of the amino acid sequence set forth in SEQ ID NO:3; and

(b) VL CDRs, wherein

VL-CDR1 consists of the amino acid sequence set forth in SEQ ID NO:4;

VL-CDR2 consists of the amino acid sequence set forth in SEQ ID NO:5; and

VL-CDR3 consists of the amino acid sequence set forth in SEQ ID NO:6, and

wherein the composition has a pH of 5.2 to 6.2.

2. The pharmaceutical composition of claim 1, wherein the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 50 mg/ml to 250 mg/ml.

3. The pharmaceutical composition of claim 1, wherein the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 75 mg/ml to 165 mg/ml.

4. The pharmaceutical composition of claim 1, wherein the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 150 mg/ml.

5. The pharmaceutical composition of claim 1, wherein the composition comprises the anti-Aβ antibody or Aβ-binding fragment thereof at a concentration of 100 mg/ml.

6. The pharmaceutical composition of any one of claims 1 to 5, wherein the composition comprises Arg.HCl at a concentration of 50 mM to 250 mM.

7. The pharmaceutical composition of any one of claims 1 to 5, wherein the composition comprises Arg.HCl at a concentration of 75 mM to 175 mM.

8. The pharmaceutical composition of any one of claims 1 to 5, wherein the composition comprises Arg.HCl at a concentration of 150 mM.

9. The pharmaceutical composition of any one of claims 1 to 8, wherein the composition comprises Polysorbate-80 (PS80).

10. The pharmaceutical composition of claim 9, wherein the composition comprises PS80 at a concentration of 0.01% to 0.1%.

11. The pharmaceutical composition of claim 9, wherein the composition comprises PS80 at a concentration of 0.03% to 0.08%.

12. The pharmaceutical composition of claim 9, wherein the composition comprises PS80 at a concentration of 0.05%.

13. The pharmaceutical composition of any one of claims 1 to 12, wherein the composition comprises a buffer selected from the group consisting of histidine, acetate, succinate, and citrate.

14. The pharmaceutical composition of claim 13, wherein the composition comprises histidine, acetate, succinate, or citrate at a concentration of 10 mM to 30 mM.

15. The pharmaceutical composition of claim 13, wherein the composition comprises histidine, acetate, succinate, or citrate at a concentration of 20 mM

16. The pharmaceutical composition of claim 13, wherein the buffer is histidine.

17. The pharmaceutical composition of claim 16, wherein histidine is at a concentration of 10 mM to 30 mM.

18. The pharmaceutical composition of claim 16, wherein histidine is at a concentration of 20 mM.

19. The pharmaceutical composition of any one of claims 1 to 18, wherein the composition comprises methionine.

20. The pharmaceutical composition of claim 19, wherein methionine is at a concentration of 0.01 mM to 150 mM.

21. The pharmaceutical composition of claim 19, wherein methionine is at a concentration of 5 mM to 15 mM.

22. The pharmaceutical composition of claim 19, wherein methionine is at a concentration of 10 mM.

23. The pharmaceutical composition of any one of claims 1 to 22, wherein the composition comprises sucrose.

24. The pharmaceutical composition of claim 23, wherein the composition comprises sucrose at a concentration of 0.01% to 3%.

25. The pharmaceutical composition of claim 23, wherein the composition comprises sucrose at a concentration of 3%.

26. The pharmaceutical composition of any one of claims 1 to 25, wherein the composition has a pH of 5.2 to 6.0.

27. The pharmaceutical composition of any one of claims 1 to 26, wherein the composition has a pH of 5.3 to 5.7.

28. The pharmaceutical composition of any one of claims 1 to 27, wherein the composition has a pH of 5.5.

29. The pharmaceutical composition of claim 1, comprising:

the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 50 mg/ml to 250 mg/ml;

Arg.HCl at a concentration of 50 mM to 200 mM;

methionine at a concentration of 0 mM to 150 mM;

histidine at a concentration of 10 mM to 30 mM;

PS80 at a concentration of 0.01% to 0.1%;

sucrose at a concentration of 0 to 3%; and

wherein the composition has a pH of 5.2 to 6.0.

