

COMBINATIONAL TREATMENT

BACKGROUND OF THE INVENTION

[0001] Related Applications

[0002] The present application claims priority to U.S. Prov. Appl. No. 63/509,854, filed on June 23, 2023, the contents of which are incorporated by reference in their entirety.

[0003] Sequence Listing Disclosure

[0004] The contents of the electronic sequence listing (1143257o014013.xml; Size: 25,446 bytes; and Date of Creation: June 17, 2024) is herein incorporated by reference in its entirety.

[0005] Sequences Not Permitted To Be Entered In St.26 Xml File Due To Sequence Length

[0006] **Table A** below lists sequences present in the priority application U.S. Provisional Application No. 63/509,854 (identified above, which is herein incorporated by reference in its entirety), but cannot be included in the 1143257o014013.xml file submitted herewith due to the length of the sequences.

Item No.	SEQ ID NO:	Length	Skipped Sequence	Sequence Name	Molecule Type	Organism	Residues
1	3	3	Yes	Eptinezumab CDR-H3	AA	synthetic construct	GDI

[0007] Field of the invention

[0008] This invention pertains to a composition comprising two antibodies or fragments thereof (including Fab fragments) with specificities to different targets. One of these antibodies or antibody fragments binds specifically to human Calcitonin Gene Related Peptide (hereinafter “CGRP”) and the other antibody or antigen binding fragments thereof specifically bind to Pituitary Adenylate Cyclase-Activating Polypeptide (“PACAP”).

[0009] Description of Related Art

[0010] Calcitonin Gene Related Peptide (CGRP) is produced as a multifunctional neuropeptide of 37 amino acids in length. Two forms of CGRP, the CGRP-alpha and CGRP-beta forms, exist in humans and have similar activities. CGRP-alpha and CGRP-beta differ by three amino acids in humans, and are derived from different genes. CGRP is released from

numerous tissues such as trigeminal nerves, which when activated release neuropeptides within the meninges, mediating neurogenic inflammation that is characterized by vasodilation, vessel leakage, and mast-cell degradation. Durham, P.L., *New Eng. J. Med.*, 350 (11):1073-75 (2004). Biological effects of CGRP are mediated via the CGRP receptor (CGRP-R), which consists of a seven-transmembrane component, in conjunction with receptor-associated membrane protein (RAMP). CGRP-R further requires the activity of the receptor component protein (RCP), which is essential for an efficient coupling to adenylate cyclase through G proteins and the production of cAMP. Doods, H., *Curr. Op. Invest. Drugs*, 2(9):1261-68 (2001).

[0011] Several antibodies have been approved for treatment of migraine. These antibodies binds either CGRP or the CGRP receptor. The FDA approved antibodies include Aimovig (Erenumab), Ajovi (Fremanezumab), Emgality (Galcanezumab) and Vyepti (Eptinezumab). The current invention relates to Vyepti (Eptinezumab or Ab6 as used herein) which is a drug approved for preventive treatment of migraine. The recommended dosage is 100 mg as an intravenous infusion every 3 months. Some patients may benefit from a dosage of 300 mg administered every 3 months.

[0012] Pituitary Adenylate Cyclase-Activating Polypeptide ("PACAP") is a member of the secretin/vasoactive intestinal peptide ("VIP")/growth hormone-releasing hormone ("GHRH") family. PACAP is a multifunctional vasodilatory peptide that exists in two α -amidated active forms, one with 38 amino acids (PACAP38) and the other with 27 amino acids (PACAP27). Both peptides have the same N-terminal 27 amino acids and are synthesized from the same precursor protein, preproPACAP (See, Moody et al., *Curr. Opin. Endocrinol. Diabetes Obes.*, 18(1):61-67, 2011). PACAP38 is the more prevalent active form, representing up to 90% of PACAP forms in mammalian tissues (See, Kaiser and Russo, *Neuropeptides*, 47:451-461, 2013). The sequence of PACAP38 is identical in all mammals and differs from the avian and amphibian orthologs by only one amino acid (See, Vaudry et al., *Pharmacol. Rev.*, 52:269-324, 2000). The secretin/VIP/GHRH family includes mammalian peptide histidine methionineamide ("PHM"), secretin, glucagon, glucagon-like peptide-1 ("GLP1"), glucagon-like peptide-2 ("GLP2"), glucose-dependent-insulinotropic-polypeptide ("GIP"), and growth-hormone-releasing-factor ("GRF"). PACAP27 has 68% sequence identity to VIP at the amino acid level (See, Vaudry et al., 2000).

[0013] The biological effects of PACAP are mediated via three different G-protein

coupled receptors: PAC1-R, vasoactive intestinal peptide receptor type 1 ("VPAC1-R"), and vasoactive intestinal peptide receptor type 2 ("VPAC2-R"). These receptors are expressed in diverse tissues. PAC1-R is particularly abundant in the nervous system (e.g., olfactory bulb, thalamus, hypothalamus, cerebellum, and spinal dorsal horn), pituitary, and adrenal glands. By contrast, VPAC1-R and VPAC2-R are expressed mainly in the lung, liver, and testis, although they have been detected in other tissues as well. VPAC1-R expression has been detected in the nervous system (e.g., cerebral cortex and hippocampus), smooth muscle cells of lung, liver, intestine, megakaryocytes, and platelets. VPAC1-R associates with receptor-associated membrane protein ("RAMP", specifically, RAMP2) (See, Christopoulos et al., *J. Biol. Chem.*, 278:3293-3297, 2002). VPAC2-R expression profile includes the nervous (e.g., thalamus, hippocampus, brain stem, and dorsal root ganglia ("DRG")), cardiovascular system, gastrointestinal system, pancreas, and reproductive systems (See, Usdin et al., *Endocrin.*, 135:2662-2680, 1994; Sheward et al., *Neurosci.*, 67:409-418, 1995).

[0014] PACAP is hypothesized to play a role in a multitude of diseases and disorders, including but not limited to migraine, headache, and pain. Migraines are believed to have a neurovascular component. Migraines affect approximately 10% of the adult population in the U.S. and are typically accompanied by intense headaches. Approximately 20-30% of migraine sufferers experience aura, comprising focal neurological phenomena that precede and/or accompany the event. A role for PACAP in migraine has been suggested by several observations: (1) plasma levels of PACAP are elevated during migraine attacks (ictal), as compared to interictal levels, in humans (see Tuka et al., *Cephalalgia*, 33(13):1085-1095, 2013); (2) an infusion of PACAP38 triggered headaches in healthy subjects, and headaches followed by migraine-like attacks in migraineurs (see Schytz et al., *Brain*, 132:16-25, 2009; and Amin et al., *Brain*, 137:779-794, 2014, respectively); (3) PACAP-induced vasodilation may play a role in neurogenic inflammation (see Kaiser and Russo, *Neuropeptides*, 47:451-461, 2013); and (4) PACAP-induced migraines are associated with photophobia, phonophobia, nausea, and respond to triptans (see Amin et al., *Brain*, 135:140-149, 2012). PACAP has also been shown to induce vasodilation, photophobia, as well as mast cell degranulation and neuronal activation (See, Markovics et al., *Neurobiology of Disease*, 45:633-644, 2012; Baun et al., *Cephalalgia*, 32(4):337-345, 2012; Chan et al., *Pharmacology & Therapeutics*, 129:332-351, 2011).

[0015] PACAP may also be involved in diseases and disorders other than migraine,

headache, and pain. For example, PACAP may correlate to or even play a causal role in anxiety disorders (WO 2012/106407); thrombocytopenia (WO 2004/062684); and inflammatory skin diseases (WO 2010/007175). PACAP and PAC1-R polymorphisms are associated with post-traumatic stress syndrome ("PTSD") in females, major depressive disorder, and generalized anxiety disorder, suggesting a role for PACAP in these conditions. Further, supporting a role for PACAP in thrombocytopenia, trisomy 18 patients have excess PACAP and exhibit defective megakaryocyte maturation (See, Schytz et al., 2010; and Moody et al., *Curr. Opin. Endocrinol. Diabetes Obes.*, 18(1):61-67, 2011).

[0016] Also, PACAP and other neuropeptides, such as Calcitonin Gene-Related Peptide ("CGRP"), substance P, neurokinin A, bradykinin, and endothelin-1, are expressed in the lower urinary tract ("LUT") (see Arms and Vizzard, *Handbook Exp. Pharmacol.*, 202:395-423, 2011) and reportedly may play a role in LUT dysfunction and urinary tract disorders such as urinary tract infection ("UTI"), abnormal voiding, urinary urgency, nocturia, urinary incontinence, overactive bladder, and the pain associated with such conditions.

[0017] PACAP and PACAP receptors have also been suggested to modulate inflammatory and neuropathic pain and have been implicated in both pronociception and antinociception (See, Davis-Taber et al., *J. Pain*, 9(5):449-56, 2008). PACAP has also been reported to be required for spinal desensitization and the induction of neuropathic pain (See, Mabuchi et al., *J. Neurosci.*, 24(33):7283-91, 2004). Additionally, morphine withdrawal behavior is reportedly modified in PACAP-receptor deficient mice further suggesting the role of PACAP in morphine withdrawal anxiolytic response (See, Martin et al., *Mol. Brain Res.*, 110(1):109-18, 2003).

[0018] The present invention relates to an anti-PACAP antibody named LuAG09222, Ab10.H3 or ALD1910 (all synonyms for the same antibody) (Moldovan Loomis et al., *J Pharmacol Exp Ther* 369:26–36, April 2019). The drug is tested in various clinical trials within migraine at different dosages and has just shown significant results in a proof of concept study in migraine (clinicaltrials.gov number NCT05133323; and *The Pharma Letter* 20 Apr 2023 "Lundbeck posts positive Phase IIa results with LuAG09222").

[0019] The present invention relates to the combined use of Eptinezumab and LuAG09222 as a combinational therapy or preferable in a composition comprising both drugs. Said combinational therapy or composition may be used in the treatment of medical conditions, optionally headache, episodic or chronic migraine, cluster headache,

endometriosis or pain.

[0020] Brief Summary

[0021] The present disclosure provides methods of treatment of headache in patient, comprising administering to a patient in need an effective amount of an anti-CGRP antibody (such as Eptinezumab) or antibody fragment thereof and an effective amount of an anti-PACAP antibody (such as LuAG09222) or antibody fragment thereof as disclosed herein.

[0022] According to one embodiment the invention relates to the treatment of migraine. Said antibody treatment may be initiated in the interictal period, *i.e.* in between migraine attacks or in the ictal phase, *i.e.* during the migraine episode. Said migraine may comprise *e.g.* chronic migraine or episodic migraine, in a specific aspect of the present invention the patient suffers from chronic migraine. In the present invention, said anti-CGRP antibody is denoted Ab6, Eptinezumab or Vyepti which are all intended to refer to the same antibody. Said anti-PACAP antibody is denoted LuAG09222, ALD1910 or Ab10.H3 which are all intended to refer to the same antibody.

[0023] The antibodies of the invention may be produced in yeast or mammalian cells, *e.g.*, *Pichia pastoris* or CHO cells. The antibodies of the invention may be in a composition comprising histidine (10 – 50 mM), polysorbate 80 or Poloxamer 188 (0.005-0.05% w/v) at pH 5.0-6.8. The composition may additionally comprise a tonicity agent, optionally NaCl (10-150 mM), sorbitol (50-250 mM) and/or arginine (50-250 mM). The total amount of both antibodies combined may be 150 mg/ml, for example so that Eptinezumab is present in 100 mg/ml and LuAG09222 is present in 50 mg/ml. The formulation may be administered subcutaneous or intravenously (iv) to a patient. Further embodiments of formulations and co-formulations are described herein and in the claims. As used in the present invention, histidine also include the L form of histidine (L-histidine), sorbitol includes the L-sorbitol form, and arginine includes the L-arginine from.

[0024] In another embodiment of the invention, the combinational therapy or the composition is useful in methods directed to reducing, treating, or preventing migraines (with or without aura), cancer or tumors, angiogenesis associated with cancer or tumor growth, angiogenesis associated with cancer or tumor survival, weight loss, pain, hemiplegic migraines, cluster headaches, migrainous neuralgia, chronic headaches, tension headaches, general headaches, hot flushes, chronic paroxysmal hemicrania, secondary headaches due to an underlying structural problem in the head or neck, cranial neuralgia, sinus headaches

(such as for example associated with sinusitis), and allergy-induced headaches or migraines. The antibodies and antibody fragments of the present invention particularly have utility in treating, preventing, ameliorating, controlling or reducing the risk of one or more of the following conditions or diseases: overactive bladder and other urinary conditions including bladder infection, pain; chronic pain; neurogenic inflammation and inflammatory pain; neuropathic pain; eye pain; tooth pain; post-surgical pain, trauma related pain, burn related pain, diabetes; non-insulin dependent diabetes mellitus and other inflammatory autoimmune disorders, vascular disorders; inflammation; arthritis; bronchial hyperreactivity, asthma; shock; sepsis; opiate withdrawal syndrome; morphine tolerance; hot flashes in men and women; allergic dermatitis; psoriasis; encephalitis; brain trauma; epilepsy; neurodegenerative diseases; skin diseases including pruritis, neurogenic cutaneous redness, skin rosaceousness and erythema; inflammatory bowel disease, irritable bowel syndrome, cystitis; dysmenorrhea, and other conditions that potentially may be treated or prevented or the symptoms ameliorated by antagonism of CGRP and/or PACAP signaling. Of particular importance is the acute or prophylactic treatment of headache, including migraine and cluster headache, and other pain related conditions as well as endometriosis.

[0025] In another embodiment of the invention, the combinational therapy or the composition is useful in methods directed to reducing, treating, or preventing gastro-esophageal reflux and/or visceral pain associated with gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, ileitis, ulcerative colitis, renal colic, dysmenorrhea, cystitis, menstrual period, labor, menopause, prostatitis, or pancreatitis.

[0026] In migraine, hyperactivation of trigeminal nerves results in increased release of Calcitonin gene-related peptide (CGRP) and other peptides that cause the release of neurogenetic proinflammatory mediators. These mediators further increase CGRP synthesis and release over time in correspondence with a typical migraine episode. CGRP mediates its effect via vasodilation of cerebral arteries and arterioles, activating adenylyl cyclase in the smooth muscle cells, predominantly in the trigeminal vascular network, and leading to aberrant activation of nociceptors and pain sensation.

[0027] Pituitary adenylyl cyclase-activating polypeptide (PACAP) is thought to contribute to the pathophysiology of headache based on several lines of evidence; studies have demonstrated that PACAP levels are elevated during ictal compared to interictal periods

in migraine patients. Furthermore, PACAP may be released during a migraine attack, and PACAP levels are elevated in patients with chronic migraine.

[0028] Additional lines of evidence come from provocation studies, where administration of both PACAP-38 and PACAP-27 resulted in producing migraine-like events in both healthy subjects and migraineurs. PACAP may also play a role in cluster headache. Similarly, studies have demonstrated that PACAP levels are also raised during ictal cluster events compared to interictal attacks.

[0029] CGRP and PACAP neuropeptides have overlapping locations and physiological similarities but also show differentiated biological effects.

[0030] This suggests that dual neutralization of CGRP and PACAP peptides will result in a profound clinical efficacy compared to single target neutralization in a group of patients in the migraine/headache franchise.

[0031] Both Eptinezumab and LuAG09222 are genetically engineered humanized antibodies directed against human CGRP and PACAP, respectively, Eptinezumab and LuAG09222 can bind these neuropeptides and thereby block their binding to the respective receptors, and consequently inhibiting downstream signaling that can lead to headache and pain sensation.

[0032] These antibodies are IgG1 kappa immunoglobulin containing human constant regions. Their light and heavy chain variable regions are comprised of human and humanized rabbit sequences.

[0033] Eptinezumab is a prescription medicine used for the preventive treatment of migraine in adults. It is dosed at 100 or 300 mg as a 30-minute intravenous infusion (iv) treatment. Patients are given 4 doses per year (i.e. one dose every 3 months).

[0034] LuAG09222 binds human PACAP with high affinity. LuAG09222 blocks migraine-associated effects (photophobia, vasodilation, temperature increase and lacrimation), and can reduce pain in preclinical mechanistic models. Data from a clinical study confirmed the safety, tolerability, and PK of LuAG09222. A human challenge study demonstrated that LuAG09222 prevents PACAP38-induced vasodilation and prevents PACAP38-induced facial flushing and heart rate increase, and a Phase 2 study of LuAG09222 in migraine (HOPE Study) provided evidence for the efficacy of targeting PACAP in Migraine prevention. Data from the phase 2 HOPE trial (NCT05133323) highlighted the effects of Lu AG09222 as a potential preventive for migraine. All told, the trial met its primary end point, with significant between-

group differences observed in the high dose group of treated patients over a 12-week double-blind period. The multinational, multisite trial featured 237 individuals with episode or chronic migraine who failed 2-4 previous preventives and were randomized to either 750 mg (n = 97) or 100 mg Lu AG09222 (n = 46) or placebo (n = 94) for 4-week treatment period with 12 weeks of safety follow-up. At the end of the 4-week period, investigators observed a 2.0-day difference (95% CI, -3.5 to -0.6; P = .0106) in the reduction of monthly migraine days (MMDs) between those in the high dose treated group and placebo.

[0035] A composition comprising both products ((Eptinezumab and LuAG09222) developed for subcutaneous administration offers added therapeutic benefit and provide a differentiated and/or superior treatment option within headache and non-headache pain disorders. Defined segments/phenotypes within migraine (patients with insufficient anti-CGRP responders or patients with parasympathetic symptoms, patients with high frequency/chronic migraine, switch/adjunct for anti-CGRPs) and in episodic cluster headache include subjects with elevated circulated CGRP and PACAP levels.

[0036] In yet another embodiment the invention, the combinational therapy or the composition is useful in treating, ameliorating, or preventing chronic or episodic migraine, cluster headache, endometriosis or pain.

[0037] In a specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 wherein Eptinezumab has the VH region as defined in SEQ ID NO.: 4 and the VL as defined in SEQ ID NO.: 10, and LU AG09222 has the VH region as defined in SEQ ID NO.: 15 and the and VL region as defined in SEQ ID NO.: 20.

[0038] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing which is formulated so as to maintain the biologic activity and/or storage stability of the Eptinezumab and LuAG09222 antibodies therein.

[0039] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing which maintains the biologic activity and/or storage stability of the Eptinezumab and LuAG09222 antibodies therein for at least 1 month, at least 2 months, at least 3 months, at least 3-6 months, at least 6-9 months, at least 9-12 months, or at least a year.

[0040] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing,

which comprises or further comprises histidine and either polysorbate 80 or Poloxamer 188.

[0041] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing which comprises or further comprises one, two or all of the following excipients NaCl, sorbitol and arginine.

[0042] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing which comprises a total concentration of Eptinezumab and LuAG09222 of 100 mg/mL to 300 mg/mL.

[0043] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing which comprises a total concentration of Eptinezumab and LuAG09222 of 100 mg/mL, 150 mg/mL, 200 mg/mL 250 mg/mL or 300 mg/mL.

[0044] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing which has a ratio of Eptinezumab to LuAG09222 of 1:1, 1:2 or 2:2.

[0045] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing wherein the composition comprises 100-300 mg/mL of Eptinezumab and 50 -100 mg/mL of LuAG09222.

[0046] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing wherein the composition comprises 100 mg/mL of Eptinezumab and 50 mg/mL of LuAG09222.

[0047] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing wherein Eptinezumab and LuAG0922 are the only active ingredients in the composition.

[0048] The pharmaceutical composition according to any one of the previous claims, wherein histidine is in a concentration ranging between 10 – 50 mM, optionally 20-40 mM, Poloxamer P188 ranging between 0.0025-0.0120 % w/v and polysorbate 80 0.005-0.05% w/v inclusive.

[0049] In another specific embodiment the invention provides a pharmaceutical

composition comprising Eptinezumab and LuAG09222 according to any of the foregoing, wherein the concentration of NaCl is between 10-150 mM, optionally 30-70 mM, sorbitol (e.g. L-sorbitol) 50-250 mM, optionally 90-180 mM, and arginine (e.g. L-arginine) ranging between 50-250 mM inclusive.

[0050] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing, wherein the pH is between 5.0-6.8 inclusive.

[0051] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing, wherein the pH is 5.0, 5.5, 5.9, 6.0, 6.5 or 6.8.

[0052] The pharmaceutical composition **according to any one of the previous claims**, which is suitable for intravenous administration or subcutaneous administration.

[0053] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing, comprising Eptinezumab and LuAG09222 in a ratio of 2:1, 1:1 or 1:2 and comprises 20-40 mM histidine buffer, 90-180 mM sorbitol, Poloxamer P188 0.0025-0.0120% w/v and 30-70 mM NaCl, and has a pH about 6, optionally pH 5.9.

[0054] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing, comprising Eptinezumab and LuAG09222 in a ratio of 2:1 and comprising 25-35 mM histidine buffer, 165-175 mM sorbitol, Poloxamer P188 0.0025-0.010% w/v and 25-35 mM NaCl, and has a pH about 6, optionally pH 5.9.

[0055] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing comprising Eptinezumab and LuAG09222 in a ratio of 1:1 and comprising 30-40 mM histidine buffer, 130-140 mM sorbitol, Poloxamer P188 0.005-0.010% w/v and 45-55 mM NaCl, and has a pH about 6, optionally pH 5.9.

[0056] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing wherein Eptinezumab and LuAG09222 in a ratio of 1:2 and comprising 35-45 mM histidine buffer, 90-100 mM sorbitol, Poloxamer P188 0.010-0.0120 % w/v and 65-75 mM NaCl, and has a pH about 6, optionally pH 5.9.

[0057] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing for use as a medicament.

[0058] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing for use in treating or preventing headache, optionally chronic or episodic migraine or cluster headache.

[0059] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing for use in treating or preventing pain.

[0060] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing for administration every month (every 4 weeks) or every 2 weeks.

[0061] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 according to any of the foregoing or use thereof wherein Eptinezumab has the heavy chain as defined in SEQ ID NO.: 5 or SEQ ID NO.: 6 and the light chain as defined in SEQ ID NO.: 11.

[0062] In another specific embodiment the invention provides a pharmaceutical composition comprising Eptinezumab and LuAG09222 or use thereof according to any of the foregoing wherein LUAG09222 has the heavy chain as defined in SEQ ID NO.: 16 or SEQ ID NO.: 26 and the light chain as defined in SEQ ID NO.: 21.

[0063] In another specific embodiment the invention provides a method of treating or preventing headache, optionally chronic or episodic migraine or cluster headache, comprising the subcutaneous or intravenous administration of the combination of Eptinezumab and LuAG09222 antibodies, wherein Eptinezumab has the VH region as defined in SEQ ID NO.: 4 and the VL as defined in SEQ ID NO.: 10, and LU AG09222 has the VH region as defined in SEQ ID NO.: 15 and the VL region as defined in SEQ ID NO.: 20, and optionally wherein the administration of said antibody combination has an additive or synergistic effect on the inhibition, alleviation or prevention of the number of, duration, and/or the intensity of migraine episodes compared to the subcutaneous or intravenous administration of Eptinezumab or LuAG09222 alone.

[0064] In another specific embodiment the invention provides a treating or preventing

pain, comprising the subcutaneous or intravenous administration of the combination of Eptinezumab and LuAG09222 antibodies, wherein Eptinezumab has the VH region as defined in SEQ ID NO.: 4 and the VL as defined in SEQ ID NO.: 10, and LU AG09222 has the VH region as defined in SEQ ID NO.: 15 and the and VL region as defined in SEQ ID NO.: 20, and optionally wherein the administration of said antibody combination has an additive or synergistic effect on the inhibition or alleviation of pain, compared to the subcutaneous or intravenous administration of Eptinezumab or LuAG09222 alone.

[0065] In another specific embodiment the invention provides a method of method of treating or preventing headache, optionally chronic or episodic migraine or cluster headache by administering Eptinezumab and LuAG09222, wherein the Eptinezumab and LuAG09222 antibodies are subcutaneously or intravenously administered using a pharmaceutical composition according to of the foregoing.

[0066] In another specific embodiment the invention provides a method of method of treating or preventing pain, e.g., acute pain, chronic pain, neuropathic pain, nociceptive pain, and/or radicular pain, by administering Eptinezumab and LuAG09222, wherein the Eptinezumab and LuAG09222 antibodies are subcutaneously or intravenously administered using a pharmaceutical composition according to of the foregoing.

[0067] BRIEF DESCRIPTION OF the DRAWINGS

[0068] **FIG. 1** shows the number of subjects in a human clinical trial described in Example 1 who were either treated with Ab6 (treatment group) or placebo groups who showed a 50, 75 or 100% reduction in migraines at each monitoring point throughout the period. The right bar in each group corresponds to patients receiving 1000 mg Ab6 and the left bar in each group corresponds to matched placebo controls. In each response rate group the patients receiving Ab6 had a significantly greater response rate than placebo-treated controls, with p values of 0.0155, 0.0034, and 0.0006 in each respective group as indicated.

[0069] **FIG. 2** shows the median ($\pm$ QR) % change from baseline in the number of migraine days per month in the placebo and Ab6 –treated group over the 12 weeks post-treatment. ($p=0.0078$). The upper line and lower line show results for placebo-treated controls and patients administered 1000 mg Ab6, respectively.

[0070] **FIG. 3** shows the median ($\pm$ QR) % change from baseline in the number of

migraine episodes per month in the placebo and Ab6 –treated group over the 12 weeks post-treatment. The upper line and lower line show results for placebo-treated controls and patients administered 1000 mg Ab6, respectively.

[0071] **FIG. 4** shows the median ($\pm$ QR) % change from baseline in the number of migraine hours per month in the placebo and Ab6 –treated group over the 12 weeks post-treatment. The upper line and lower line show results for placebo-treated controls and patients administered 1000 mg Ab6, respectively.

[0072] **FIG. 5** summarizes the screening of patients, allocation into the treatment and control groups, and loss of patients through follow-up.

[0073] **FIG. 6** compares the HIT-6 responder analysis for the Ab6-treated and placebo groups at baseline, week 4 after treatment, week 8 after treatment and week 12 after treatment.

[0074] **FIG. 7** shows the percentage of patients for whom the HIT-6 analysis indicated that the effect of headaches was only “some” or “little/none” at baseline and after Ab6 administration. At baseline most patients had either “substantial” or “severe” impact from migraines. At each subsequent time point, a significantly greater percentage of patients administered 1000 mg Ab6 had only “some” or “little/none” HIT-6 impact (left bar in each group, colored blue) as compared to placebo controls (right bar in each group, colored red).

[0075] **FIG. 8** contains the pharmacokinetic (PK) profile for Ab6 administered intravenously at a single dosage of 1000 mg.

[0076] **FIG. 9** contains plasma-free pharmacokinetic (PK) parameters N (number of patients), mean, and standard deviation (SD) for a single 1000 mg intravenous dosage of Ab6. The parameters shown in the table and the units are $C_{\max}$ ($\mu\text{g/mL}$), $\text{AUC}_{0-\infty}$ ($\text{mg}\cdot\text{hr/mL}$), half-life (days), V_z (L) and CL (mL/hr).

[0077] **FIG. 10** shows the change (mean $\pm$ SEM) change from baseline in migraine days per month for Ab6 (1000 mg i.v.) versus placebo as a single dose for the study described in Example 1.

[0078] **FIG. 11** shows the average migraine days ($\pm$ SD) over time for the full analysis population for the study described in Example 1. Normalization was applied to visit intervals where eDiaries were completed for 21-27 days by multiplying the observed frequency by the inverse of the completion rate.

[0079] **FIG. 12** shows the distribution of migraine days actual and change for the Ab6

treatment group during weeks 1-4 for the study described in Example 1.

[0080] **FIG. 13** shows the distribution of migraine days actual and change for the placebo group during weeks 1-4 for the study described in Example 1.

[0081] **FIG. 14** shows the distribution of migraine days actual and change for the Ab6 treatment group during weeks 5-8 for the study described in Example 1.

[0082] **FIG. 15** shows the distribution of migraine days actual and change for the placebo group during weeks 5-8 for the study described in Example 1.

[0083] **FIG. 16** shows the distribution of migraine days actual and change for the Ab6 treatment group during weeks 9-12 for the study described in Example 1.

[0084] **FIG. 17** shows the distribution of migraine days actual and change for the placebo group during weeks 9-12 for the study described in Example 1.

[0085] **FIG. 18** shows the 50% responder rate for the Ab6 and placebo treatment groups for the study described in Example 1. Subjects with $\geq 50\%$ reduction in migraine frequency were considered to be a 50% responder. Normalization was applied to visit intervals where eDiary was completed for 21-27 days by multiplying the observed frequency by the inverse of the completion rate.

[0086] **FIG. 19** shows the 75% responder rate for the Ab6 and placebo treatment groups for the study described in Example 1. Subjects with $\geq 75\%$ reduction in migraine frequency were considered to be a 75% responder. Normalization was applied as described with **FIG. 18**.

[0087] **FIG. 20** shows the 100% responder rate for the Ab6 and placebo treatment group for the study described in Example 1. Subjects with 100% reduction in migraine frequency were considered to be a 100% responder. Normalization was applied as described with **FIG. 18**.

[0088] **FIG. 21** shows the mean migraine severity over time for the full analysis population for the study described in Example 1. On the scale used, a mean migraine score of 3 represents "moderate pain."

[0089] **FIG. 22** summarizes the change from baseline in measured attributes for the placebo and treatment groups in the study described in Example 1.

[0090] **FIG. 23** shows the percentages of patients with migraine in the 300 mg, 100 mg, and placebo treatment groups at days 1, 7, 14, 21, and 28 in the clinical trial described in Example 2. The uppermost line shows results for placebo, the lowest line shows results for

the 300 mg dosage, and the middle line shows results for the 100 mg dosage.

[0091] **FIG. 24** show the percentage of patients in the 300 mg and 100 mg treatment groups achieving a 50% reduction in migraine days in month 1, over months 1-3 (after the 1st infusion), and over months 4-5 (after the 2nd infusion) in the clinical trial described in Example 2. In each graph, the data bars, from left to right, show results for the 100 mg, 300 mg, and placebo groups. Statistical significance is as shown. ++ indicates a statistically significant difference from placebo; + indicates a statistically significant difference from placebo (unadjusted); and § indicates a statistically significant difference from placebo (post hoc).

[0092] **FIG. 25** show the percentage of patients in the 300 mg and 100 mg treatment groups achieving a 75% reduction in migraine days in month 1, over months 1-3 (after the 1st infusion), and over months 4-5 (after the 2nd infusion) in the clinical trial described in Example 2. Data order and statistical significance labels are as indicated with **FIG. 24**.

[0093] **FIG. 26** show the percentage of patients in the 300 mg and 100 mg treatment groups achieving a 100% reduction in migraine days in month 1, over months 1-3 (after the 1st infusion), and over months 4-5 (after the 2nd infusion) in the clinical trial described in Example 2. Data order and statistical significance labels are as indicated with **FIG. 24**.

[0094] **FIG. 27** summarizes the characteristics of patients in each treatment group in the clinical trial described in Example 3. * According to the American Academy of Neurology/American Headache Society guidelines for migraine preventative treatment (medications identified by clinical review of coded medical data); SD, standard deviation; BMI, body mass index.

[0095] **FIG. 28.** Difference from placebo in change from baseline in mean migraine days (MMD) over months 1-3 by baseline subgroup for a human clinical trial of chronic migraine patients. In the graph, the data point refers to the mean value and the line shows the 95% confidence interval (CI) of the change from placebo for the 100 mg (upper line) or 300 mg (lower line) treatment group, for each subgroup as labeled at the far left.

[0096] **FIG. 29.** Difference from placebo in change from baseline in mean migraine days (MMD) over months 1-3 by baseline subgroup for a human clinical trial of episodic migraine patients.

[0097] **FIG. 30.** Change from baseline in mean migraine days (MMDs) across 2 dose intervals in chronic migraine patients with at least 1 day of acute medication use per month

at baseline. Triangle: placebo (n=366). Circle: 100 mg Ab6 per dose (n=356). Square: 300 mg Ab6 per dose (n=350).

[0098] **FIG. 31.** Mean days with acute medication use in chronic migraine patients with at least one day per month of acute medication use at baseline. Triangle: placebo (n=366). Circle: 100 mg Ab6 per dose (n=356). Square: 300 mg Ab6 per dose (n=350).

[0099] **FIG. 32.** Change from baseline in acute medication use by subgroups of chronic migraine patients with differing baseline days of acute medication use. Solid lines: patients with 10 or more days of acute medication use per month at baseline. Dashed lines: patients with at least 1 and less than 10 days of acute medication use per month at baseline.

Triangle: placebo. Circle: 100 mg Ab6 per dose. Square: 300 mg Ab6 per dose.

[0100] **FIG. 33.** Summary of Acute Medication Days by Subgroups of Chronic Migraine Patients with Baseline Acute Medication Use.

[0101] **FIG. 34.** Change from baseline in mean migraine days (MMDs) across 2 dose intervals in episodic migraine patients with at least 1 day of acute medication use per month at baseline. Triangle: placebo (n=222). Circle: 100 mg Ab6 per dose (n=221). Square: 300 mg Ab6 per dose (n=222).

[0102] **FIG. 35.** Mean days with acute medication use in episodic migraine patients with at least one day per month of acute medication use at baseline. Triangle: placebo (n=222). Circle: 100 mg Ab6 per dose (n=221). Square: 300 mg Ab6 per dose (n=222).

[0103] **FIG. 36.** Change from baseline in acute medication use by subgroups of episodic migraine patients with differing baseline days of acute medication use. Solid lines: patients with 10 or more days of acute medication use per month at baseline. Dashed lines: patients with at least 1 and less than 10 days of acute medication use per month at baseline.

Triangle: placebo. Circle: 100 mg Ab6 per dose. Square: 300 mg Ab6 per dose.

[0104] **FIG. 37.** Summary of Acute Medication Days by Subgroups of Episodic Migraine Patients with Baseline Acute Medication Use.

[0105] **FIG. 38.** Inclusion of Day -1 in the Migraine Data. Day 0 is defined as the day of the infusion. Thus, the data on Day 0 are indicative of the treatment effect post-infusion.

[0106] **Fig 39.** Based on clinical data from trials with LuAG09222 (Ab 10.H3) and in particular from the Phase II trial in migraine patients a dosage prediction has been made using R software (nlmixr). Dosed every months for 7 months and then discontinued.

DETAILED DESCRIPTION

[0107] Combining the population PK models for Eptinezumab and LuAG09222, allowed establishment of a PKPD model to determine the ratio of Eptinezumab and LuAG09222 needed to have below 50% free of each target (CGRP and PACAP). Dosing was explored as bolus administration at same time for both compounds. Dose frequency was defined as once monthly and route of administration was subcutaneous.

[0108] Eptinezumab has a terminal elimination half-life of 27 days, and is used at 100 or 300 mg in migraine, while LuAG09222 has a terminal elimination half-life of approximately 15 days.

[0109] If below 50% free targets is to be obtained with monthly s.c. dosing intervals, a 100 mg dose of Eptinezumab and a 50 mg dose of LuAG09222 is estimated to be needed.

[0110] When administered as single-agents, no treatment-related mortalities or adverse findings attributed to the pharmacological activity of Eptinezumab or LuAG09222 were observed during single or repeat-dose studies in rats or cynomolgus monkeys. Following Eptinezumab administration no effects on reproductive function or performance, fertility or early embryonic development in rats were observed. For Eptinezumab or LuAG09222 administration, no parental effects or evidence of embryoletality, fetotoxicity, or teratogenicity in rats or rabbits were observed. There were no effects on the survival, physical development, behavior, or reproductive performance of the F1 generation during a pre- and postnatal development study with eptinezumab in rats.

[0111] Across all nonclinical studies, the NOEL/NOAEL for IV administration of eptinezumab or LuAG09222 as single agents was the highest dose administered (up to 150 mg/kg/dose).

[0112] As both Eptinezumab and LuAG09222 are humanized monoclonal antibodies, no pharmacokinetic interactions are anticipated from the administration of a combination product or co-administration.

[0113] Definitions

[0114] It is to be understood that this invention is not limited to the particular methodology, protocols, cell lines, animal species or genera, and reagents described, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. As used herein the singular forms "a", "and", and "the" include plural referents unless the context clearly

dictates otherwise. Thus, for example, reference to "a cell" includes a plurality of such cells and reference to "the protein" includes reference to one or more proteins and equivalents thereof known to those skilled in the art, and so forth. All technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs unless clearly indicated otherwise.

[0115] As used herein, the term "chronic migraine" refers to a condition wherein a patient exhibits, on average, at least 15 headache per month with a subset of these headache days fulling the ICHD – 3 criteria for migraine with or without aura. The term "episodic migraine" refers to a condition wherein a patient exhibits, on average, less than 15 day a month of headache with typically 4 – 15 being a migraine phenotype meeting the ICHD-3 definition of migraine with or without aura.

[0116] As used herein, the term "diagnosed with chronic migraine" refers to a patient meeting the clinical criteria for chronic migraine, whether or not a formal diagnosis of that patient was performed. The term "diagnosed with episodic migraine" refers to a patient meeting the clinical criteria for episodic migraine, whether or not a formal diagnosis of that patient was performed.

[0117] As used herein, the term "intravenously administering" refers to a mode of administration wherein a substance, *e.g.*, an antibody, is introduced directly into the circulation of that patient, most typically into the venous circulation. The substance may be introduced in a carrier fluid, optionally an aqueous solution, *e.g.*, normal saline. The substance may be administered in a single formulation or in multiple formulations, as long as the administration is completed over a short period of time (*e.g.*, within 1 day, preferably within 12 hours, more preferably within 6 hours, and most preferably within 1-2 hours). The term "subcutaneous administering" (or *s.c.* administering) refers to a mode of administration wherein a substance, *e.g.*, an antibody, is administered to the layer of skin referred to as cutis, just below the dermis and epidermis layers. Subcutaneous medication can be administered to various sites, including the upper arm's outer area and abdomen, the front of the thigh, the upper back, or the upper buttock area behind the hip bone.

[0118] As used herein, the term "the baseline number of migraine days" refers to the number of migraine days exhibited by a patient in a specified time period, *e.g.*, prior to treatment. For example, the baseline number of migraine days may be determined over a period of one month, or longer, *e.g.*, by recording each day whether or not a migraine

occurred.

[0119] As used herein, the term "migraine days per month" refers to the number of days per month on which a patient has a migraine, *i.e.*, at any time during that day, the patient has symptoms that meet the clinical definition of migraine. The number of migraine days per month may be determined by recording each day whether or not a migraine occurred.

[0120] As used herein, the term "headache days per month" refers to the number of days per month on which a patient has a headache, *i.e.*, at any time during that day, the patient has symptoms that meet the clinical definition of a headache. The number of headache days per month may be determined by recording each day whether or not a headache occurred.

[0121] *Calcitonin Gene Related Peptide (CGRP)*: As used herein, CGRP encompasses *Homo sapiens* CGRP-alpha and *Homo sapiens* CGRP-beta amino acid sequences available from American Peptides (Sunnyvale CA) and Bachem (Torrance, CA).

[0122] *CGRP-alpha*: ACDTATCVTHRLAGLLSRSGGVKNNFVPTNVGSKAF-NH₂ (**SEQ ID NO.: 22**), wherein the terminal phenylalanine is amidated;

[0123] *CGRP-beta*: ACNTATCVTHRLAGLLSRSGGMVKS NFVPTNVGSKAF-NH₂ (**SEQ ID NO.: 23**), wherein the terminal phenylalanine is amidated; but also any membrane-bound forms of these CGRP amino acid sequences, as well as mutants (mutiens), splice variants, isoforms, orthologs, homologues and variants of this sequence.

[0124] *Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP)*: As used herein, unless stated otherwise PACAP includes any mammalian form of PACAP, and in particular encompasses the following *Homo sapiens* PACAP27 and *Homo sapiens* PACAP38 amino acid sequences.

[0125] PACAP38:

[0126] HSDGIFTDSYSRYRKQMAVKKYLA AVL GKRYKQ RVKNK (**SEQ ID NO.: 24**), but also any mutants, splice variants, isoforms, orthologs, homologs, and variants of this sequence.

[0127] PACAP27:

[0128] HSDGIFTDSYSRYRKQMAVKKYLA AVL (**SEQ ID NO.: 25**), but also any mutants, splice variants, isoforms, orthologs, homologs, and variants of this sequence.

[0129] *Expression Vector*: These DNA vectors contain elements that facilitate manipulation for the expression of a foreign protein within the target host cell, *e.g.*, a yeast

or mammalian cell optionally *Pichia pastoris* or CHO cells. Conveniently, manipulation of sequences and production of DNA for transformation is first performed in a bacterial host, *e.g.* *E. coli*, and usually vectors will include sequences to facilitate such manipulations, including a bacterial origin of replication and appropriate bacterial selection marker. Selection markers encode proteins necessary for the survival or growth of transformed host cells grown in a selective culture medium. Host cells not transformed with the vector containing the selection gene will not survive in the culture medium. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media. Exemplary vectors and methods for transformation of yeast are described, for example, in Burke, D., Dawson, D., & Stearns, T. (2000). *Methods in yeast genetics: a Cold Spring Harbor Laboratory course manual*. Plainview, N.Y.: Cold Spring Harbor Laboratory Press.

[0130] Expression vectors for use in yeast or mammalian cells will generally further include yeast or mammalian specific sequences, including a selectable auxotrophic or drug marker for identifying transformed yeast strains or transformed mammalian cells. A drug marker may further be used to amplify copy number of the vector in the host cell.

[0131] The polypeptide coding sequence of interest is operably linked to transcriptional and translational regulatory sequences that provide for expression of the polypeptide in host cells, *e.g.*, *Pichia pastoris* or CHO cells. These vector components may include, but are not limited to, one or more of the following: an enhancer element, a promoter, and a transcription termination sequence. Sequences for the secretion of the polypeptide may also be included, *e.g.* a signal sequence, and the like. A yeast or mammalian origin of replication is optional, as expression vectors are often integrated into the host cell genome. In one embodiment of the invention, the polypeptide of interest is operably linked, or fused, to sequences providing for optimized secretion of the polypeptide from yeast diploid cells.