30. The pharmaceutical composition of claim 1, comprising:

the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 150 mg/ml;

Arg.HCl at a concentration of 150 mM;

methionine at a concentration of 10 mM;

histidine at a concentration of 20 mM; and

PS80 at a concentration of 0.05%,

wherein the composition has a pH of 5.5.

31. The pharmaceutical composition of claim 1, comprising:

the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 100 mg/ml;

Arg.HCl at a concentration of 150 mM;

methionine at a concentration of 10 mM;

histidine at a concentration of 20 mM; and

PS80 at a concentration of 0.05%,

wherein the composition has a pH of 5.5.

32. The pharmaceutical composition of any one of claims 1 to 31, wherein:

(i) the VH consists of a sequence at least 80% identical to SEQ ID NO:7 and the VL consists of a sequence at least 80% identical to SEQ ID NO:8;

(ii) the VH consists of a sequence at least 90% identical to SEQ ID NO:7 and the VL consists of a sequence at least 90% identical to SEQ ID NO:8; or

(iii) the VH consists of the amino acid sequence set forth in SEQ ID NO:7 and the VL consists of the amino acid sequence set forth in SEQ ID NO:8.

33. The pharmaceutical composition of any one of claims 1 to 32, wherein the anti-Aβ antibody comprises an immunoglobulin heavy chain and an immunoglobulin light chain, wherein:

(i) the heavy chain consists of a sequence at least 80% identical to SEQ ID NO:9 and the light chain consists of a sequence at least 80% identical to SEQ ID NO:10;

(ii) the heavy chain consists of a sequence at least 90% identical to SEQ ID NO:9 and the light chain consists of a sequence at least 90% identical to SEQ ID NO:10; or

(iii) the heavy chain consists of the amino acid sequence set forth in SEQ ID NO:9 and the light chain consists of the amino acid sequence set forth in SEQ ID NO:10.

34. A method of treating abnormal accumulation or deposition of Aβ in the central nervous system in a human subject in need thereof, the method comprising administering to the human subject the pharmaceutical composition of any one of claims 1 to 33.

35. A method of treating mild cognitive impairment in a human subject in need thereof, the method comprising administering to the human subject the pharmaceutical composition of any one of claims 1 to 33.

36. A method of treating Alzheimer's disease in a human subject in need thereof, the method comprising administering to the human subject the pharmaceutical composition of any one of claims 1 to 33.

37. The method of any one of claims 34 to 36, wherein the pharmaceutical composition is administered subcutaneously to the human subject.

38. The method of any one of claims 34 to 36, wherein the pharmaceutical composition is administered intravenously to the human subject.

39. A pharmaceutical composition comprising an anti-beta amyloid (Aβ) antibody or Aβ-binding fragment thereof, a thiol-containing antioxidant, and arginine hydrochloride (Arg.HCl), wherein the anti-Aβ antibody or Aβ-binding fragment thereof comprises an immunoglobulin heavy chain variable domain (VH) and an immunoglobulin light chain variable domain (VL), the VH and VL, respectively, comprising:

(a) VH complementarity determining regions (CDRs), wherein

VH-CDR1 consists of the amino acid sequence set forth in SEQ ID NO:1;

VH-CDR2 consists of the amino acid sequence set forth in SEQ ID NO:2; and

VH-CDR3 consists of the amino acid sequence set forth in SEQ ID NO:3; and

(b) VL CDRs, wherein

VL-CDR1 consists of the amino acid sequence set forth in SEQ ID NO:4;

VL-CDR2 consists of the amino acid sequence set forth in SEQ ID NO:5; and

VL-CDR3 consists of the amino acid sequence set forth in SEQ ID NO:6, and

wherein the composition has a pH of 5.2 to 6.2.

40. The pharmaceutical composition of claim 39, wherein the composition comprises the anti- Aβ antibody or Aβ-binding fragment thereof at a concentration of 50 mg/ml to 250 mg/ml.

41. The pharmaceutical composition of claim 39, wherein the composition comprises the anti- Aβ antibody or Aβ-binding fragment thereof at a concentration of 75 mg/ml to 165 mg/ml.

42. The pharmaceutical composition of claim 39, wherein the composition comprises the anti- Aβ antibody or Aβ-binding fragment thereof at a concentration of 150 mg/ml.