[0132] Nucleic acids are "operably linked" when placed into a functional relationship with another nucleic acid sequence. For example, DNA for a signal sequence is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading frame. However, enhancers do not have to be contiguous. Linking

is accomplished by ligation at convenient restriction sites or alternatively via a PCR/recombination method familiar to those skilled in the art (Gateway[®] Technology; Invitrogen, Carlsbad California). If such sites do not exist, the synthetic oligonucleotide adapters or linkers are used in accordance with conventional practice.

[0133] Promoters are untranslated sequences located upstream (5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control the transcription and translation of particular nucleic acid sequences to which they are operably linked. Such promoters fall into several classes: inducible, constitutive, and repressible promoters (that increase levels of transcription in response to absence of a repressor). Inducible promoters may initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, *e.g.*, the presence or absence of a nutrient or a change in temperature.

[0134] The promoter fragment may also serve as the site for homologous recombination and integration of the expression vector into the same site in the host genome; alternatively a selectable marker is used as the site for homologous recombination. Examples of suitable promoters from *Pichia* include the AOX1 and promoter (Cregg *et al.* (1989) *Mol. Cell. Biol.* 9:1316-1323); ICL1 promoter (Menendez *et al.* (2003) *Yeast* 20(13):1097-108); glyceraldehyde-3-phosphate dehydrogenase promoter (GAP) (Waterham *et al.* (1997) *Gene* 186(1):37-44); and FLD1 promoter (Shen *et al.* (1998) *Gene* 216(1):93-102). The GAP promoter is a strong constitutive promoter and the AOX and FLD1 promoters are inducible.

[0135] Other yeast promoters include ADH1, alcohol dehydrogenase II, GAL4, PHO3, PHO5, Pyk, and chimeric promoters derived therefrom. Additionally, non-yeast promoters may be used in the invention optionally mammalian, insect, plant, reptile, amphibian, viral, and avian promoters. Most typically the promoter will comprise a mammalian promoter (potentially endogenous to the expressed genes) or will comprise a yeast or viral promoter that provides for efficient transcription in yeast systems.

[0136] Examples of mammalian promoters include cytomegalovirus (CMV) derived promoters, chicken 3-actin (CBM) derived promoters, adenomatous polyposis coli (APC) derived promoters, leucine-rich repeat containing G protein-coupled receptor 5 (LGR5) promoters, CAG promoter, Beta actin promoter, elongation factor-1 (EF1) promoter, early growth response 1 (EGR-1) promoter, eukaryotic initiation factor 4A (EIF4A1) promoter, simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), human

immunodeficiency virus (HIV) long terminal repeat (LTR) promoter, MoMuLV promoter, an avian leukemia virus promoter, an Epstein-Barr virus immediate early promoter, a Rous sarcoma virus promoter, as well as human gene promoters optionally, but not limited to, the actin promoter, the myosin promoter, the hemoglobin promoter, and the creatine kinase promoter, among others. Combinations of two or more of the foregoing promoters may also be used. Further, inducible promoters may be used. The use of an inducible promoter provides a molecular switch capable of turning on expression of the polynucleotide sequence which it is operatively linked when such expression is desired, or turning off the expression when expression is not desired. Examples of inducible promoters include, but are not limited to a metallothionine promoter, a glucocorticoid promoter, a progesterone promoter, and a tetracycline promoter.

[0137] The antibodies of the invention may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, *e.g.* a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the polypeptide coding sequence that is inserted into the vector. The heterologous signal sequence selected preferably is one that is recognized and processed through one of the standard pathways available within the host cell. The *S. cerevisiae* alpha factor pre-pro signal has proven effective in the secretion of a variety of recombinant proteins from *P. pastoris*. Other yeast signal sequences include the alpha mating factor signal sequence, the invertase signal sequence, and signal sequences derived from other secreted yeast polypeptides. Additionally, these signal peptide sequences may be engineered to provide for enhanced secretion in diploid yeast expression systems. Secretion signals for use in mammalian as well as yeast cells include mammalian signal sequences, which may be heterologous to the protein being secreted, or may be a native sequence for the protein being secreted. Signal sequences include pre-peptide sequences, and in some instances may include propeptide sequences. Many such signal sequences are known in the art, including the signal sequences found on immunoglobulin chains, *e.g.*, K28 preprotoxin sequence, PHA-E, FACE, human MCP-1, human serum albumin signal sequences, human Ig heavy chain, human Ig light chain, and the like. For example, see Hashimoto *et. al. Protein Eng* 11(2) 75 (1998); and Kobayashi *et. al. Therapeutic Apheresis* 2(4) 257 (1998).

[0138] Transcription may be increased by inserting a transcriptional activator sequence into the vector. These activators are cis-acting elements of DNA, usually about from 10 to 300 bp, which act on a promoter to increase its transcription. Transcriptional enhancers are relatively orientation and position independent, having been found 5' and 3' to the transcription unit, within an intron, as well as within the coding sequence itself. The enhancer may be spliced into the expression vector at a position 5' or 3' to the coding sequence, but is preferably located at a site 5' from the promoter.

[0139] Expression vectors used in eukaryotic host cells may also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from 3' to the translation termination codon, in untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA.

[0140] Construction of suitable vectors containing one or more of the above-listed components employs standard ligation techniques or PCR/recombination methods. Isolated plasmids or DNA fragments are cleaved, tailored, and re-ligated in the form desired to generate the plasmids required or via recombination methods. For analysis to confirm correct sequences in plasmids constructed, the ligation mixtures are used to transform host cells, and successful transformants selected by antibiotic resistance (e.g. ampicillin or Zeocin) where appropriate. Plasmids from the transformants are prepared, analyzed by restriction endonuclease digestion and/or sequenced.

[0141] As an alternative to restriction and ligation of fragments, recombination methods based on att sites and recombination enzymes may be used to insert DNA sequences into a vector. Such methods are described, for example, by Landy (1989) *Ann. Rev. Biochem.* 58:913-949; and are known to those of skill in the art. Such methods utilize intermolecular DNA recombination that is mediated by a mixture of lambda and *E. coli* -encoded recombination proteins. Recombination occurs between specific attachment (*att*) sites on the interacting DNA molecules. For a description of att sites see Weisberg and Landy (1983) Site-Specific Recombination in Phage Lambda, in *Lambda II*, Weisberg, ed.(Cold Spring Harbor, NY:Cold Spring Harbor Press), pp. 211-250. The DNA segments flanking the recombination sites are switched, such that after recombination, the *att* sites are hybrid sequences comprised of sequences donated by each parental vector. The recombination can occur between DNAs of any topology.

[0142] *Att* sites may be introduced into a sequence of interest by ligating the sequence of interest into an appropriate vector; generating a PCR product containing *att* B sites through the use of specific primers; generating a cDNA library cloned into an appropriate vector containing *att* sites; and the like.

[0143] *Folding*, as used herein, refers to the three-dimensional structure of polypeptides and proteins, where interactions between amino acid residues act to stabilize the structure. Proper folding is typically the arrangement of a polypeptide that results in optimal biological activity, and in the case of antibodies can conveniently be monitored by assays for activity, *e.g.* antigen binding.

[0144] The expression host may be further modified by the introduction of sequences encoding one or more enzymes that enhance folding and disulfide bond formation, *i.e.* foldases, chaperonins, *etc.* Such sequences may be constitutively or inducibly expressed in the yeast host cell, using vectors, markers, *etc.* as known in the art. Preferably the sequences, including transcriptional regulatory elements sufficient for the desired pattern of expression, are stably integrated in the yeast genome through a targeted methodology.

[0145] For example, the eukaryotic PDI is not only an efficient catalyst of protein cysteine oxidation and disulfide bond isomerization, but also exhibits chaperone activity. Co-expression of PDI can facilitate the production of active proteins having multiple disulfide bonds. Also of interest is the expression of BIP (immunoglobulin heavy chain binding protein); cyclophilin; and the like. In one embodiment of the invention, each of the haploid parental strains expresses a distinct folding enzyme, *e.g.* one strain may express BIP, and the other strain may express PDI or combinations thereof.

[0146] The terms "*desired protein*" or "*desired antibody*" are used interchangeably and refer generally to a parent antibody specific to a target, *i.e.*, CGRP, PACAP or a chimeric or humanized antibody or a binding portion thereof derived therefrom as described herein. The term "antibody" is intended to include any polypeptide chain-containing molecular structure with a specific shape that fits to and recognizes an epitope, where one or more non-covalent binding interactions stabilize the complex between the molecular structure and the epitope. The archetypal antibody molecule is the immunoglobulin, and in particular IgGs, from all sources, *e.g.* human, rodent, rabbit, cow, sheep, pig, dog, other mammals, chicken, other avians, *etc.*, are considered to be "antibodies. Numerous antibody coding sequences have been described; and others may be raised by methods well-known in the

art. Examples thereof include chimeric antibodies, human antibodies and other non-human mammalian antibodies, humanized antibodies, single chain antibodies (such as scFvs), camelbodies, nanobodies, IgNAR (single-chain antibodies derived from sharks), small-modular immunopharmaceuticals (SMIPs), and antibody fragments such as Fabs, Fab', F(ab')₂ and the like. See Streltsov VA, et al., Structure of a shark IgNAR antibody variable domain and modeling of an early-developmental isotype, *Protein Sci.* 2005 Nov;14(11):2901-9. Epub 2005 Sep 30; Greenberg AS, et al., A new antigen receptor gene family that undergoes rearrangement and extensive somatic diversification in sharks, *Nature*. 1995 Mar 9;374(6518):168-73; Nuttall SD, et al., Isolation of the new antigen receptor from wobbegong sharks, and use as a scaffold for the display of protein loop libraries, *Mol Immunol.* 2001 Aug;38(4):313-26; Hamers-Casterman C, et al., Naturally occurring antibodies devoid of light chains, *Nature*. 1993 Jun 3;363(6428):446-8; Gill DS, et al., Biopharmaceutical drug discovery using novel protein scaffolds, *Curr Opin Biotechnol.* 2006 Dec; 17(6):653-8. Epub 2006 Oct 19.

[0147] For example, antibodies or antigen binding fragments may be produced by genetic engineering. In this technique, as with other methods, antibody-producing cells are sensitized to the desired antigen or immunogen. The messenger RNA isolated from antibody producing cells is used as a template to make cDNA using PCR amplification. A library of vectors, each containing one heavy chain gene and one light chain gene retaining the initial antigen specificity, is produced by insertion of appropriate sections of the amplified immunoglobulin cDNA into the expression vectors. A combinatorial library is constructed by combining the heavy chain gene library with the light chain gene library. This results in a library of clones which co-express a heavy and light chain (resembling the Fab fragment or antigen binding fragment of an antibody molecule). The vectors that carry these genes are co-transfected into a host cell. When antibody gene synthesis is induced in the transfected host, the heavy and light chain proteins self-assemble to produce active antibodies that can be detected by screening with the antigen or immunogen.

[0148] Antibody coding sequences of interest include those encoded by native sequences, as well as nucleic acids that, by virtue of the degeneracy of the genetic code, are not identical in sequence to the disclosed nucleic acids, and variants thereof. Variant polypeptides can include amino acid (aa) substitutions, additions or deletions. The amino acid substitutions can be conservative amino acid substitutions or substitutions to eliminate

non-essential amino acids, such as to alter a glycosylation site, or to minimize misfolding by substitution or deletion of one or more cysteine residues that are not necessary for function. Variants can be designed so as to retain or have enhanced biological activity of a particular region of the protein (*e.g.*, a functional domain, catalytic amino acid residues, *etc.*). Variants also include fragments of the polypeptides disclosed herein, particularly biologically active fragments and/or fragments corresponding to functional domains. Techniques for *in vitro* mutagenesis of cloned genes are known. Also included in the subject invention are polypeptides that have been modified using ordinary molecular biological techniques so as to improve their resistance to proteolytic degradation or to optimize solubility properties or to render them more suitable as a therapeutic agent.

[0149] Chimeric antibodies may be made by recombinant means by combining the variable light and heavy chain regions (V_L and V_H), obtained from antibody producing cells of one species with the constant light and heavy chain regions from another. Typically chimeric antibodies utilize rodent or rabbit variable regions and human constant regions, in order to produce an antibody with predominantly human domains. The production of such chimeric antibodies is well known in the art, and may be achieved by standard means (as described, *e.g.*, in U.S. Patent No. 5,624,659, incorporated herein by reference in its entirety). It is further contemplated that the human constant regions of chimeric antibodies of the invention may be selected from IgG1, IgG2, IgG3, and IgG4 constant regions.

[0150] Humanized antibodies are engineered to contain even more human-like immunoglobulin domains, and incorporate only the complementarity-determining regions of the animal-derived antibody. This is accomplished by carefully examining the sequence of the hyper-variable loops of the variable regions of the monoclonal antibody, and fitting them to the structure of the human antibody chains. Although facially complex, the process is straightforward in practice. *See, e.g.*, U.S. Patent No. 6,187,287, incorporated fully herein by reference.

[0151] In addition to entire immunoglobulins (or their recombinant counterparts), immunoglobulin fragments comprising the epitope binding site (*e.g.*, Fab', F(ab')₂, or other fragments) may be synthesized. "Fragment," or minimal immunoglobulins may be designed utilizing recombinant immunoglobulin techniques. For instance "Fv" immunoglobulins for use in the present invention may be produced by synthesizing a fused variable light chain region and a variable heavy chain region. Combinations of antibodies are also of interest,

e.g. diabodies, which comprise two distinct Fv specificities. In another embodiment of the invention, SMIPs (small molecule immunopharmaceuticals), camelbodies, nanobodies, and IgNAR are encompassed by immunoglobulin fragments.

[0152] Immunoglobulins and fragments thereof may be modified post-translationally, *e.g.* to add effector moieties such as chemical linkers, detectable moieties, such as fluorescent dyes, enzymes, toxins, substrates, bioluminescent materials, radioactive materials, chemiluminescent moieties and the like, or specific binding moieties, such as streptavidin, avidin, or biotin, and the like may be utilized in the methods and compositions of the present invention. Examples of additional effector molecules are provided *infra*.

[0153] A polynucleotide sequence "corresponds" to a polypeptide sequence if translation of the polynucleotide sequence in accordance with the genetic code yields the polypeptide sequence (*i.e.*, the polynucleotide sequence "encodes" the polypeptide sequence), one polynucleotide sequence "corresponds" to another polynucleotide sequence if the two sequences encode the same polypeptide sequence.

[0154] A "heterologous" region or domain of a DNA construct is an identifiable segment of DNA within a larger DNA molecule that is not found in association with the larger molecule in nature. Thus, when the heterologous region encodes a mammalian gene, the gene will usually be flanked by DNA that does not flank the mammalian genomic DNA in the genome of the source organism. Another example of a heterologous region is a construct where the coding sequence itself is not found in nature (*e.g.*, a cDNA where the genomic coding sequence contains introns, or synthetic sequences having codons different than the native gene). Allelic variations or naturally-occurring mutational events do not give rise to a heterologous region of DNA as defined herein.

[0155] A "coding sequence" is an in-frame sequence of codons that (in view of the genetic code) correspond to or encode a protein or peptide sequence. Two coding sequences correspond to each other if the sequences or their complementary sequences encode the same amino acid sequences. A coding sequence in association with appropriate regulatory sequences may be transcribed and translated into a polypeptide. A polyadenylation signal and transcription termination sequence will usually be located 3' to the coding sequence. A "promoter sequence" is a DNA regulatory region capable of binding RNA polymerase in a cell and initiating transcription of a downstream (3' direction) coding sequence. Promoter sequences typically contain additional sites for binding of regulatory

molecules (*e.g.*, transcription factors) which affect the transcription of the coding sequence. A coding sequence is "under the control" of the promoter sequence or "operatively linked" to the promoter when RNA polymerase binds the promoter sequence in a cell and transcribes the coding sequence into mRNA, which is then in turn translated into the protein encoded by the coding sequence.

[0156] Vectors are used to introduce a foreign substance, such as DNA, RNA or protein, into an organism or host cell. Typical vectors include recombinant viruses (for polynucleotides) and liposomes (for polypeptides). A "DNA vector" is a replicon, such as plasmid, phage or cosmid, to which another polynucleotide segment may be attached so as to bring about the replication of the attached segment. An "expression vector" is a DNA vector which contains regulatory sequences which will direct polypeptide synthesis by an appropriate host cell. This usually means a promoter to bind RNA polymerase and initiate transcription of mRNA, as well as ribosome binding sites and initiation signals to direct translation of the mRNA into a polypeptide(s). Incorporation of a polynucleotide sequence into an expression vector at the proper site and in correct reading frame, followed by transformation of an appropriate host cell by the vector, enables the production of a polypeptide encoded by said polynucleotide sequence.

[0157] "Amplification" of polynucleotide sequences is the *in vitro* production of multiple copies of a particular nucleic acid sequence. The amplified sequence is usually in the form of DNA. A variety of techniques for carrying out such amplification are described in a review article by Van Brunt (1990, *Bio/Technol.*, 8(4):291-294). Polymerase chain reaction or PCR is a prototype of nucleic acid amplification, and use of PCR herein should be considered exemplary of other suitable amplification techniques.

[0158] The general structure of antibodies in vertebrates now is well understood (Edelman, G. M., *Ann. N.Y. Acad. Sci.*, 190: 5 (1971)). Antibodies consist of two identical light polypeptide chains of molecular weight approximately 23,000 Daltons (the "light chain"), and two identical heavy chains of molecular weight 53,000-70,000 (the "heavy chain"). The four chains are joined by disulfide bonds in a "Y" configuration wherein the light chains bracket the heavy chains starting at the mouth of the "Y" configuration. The "branch" portion of the "Y" configuration is designated the F_{ab} region; the stem portion of the "Y" configuration is designated the F_c region. The amino acid sequence orientation runs from the N-terminal end at the top of the "Y" configuration to the C-terminal end at the bottom

of each chain. The N-terminal end possesses the variable region having specificity for the antigen that elicited it, and is approximately 100 amino acids in length, there being slight variations between light and heavy chain and from antibody to antibody.

[0159] The variable region is linked in each chain to a constant region that extends the remaining length of the chain and that within a particular class of antibody does not vary with the specificity of the antibody (*i.e.*, the antigen eliciting it). There are five known major classes of constant regions that determine the class of the immunoglobulin molecule (IgG, IgM, IgA, IgD, and IgE corresponding to γ , μ , α , δ , and ϵ (gamma, mu, alpha, delta, or epsilon) heavy chain constant regions). The constant region or class determines subsequent effector function of the antibody, including activation of complement (Kabat, E. A., *Structural Concepts in Immunology and Immunochemistry*, 2nd Ed., p. 413-436, Holt, Rinehart, Winston (1976)), and other cellular responses (Andrews, D. W., *et al.*, *Clinical Immunobiology*, pp 1-18, W. B. Sanders (1980); Kohl, S., *et al.*, *Immunology*, 48: 187 (1983)); while the variable region determines the antigen with which it will react. Light chains are classified as either κ (kappa) or λ (lambda). Each heavy chain class can be prepared with either kappa or lambda light chain. The light and heavy chains are covalently bonded to each other, and the "tail" portions of the two heavy chains are bonded to each other by covalent disulfide linkages when the immunoglobulins are generated either by hybridomas or by B cells.

[0160] The expression "variable region" or "VR" refers to the domains within each pair of light and heavy chains in an antibody that are involved directly in binding the antibody to the antigen. Each heavy chain has at one end a variable domain (V_H) followed by a number of constant domains. Each light chain has a variable domain (V_L) at one end and a constant domain at its other end; the constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[0161] The expressions "complementarity determining region," "hypervariable region," or "CDR" refer to one or more of the hyper-variable or complementarity determining regions (CDRs) found in the variable regions of light or heavy chains of an antibody (See Kabat, E. A. *et al.*, *Sequences of Proteins of Immunological Interest*, National Institutes of Health, Bethesda, Md., (1987)). These expressions include the hypervariable regions as defined by Kabat *et al.* ("Sequences of Proteins of Immunological Interest," Kabat E., *et al.*,

US Dept. of Health and Human Services, 1983) or the hypervariable loops in 3-dimensional structures of antibodies (Chothia and Lesk, *J Mol. Biol.* 196 901-917 (1987)). The CDRs in each chain are held in close proximity by framework regions and, with the CDRs from the other chain, contribute to the formation of the antigen binding site. Within the CDRs there are select amino acids that have been described as the selectivity determining regions (SDRs) which represent the critical contact residues used by the CDR in the antibody-antigen interaction (Kashmiri, S., *Methods*, 36:25-34 (2005)). In the present invention when specific antibody amino acid or nucleic acid residues are referenced by number this generally refers to its position within a specified amino acid or nucleic acid sequence (*i.e.*, particular sequence identifier) and/or in accordance with Kabat *et al* numbering.

[0162] The expressions “framework region” or “FR” refer to one or more of the framework regions within the variable regions of the light and heavy chains of an antibody (See Kabat, E. A. *et al.*, Sequences of Proteins of Immunological Interest, National Institutes of Health, Bethesda, Md., (1987)). These expressions include those amino acid sequence regions interposed between the CDRs within the variable regions of the light and heavy chains of an antibody.

[0163] “C_{max}” refers to the maximum (or peak) concentration that an antibody or other compound achieves in tested area (*e.g.*, in the serum or another compartment such as cerebrospinal fluid) after the drug has been administered. For example, serum C_{max} may be measured from serum, *e.g.*, prepared by collecting a blood sample, allowing it to clot and separating solid components by centrifugation or other means to yield serum (blood containing neither blood cells nor clotting factors), and then detecting the concentration of the analyte in the serum by ELISA or other means known in the art.

[0164] “AUC” refers to the area under the concentration-time curve which is expressed in units of mg/mL * hr (or equivalently mg*hr/ml) unless otherwise specified. “AUC_{0-t}” refers to the area under the concentration-time curve from time=0 to last quantifiable concentration. “AUC_{0-inf}” refers to the area under the concentration-time curve from time=0 extrapolated to infinity.

[0165] “I_{max}” refers to the maximal pharmacodynamic response elicited by an anti-CGRP antibody dosage, preferably a dosage of 350 mg or more, more typically at least 750 or 1000 mg, as compared to the response elicited by a lower anti-CGRP antibody doses, *e.g.*, wherein such response may be detected by the inhibition of vasodilation after topical

application of capsaicin.

[0166] Antibody Ab6 (Eptinezumab) sequence

[0167] Antibody Ab6 (Eptinezumab) contains a variable light chain sequence as set forth below:

QVLTQSPSSLSASVGDRVINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTLASGVPSRFSGSGSGT
DFTLTISLQPEDVATYYCLGSYDCTNGDCVFVGGGTKVEIKR (SEQ ID NO.: 10).

[0168] Antibody Ab6 (Eptinezumab) contains a light chain sequence as set forth below:

QVLTQSPSSLSASVGDRVINCQASQSVYHNTYLAWYQQKPGKVPKQLIYDASTLASGVPSRFSGSGSGT
DFTLTISLQPEDVATYYCLGSYDCTNGDCVFVGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLN
NFYPREAKVQWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTK
SFNRGEC (SEQ ID NO.: 11).

[0169] Antibody Ab6 (Eptinezumab) contains a variable heavy chain as set forth below:

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYIMNWVRQAPGKGLEWVGIVIGINGATYYASWAKGRF
TISRDNSTTVYLQMNSLR AEDTAVYFCARGDIWGQGT LVT VSS (SEQ ID NO.: 4).

[0170] Antibody Ab6 (Eptinezumab) contains a heavy chain sequence as set forth below:

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYIMNWVRQAPGKGLEWVGIVIGINGATYYASWAKGRF
TISRDNSTTVYLQMNSLR AEDTAVYFCARGDIWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALG
CLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTPSSSLGTQTYICNVNHKPSNTKVDAR
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
SCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO.: 6)

[0171] Alternatively, the heavy chain of Ab6 (Eptinezumab) may lack the C-terminal

lysine, *i.e.*, a heavy chain sequence comprising the sequence set forth below:

EVQLVESGGGLVQPGGSLRLSCAVSGIDLSGYIMNWVRQAPGKGLEWVGIVIGINGATYYASWAKGRF
TISRDNSTTVYLQMNSLR AEDTAVYFCARGDIWGQGT LVT VSSASTKGPSVFPLAPSSKSTSGGTAALG
CLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSV VTPSSSLGTQTYICNVNHKPSNTKVDAR
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV
HNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNV
SCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO.: 5).

[0172] In one embodiment of the invention described herein (*infra*), Fab fragments may

be produced by enzymatic digestion (*e.g.*, papain) of Ab6. In another embodiment of the invention, Ab6 or Fab fragments thereof may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

[0173] The CDR regions of Ab6 (Eptinezumab) are as outlined below

[0174] Light Chain CDR 1 QASQSVYHNTYLA (SEQ ID NO.: 7)

[0175] Light Chain CDR 2 DASTLAS (SEQ ID NO.: 8)

[0176] Light Chain CDR 3 LGSYDCTNGDCFV (SEQ ID NO.: 9)

[0177] Heavy Chain CDR 1 GYYMN (SEQ ID NO.: 1)

[0178] Heavy Chain CDR 2 VIGINGATYYASWAKG (SEQ ID NO.: 2)

[0179] Heavy Chain CDR 3 GDI (SEQ ID NO.: 3)

Antibody LuAG09222

[0180] LuAG09222 contains a variable heavy chain sequence as set forth below:

[0181] EVQLVESGGGLVQPGGSLRLSCAASGIDLSYMTWVRQAPGKGLEWIGFIDAGGDAYYA
SWAKGRFTISRDNKNTVYLQMNSLRAEDTAVYFCARDLDLWGQGTLLTVSS (SEQ ID NO.: 15)

[0182] LuAG09222 contains a heavy chain sequence set forth below:

[0183] EVQLVESGGGLVQPGGSLRLSCAASGIDLSYMTWVRQAPGKGLEWIGFIDAGGDAYYA
SWAKGRFTISRDNKNTVYLQMNSLRAEDTAVYFCARDLDLWGQGTLLTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHK
PSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE
PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO.: 16).

[0184] According to some aspect of the invention LuAG09222 may have a terminal lysine in the heavy chain as set forth below

[0185] EVQLVESGGGLVQPGGSLRLSCAASGIDLSYMTWVRQAPGKGLEWIGFIDAGGDAYYA
SWAKGRFTISRDNKNTVYLQMNSLRAEDTAVYFCARDLDLWGQGTLLTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHK
PSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE

PQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO.: 26)

[0186] LuAG09222 contains a variable light chain sequence comprising the sequence set forth below:

[0187] DIQLTQSPSTLSASVGDRVTITCQSSSESVYGNYLAWFQQKPGKAPKFLIYEASKLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCAGGDISEGVAFGGGTKVEIKR (SEQ ID NO.:20).

[0188] LuAG09222 contains a light chain sequence comprising the sequence set forth below:

[0189] DIQLTQSPSTLSASVGDRVTITCQSSSESVYGNYLAWFQQKPGKAPKFLIYEASKLESGVPSRFSGSGSGTEFTLTISSLQPDDFATYYCAGGDISEGVAFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNFPYPREAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO.:21).

[0190] In one embodiment of the invention described herein (infra), Fab fragments may be produced by enzymatic digestion (*e.g.*, papain) of Ab10.H3. In another embodiment of the invention, LuAG09222 may be produced via expression in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or microbial systems such as yeast cells (for example diploid yeast such as diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

[0191] The CDR regions of LuAG09222 are as outlined below

[0192] Light Chain CDR 1 QSSSESVYGNYL (SEQ ID NO.: 17)

[0193] Light Chain CDR 2 EASKLES (SEQ ID NO.: 18)

[0194] Light Chain CDR 3 AGGDISEGVA (SEQ ID NO.: 19)

[0195] Heavy Chain CDR 1 SYMT (SEQ ID NO.: 12)

[0196] Heavy Chain CDR 2 FIDAGGDAYYASWAKG (SEQ ID NO.:13)

[0197] Heavy Chain CDR 3 DLDL (SEQ ID NO.: 14)

[0198] As stated herein, antibodies and fragments thereof may be modified post-translationally to add effector moieties such as chemical linkers, detectable moieties such as for example fluorescent dyes, enzymes, substrates, bioluminescent materials, radioactive materials, and chemiluminescent moieties, or functional moieties such as for example streptavidin, avidin, biotin, a cytotoxin, a cytotoxic agent, and radioactive materials.

[0199] Antibodies or fragments thereof may also be chemically modified to provide

additional advantages such as increased solubility, stability and circulating time (*in vivo* half-life) of the polypeptide, or decreased immunogenicity (See U.S. Pat. No. 4,179,337). The chemical moieties for derivatization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The antibodies and fragments thereof may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0200] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (*e.g.*, the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500, 14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa. Branched polyethylene glycols are described, for example, in U.S. Pat. No. 5,643,575; Morpurgo et al., *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev et al., *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti et al., *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[0201] There are a number of attachment methods available to those skilled in the art, See *e.g.*, EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), See also Malik et al., *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino

acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0202] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to polypeptides via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (*e.g.*, lysine, histidine, aspartic acid, glutamic acid, or cysteine) or to more than one type of amino acid residue (*e.g.*, lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof).

[0203] Alternatively, antibodies or fragments thereof may have increased *in vivo* half-lives via fusion with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (See, *e.g.*, U.S. Pat. No. 5,876,969, issued Mar. 2, 1999, EP Patent 0 413 622, and U.S. Pat. No. 5,766,883, issued Jun. 16, 1998, herein incorporated by reference in their entirety)) or other circulating blood proteins such as transferrin or ferritin. In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (*i.e.*, amino acids 1-585 of human serum albumin as shown in FIGS. 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

[0204] Regarding detectable moieties, further exemplary enzymes include, but are not limited to, horseradish peroxidase, acetylcholinesterase, alkaline phosphatase, beta-galactosidase and luciferase. Further exemplary fluorescent materials include, but are not limited to, rhodamine, fluorescein, fluorescein isothiocyanate, umbelliferone, dichlorotriazinylamine, phycoerythrin and dansyl chloride. Further exemplary chemiluminescent moieties include, but are not limited to, luminol. Further exemplary bioluminescent materials include, but are not limited to, luciferin and aequorin. Further exemplary radioactive materials include, but are not limited to, Iodine 125 (¹²⁵I), Carbon 14 (¹⁴C), Sulfur 35 (³⁵S), Tritium (³H) and Phosphorus 32 (³²P).

[0205] Regarding functional moieties, exemplary cytotoxic agents include, but are not limited to, methotrexate, aminopterin, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine; alkylating agents such as mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU), mitomycin C, lomustine (CCNU), 1-methylnitrosourea, cyclophosphamide, mechlorethamine, busulfan, dibromomannitol, streptozotocin, mitomycin C, cis-dichlorodiamine platinum (II) (DDP) cisplatin and carboplatin (paraplatin); anthracyclines include daunorubicin (formerly daunomycin), doxorubicin (adriamycin), detorubicin, carminomycin, idarubicin, epirubicin, mitoxantrone and bisantrene; antibiotics include dactinomycin (actinomycin D), bleomycin, calicheamicin, mithramycin, and anthramycin (AMC); and antimetabolic agents such as the vinca alkaloids, vincristine and vinblastine. Other cytotoxic agents include paclitaxel (taxol), ricin, *Pseudomonas* exotoxin, gemcitabine, cytochalasin B, gramicidin D, ethidium bromide, emetine, etoposide, teniposide, colchicine, dihydroxy anthracin dione, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, puromycin, procarbazine, hydroxyurea, asparaginase, corticosteroids, mytostane (O,P'-(DDD)), interferons, and mixtures of these cytotoxic agents.

[0206] Further cytotoxic agents include, but are not limited to, chemotherapeutic agents such as carboplatin, cisplatin, paclitaxel, gemcitabine, calicheamicin, doxorubicin, 5-fluorouracil, mitomycin C, actinomycin D, cyclophosphamide, vincristine and bleomycin. Toxic enzymes from plants and bacteria such as ricin, diphtheria toxin and *Pseudomonas* toxin may be conjugated to the humanized or chimeric antibodies, or binding fragments thereof, to generate cell-type-specific-killing reagents (Youle, et al., *Proc. Nat'l Acad. Sci. USA* 77:5483 (1980); Gilliland, et al., *Proc. Nat'l Acad. Sci. USA* 77:4539 (1980); Krolick, et al., *Proc. Nat'l Acad. Sci. USA* 77:5419 (1980)).

[0207] Other cytotoxic agents include cytotoxic ribonucleases as described by Goldenberg in U.S. Pat. No. 6,653,104. Embodiments of the invention also relate to radioimmunoconjugates where a radionuclide that emits alpha or beta particles is stably coupled to the antibody, or binding fragments thereof, with or without the use of a complex-forming agent. Such radionuclides include beta-emitters such as Phosphorus-32 (³²P), Scandium-47 (⁴⁷Sc), Copper-67 (⁶⁷Cu), Gallium-67 (⁶⁷Ga), Yttrium-88 (⁸⁸Y), Yttrium-90 (⁹⁰Y), Iodine-125 (¹²⁵I), Iodine-131 (¹³¹I), Samarium-153 (¹⁵³Sm), Lutetium-177 (¹⁷⁷Lu), Rhenium-186 (¹⁸⁶Re) or Rhenium-188 (¹⁸⁸Re), and alpha-emitters such as Astatine-211

(²¹¹At), Lead-212 (²¹²Pb), Bismuth-212 (²¹²Bi) or -213 (²¹³Bi) or Actinium-225 (²²⁵Ac).

[0208] Methods are known in the art for conjugating an antibody or binding fragment thereof to a detectable moiety and the like, such as for example those methods described by Hunter et al, *Nature* 144:945 (1962); David et al, *Biochemistry* 13:1014 (1974); Pain et al, *J. Immunol. Meth.* 40:219 (1981); and Nygren, J., *Histochem. and Cytochem.* 30:407 (1982).

[0209] Embodiments described herein further include variants and equivalents that are substantially homologous to the antibodies, antibody fragments, diabodies, SMIPs, camelbodies, nanobodies, IgNAR, polypeptides, variable regions and CDRs set forth herein. These may contain, *e.g.*, conservative substitution mutations, (*i.e.*, the substitution of one or more amino acids by similar amino acids). For example, conservative substitution refers to the substitution of an amino acid with another within the same general class, *e.g.*, one acidic amino acid with another acidic amino acid, one basic amino acid with another basic amino acid, or one neutral amino acid by another neutral amino acid. What is intended by a conservative amino acid substitution is well known in the art.

[0210] In another embodiment, the invention contemplates polypeptide sequences having at least 90% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. More preferably, the invention contemplates polypeptide sequences having at least 95% or greater sequence homology, even more preferably at least 98% or greater sequence homology, and still more preferably at least 99% or greater sequence homology to any one or more of the polypeptide sequences of antibody fragments, variable regions and CDRs set forth herein. Methods for determining homology between nucleic acid and amino acid sequences are well known to those of ordinary skill in the art.

[0211] Another embodiment of the invention contemplates these polynucleotides incorporated into an expression vector for expression in mammalian cells such as CHO, NSO, HEK-293, or in fungal, insect, or microbial systems such as yeast cells such as the yeast *Pichia*. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*. In one embodiment of the invention described herein (*infra*), Fab fragments may be produced by enzymatic digestion (*e.g.*, papain) of Ab6 following expression of the full-length polynucleotides in a suitable host. In another embodiment of the invention, anti-CGRP antibodies such as Ab6 or Fab fragments thereof may be produced via expression of Ab6 polynucleotides in mammalian cells such as CHO, NSO or HEK 293 cells, fungal, insect, or

microbial systems such as yeast cells (for example diploid yeast such as diploid *Pichia*) and other yeast strains. Suitable *Pichia* species include, but are not limited to, *Pichia pastoris*.

[0212] Host cells and vectors comprising said polynucleotides are also contemplated.

[0213] The invention further contemplates vectors comprising the polynucleotide sequences encoding the variable heavy and light chain polypeptide sequences, as well as the individual complementarity-determining regions (CDRs, or hypervariable regions), as set forth herein, as well as host cells comprising said vector sequences. In one embodiment of the invention, the host cell is a yeast cell. In another embodiment of the invention, the yeast host cell belongs to the genus *Pichia*.

[0214] Methods of Producing Antibodies and Fragments thereof

[0215] In another embodiment, the present invention contemplates methods for producing anti-CGRP antibodies and fragments thereof. Methods for producing antibodies and fragments thereof secreted from polyploid, preferably diploid or tetraploid strains of mating competent yeast are taught, for example, in U.S. patent application publication no. US 2009/0022659 to Olson et al., and in U.S. patent no. 7,935,340 to Garcia-Martinez et al., the disclosures of each of which are herein incorporated by reference in their entireties. Methods for producing antibodies and fragments thereof in mammalian cells, *e.g.*, CHO cells are further well known in the art.

[0216] Other methods of producing antibodies are also well known to those of ordinary skill in the art. For example, methods of producing chimeric antibodies are now well known in the art (*See*, for example, U.S. Patent No. 4,816,567 to Cabilly et al.; Morrison et al., *P.N.A.S. USA*, 81:8651-55 (1984); Neuberger, M.S. et al., *Nature*, 314:268-270 (1985); Boulianne, G.L. et al., *Nature*, 312:643-46 (1984), the disclosures of each of which are herein incorporated by reference in their entireties).

[0217] Likewise, other methods of producing humanized antibodies are now well known in the art (*See*, for example, U.S. Patent Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370 to Queen et al; U.S. Patent Nos. 5,225,539 and 6,548,640 to Winter; U.S. Patent Nos. 6,054,297, 6,407,213 and 6,639,055 to Carter et al; U.S. Patent No. 6,632,927 to Adair; Jones, P.T. et al, *Nature*, 321:522-525 (1986); Reichmann, L., et al, *Nature*, 332:323-327 (1988); Verhoeven, M, et al, *Science*, 239:1534-36 (1988), the disclosures of each of which are herein incorporated by reference in their entireties).

[0218] Administration

[0219] A “pharmaceutical composition” refers to a chemical or biological composition suitable for administration to a mammal. Such compositions may be specifically formulated for administration via one or more of a number of routes, including but not limited to intravenous or subcutaneous. The administration may be every 2 weeks, once monthly (every 4 weeks), every second month or every third month.

[0220] A “pharmaceutical excipient” or a “pharmaceutically acceptable excipient” is a carrier, usually a liquid, in which an active therapeutic agent is formulated. In one embodiment of the invention, the active therapeutic agent is a humanized antibody described herein, or one or more fragments thereof. The excipient generally does not provide any pharmacological activity to the formulation, though it may provide chemical and/or biological stability, and release characteristics. Exemplary formulations can be found, for example, in Remington’s Pharmaceutical Sciences, 19th Ed., Grennaro, A., Ed., 1995 which is incorporated by reference.

[0221] As used herein “pharmaceutically acceptable carrier” or “excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one embodiment, the carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, or sublingual administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0222] Pharmaceutical compositions typically must be sterile and stable under the conditions of manufacture and storage. The invention contemplates that the pharmaceutical composition is present in lyophilized form. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The invention further contemplates the

inclusion of a stabilizer in the pharmaceutical composition. The proper fluidity can be maintained, for example, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

[0223] In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the alkaline polypeptide can be formulated in a time release formulation, for example in a composition which includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

[0224] **According to the invention LuAG09222 and Eptinezumab may be co-formulated according to the following embodiments.**

[0225] Unless otherwise described in the following embodiments the total amount of Eptinezumab and LuAG09222 is between 100 mg/mL and 300 mg/mL in the pharmaceutical formulations (optionally about. 100 mg/mL, 150 mg/mL, 200 mg/mL, 250 mg/mL or 300 mg/mL) wherein the ratio of Eptinezumab and LuAG09222 may be varied. In one embodiment the ratio of Eptinezumab and LuAG09222 are 1:1, 1:2 and 2:1, meaning that a ratio of e.g., 1:1 in a 100 mg/mL pharmaceutical formulation will contain 50 mg/mL Eptinezumab and 50 mg/mL LuAG09222. Below is given embodiments of pharmaceutical compositions according to the invention.

[0226] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio selected from 2:1, 1:1 or 1:2 and further comprises 20-40 mM histidine buffer, 90-180 mM sorbitol, Poloxamer P188

0.0025-0.0120% w/v and 30-70 mM NaCl, and has a pH about 6 (optionally between pH 5.5 and 6.4, optionally pH 5.9).

[0227] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio 2:1 and comprising 25-35 mM histidine buffer, 165-175 mM sorbitol, Poloxamer P188 0.0025-0.010% w/v and 25-35 mM NaCl, and has a pH about 6 (optionally pH 5.9).

[0228] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio 2:1 and comprising 30 mM histidine buffer, 169 mM sorbitol, Poloxamer P188 0.005% w/v and 30 mM NaCl, and has a pH about 6 (optionally pH 5.9). The total combined protein concentration of Eptinezumab and LuAG90222 in the composition may be 113 mg/mL.

[0229] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio 2:1 and comprising 30-50 mM histidine buffer, 80-150 mM sorbitol, L-arginine hydrochloride 150-250 mM and Poloxamer P188 0.02 % w/v, and has a pH about 6 (optionally pH 6.125). The total combined protein concentration of Eptinezumab and LuAG90222 in the composition may be 140-150 mg/mL.

[0230] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio 2:1 and comprising 30 mM histidine buffer, 80 mM sorbitol, 150 mM L-arginine hydrochloride and Poloxamer P188 0.02 % w/v, and has a pH about 6 (optionally pH 6.125)). The total combined protein concentration of Eptinezumab and LuAG90222 may be about 150 mg/mL.

[0231] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio 2:1 and comprising 50 mM histidine buffer, 150 mM sorbitol, L-arginine hydrochloride 250 mM and Poloxamer P188 0.02 %, and has a pH about 6 (optionally pH 6.125). The total combined protein concentration of Eptinezumab and LuAG90222 may be about 145 mg/mL.

[0232] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio 1:1 and comprising 30-40 mM histidine buffer, 130-140 mM sorbitol, Poloxamer P188 0.005-0.010% w/v and 45-55 mM NaCl, and has a pH about 6 (optionally pH 5.9).