43. The pharmaceutical composition of claim 39, wherein the composition comprises the anti- Aβ antibody or Aβ-binding fragment thereof at a concentration of 100 mg/ml.

44. The pharmaceutical composition of any one of claims 39 to 43, wherein the thiol-containing antioxidant is selected from the group consisting of GSH, GSSG, the combination of GSH and GSSG, cystine, cysteine, and the combination of cysteine and cystine.

45. The pharmaceutical composition of claim 44, wherein the thiol-containing antioxidant is GSH.

46. The pharmaceutical composition of claim 44, wherein the thiol-containing antioxidant is GSSG.

47. The pharmaceutical composition of claim 44, wherein the thiol-containing antioxidant is the combination of GSH and GSSG.

48. The pharmaceutical composition of any one of claims 39 to 47, wherein the thiol-containing antioxidant is at a concentration of 0.02 mM to 4 mM.

49. The pharmaceutical composition of any one of claims 39 to 47, wherein the thiol-containing antioxidant is at a concentration of 0.2 mM.

50. The pharmaceutical composition of any one of claims 39 to 47, wherein the thiol-containing antioxidant is at a concentration of 0.4 mM.

51. The pharmaceutical composition of any one of claims 39 to 47, wherein the thiol-containing antioxidant is at a concentration of 1 mM.

52. The pharmaceutical composition of claim 47, wherein the GSH is at a concentration of 0.4 mM and the GSSG is at a concentration of 0.2 mM.

53. The pharmaceutical composition of claim 44, wherein the thiol-containing antioxidant is the combination of cysteine and cystine, wherein the cysteine is at a concentration of 0.4 mM and the cystine is at a concentration of 0.2 mM.

54. The pharmaceutical composition of any one of claims 39 to 53, wherein the composition comprises Arg.HCl at a concentration of 50 mM to 250 mM.

55. The pharmaceutical composition of any one of claims 39 to 53, wherein the composition comprises Arg.HCl at a concentration of 75 mM to 175 mM.

56. The pharmaceutical composition of any one of claims 39 to 53, wherein the composition comprises Arg.HCl at a concentration of 150 mM.

57. The pharmaceutical composition of any one of claims 39 to 56, wherein the composition comprises Polysorbate-80 (PS80).

58. The pharmaceutical composition of claim 57, wherein the composition comprises PS80 at a concentration of 0.01% to 0.1%.

59. The pharmaceutical composition of claim 57, wherein the composition comprises PS80 at a concentration of 0.03% to 0.08%.

60. The pharmaceutical composition of claim 57, wherein the composition comprises PS80 at a concentration of 0.05%.

61. The pharmaceutical composition of any one of claims 39 to 60, wherein the composition comprises a buffer selected from the group consisting of histidine, acetate, succinate, and citrate.

62. The pharmaceutical composition of claim 61, wherein the composition comprises histidine, acetate, succinate, or citrate at a concentration of 10 mM to 30 mM.

63. The pharmaceutical composition of claim 61, wherein the composition comprises histidine, acetate, succinate, or citrate at a concentration of 20 mM

64. The pharmaceutical composition of claim 61, wherein the buffer is histidine.

65. The pharmaceutical composition of claim 64, wherein histidine is at a concentration of 10 mM to 30 mM.

66. The pharmaceutical composition of claim 64, wherein histidine is at a concentration of 20 mM.

67. The pharmaceutical composition of any one of claims 39 to 66, wherein the composition comprises sucrose.

68. The pharmaceutical composition of claim 67, wherein the composition comprises sucrose at a concentration of 0.01% to 3%.

69. The pharmaceutical composition of claim 67, wherein the composition comprises sucrose at a concentration of 1% to 3%.