[0233] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio 1:1 and comprising 34 mM histidine buffer, 135 mM sorbitol, Poloxamer P188 0.008% w/v and 48 mM NaCl, and has a pH about 6 (optionally pH 5.9). The total protein concentration of Eptinezumab and LuAG09222 may be 120 mg/mL

[0234] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio 1:1 and comprising 30 mM histidine buffer, 80 mM sorbitol, L-arginine 150 mM and Poloxamer P188 0.02 % w/v, and has a pH about 6 (optionally pH 6.125). The total protein concentration of Eptinezumab and LuAG09222 may be about 130 mg/mL.

[0235] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio 1:1 and comprising 10 mM histidine buffer, 10 mM sorbitol, L-arginine hydrochloride 50 mM and Poloxamer P188 0.02 % w/v, and has a pH about 6 (optionally pH 6.125). The total protein concentration of Eptinezumab and LuAG09222 may be about 140 mg/mL

[0236] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio 1:2 and comprising 35-45 mM histidine buffer, 90-100 mM sorbitol, Poloxamer P188 0.010-0.0120 % w/v and 65-75 mM NaCl, and has a pH about 6 (optionally pH 5.9).

[0237] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio 1:2 and comprising 38 mM histidine buffer, 96 mM sorbitol, Poloxamer P188 0.0114% w/v and 69 mM NaCl, and has a

pH about 6 (optionally pH 5.9). The total protein concentration of Eptinezumab and LuAG09222 may be 129 mg/mL.

[0238] In the above-mentioned embodiments arginine (optionally L-arginine) may be added at a concentration of 10-150 mM, optionally 10 mM, 50 mM, 80 mM, 100 mM or 120 mM or 150 mM.

[0239] Further, an embodiment including arginine, the pharmaceutical formulations may comprise Eptinezumab and LuAG90222 in a ratio selected from 1:2, 1:1 or 2:1 and further comprises 30-50 mM histidine buffer, 50-250 mM sorbitol and 10-150 mM NaCl, Poloxamer 188 0.005-0.05% w/v, 10-150 mM L-arginine hydrochloride and a pH about 6 (optionally pH 5.9).

[0240] In another embodiment, the pharmaceutical formulations may comprise Eptinezumab and LuAG90222 in a selected from 1:2, 1:1 or 2:1 and comprising 30-50 mM histidine buffer, 150-250 mM sorbitol and 80-150 mM NaCl, 0.005-0,05% w/v Poloxamer P188, 80-150 mM L-arginine hydrochloride and has a pH about 6 (optionally pH 5.9). The total protein concentration of Eptinezumab and LuAG09222 may be between 125-150 mg/mL.

[0241] In another embodiment, the pharmaceutical formulations may comprise Eptinezumab and LuAG90222 in a ratio of 1:2 and comprising 10-50 mM histidine buffer, 50-250 mM sorbitol and 10 -150 mM NaCl, 0.005-0,05% w/v Poloxamer P188, 10-150 mM L-arginine hydrochloride and has a pH about 6 (optionally pH 5.9). The total protein concentration of Eptinezumab and LuAG09222 may be between 100-150 mg/mL.

[0242] In another embodiment, the pharmaceutical formulations may comprise Eptinezumab and LuAG90222 in a ratio selected from 1:2, 2:1 and 1:1 and comprising 10-50 mM histidine buffer, 50-250 mM sorbitol and 10 -150 mM NaCl, 0.005-0,05% w/v Poloxamer P188, 10-150 mM L-arginine hydrochloride and has a pH about 7 (optionally pH 6.75) or about 5 (optionally about 5.25). The total protein concentration of Eptinezumab and LuAG09222 may be between 100-125 mg/mL.

[0243] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio selected from 1:1, 1:2 or 2:1 and comprises 10-50 mM histidine buffer, 10-150 mM sorbitol, L-arginine hydrochloride 50-250 mM and Poloxamer P188 0.02 % w/v, and has a pH about 5 (optionally pH 5.5). The total protein concentration of Eptinezumab and LuAG09222 may be between 140-155 mg/mL (optionally 140 mg/mL, 145 mg/mL, 150 mg/mL or 155 mg/mL).

[0244] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio selected from 1:1, 1:2 or 2:1 and comprises 10-50 mM histidine buffer, 10-150 mM sorbitol, L-arginine hydrochloride 50-250 mM and Poloxamer P188 0.02 % w/v, and has a pH about 5 (optionally pH 5.5). The total protein concentration of Eptinezumab and LuAG09222 may be between 140-155 mg/mL (optionally 140 mg/mL, 145 mg/mL, 150 mg/mL or 155 mg/mL).

[0245] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio selected from 1:1, 1:2 or 2:1 and comprises 10-50 mM histidine buffer, 10-150 mM sorbitol, L-arginine hydrochloride 50-250 mM and Poloxamer P188 0.02 % w/v, and has a pH about 5 (optionally pH 5.5). The total protein concentration of Eptinezumab and LuAG09222 may be between 140-155 mg/mL (optionally 140 mg/mL, 145 mg/mL, 150 mg/mL or 155 mg/mL).

[0246] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio selected from 1:1, 1:2 or 2:1 and comprises 10-50 mM histidine buffer, 10-150 mM sorbitol, L-arginine hydrochloride 50-250 mM and Poloxamer P188 0.02 % w/v, and has a pH about 7 (optionally pH 6.75). The total protein concentration of Eptinezumab and LuAG09222 may be between 140-160 mg/mL (optionally 140 mg/mL, 145 mg/mL, 150 mg/mL, 155 mg/mL or 160 mg/mL).

[0247] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG90222 in a ratio selected from 1:1 or 1:2 and comprising 10-50 mM histidine buffer, 10-150 mM sorbitol, L-arginine hydrochloride 50-250

mM and Poloxamer P188 0.02 % w/v, and has a pH about 7 (optionally pH 6.75). The total protein concentration of Eptinezumab and LuAG09222 may be between 140-160 mg/mL (optionally 140 mg/mL, 145 mg/mL, 150 mg/mL, 155 mg/mL or 160 mg/mL).

[0248] According to one embodiment the invention relates to a pharmaceutical composition comprising Eptinezumab and LuAG09222 in a ratio 2:1 and comprising 30-50 mM histidine buffer, 80-150 mM sorbitol, L-arginine hydrochloride 50-250 mM and Poloxamer P188 0.02 % w/v, and has a pH about 7 (optionally pH 6.75). The total protein concentration of Eptinezumab and LuAG09222 may be between 140-160 mg/mL (optionally 140 mg/mL, 145 mg/mL, 150 mg/mL, 155 mg/mL).

[0249] FURTHER EXEMPLARY EMBODIMENTS

[0250] Embodiment 1 (E1) A composition comprising Eptinezumab and LuAG09222.

[0251] E2. The composition of E1 further comprising histidine and either Poloxamer 188 or polysorbate 80.

[0252] E3. The composition of E1 and E2 further comprising one, two or all of the following excipients NaCl, sorbitol (e.g. L-sorbitol) and arginine (e.g. L-arginine).

[0253] E4. The pharmaceutical composition according to any of the previous Embodiments, which comprises a total concentration of Eptinezumab and LuAG09222 of 100 mg/mL to 300 mg/mL.

[0254] E5. The pharmaceutical composition according to any of the previous Embodiments which comprises a total concentration of Eptinezumab and LuAG09222 of 100 mg/mL, 150 mg/mL, 200 mg/mL 250 mg/mL or 300 mg/mL.

[0255] E6. The pharmaceutical composition according to Embodiments 4 or 5 which has a ratio of Eptinezumab to LuAG09222 of 1:1, 1:2 or 2:1.

[0256] E7. The pharmaceutical composition according to any of the previous Embodiments wherein the composition comprises 100-300 mg/mL of Eptinezumab and 50 - 100 mg/mL of LuAG09222.

[0257] E8. The composition according to any of the previous Embodiments wherein the composition comprises 100, 150, 200 or 300 mg/ml of Eptinezumab.

[0258] E9. The composition according to any of the previous Embodiments wherein the

composition comprises and 50, 75, 100 or 150 mg/ml of LuAG09222.

[0259] E10. The composition according to any one of the previous Embodiments wherein the composition comprises 100 mg/ml of Eptinezumab and 50 mg/ml of LuAG09222.

[0260] E11. The composition according to any one of the previous Embodiments, wherein Eptinezumab and LuAG09222 are the only active ingredients in the composition.

[0261] E12. The composition according to any one of the previous Embodiments, wherein histidine is in the composition in a concentration between 10–50 mM, optionally at 10 mM, 20 mM, 25 mM, 30 mM, 40 mM or 50 mM.

[0262] E13. The composition according to any one of the previous Embodiments wherein polysorbate 80 or Poloxamer P188 is in the composition 0.005-0.05% w/v.

[0263] E14. The composition according to any one of the previous Embodiments, wherein one, two or three of the following excipients are present in the composition NaCl, sorbitol and arginine.

[0264] E15. The composition according to any one of the previous Embodiments, wherein the concentration of NaCl in the composition is between 10-150 mM, optionally at 25 mM, 50 mM, 100 mM or 150 mM.

[0265] E16. The composition according to any one of the previous Embodiments, wherein sorbitol is present in the composition at a concentration between 50-250 mM, optionally at 50 mM, 100 mM, 150 mM, 200 mM or 250 mM.

[0266] E17. The composition according to any one of the previous Embodiments, wherein arginine is present in the composition at a concentration between 50-250 mM, optionally at 50 mM, 100 mM, 150 mM, 200 mM or 250 mM.

[0267] E18. The composition according to any one of the previous Embodiments, wherein the pH is between 5.0-6.8, optionally at pH 5.0, pH 5.5, pH 5.9, pH 6.0, pH 6.5 or pH 6.8.

[0268] E19. The pharmaceutical composition according to any one of the previous claims, wherein histidine is in a concentration ranging between 10 – 50 mM, optionally 20-40 mM, Poloxamer P188 ranging between 0.0025-0.0120 % w/v and polysorbate 80 0.005-0.05% w/v inclusive.

[0269] E20. The pharmaceutical composition according to any one of the previous Embodiments, wherein the concentration of NaCl is between 10-150 mM, optionally 30-70 mM, sorbitol 50-250 mM, optionally 90-180 mM, and arginine (e.g. L-arginine) ranging

between 50-250 mM inclusive.

[0270] E21. The pharmaceutical composition according to any one of the previous Embodiments, which comprising Eptinezumab and LuAG90222 in a ratio 2:1, 1:1 or 1:2 and comprises 20-40 mM histidine buffer, 90-180 mM sorbitol, Poloxamer P188 0.0025-0.0120% w/v and 30-70 mM NaCl, and has a pH about 6 (optionally pH 5.9).

[0271] E22. The pharmaceutical composition according to any one of the previous Embodiments, comprising Eptinezumab and LuAG90222 in a ratio 2:1 and comprising 25-35 mM histidine buffer, 165-175 mM sorbitol, Poloxamer P188 0.0025-0.010% w/v and 25-35 mM NaCl, and has a pH about 6 (optionally pH 5.9).

[0272] E23. The pharmaceutical composition according to any one of the previous Embodiments, comprising Eptinezumab and LuAG90222 in a ratio of 1:1 and comprising 30-40 mM histidine buffer, 130-140 mM sorbitol, Poloxamer P188 0.005-0.010% w/v and 45-55 mM NaCl, and has a pH about 6 (optionally pH 5.9).

[0273] E24. The pharmaceutical composition according to any one of the previous Embodiments, Eptinezumab and LuAG90222 in a ratio 1:2 and comprising 35-45 mM histidine buffer, 90-100 mM sorbitol, Poloxamer P188 0.010-0.0120 % w/v and 65-75 mM NaCl, and has a pH about 6 (optionally pH 5.9).

[0274] E25. The composition according to any one of the previous Embodiments for use as a medicament.

[0275] E26. The composition according to any one of the previous Embodiments for use in subcutaneous administration.

[0276] E27. The composition according to any one of the previous Embodiments for use in treating or preventing headache.

[0277] E28. The composition according to any one of the previous Embodiments for use in treating or preventing pain

[0278] E29. The composition according to any one of the previous Embodiments for use treating or preventing chronic or episodic migraine.

[0279] E30. The composition according to any one of the previous Embodiments for use in treating or preventing cluster headache.

[0280] E31. The composition according to any one of the previous Embodiments for use in treating or preventing endometriosis.

[0281] E32. The composition according to any one of the previous Embodiments for use

in treating or preventing migraine (with or without aura), weight loss, cancer or tumors, angiogenesis associated with cancer or tumor growth, angiogenesis associated with cancer or tumor survival, hemiplegic migraines, cluster headaches, migrainous neuralgia, chronic headaches, tension headaches, general headaches, hot flushes, chronic paroxysmal hemicrania, secondary headaches due to an underlying structural problem in the head or neck, cranial neuralgia, sinus headaches (optionally for example associated with sinusitis), allergy-induced headaches or migraines, pain, inflammatory pain, post-operative incision pain, complex regional pain syndrome, cancer pain, primary or metastatic bone cancer pain, fracture pain, osteoporotic fracture pain, pain resulting from burn, osteoporosis, gout joint pain, pain associated with sickle cell crises, and other nociceptive pain, as well as hepatocellular carcinoma, breast cancer, liver cirrhosis, neurogenic pain, neuropathic pain, nociceptive pain, trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, fibromyalgia, menstrual pain, ovarialgia, reflex sympathetic dystrophy, neurogenic pain, osteoarthritis or rheumatoid arthritis pain, lower back pain, diabetic neuropathy, sciatica, or visceral pain associated with gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, ileitis, ulcerative colitis, renal colic, dysmenorrhea, cystitis, menstrual period, labor, menopause, prostatitis, or pancreatitis.

[0282] E33. The composition according to any one of the previous Embodiments for use in treating or preventing chronic pain; neurogenic inflammation and inflammatory pain; neuropathic pain; eye pain; tooth pain; post-surgical pain, trauma related pain, diabetes; non-insulin dependent diabetes mellitus and other inflammatory autoimmune disorders, vascular disorders; inflammation; arthritis; sarcoidosis, bronchial hyperreactivity, asthma; shock; sepsis; opiate withdrawal syndrome; morphine tolerance; hot flashes in men and women; allergic dermatitis; psoriasis; encephalitis; brain trauma; epilepsy; neurodegenerative diseases; skin diseases including pruritis, neurogenic cutaneous redness, skin rosaceousness and erythema; inflammatory bowel disease, irritable bowel syndrome, cystitis; and dysmenorrhea.

[0283] E34. The composition according to any one of the previous Embodiments for administration every month or every 2 weeks.

[0284] E35. The composition according to any one of the previous Embodiments wherein the composition comprises a fragment of Eptinezumab and LuAG09222.

[0285] E36. The composition according to Embodiment 26 wherein the fragment of

Eptinezumab and LuAG09222 comprises all 6 the CDR regions of said antibodies, respectively.

[0286] E37. The composition according to Embodiment 26 wherein the fragment comprises or consist of the VH and VL region of Eptinezumab and LuAG09222.

[0287] E38. The composition according to any one of the previous Embodiments, wherein the composition comprises 50- 150 mg/ml Eptinezumab, optionally 50 mg/ml, 75 mg/ml, 100 mg/ml, or 150 mg/ml.

[0288] E39. The composition according to any one of the previous Embodiments, wherein the composition comprises 25- 100 mg/ml LuAG09222, optionally 25 mg/ml, 50 mg/ml, 75 mg/ml or 100 mg/ml.

[0289] E40. The composition according to any one of the previous Embodiments for use in a method for subcutaneous administration.

[0290] E41. A method for treating or preventing headache comprising administering to a patient in the need thereof a composition according to any one of E1-E30.

[0291] E42. A method for treating or preventing pain comprising administering to a patient in the need thereof a composition according to any one of E1-E30.

[0292] E43. A method for treating or preventing chronic or episodic migraine comprising administering to a patient in the need thereof a composition according to any one of E1-E30.

[0293] E44. A method for treating or preventing cluster headache comprising administering to a patient in the need thereof a composition according to any one of E1-E30.

[0294] E45. A method for treating or preventing endometriosis comprising administering to a patient in the need thereof a composition according to any one of E1-E30.

[0295] E46. A method for treating or preventing migraine (with or without aura), weight loss, cancer or tumors, angiogenesis associated with cancer or tumor growth, angiogenesis associated with cancer or tumor survival, hemiplegic migraines, cluster headaches, migrainous neuralgia, chronic headaches, tension headaches, general headaches, hot flushes, chronic paroxysmal hemicrania, secondary headaches due to an underlying structural problem in the head or neck, cranial neuralgia, sinus headaches (optionally for example associated with sinusitis), allergy-induced headaches or migraines, pain,

inflammatory pain, post-operative incision pain, complex regional pain syndrome, cancer pain, primary or metastatic bone cancer pain, fracture pain, osteoporotic fracture pain, pain resulting from burn, osteoporosis, gout joint pain, pain associated with sickle cell crises, and other nociceptive pain, as well as hepatocellular carcinoma, breast cancer, liver cirrhosis, neurogenic pain, neuropathic pain, nociceptive pain, trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, fibromyalgia, menstrual pain, ovarialgia, reflex sympathetic dystrophy, neurogenic pain, osteoarthritis or rheumatoid arthritis pain, lower back pain, diabetic neuropathy, sciatica, or visceral pain associated with gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, ileitis, ulcerative colitis, renal colic, dysmenorrhea, cystitis, menstrual period, labor, menopause, prostatitis, or pancreatitis

comprising administering to a patient in the need thereof a composition according to any one of E1-E40.

[0296] E47. A method for treating or preventing chronic pain; neurogenic inflammation and inflammatory pain; neuropathic pain; eye pain; tooth pain; post-surgical pain, trauma related pain, diabetes; non-insulin dependent diabetes mellitus and other inflammatory autoimmune disorders, vascular disorders; inflammation; arthritis; sarcoidosis, bronchial hyperreactivity, asthma; shock; sepsis; opiate withdrawal syndrome; morphine tolerance; hot flashes in men and women; allergic dermatitis; psoriasis; encephalitis; brain trauma; epilepsy; neurodegenerative diseases; skin diseases including pruritis, neurogenic cutaneous redness, skin rosaceousness and erythema; inflammatory bowel disease, irritable bowel syndrome, cystitis; and dysmenorrhea.

comprising administering to a patient in the need thereof a composition according to any one of E1-40

[0297] E48. Use of a composition according to E1-E40 for the manufacture of a medicament for the treatment or prevention of headache.

[0298] E49. Use of a composition according to E1-E40 for the manufacture of a medicament for the treatment or prevention of pain.

[0299] E50. Use of a composition according to E1-E40 for the manufacture of a medicament for the treatment or prevention of chronic or episodic migraine.

[0300] E51. Use of a composition according to E1-E40 for the manufacture of a medicament for the treatment or prevention of cluster headache.

[0301] E52. Use of a composition according to E1-E40 for the manufacture of a medicament for the treatment of prevention of endometriosis.

[0302] E53. Use of a composition according to E1-E40 for the manufacture of a medicament for the treatment of prevention of migraine (with or without aura), weight loss, cancer or tumors, angiogenesis associated with cancer or tumor growth, angiogenesis associated with cancer or tumor survival, hemiplegic migraines, cluster headaches, migrainous neuralgia, chronic headaches, tension headaches, general headaches, hot flushes, chronic paroxysmal hemicrania, secondary headaches due to an underlying structural problem in the head or neck, cranial neuralgia, sinus headaches (optionally for example associated with sinusitis), allergy-induced headaches or migraines, pain, inflammatory pain, post-operative incision pain, complex regional pain syndrome, cancer pain, primary or metastatic bone cancer pain, fracture pain, osteoporotic fracture pain, pain resulting from burn, osteoporosis, gout joint pain, pain associated with sickle cell crises, and other nociceptive pain, as well as hepatocellular carcinoma, breast cancer, liver cirrhosis, neurogenic pain, neuropathic pain, nociceptive pain, trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, fibromyalgia, menstrual pain, ovarialgia, reflex sympathetic dystrophy, neurogenic pain, osteoarthritis or rheumatoid arthritis pain, lower back pain, diabetic neuropathy, sciatica, or visceral pain associated with gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, ileitis, ulcerative colitis, renal colic, dysmenorrhea, cystitis, menstrual period, labor, menopause, prostatitis, or pancreatitis.

[0303] E54. Use of a composition according to E1-E40 for the manufacture of a medicament for the treatment of prevention of chronic pain; neurogenic inflammation and inflammatory pain; neuropathic pain; eye pain; tooth pain; post-surgical pain, trauma related pain, diabetes; non-insulin dependent diabetes mellitus and other inflammatory autoimmune disorders, vascular disorders; inflammation; arthritis; sarcoidosis, bronchial hyperreactivity, asthma; shock; sepsis; opiate withdrawal syndrome; morphine tolerance; hot flashes in men and women; allergic dermatitis; psoriasis; encephalitis; brain trauma; epilepsy; neurodegenerative diseases; skin diseases including pruritis, neurogenic cutaneous redness, skin rosaceousness and erythema; inflammatory bowel disease, irritable bowel syndrome, cystitis; and dysmenorrhea.

[0304] E55. The composition, method or use according to any of the previous

embodiments wherein Eptinezumab comprises all six CDR sequences:

Light Chain CDR 1 SEQ ID NO.: 7, Light Chain CDR 2 SEQ ID NO.: 8, Light Chain CDR 3 SEQ ID NO.: 9, Heavy Chain CDR 1 SEQ ID NO.: 1, Heavy Chain CDR 2 SEQ ID NO.: 2, and Heavy Chain CDR 3 SEQ ID NO.: 3.

[0305] E56. The composition, method or use according to any of the previous embodiments wherein LU AG 09222 comprises all six CDR sequences:

Light Chain CDR 1 SEQ ID NO.: 17, Light Chain CDR 2 SEQ ID NO.: 18, Light Chain CDR 3 SEQ ID NO.: 19, Heavy Chain CDR 1 SEQ ID NO.: 12, Heavy Chain CDR 2 SEQ ID NO.: 13, and Heavy Chain CDR 3 SEQ ID NO.: 14.

[0306] E57. The composition, method or use according to any of the previous embodiments wherein Eptinezumab has the VH region as defined in SEQ ID NO.: 4 and the VL as defined in SEQ ID NO.: 10.

[0307] E58. The composition, method or use according to any of the previous embodiments wherein LU AG09222 has the VH region as defined in SEQ ID NO.: 15 and the VL region as defined in SEQ ID NO.: 20.

[0308] E59. The composition, method or use according to any of the previous embodiments wherein the Eptinezumab has the heavy chain as defined in SEQ ID NO.: 5 or SEQ ID NO.: 6 and the light chain as defined in SEQ ID NO.: 11.

[0309] E60. The composition, method or use according to any of the previous embodiments wherein the LU AG09222 has the heavy chain as defined in SEQ ID NO.: 16 or SEQ ID No.: 26 and the light chain as defined in SEQ ID NO.: 21

[0310] E61. The composition, method or use according to any of the previous embodiments wherein histidine is in the form of L-histidine and/or sorbitol is in the L-sorbitol form and arginine is in the L-arginine form.

[0311] ADDITIONAL EXEMPLARY EMBODIMENTS (EE)

[0312] Embodiment 1 (EE1) A method for treating a patient in the need thereof by administering Eptinezumab and LuAG09222 in an effective amount.

[0313] EE2. The method of EE1 wherein Eptinezumab and LuAG09222 are administered simultaneously or sequentially.

[0314] EE3. The method according to any one of the previous Embodiments wherein Eptinezumab and LuAG09222 are administered sequentially within a time period of ½-2

hours, such as within ½ hour or 1 hour.

[0315] EE4. The method according to any one of the previous Embodiments, wherein 50- 150 mg/ml Eptinezumab is administered, optionally 50 mg/ml, 75 mg/ml, 100 mg/ml, or 150 mg/ml.

[0316] EE5. The method according to any one of the previous Embodiments, wherein 25- 100 mg/ml LuAG09222 is administered , optionally 25 mg/ml, 50 mg/ml, 75 mg/ml or 100 mg/ml.

[0317] EE6. The method according to any one of the previous Embodiments wherein Eptinezumab is administered subcutaneously or intravenously and LuAG09222 is administered subcutaneously or intravenously.

[0318] EE7. The method according to any one of the previous Embodiments for treating or preventing headache.

[0319] EE8. The method according to any one of the previous Embodiments for treating or preventing pain.

[0320] EE9. The method according to any one of the previous Embodiments for treating or preventing chronic or episodic migraine.

[0321] EE10. The method according to any one of the previous Embodiments for treating or preventing cluster headache.

[0322] EE11 The method according to any one of the previous Embodiments for treating or preventing endometriosis.

[0323] EE12. The method according to any one of the previous Embodiments for treating or preventing migraine (with or without aura), weight loss, cancer or tumors, angiogenesis associated with cancer or tumor growth, angiogenesis associated with cancer or tumor survival, hemiplegic migraines, cluster headaches, migrainous neuralgia, chronic headaches, tension headaches, general headaches, hot flushes, chronic paroxysmal hemicrania, secondary headaches due to an underlying structural problem in the head or neck, cranial neuralgia, sinus headaches (such as for example associated with sinusitis), allergy-induced headaches or migraines, pain, inflammatory pain, post-operative incision pain, complex regional pain syndrome, cancer pain, primary or metastatic bone cancer pain, fracture pain, osteoporotic fracture pain, pain resulting from burn, osteoporosis, gout joint pain, pain associated with sickle cell crises, and other nociceptive pain, as well as hepatocellular carcinoma, breast cancer, liver cirrhosis, neurogenic pain, neuropathic pain,

nociceptive pain, trigeminal neuralgia, post-herpetic neuralgia, phantom limb pain, fibromyalgia, menstrual pain, ovariangia, reflex sympathetic dystrophy, neurogenic pain, osteoarthritis or rheumatoid arthritis pain, lower back pain, diabetic neuropathy, sciatica, or visceral pain associated with gastro-esophageal reflux, dyspepsia, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, ileitis, ulcerative colitis, renal colic, dysmenorrhea, cystitis, menstrual period, labor, menopause, prostatitis, or pancreatitis.

[0324] EE13. The method according to any one of the previous Embodiments for treating or preventing chronic pain; neurogenic inflammation and inflammatory pain; neuropathic pain; eye pain; tooth pain; post-surgical pain, trauma related pain, diabetes; non-insulin dependent diabetes mellitus and other inflammatory autoimmune disorders, vascular disorders; inflammation; arthritis; sarcoidosis, bronchial hyperreactivity, asthma; shock; sepsis; opiate withdrawal syndrome; morphine tolerance; hot flashes in men and women; allergic dermatitis; psoriasis; encephalitis; brain trauma; epilepsy; neurodegenerative diseases; skin diseases including pruritis, neurogenic cutaneous redness, skin rosaceousness and erythema; inflammatory bowel disease, irritable bowel syndrome, cystitis; and dysmenorrhea.

[0325] EE14. The method according to any one of the previous Embodiments wherein Eptinezumab and LUAG09222 is administered every month (every 4 weeks) or every 2 weeks.

[0326] EE15. The method according to any of the previous embodiments wherein Eptinezumab comprises all six CDR sequences:

Light Chain CDR 1 SEQ ID NO.: 7, Light Chain CDR 2 SEQ ID NO.: 8, Light Chain CDR 3 SEQ ID NO.:9, Heavy Chain CDR 1 SEQ ID NO.:1, Heavy Chain CDR 2 SEQ ID NO.:2, and Heavy Chain CDR 3 SEQ ID NO.:3.

[0327] EE16 The method according to any of the previous embodiments wherein LUAG09222 comprises all six CDR sequences:

Light Chain CDR 1 SEQ ID NO.: 17, Light Chain CDR 2 SEQ ID NO.: 18, Light Chain CDR 3 SEQ ID NO.: 19, Heavy Chain CDR 1 SEQ ID NO.: 12, Heavy Chain CDR 2 SEQ ID NO.:13, and Heavy Chain CDR 3 SEQ ID NO.: 14.

[0328] EE17 The method according to any of the previous embodiments wherein Eptinezumab has the VH region as defined in SEQ ID NO.: 4 and the VL as defined in SEQ ID NO.: 10.

[0329] EE18 The method according to any of the previous embodiments wherein LU AG09222 has the VH region as defined in SEQ ID NO.: 15 and the VL region as defined in SEQ ID NO.: 20.

[0330] EE19 The method according to any of the previous embodiments wherein the Eptinezumab has the heavy chain as defined in SEQ ID NO.: 5 or SEQ ID NO.: 6 and the light chain as defined in SEQ ID NO.: 11.

[0331] EE20 The method according to any of the previous embodiments wherein the LU AG09222 has the heavy chain as defined in SEQ ID NO.: 16 or SEQ ID NO.: 26 and the light chain as defined in SEQ ID NO.: 21

[0332] The above description of various illustrated embodiments of the invention is not intended to be exhaustive or to limit the invention to the precise form disclosed. While specific embodiments of, and examples for, the invention are described herein for illustrative purposes, various equivalent modifications are possible within the scope of the invention, as those skilled in the relevant art will recognize. The teachings provided herein of the invention can be applied to other purposes, other than the examples described above.

[0333] These and other changes can be made to the invention in light of the above detailed description. In general, in the following claims, the terms used should not be construed to limit the invention to the specific embodiments disclosed in the specification and the claims. Accordingly, the invention is not limited by the disclosure, but instead the scope of the invention is to be determined entirely by the following claims.

[0334] The invention may be practiced in ways other than those particularly described in the foregoing description and examples. Numerous modifications and variations of the invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

[0335] The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is herein incorporated by reference in their entireties.

[0336] The following examples are put forth so as to provide those of ordinary skill in

the art with a complete disclosure and description of how to make and use the subject invention, and are not intended to limit the scope of what is regarded as the invention. Efforts have been made to ensure accuracy with respect to the numbers used (*e.g.* amounts, temperature, concentrations, etc.) but some experimental errors and deviations should be allowed for. Unless otherwise indicated, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees centigrade; and pressure is at or near atmospheric.

[0337] EXAMPLES

[0338] The following examples are provided in order to illustrate the invention, but are not to be construed as limiting the scope of the claims in any way.

[0339] **EXAMPLE 1**

[0340] Human Clinical Study Evaluating the Safety and Efficacy of an Anti-CGRP Antibody According to the Invention

[0341] CLINICAL TREATMENT PROTOCOL

[0342] The humanized anti-CGRP IgG1 antibody identified herein as Ab6 (Eptinezumab) was assessed in human subjects for its ability to inhibit, alleviate or prevent the number of, duration, and/or the intensity of migraine episodes.

[0343] Specifically, the clinical efficacy of the Ab6 antibody was tested in a placebo controlled double-blind, randomized study. The individuals in the study were all selected based on specific criteria. Particularly all were diagnosed as migraine sufferers at ≤ 50 years of age (ICHD-II, 2004 Section 1), and further had a history of migraine ≥ 12 months with ≥ 5 and ≤ 14 migraine days in each 28 day period in the 3 months prior to screening.

[0344] Further, all of the individuals in the study used acute migraine medications ≤ 14 days per 28 day period and, within those days, ≤ 10 days of triptan use per 28 day period in the 3 months prior to screening and the 28 day period of completion of eDiary prior to randomization.

[0345] **TABLE 1** summarizes the demographic characteristics of the study population.

Table 1: Baseline Demographics and Clinical Characteristics		
Characteristic	Placebo iv	Ab6 1000mg iv

	(n=82)	(n=81)
Mean $\pm$SD Age (years)	39.0 (9.6)	38.6 (10.8)
Mean $\pm$SD Weight (kg)	75.4 (14.4)	75.0 (16.5)
Female Gender	66 (80%)	67 (83%)
Race:		
Caucasian	66 (80.5%)	66 (81.5%)
African American	9 (11.0%)	10 (12.4%)
Asian	3 (3.7%)	4 (5.0%)
Other	4 (4.8%)	1 (1.1%)
Baseline (per 28 days):		
Mean $\pm$SD Migraine Days	8.8 (2.7)	8.4 (2.1)
Mean $\pm$SD Migraine Episodes	6.7 (2.4)	6.0 (2.2)
Mean $\pm$SD Headache Frequency	9.6 (2.8)	9.2 (2.6)
Mean $\pm$SD Migraine Hours	72.2 (51.0)	80.1 (49.1)
Mean $\pm$SD HIT-6 Score	64.5 (4.44)	63.8 (5.21)
Mean $\pm$SD MSQ RFP Score	49.0 (17.9)	49.5 (21.2)
Mean $\pm$SD MSQ RFR Score	61.9 (22.7)	63.9 (24.0)
Mean $\pm$SD MSQ EF Score	59.5 (22.9)	59.8 (27.0)

[0346] Throughout the study all of the individuals were required to record their migraine status daily using an e-diary. In the e-diary the subjects in the study were required to record the number of migraine days/month, migraine episodes/month, migraine hours/month, migraine severity, and the use of any abortive medicine such as triptans.

[0347] In addition, the study participants were required to use the e-diary to record their migraine status in the 28 day period prior to treatment with antibody or placebo in order to establish a migraine day/hour/episode baseline per month. Also, this allowed the

subjects in the study to become familiar with the use of the e-diary.

[0348] After the 28-day run-in the subjects in the study were broken into two groups, each including 80 subjects (**FIG. 5**). In the first group, i.e., the antibody treatment group, (n=80) each subject in the group was administered intravenously a single 1000 mg dose of Ab6. In the second group (n=80), i.e., the placebo group, each of the subjects was given an intravenous injection containing only the aqueous antibody carrier solution.

[0349] The individuals in the treated and placebo groups were assessed in the 24 weeks post-dose administration. Initially, a 12 week interim analysis was conducted. Subsequent to the 12 week interim analysis, a refined analysis was conducted. This refined analysis potentially included, for example, addition or removal of patient data in accord with the study protocol, e.g., updating data that had not been fully loaded from the e-diaries. This refinement resulted in slight changes but did not alter the overall conclusions.

[0350] The efficacy of the antibody versus the placebo was assessed in part based on the recorded data in the e-diary entries. For example, this analysis included a comparison of the number of recorded migraine days/month, migraine episodes/month, migraine hours/month in the subjects in the treated versus the placebo group. The percentage of responders in each group (i.e., the subjects with 50%, 75%, and 100% reduction in migraine days) in both groups was also compared.

[0351] In addition, the responses of the Ab6- and placebo-treated subjects in both groups to MSQ and HIT-6 questionnaires are to be evaluated and compared. MSQ is a frequently utilized disease-specific tool to assess the impact of migraine on health-related quality of life (HRQL). MSQ comprises a 16-item Migraine-Specific Quality-of-Life Questionnaire (Version 1.0), which was developed by Glaxo Wellcome Inc. MSQ is hypothesized to measure 3 parameters: (i) Role Function-Restrictive; (ii) Role Function-Preventive; and (iii) Emotional Function.

[0352] The HIT-6 or functional impact (also called the Headache Impact Test or HIT-6) similarly is a well-known tool for assessing migraine intensity. This test uses six questions to capture the impact of headache and its treatment on an individual's functional health and well-being.

[0353] CLINICAL RESULTS AND ANALYSIS

[0354] The results of this human clinical trial and analysis through week 12 in the treated subjects are summarized in the **TABLE 2** below.

[0355] **TABLE 2.** Responder analysis for migraine days

Time period	% reduction migraine days	Placebo iv	Ab6 1000mg iv	P value
Week 1-4		n=80	n=75	
	50	40 (50.0)	58 (77.3)	p=0.0005
	75	19 (23.8)	39 (52.0)	p=0.0005
	100	4 (5.0)	21 (28.0)	p=0.0001
Week 5-8		n=80	n=78	
	50	43 (53.8)	59 (75.6)	p=0.0048
	75	28 (35.0)	35 (44.9)	p=0.2555
	100	12 (15.0)	21 (26.9)	p=0.0791
Week 9-12		n=77	n=72	
	50	51 (66.2)	54 (75.0)	p=0.2827
	75	24 (31.2)	38 (52.8)	p=0.0083
	100	13 (16.9)	29 (40.3)	p=0.0019

[0356] In addition, the results of the clinical study were compared based on the number of responders in the treatment and placebo groups. As shown in **FIG. 1** the number of subjects who showed a 50, 75 or 100% reduction in migraine days for each month of the interim period were compared in the treatment and placebo groups. As shown in the figure, 60% of the Ab6- treated group had at least 50 % reduction in headache days, 31% of the Ab6- treated group had at least 75 % reduction in headache days and 15 % of the Ab6 treated group had 100 % reduction in headache days.

[0357] By contrast, 33% of the placebo-treated group had at least 50 % reduction in headache days, 9% of the placebo-treated group had at least 75 % reduction in headache days, and 0 % (none) of the placebo- treated group had 100 % reduction in headache days.

[0358] These results clearly show that the reduction in the number of migraine days was much greater in the Ab6-treated group. But for the significant placebo effect, the difference in these numbers would have been more pronounced. (Elevated placebo effect is not surprising as the phenomenon is often very high for migraine and other neurological drugs).

[0359] In addition, the % change from baseline in the number of migraine days per month in the placebo and Ab6 –treated group was compared. As shown in **FIG. 2**, the median ($\pm$ QR) % change from baseline in the number of migraine days per month in the placebo and Ab6 –treated group was compared for the 2 groups during the 12 weeks post-treatment. These results which are statistically significant ($p=0.0078$) clearly show the Ab6-treated group had a much greater reduction in the number of headache days per month compared to baseline than the placebo-treated group.

[0360] Also, the % change from baseline in the number of migraine episodes per month in the placebo and Ab6 –treated group was compared. As shown in **FIG. 3** the median ($\pm$ QR) % change from baseline in the number of migraine episodes per month in the placebo and Ab6 –treated group was compared during the 12 weeks post-treatment. These results indicate that the Ab6-treated group had a significantly greater reduction in the number of migraine episodes per month compared to baseline than the placebo-treated group.

[0361] Further, the % change from baseline in the number of migraine hours per month in the placebo and Ab6-treated group was compared. As shown in **FIG. 4**, the median ($\pm$ QR) % change from baseline in the number of migraine hours per month in the placebo and Ab6 –treated group was compared for the 2 groups during the 12 weeks post-treatment. These results clearly show the Ab6-treated group had a greater reduction in the number of migraine hours per month compared to baseline than the placebo-treated group.

[0362] In addition, the HIT-6 results were compared for both groups. As noted, this questionnaire finds well accepted usage in assessing the migraine status of individuals with frequent/chronic migraine. **FIG. 6** compares the HIT-6 responder analysis for the Ab6-treated and placebo groups at baseline, week 4 after treatment, week 8 after treatment and week 12 after treatment. The results at each time point reveal that the Ab6-treated group had a statistically significant improvement in the HIT-6 scores relative to the placebo group,

i.e., 54.4% for the Ab6-treated compared to 30% for the placebo at week 4 ($p=0.0023$), 51.3% for the Ab6-treated compared to 38.0% for the placebo at week 8 ($p=0.1094$) and 61.1% for the Ab6-treated compared to 33.3% for the placebo at week 12 ($p=0.0007$). **FIG. 7** shows the percentage of patients having a HIG-6 score of some or little/none over time in the placebo and Ab6 treatment groups (statistical significance a shown).

[0363] In addition, **FIG. 8** contains the pharmacokinetic (PK) profile for Ab6 administered intravenously at a single dosage of 1000 mg in mg/mL over the 24 week period following Ab6 administration.

[0364] **FIG. 9** contains plasma-free pharmacokinetic (PK) parameters N (number of patients), mean, and standard deviation (SD) for a single 1000 mg intravenous dosage of Ab6. The parameters shown in the table and the units are C_{max} ($\mu\text{g/mL}$), $AUC_{0-\infty}$ ($\text{mg}\cdot\text{hr/mL}$), half-life (days), V_z (L) and CL (mL/hr).

[0365] Further analysis was conducted for patient data between 12-weeks and 24-weeks. The treatment group continued to exhibit decreased migraine days relative to the control group, however, the magnitude of the difference decreased over time. Additionally, the control group exhibited fewer migraine days per month than at baseline. This was thought to result at least in part from “diary fatigue” wherein patients potentially report no migraine on a day in which a migraine actually occurred, in order to avoid the time and effort of answering further queries about the migraine that would result from giving an affirmative answer to the question of whether they had a migraine on a given day.

[0366] Further analysis of the study results are shown in **FIGs. 10-21**. These result include analysis of the change (mean $\pm$ SEM) from baseline in migraine days per month for Ab6 (1000 mg i.v.) versus placebo (**FIG. 22**), change in average migraine days ($\pm$ SD) over time for the full analysis population (**FIG. 23**). Additionally, shown are the distribution of migraine days actual and change for the Ab6 treatment group during weeks 1-4 (**FIG. 12**), distribution of migraine days actual and change for the placebo group during weeks 1-4 (**FIG. 13**), distribution of migraine days actual and change for the Ab6 treatment group during weeks 5-8 (**FIG. 14**), distribution of migraine days actual and change for the placebo group during weeks 5-8 (**FIG. 15**), distribution of migraine days actual and change for the Ab6 treatment group during weeks 9-12 (**FIG. 16**), and distribution of migraine days actual and change for the placebo group during weeks 9-12 (**FIG. 17**).

[0367] Responder rate analysis was also performed (**FIGs. 18-20**). These figures

respectively show the 50%, 75%, and 100% responder rate for the Ab6 and placebo treatment groups. Subjects with $\geq 50\%$ reduction in migraine frequency were considered to be a 50% responder. Subjects with $\geq 75\%$ reduction in migraine frequency were considered to be a 75% responder. Likewise, subjects with 100% reduction in migraine frequency were considered to be a 100% responder.

[0368] In **FIGs. 10 and 18-20**, normalization was applied to visit intervals where eDiaries were completed for 21-27 days by multiplying the observed frequency by the inverse of the completion rate.

[0369] Migraine severity was also analyzed. **FIG. 21** shows the mean migraine severity over time for the full analysis population. On the scale used, a mean migraine score of 3 represents “moderate pain.”