70. The pharmaceutical composition of claim 67, wherein the composition comprises sucrose at a concentration of 3%.

71. The pharmaceutical composition of any one of claims 39 to 70, wherein the composition has a pH of 5.2 to 6.0.

72. The pharmaceutical composition of any one of claims 39 to 70, wherein the composition has a pH of 5.3 to 5.7.

73. The pharmaceutical composition of any one of claims 39 to 70, wherein the composition has a pH of 5.5.

74. The pharmaceutical composition of claim 39, comprising:

the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 50 mg/ml to 250 mg/ml;

Arg.HCl at a concentration of 50 mM to 200 mM;

a thiol-containing antioxidant at a concentration of 0.02 mM to 4 mM;

histidine at a concentration of 10 mM to 30 mM;

PS80 at a concentration of 0.01% to 0.1%;

sucrose at a concentration of 0 to 3%; and

wherein the composition has a pH of 5.2 to 6.0.

75. The pharmaceutical composition of claim 39, comprising:

the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 150 mg/ml;

Arg.HCl at a concentration of 150 mM;

a thiol-containing antioxidant at a concentration of 0.02 mM to 4 mM;

histidine at a concentration of 20 mM; and

PS80 at a concentration of 0.05%,

wherein the composition has a pH of 5.5.

76. The pharmaceutical composition of claim 39, comprising:

the anti-Aβ antibody or the Aβ-binding fragment thereof at a concentration of 100 mg/ml;

Arg.HCl at a concentration of 150 mM;

a thiol-containing antioxidant at a concentration of 0.02 mM to 2 mM;

histidine at a concentration of 20 mM; and

PS80 at a concentration of 0.05%,

wherein the composition has a pH of 5.5.

77. The pharmaceutical composition of any one of claims 74 to 76, wherein the thiol-containing antioxidant is selected from the group consisting of GSH, GSSG, the combination of GSH and GSSG, cystine, cysteine, and the combination of cysteine and cystine.

78. The pharmaceutical composition of claim 77, wherein the thiol-containing antioxidant is GSH.

79. The pharmaceutical composition of claim 77, wherein the thiol-containing antioxidant is GSSG.

80. The pharmaceutical composition of claim 77, wherein the thiol-containing antioxidant is the combination of GSH and GSSG.

81. The pharmaceutical composition of any one of claims 39 to 80, further comprising methionine.

82. The pharmaceutical composition of claim 81, wherein methionine is at a concentration of 0.01 mM to 150 mM.

83. The pharmaceutical composition of claim 81, wherein methionine is at a concentration of 5 mM to 20 mM.

84. The pharmaceutical composition of any one of claims 39 to 83, wherein:

(i) the VH consists of a sequence at least 80% identical to SEQ ID NO:7 and the VL consists of a sequence at least 80% identical to SEQ ID NO:8;

(ii) the VH consists of a sequence at least 90% identical to SEQ ID NO:7 and the VL consists of a sequence at least 90% identical to SEQ ID NO:8; or

(iii) the VH consists of the amino acid sequence set forth in SEQ ID NO:7 and the VL consists of the amino acid sequence set forth in SEQ ID NO:8.

85. The pharmaceutical composition of any one of claims 39 to 84, wherein the anti-Aβ antibody comprises an immunoglobulin heavy chain and an immunoglobulin light chain, wherein:

(i) the heavy chain consists of a sequence at least 80% identical to SEQ ID NO:9 and the light chain consists of a sequence at least 80% identical to SEQ ID NO:10;

(ii) the heavy chain consists of a sequence at least 90% identical to SEQ ID NO:9 and the light chain consists of a sequence at least 90% identical to SEQ ID NO:10; or

(iii) the heavy chain consists of the amino acid sequence set forth in SEQ ID NO:9 and the light chain consists of the amino acid sequence set forth in SEQ ID NO:10.

86. A method of treating abnormal accumulation or deposition of Aβ in the central nervous system in a human subject in need thereof, the method comprising administering to the human subject the pharmaceutical composition of any one of claims 39 to 85.

87. A method of treating mild cognitive impairment in a human subject in need thereof, the method comprising administering to the human subject the pharmaceutical composition of any one of claims 39 to 85.

88. A method of treating Alzheimer's disease in a human subject in need thereof, the method comprising administering to the human subject the pharmaceutical composition of any one of claims 39 to 85.

89. The method of any one of claims 86 to 88, wherein the pharmaceutical composition is administered subcutaneously to the human subject.

90. The method of any one of claims 86 to 88, wherein the pharmaceutical composition is administered intravenously to the human subject.