[0370] **FIG. 22** summarizes the change from baseline in migraine days, migraine episodes, migraine hours, average migraine severity, headache frequency, and outcome measures including the HIT-6 score, MSQ (Migraine Specific Quality of Life Questionnaire) RFP (Role Function-Preventative), MSQ RFR (Role Function-Restrictive), and MSQ EF (Emotional Function).

[0371] **EXAMPLE 2**

[0372] Human Clinical Study Evaluating the Safety and Efficacy of an Anti-CGRP Antibody in Chronic Migraine Patients

[0373] This example describes a randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of Ab6 (eptinezumab) for chronic migraine prevention. In the study, 1,072 patients were randomized to receive Ab6 (300 mg or 100 mg), or placebo administered by infusion once every 12 weeks. To be eligible for the trial, patients must have experienced at least 15 headache days per month, of which at least eight met criteria for migraine. Patients that participated in the trial had an average of 16.1 migraine days per month at baseline. Study endpoints included the mean change from baseline in monthly migraine days, reduction in migraine prevalence at day 1 and over days 1-28, and reduction of at least 50%, 75%, and 100% from baseline in mean monthly migraine days, change from baseline in mean monthly acute migraine-specific medication days, and reductions from baseline in patient-reported impact scores on the Headache Impact Test (HIT-6).

[0374] Patient characteristics are summarized in **FIG. 27**, with separate columns for

patients receiving placebo, 100 mg of the antibody, or 300 mg of the antibody. Patients had a mean number of years from migraine diagnosis of between 17.0 and 19.0 years, a mean duration of suffering from chronic migraine of between 11.5 and 12.4 years, and between 44.3% and 45.2% of patients utilized at least one prophylactic medication. At baseline, in both antibody treatment groups the mean number of migraine days per month was 16.1, while for the placebo group, the mean number of migraine days per month was 16.2.

[0375] The reduction in a specified percentage (50%, 75%, or 100%) from baseline in mean monthly migraine days refers to the number or percentage of patients in a treatment group that exhibited the given percentage reduction in the number of migraine days per month. For example, a patient exhibiting 16 migraine days per month at baseline would be a 75% responder if the number of migraine days per month was decreased by at least 12 days per month over specified period.

[0376] The results are shown in **FIGs. 23-27**. **FIG. 23** shows the percentages of patients with migraine in the 300 mg, 100 mg, and placebo treatment groups at days 1, 7, 14, 21, and 28. The uppermost line shows results for placebo, the lowest line shows results for the 300 mg dosage, and the middle line shows results for the 100 mg dosage.

[0377] As shown in **FIG. 23**, at day 1 the percentage reduction in migraine prevalence was 52% for the 300 mg dosage, 50% at the 100 mg dosage, and 27% for placebo. The decrease was statistically significant compared to the placebo group for both the 100 mg and 300 mg treatment groups.

[0378] **FIGs. 24-26** show the percentage of patients in the 300 mg and 100 mg treatment groups achieving, respectively, 50%, 75%, and 100% reduction in migraine days in month 1, over months 1-3 (after the 1st infusion), and over months 4-5 (after the 2nd infusion). In each graph, the data bars, from left to right, show results for the 100 mg, 300 mg, and placebo groups. Statistical significance is as shown. ++ indicates a statistically significant difference from placebo; + indicates a statistically significant difference from placebo (unadjusted); and § indicates a statistically significant difference from placebo (post hoc).

[0379] **EXAMPLE 3**

[0380] Baseline Subgroup Analysis for Human Clinical Studies Evaluating the Safety and Efficacy of an Anti-CGRP Antibody in Chronic or Episodic Migraine Patients

[0381] In the study of Chronic Migraine described in Example 3, at intake, each patient

was assessed for potential medication overuse headache (MOH). MOH was present in 39.9% (139 patients) in the 100 mg treatment group, 42.0% (147 patients) in the 300 mg treatment group, and 39.6% (145 patients) in the placebo group. Assessment of the treatment outcomes in this patient subset indicated that treatment with the anti-CGRP antibody was efficacious for MOH (**FIG. 29**). Specifically, in the 100 mg treatment group, mean migraine days per month changed by -3.0 days (95% CI, -4.56 to -1.52 days) in the patients having MOH at baseline, compared to MOH patients receiving placebo. Similarly, in the 300 mg treatment group, mean migraine days per month changed by -3.2 days (95% CI, -4.66 to -1.78 days) in the patients having MOH at baseline, compared to MOH patients receiving placebo. By contrast, for patients without MOH at baseline, in the 100 mg treatment group, mean migraine days per month changed by -1.3 days (95% CI, -2.43 to -0.16 days), compared to patients without MOH at baseline receiving placebo. Likewise, for patients without MOH at baseline in the 300 mg treatment group, mean migraine days per month changed by -2.1 days (95% CI, -3.24 to -0.88 days), compared to patients without MOH at baseline receiving placebo. Efficacy for other subgroups was shown as well, including efficacy for patients with mean migraine day (MMD) frequency less than 17 days or greater than or equal to 17 days, patients with an age at diagnosis of less than or equal to 21 years or greater than 21 years, patients having a duration of migraine of less than or equal to 15 year or greater than 15 years, patients suffering from migraine with aura or migraine with no aura, patients with prior prophylactic medication use or no prior prophylactic medication use, patients with concomitant prophylactic medication use or no concomitant prophylactic medication use, ant patients with triptan use on greater than or equal to 33% of days, or less than 33% of days. In each case, efficacy for each subgroup was shown (**FIG. 29**).

[0382] In another human clinical trial of patients with episodic migraine, patients were randomized to receive Ab6 100 mg (n=221), 300 mg (n=222), or placebo (n=222) in a double blind, parallel study. After a 28 day screening period, patients were administered the drug or placebo intravenously every 3 months for 4 total infusions (**FIG. 28**). Efficacy was shown over months 1-3 for both the 100 mg and 300 mg treatment groups, with a mean change in migraine days of -3.9 for the 100 mg treatment group and -4.3 days for the 300 mg treatment group, compared to -3.2 days for the placebo group. Efficacy for subgroups of patients was also shown, including efficacy for patients with mean migraine day (MMD)

frequency less than or equal to 9 days or greater than 9 days, patients with an age at diagnosis of less than or equal to 21 years or greater than 21 years, patients having a duration of migraine of less than or equal to 15 year or greater than 15 years, and patients suffering from migraine with aura or migraine with no aura.

[0383] **EXAMPLE 4**

[0384] Effects of Ab6 treatment on medication use in chronic and episodic migraine patients.

[0385] During the studies of chronic migraine patients described in Example 3 and episodic migraine patients described in Example 4, patients also recorded use of acute medication in a daily eDiary and were allowed to use acute medication at their own discretion. Acute medications for migraine included ergots, triptans, and analgesics (e.g., NSAIDS, opioids, and caffeine-containing combination analgesics).

[0386] For further analysis, patients were stratified by the number of days with acute medication use during the 28-day screening period (1-9 or ≥ 10 days; “baseline”). Acute medication days were calculated for individual types of acute medications and combined, meaning that if 2 or more types medications were used on the same calendar days, they were counted as separate medication use days. For example, if a patient took an opioid and a triptan on the same day, it counted as 2 days of acute medication use. These analyses included patients with at least 1 acute medication use day during the 28-day baseline screening period.

[0387] In both chronic migraine and episodic migraine patients who used acute medication during the 28-day baseline period, Ab6 treatment resulted in greater average reductions in monthly migraine days and acute medication days than placebo as early as Month 1 after dosing, with similar results across 2 dose intervals over 6 months.

[0388] Ab6 consistently demonstrated greater reductions in mean monthly migraine days over 6 months of treatment than placebo in chronic migraine patients taking ≥ 1 day of acute medication use during baseline (**FIG. 30**). Chronic migraine patients who had at least one day of acute medication use per month during baseline demonstrated greater decreases in acute medication use than placebo as early as month 1 after treatment and across the entire 6 month treatment period (**FIG. 31**). In the subgroup of chronic migraine patients who were taking 1–9 days of acute medication during baseline, the change from baseline in days of acute medication use was greater in the 300 mg Ab6 group than placebo

across 6 months of treatment (**FIG. 32**). A clear decrease in medication days per month was observed for patients with at least 10 days of medication use per month at baseline for both Ab6 treatment group compared to placebo over the entire 6 month period. **FIG. 33** shows the changes in medication use days at Month 1 and Month 6 in the subgroups of chronic migraine patients with ≥ 1 , 1–9, and ≥ 10 days of acute medication use at baseline. With the exception of Ab6 100 mg at month 6 in patients with 1–9 days/month of use at baseline, Ab6 demonstrated a greater treatment effect in reducing acute medication use than placebo.

[0389] Similarly, across 2 dose intervals over 6 months, episodic migraine patients with one or more days of acute medication use during baseline experienced greater reductions in mean monthly migraine days with Ab6 than Placebo (**FIG. 34**). Episodic migraine patients who had at least one day of acute medication use per month during baseline demonstrated greater decreases in acute medication use than placebo as early as month 1 after treatment and across the entire 6 month treatment period (**FIG. 35**). In the subgroup of episodic migraine patients who were taking 1–9 days of acute medication during baseline, the change from baseline in days of acute medication use was greater with Ab6 than placebo across 6 months of treatment (**FIG. 36**). A similar pattern was observed in the subgroup of patients who were taking ≥ 10 days of acute medication during baseline, though smaller sample sizes may have contributed to the less consistent pattern over time. **FIG. 37** shows the changes in medication use days at Month 1 and Month 6 in the subgroups of episodic migraine patients with ≥ 1 , 1–9, and ≥ 10 days of acute medication use at baseline. With the exception of Ab6 100 mg at Month 6 in patients with ≥ 10 days/month of use at baseline, the reduction in acute medication use was greater in the Ab6 treatment groups than placebo.

[0390] The results show that both episodic migraine and chronic migraine patients who were at risk for medication-overuse headache (≥ 10 days/month of acute medication use) demonstrated the greatest reductions in acute medication use, with Ab6 treatment generally resulting in larger decreases in medication use days than placebo.

[0391] The most frequently reported acute headache medications in > 10% of subjects included Thomapyrin N (44.5%) (a combination of paracetamol, aspirin, and caffeine), ibuprofen (40.6%), sumatriptan (33.6%), paracetamol (acetaminophen) (20.3%), and naproxen sodium (10.2%). The most frequently reported preventive headache medication in > 10% of subjects was topiramate (12.5%).

[0392] **Example 5**

[0393] Efficacy of anti-CGRP Antibodies in Subjects Experiencing an Acute Attack of Migraine

[0394] This example describes a randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of Ab6 for the acute treatment of migraine. In the study, approximately 450 patients are randomized 1:1 to receive either 100 mg Ab6 or placebo. During a screening period (approx. 1-8 weeks) patients are assessed for migraine frequency and medication use frequency. Eligible patients have a migraine attack frequency of about 4-15 migraine days per month in the 3 months prior to screening. By history, the subject's typical migraine attack, if untreated, would be associated with headache pain of moderate to severe intensity and a most bothersome symptom of nausea, photophobia, or phonophobia. Subjects must be headache free for at least 24 hours prior to onset of a qualifying migraine in order to participate in the trial. On the day of treatment, the patient will travel to the study site and intravenous infusion of 100 mg Ab6 or placebo will commence between about 1-6 hours from the start of the attack. Patients will not have received any other monoclonal antibody (e.g., any CGRP antagonist antibody) within the 6 month period prior to screening.

[0395] Co-Primary Endpoints are time to headache pain freedom and time to absence of most bothersome symptom. Co-Key secondary are headache pain freedom at 2 hours and absence of most bothersome symptom at 2 hours. Secondary endpoints are time to headache pain relief, headache pain freedom at 2 hours with sustained headache pain freedom for 24 and 48 hours, use of rescue medication by 24 hours and by 48 hours, absence of photophobia at 2 hours, absence of phonophobia at 2 hours, absence of nausea at 2 hours, change from Baseline in Headache Impact Test (HIT 6) at Week 4, and change from Baseline in Migraine Treatment Optimization Questionnaire-6 (mTOQ-6) at Week 4. Exploratory Endpoints are absence of headache pain at all timepoints other than 2 hours, absence of photophobia at all timepoints other than 2 hours, absence of phonophobia at all timepoints other than 2 hours, absence of nausea at all timepoints other than 2 hours, pain relapse when the subject was headache pain-free at 2 hours, patient Global Impression of Change (PGIC) at Week 4, and time to next migraine. Headache pain is collected on a 4-point scale with 3 being severe, 2 being moderate, 1 being mild, and 0 being no pain. Pain freedom is no pain (0) with the absence of rescue medication (note that in the trial rescue

medication is not to be used for 2 hours post completion of infusion in order to separate the effects of the antibody from the rescue medication, however, in the course of normal use, rescue medication optionally may be used; any use of rescue medication is collected as data).

[0396] Statistical analysis is performed to determine significance of the difference in endpoints between patients receiving Ab6 or placebo, including the time to pain freedom and time to absence of most bothersome symptom, and each of the other aforementioned endpoints.

[0397] Use of rescue medication refers to any intervention (medical or device) provided to the subject to provide relief of migraine. In the study this should not be provided sooner than 2 hours following completion of the study drug administration in order to separate the effects of the antibody from the effects of said rescue medication, however, rescue medication is not contraindicated. The proportion of subjects requiring rescue medication use is summarized in the study. Acute rescue medication includes any medication to treat migraine or migraine associated symptoms, e.g., triptans, analgesics such as non-opioids or opioids/narcotics, acetaminophen, NSAIDS, combination medications such as EXCEDRIN® or EXCEDRIN MIGRAINE®, antiemetic medications, ergotamines, ergot derivatives, etc.

[0398] Absence of Migraine-Associated Symptoms (Photophobia, Phonophobia and Nausea) refers to the absence or presence of each of the aforementioned migraine-associated symptoms, as reported by the subject. The proportion of subjects absent the symptoms, with no administration of rescue medication, is summarized in the study.

[0399] Headache Impact Test (HIT-6) is assessed as the change from baseline of the total score, and is summarized and compared between treatment groups in the study.

[0400] Migraine Treatment Optimization Questionnaire-6 (mTOQ-6) is assessed as the change from baseline of the total score and is summarized and compared between the treatment groups in the study.

[0401] Time to Headache Pain Relief is assessed as the first time point post completion of infusion at which the subject reports relief of pain meaning their headache pain has gone from moderate or severe (2 or 3) to mild or no pain (1 or 0) with no administration of rescue medication.

[0402] Pain Relapse is assessed as the occurrence of headache of any severity within 48 hours of drug administration for a patient who has no headache pain (0) at 2 hours. The

proportion of subjects with recurrence of headache pain of any severity is summarized in the study.

[0403] The study shows that Ab6 is effective and safe for acute migraine treatment.

[0404] **Example 6**

[0405] In the pivotal clinical studies the patients received Ab6 as 100 mg or 300 mg dosages, as described in Example 2. Including day -1 (post infusion of Ab6) in the statistical analysis shows that an apparent treatment effect is present immediately after infusion when the treatment effect is assessed (**FIG. 38**). In the Figure Day 0 is defined as the day of the infusion and Day -1 data represent the pre-infusion condition. A substantial decrease in the percentage of migraines from Day -1 (baseline, the day prior to infusion) to Day 0 is apparent. Moreover, the magnitude of the effect is greater with the 300 mg dosage than the 100 mg dosage, and both show a greater effect than the placebo group.

[0406] **Example 7**

[0407] This example relates to Antibody Ab10.H3 (LuAG09222). Ab10.H3 has been studied in several clinical trials including a phase I trials to determine the safety and tolerability of ascending doses and lately also in phase II (called HOPE study, mentioned earlier herein) showing an effect in preventing migraine. Ab 10.H3 has thus been shown to be safe and useful in treating migraine patients.

[0408] Ab10.H3 is described in patent application WO2017181039 the contents of which including the SEQUENCE LISTING are incorporated by reference in their entirety herein. Ab10.H3 is a humanized version of the antibody Ab10 described in WO2017181039. WO2017181039 describes that Ab10 and AB10.H3 have increased inhibition specificity for the PCAP1 receptor pathway over the VPAC1 or VPAC2 pathway: In case of Ab10, humanization of Ab10 reduced IC50 (pM) of PACAP38-induced PCA1-R mediated cAMP increase while humanization increased IC50 (pM) of PACAP38-induced VPAC1-R mediated and VPAC2-mediated cAMP increase, which overall indicates increased inhibition specificity for the PCAP1 receptor. Considering the abundant expression of VCAP1 and VCAP2 receptors outside the nervous system (*see* paragraph [0005] in WO2017181039), the reduced relative specificity for VCAP1 and VCAP2 receptors may reduce unintended effects, *i.e.*, interaction with undesired target cells when the antibody is used as a therapeutic or prophylactic agent, which is a desired property.

[0409] Therefore, humanized antibodies provide an additional technical feature, *i.e.*,

increased inhibition specificity for the PCAP1 receptor pathway over the VPAC1 or VPAC2 pathway that further supplements the above-mentioned technical difference. The Table below summarize these points from WO2017181039. **TABLE 2** is generated from WO2017181039 on the basis of the cited Tables from WO2017181039.

Source	Tables 2 and 3 from WO2017181039	Table 7 from WO2017181039	Table 8 from WO2017181039	Table 7 value divided by Table 2 or 3 value from WO2017181039	Table 8 value divided by Table 2 or 3 value from WO2017181039
Ab name	Inhibition of 0.1 nM PACAP38- induced PAC1-R mediated cAMP increase IC ₅₀ (pM)	Inhibition of 5 nM PACAP38- induced VPAC1- R mediated cAMP increase IC ₅₀ (pM)	Inhibition of 1 nM PACAP38- induced VPAC2- R mediated cAMP increase IC ₅₀ (pM)	VPAC1R/PAC1R IC50 ratio	VPAC2R/PAC1R IC50 ratio
10	180.3	649.1	188.5	3.60	1.05
10.H3	30.7	1516	301	49.38	9.80

[0410] **Ab10 and AB10.H3 antibodies provide neural effects *in vivo*:** As demonstrated in Example 11 of WO2017181039, Ab10.H and Ab10.H3 reduce light sensitivity in a mouse model of PACAP-induced photophobia (*see*, for example, paragraph [956] in WO2017181039). Photophobia, an extreme light sensitivity, is a symptom commonly experienced by patients with a neural disorder such as migraine, and therefore the currently claimed antibodies are antibodies that can be used for treating or preventing such neural disorders or symptoms. In Example 13 of WO2017181039, Ab10.H3 decreased the trigeminal parasympathetic reflex as measured by lacrimation and nose temperature upon intranasal administration of Umbellulone in a rat model of vascular dysfunction in cluster

headache, trigeminal neuralgia, and possibly migraine (see paragraphs [967]–[972] and FIGS 34 and 35 in WO2017181039). In addition, Example 8 WO2017181039 shows that Ab10 inhibits PACAP-induced dermal vasodilation in rabbits. Although the dermal vascular effects were investigated in this experiment, the neural mechanism of vasoconstriction/vasodilation is largely the same in the brain, and vasodilation is one of the causative mechanisms for various types of headache. Taken together, the antibodies can be used for treating or preventing neural disorders or symptoms such as headache.

[0411] **Ab10 and AB10.H3 recognize a unique epitope within PACAP:** As demonstrated in Example 12 of WO2017181039, Ab10 and Ab 10.H3 recognize residues 19, 22, 23, and 27 of PACAP. Currently claimed humanized versions of Ab10 are also expected to recognize the same residues as they share the same 6 CDR sequences as their parent Ab10. Binding to this particular epitope, particularly residues 23 and 27, seems to provide the unique and beneficial feature described in, the inability to bind PAC1 receptor-expressing cells via PACAP.

[0412] **Affinity:** Humanization of Ab10 increased affinity for PACAP38 from $7.5\text{E-}11$ to $2.9\text{E-}11$ (Ab10.H), $2.2\text{E-}11$ (Ab10.H2), $2.2\text{E-}11$ (Ab10.H3), or $1.9\text{E-}11$ (Ab10.H4) (Table 4 of WO2017181039).

[0413] **IC50:** Humanization of Ab10 reduced IC50 (pM) of PACAP38-induced PCA1-R mediated cAMP increase from 180.3 to 163.4 (Ab10.H), 21.3 (Ab10.H2), 30.7 (Ab10.H3), 22.8 (Ab10.H4), 22.7 (Ab10.H5) pM (see Tables 2 and 3 of WO2017181039).

Example 7

The high concentration co-formulation of Eptinezumab-LuAG00922 requires a delicate balance of formulation components and pH. The correct balance of components and pH will provide a low viscosity which enables subcutaneous administration, and in addition a stable formulation with long shelf-life may also be achieved. For typical monoclonal antibody (mAb) drug product formulations, the conformational and colloidal stability would be optimized based on the unique biophysical properties of the specific antibody. For a coformulation of two mAbs, the formulation development becomes challenging when the biophysical properties of each mAb is distinct and different from each other. In this case, the isoelectric point of Eptinezumab is approximately 8.1, while that of LuAG00922 is approximately 6.9. Often it is desirable to formulate mAbs in compositions having a few pH units distance to the isoelectric point to improve colloidal stability and solubility, which are

key for stability at high concentration. Furthermore, the behavior of LuAG00922 as sole antibody component in high concentration formulations exhibits unique pH-dependent viscosity; at pH 5.5, LuAG00922 formulations have relatively high viscosity >70 cP when the concentration of LuAG00922 is above 158 mg/mL. As pH increases from 5.5 to 6.0 and further to 6.5, the viscosity LuAG00922 shows pH dependent charge patch changing from protonated positively charged patch at pH 5.5 to deprotonated neutrally charged patch at 6.0 and 6.5 resulting in a decrease in viscosity as pH increases.

Design of Experiments (DOE)

The formulation design space was created by varying the pH and the amounts of L-histidine, sorbitol, L-arginine hydrochloride, poloxamer 188, and protein concentration. The pH range of 5.25 to 6.75 was investigated due to the desired pH range using a 10 to 50 mM histidine buffer, which was desired to provide buffering capacity for a mAb subcutaneous formulation. NaCl and L-arginine hydrochloride excipient levels were investigated at 3 levels of 10, 80, 150 mM and desired as a potential stabilizer, viscosity reducer, and tonicity modifier. L-sorbitol excipient levels were chosen at 50, 150, and 250 mM and desired as a potential stabilizer, cryo-protectant, and tonicity modifier. Poloxamer 188 was investigated at 0.005, 0.0275 and 0.05% (w/v) and desired as a surfactant to prevent against protein aggregation and particle formation. The total antibody concentration levels were investigated at 100, 125, and 150 mg/mL to provide concentrations high enough to enable subcutaneous administration of the formulation. JMP statistical software was used to create a Definitive Screening Design of Experiments (DOE) using 7 factors with 3 levels each resulting in 18 formulations. This DOE was applied to Eptinezumab-LuAG00922 coformulation ratios of 1:1, 1:2, and 2:1, resulting in a total of 54 formulations.

Formulation composition and buffer-exchange

Reagents used in preparing formulations were in **TABLE 3** below. Working stock solutions of each formulation component were prepared by the following: 0.20 M L-histidine, 1.0 M sodium chloride (NaCl), 3.5 M sorbitol, 0.9 M L-arginine hydrochloride, and 10.0 % (w/v) of Poloxamer 188. 18 formulation buffers in **TABLE 4** were created by diluting the appropriate amount of each of the working stock solutions of each formulation component into distilled

deionized water (Milli-Q water). The final pH of each formulation buffer was adjusted using 5M hydrochloric acid and then formulations were filtered with 0.22µm PES filter.

TABLE 3: Reagents used in formulations.

Reagent	Supplier	Part Number
L-histidine	J.T. Baker	2080-06
Sodium Chloride (NaCl)	Fisher Chemical	S640-3
L-sorbitol	Thermo Fisher	1.11597.2500
L-arginine hydrochloride (arginine)	J.T. Baker	2067-06
Poloxamer 188 (P188)	Spectrum	P1169
Eptinezumab (LuAG09221)	Lundbeck	N/A
LuAG09222	Lundbeck	N/A

18 formulation buffers containing L-histidine, L- sorbitol, and L-arginine hydrochloride were prepared by mixing the appropriate volume of the working stock solutions together and diluting with distilled deionized water (Milli-Q water) to achieve the compositions in the **TABLE** below. Three ratios of Eptinezumab:LuAG00922 were chosen 1:2, 1:1, 2:1 and were each buffer-exchanged into the 18 formulations to create a total of 54 protein formulations using the Big Tuna (Unchained Labs).

TABLE 4: 18 formulation buffer compositions for Eptinezumab: LuAG00922 ratios of 1:2, 1:1, and 2:1.

Formulation Number	pH	histidine (mM)	NaCl (mM)	sorbitol (mM)	arginine (mM)	P188 (w/v)	Total antibody Conc (mg/mL)
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1	6.75	50	150	50	150	0.005	100
2	6.75	30	150	250	10	0.05	100
3	6.75	10	10	150	150	0.05	100
4	6	10	10	50	10	0.005	100
5	5.25	10	150	250	80	0.005	100
6	5.25	50	80	50	10	0.05	100
7	5.25	50	10	250	150	0.0275	100
8	6.75	50	10	250	10	0.005	125
9	6	30	80	150	80	0.0275	125
10	6	30	80	150	80	0.0275	125
11	5.25	10	150	50	150	0.05	125
12	6.75	10	80	250	150	0.005	150
13	6.75	50	10	50	80	0.05	150
14	6.75	10	150	50	10	0.0275	150
15	6	50	150	250	150	0.05	150
16	5.25	30	10	50	150	0.005	150
17	5.25	10	10	250	10	0.05	150
18	5.25	50	150	150	10	0.005	150

The stability of 54 formulations was evaluated using size-exclusion column with ultra-high pressure liquid chromatography at the following conditions and timepoints.

- 5°C (0, 1, 4, 7 Month)
- 25°C (1, 4, 7 Month)
- 40°C (1 Month)

Methods

Protein Concentration Measurement:

After buffer-exchange into the desired coformulation, the protein concentration was measured using Solo VPE and an Agilent Cary 60 UV-Vis spectrophotometer or the Lunatic

spectrophotometer (Unchained Labs) and known A280 extinction coefficient for Eptinezumab and LuAG00922.

High-throughput Assays:

- Size exclusion chromatography with ultra-high pressure liquid chromatography (SE-UPLC) was performed using a Waters Acquity H-class UPLC with a TUV detector connected to a Waters BEH SEC column (P/N 186005225). SE-UPLC analysis was performed at T=0 and each timepoint at 5°C, 25°C, 30°C, and 40°C to assess the percentage of high molecular weight (HMW%) species. The initial HMW% of Eptinezumab was 0.32% and that of LuAG00922 was 0.94%. Total HMW% results at T=0 for each of the 54 coformulations after buffer-exchange ranged from 0.39% to 1.40%. JMP DOE model analysis showed significant effects in HMW% response with changes in the protein concentration, ratio of Eptinezumab:LuAG00922, histidine concentration, L-arginine hydrochloride concentration, pH, and sorbitol concentration. Sodium chloride concentration and poloxamer (P188) concentrations did not show a significant change in HMW% response.
- High-throughput viscosity measurements were performed using Uncle (Unchained Labs) dynamic light scattering (DLS) based bead method (He et al. 2010, Analytical Biochemistry, Volume 399, Issue 1, Pages 141-143, High-throughput dynamic light scattering method for measuring viscosity of concentrated protein solutions) . Protein formulations were spiked with 100 nm diameter polystyrene beads (ThermoScientific: P/N 3100A).

TABLE 5: Results for Eptinezumab:LuAG00922 Ratio 2:1

Formulation Number	Total antibody Conc (mg/ml)	Viscosity (cP)	HMW%									
			T=0	5°C T=1M	5°C T=4M	5°C T=7M	Δ5°C T=7M	25°C T=1M	25°C T=4M	25°C T=7M	Δ25°C T=7M	40°C T=1M
1	98.8	2.42	0.48	0.57	0.60	0.65	0.17	0.68	0.77	0.88	0.40	9.41
2	99.2	2.86	0.60	0.74	0.81	0.97	0.37	1.01	1.14	1.57	0.97	2.62
3	99.5	2.55	0.55	0.64	0.74	0.87	0.32	0.91	1.06	1.28	0.73	3.78
4	99.6	3.26	0.63	0.88	1.11	1.25	0.62	1.40	2.27	Gel	N/A	11.32
5	101.3	3.58	0.44	0.55	0.68	0.81	0.37	1.01	1.56	1.83	1.39	92.56
6	100.3	3.22	0.43	0.61	0.80	0.97	0.54	1.08	1.89	4.97	4.54	97.94
7	99.2	2.97	0.42	0.48	0.54	0.63	0.21	0.73	1.10	1.92	1.5	96.77
8	128.6	4.29	0.60	0.75	0.93	1.04	0.44	1.08	1.33	1.81	1.21	2.33
9	132.2	3.67	0.51	0.62	0.72	0.85	0.34	0.94	1.32	1.63	1.12	24.16
10	130.9	4.53	0.51	0.65	0.72	0.87	0.36	0.92	1.28	1.65	1.14	22.27
11	130.8	6.82	0.51	0.71	0.91	1.08	0.57	1.25	1.65	4.49	3.98	90.92
12	157.9	6.96	0.70	0.77	0.86	0.96	0.26	1.18	Gel	1.80	1.10	11.91
13	151.4	5.2	0.71	0.87	0.87	0.96	0.25	1.13	1.28	1.56	0.85	5.12
14	152.1	>10	1.09	1.47	1.51	1.70	0.61	2.17	2.44	2.73	1.64	7.24
15	154.3	6.64	0.51	0.60	0.65	0.72	0.21	0.84	1.15	1.36	0.85	69.11
16	154.5	8.54	0.73	0.91	1.11	1.23	0.50	1.67	2.22	5.17	4.44	97.81
17	161.8	>10	0.87	0.98	1.04	1.21	0.34	1.83	2.71	Gel	N/A	70.59
18	158.8	9.21	0.68	0.86	1.02	1.30	0.62	2.87	Gel	5.52	4.84	97.59

TABLE 6: Results for Eptinezumab:LuAG00922 Ratio 1:1

Formulation Number	Total antibody Conc (mg/ml)	Viscosity (cP)	HMW%									
			T=0	5°C T=1M	5°C T=4M	5°C T=7M	Δ5°C T=7M	25°C T=1M	25°C T=4M	25°C T=7M	Δ25°C T=7M	40°C T=1M
1	97.8	2.49	0.52	0.67	0.70	0.74	0.22	0.73	0.85	0.93	0.41	12.26
2	98.7	2.98	0.64	0.87	0.98	1.07	0.43	1.13	1.32	1.49	0.85	3.07
3	99.7	2.83	0.61	0.72	0.83	0.96	0.35	1.01	1.13	1.31	0.70	4.63
4	99.1	3.62	0.66	1.02	1.23	1.38	0.72	1.56	2.12	Gel	N/A	12.32
5	99.5	3.5	0.52	0.58	0.71	0.87	0.35	1.07	1.52	2.48	1.96	92.78
6	100.3	4.65	0.45	0.65	0.85	1.00	0.55	1.13	1.67	4.22	3.77	98.48
7	99.2	3.30	0.39	0.50	0.58	0.69	0.30	0.85	1.11	1.83	1.44	97.03
8	126.5	5.00	0.74	0.96	1.08	1.26	0.52	1.30	1.5	1.91	1.17	2.59
9	129.1	3.96	0.57	0.74	0.81	0.94	0.37	1.03	1.48	1.82	1.25	26.01
10	130.6	4.64	0.59	0.71	0.84	0.96	0.37	1.08	1.46	Gel	N/A	21.73
11	131.5	4.66	0.60	0.78	1.01	1.13	0.53	1.28	1.89	Gel	N/A	88.82
12	149.9	5.35	0.84	0.94	1.08	1.18	0.34	1.29	1.54	1.79	0.95	100
13	152.0	5.35	0.85	0.99	1.03	1.15	0.3	1.24	1.44	1.71	0.86	16.52
14	151.6	6.30	1.29	1.50	1.77	1.95	0.66	2.20	2.57	3.10	1.81	9.59
15	151.7	5.22	0.64	0.69	0.75	0.85	0.21	0.96	1.28	1.48	0.84	70.34
16	155.7	9.58	0.82	0.98	1.20	1.32	0.5	1.65	2.48	4.58	3.76	97.63
17	157.5	>10	0.98	1.03	1.19	1.36	0.38	1.76	Gel	3.10	2.12	66.08
18	153.0	>10	0.76	0.81	1.03	1.24	0.48	1.57	2.27	4.61	3.85	100

TABLE 7: Results for Eptinezumab:LuAG00922 Ratio 1:2

Formulation Number	Total antibody Conc (mg/ml)	Viscosity (cP)	HMW%									
			T=0	5°C T=1M	5°C T=4M	5°C T=7M	Δ5°C T=7M	25°C T=1M	25°C T=4M	25°C T=7M	Δ25°C T=7M	40°C T=1M
1	96.8	2.49	0.67	0.68	0.76	0.87	0.20	0.82	0.90	1.09	0.42	11.04
2	95.8	2.55	0.65	0.94	1.05	1.26	0.61	1.26	1.41	1.62	0.97	3.25
3	96.6	2.55	0.68	0.84	0.96	1.07	0.39	1.04	1.28	1.47	0.79	4.31
4	97.6	4.78	0.80	1.13	1.37	1.61	0.81	1.81	2.3	2.91	2.11	12.48
5	97.2	3.39	0.58	0.70	0.80	0.95	0.37	1.17	1.73	1.95	1.37	90.85
6	98.4	3.39	0.53	0.65	0.84	1.07	0.54	1.19	1.73	2.93	2.4	98.14
7	98.5	3.79	0.50	0.53	0.65	0.77	0.27	0.91	1.23	1.77	1.27	96.40
8	130.4	5.40	0.84	1.11	1.23	1.43	0.59	1.50	1.75	2.16	1.32	2.93
9	131.9	4.51	0.69	0.77	0.97	1.15	0.46	1.23	1.63	1.98	1.29	21.24
10	128.0	3.53	0.68	0.85	0.95	1.11	0.43	1.18	1.57	1.94	1.26	18.10
11	128.8	4.75	0.67	0.77	1.02	1.23	0.56	1.71	1.83	Gel	N/A	90.60
12	147.2	5.79	0.90	1.13	1.21	1.32	0.42	1.50	1.65	1.98	1.08	5.86
13	147.4	>10	0.93	1.16	1.20	1.31	0.38	1.62	1.83	1.84	0.91	5.79
14	148.7	5.66	1.40	1.80	1.96	2.19	0.79	2.86	3.27	3.28	1.88	8.05
15	149.0	5.66	0.67	0.76	0.85	0.95	0.28	1.11	1.37	1.62	0.95	59.06
16	153.6	>10	0.80	0.98	1.13	1.34	0.54	1.69	2.09	4.08	3.28	96.47
17	159.0	>10	1.11	1.23	1.38	1.50	0.39	2.01	2.60	3.25	2.14	45.62
18	150.3	>10	0.75	0.96	1.03	1.23	0.48	1.61	2.14	3.91	3.16	96.34

Example 8

The following data was obtained as in Example 7 but the stability study was performed at 30°C and SE-UPLC analysis was performed at T=10 days and T=20 days.

TABLE 8

Ratio Eptinezumab:LuAG00922	pH	histidine (mM)	NaCl (mM)	sorbitol (mM)	P188 (w/v)	Total antibody Conc (mg/mL)	HMW%		
							T=0	30°C T=10 day	30°C T=20 day
							113 mg/mL	1.03	1.14
							120 mg/mL	1.15	1.31
2:1	~5.9	30	169	30	0.0050 %	113 mg/mL	0.93	1.03	1.14
1:1	~5.9	34	135	48	0.0080 %	120 mg/mL	1.19	1.15	1.31
1:2	~5.9	38	96	69	0.0114 %	129 mg/mL	1.36	1.36	1.53

Example 9

The following data was obtained as in Example 7 but the stability study was performed at 30°C and SE-UPLC analysis was performed at T=10 days and T=20 days.

TABLE 9 using ratios of Eptinezumab:LuAG00922 of 2:1

pH	histidine (mM)	sorbitol (mM)	arginine HCl (mM)	Total antibody Conc (mg/mL)	P188 (w/v)	HMW%		
						T=0	30°C T=10D	30°C T=20D
6.125	30	80	150	149.8	0.02	0.61	1.25	1.37
6.75	10	150	250	150.5	0.02	0.66	1.10	1.20
6.125	50	150	250	144.0	0.02	0.52	0.88	0.96
6.75	10	10	150	150.7	0.02	0.89	2.12	2.23
5.5	50	150	150	151.1	0.02	0.49	1.21	1.57
6.125	10	10	50	149.1	0.02	0.81	1.78	2.11
5.5	50	10	50	150.7	0.02	0.53	1.48	1.71
5.5	30	10	250	150.4	0.02	0.55	1.31	1.56
6.75	50	80	50	156.8	0.02	0.64	1.12	1.23
5.5	10	150	50	153.1	0.02	0.57	1.48	1.60
6.75	30	150	50	149.9	0.02	0.64	1.06	1.21
6.75	50	10	250	149.8	0.02	0.67	1.17	1.31
5.5	10	80	250	146.7	0.02	0.57	1.33	1.54

TABLE 10 using ratios of Eptinezumab:LuAG00922 of 1:1

pH	histidine (mM)	sorbitol (mM)	arginine HCl (mM)	Total antibody Conc (mg/mL)	P188 (w/v)	HMW%		
						T=0	30°C T=10D	30°C T=20D
6.125	30	80	150	133.7	0.02	0.66	1.21	1.49
6.75	10	150	250	160.3	0.02	0.69	1.43	1.77
6.125	50	150	250	141.2	0.02	0.55	1.78	2.16
6.75	10	10	150	144.9	0.02	0.88	1.25	1.42
5.5	50	150	150	159.6	0.02	0.53	1.87	2.24
6.125	10	10	50	141.5	0.02	0.83	0.84	1.05
5.5	50	10	50	156.4	0.02	0.55	1.18	1.37
5.5	30	10	250	148.6	0.02	0.57	1.08	1.38
6.75	50	80	50	142.8	0.02	0.69	1.32	1.60
5.5	10	150	50	142.5	0.02	0.59	1.28	1.58
6.75	30	150	50	142.4	0.02	0.68	0.99	1.17
6.75	50	10	250	157.5	0.02	0.71	1.35	1.66
5.5	10	80	250	150.7	0.02	0.57	1.07	1.26

TABLE 11 using ratios of Eptinezumab:LuAG00922 of 1:1

pH	Buffer	Excipients	HMW%		
			T=0	30°C T=10D	30°C T=20D
5.0	25 mM Sodium Acetate	250 mM sorbitol, 0.02% P188	0.79	2.37	2.63
5.0	25 mM sodium Citrate	250 mM sorbitol, 0.02% P188	0.67	2.74	3.53
7.4	10 mM Sodium Phosphate	137 mM NaCl 2.7 mM NaCl, 0.02% P188	1.55	3.68	4.19
7.4	25 mM Tris hydrochloride	250 mM sorbitol, 0.05% 0.02% P188	1.28	3.00	3.50
6.0	25 mM histidine hydrochloride	250 mM sorbitol, 0.05% polysorbate 80	0.72	1.45	1.62

CLAIMS

What is claimed is:

1. A pharmaceutical composition comprising Eptinezumab and LuAG09222 wherein Eptinezumab comprises the VH region as defined in SEQ ID NO.: 4 and the VL as defined in SEQ ID NO.: 10, and LU AG09222 comprises the VH region as defined in SEQ ID NO.: 15 and the and VL region as defined in SEQ ID NO.: 20.
2. The pharmaceutical composition **of claim 1** which is formulated so as to maintain the biologic activity and/or storage stability of the Eptinezumab and LuAG09222 antibodies therein.
3. The pharmaceutical composition **of claim 1 or 2**, which maintains the biologic activity and/or storage stability of the Eptinezumab and LuAG09222 antibodies therein for at least 1 month, at least 2 months, at least 3 months, at least 3-6 months, at least 6-9 months, at least 9-12 months, or at least a year.
4. The pharmaceutical composition **according to any of the previous claims**, which comprises or further comprises histidine and either polysorbate 80 or poloxamer 188.
5. The pharmaceutical composition according to any of the previous claims which comprises or further comprises one, two or all of the following excipients NaCl, sorbitol and arginine.
6. The pharmaceutical composition **according to any of the previous claims**, which comprises a total concentration of Eptinezumab and LuAG09222 of 100 mg/mL to 300 mg/mL.
7. The pharmaceutical composition **according to any of the previous claims** which comprises a total concentration of Eptinezumab and LuAG09222 of about 100 mg/mL, about 150 mg/mL, about 200 mg/mL, about 250 mg/mL or about 300 mg/mL.
8. The pharmaceutical composition **according to claim 6 or 7** which comprises a ratio of Eptinezumab to LuAG09222 of about 1:1, 1:2 or 2:2.
9. The pharmaceutical composition **according to any of the previous claims** wherein the composition comprises about 100-300 mg/mL of Eptinezumab and about 50 -100 mg/mL of LuAG09222.
10. The pharmaceutical composition **according to any one of the previous claims** wherein the composition comprises about 100 mg/mL of Eptinezumab and about 50 mg/mL of LuAG09222.
11. The pharmaceutical composition **according to any one of the previous claims**, wherein

Eptinezumab and LuAG0922 are the only active ingredients in the composition.

12. The pharmaceutical composition **according to any one of the previous claims**, wherein histidine is in a concentration ranging between 10 – 50 mM, optionally about 20-40 mM, Poloxamer P188 ranging between 0.0025-0.0120 % w/v and polysorbate 80 0.005-0.05% w/v inclusive.
13. The pharmaceutical composition **according to any one of the previous claims**, wherein the concentration of NaCl is between about 10-150 mM, optionally about 30-70 mM, 50-250 mM sorbitol (optionally L-sorbitol), optionally about 90-180 mM sorbitol, and between 50-250 mM inclusive of arginine (optionally L-arginine).
14. The pharmaceutical composition **according to any one of the previous claims**, wherein the pH is between about 5.0-6.8 inclusive.
15. The pharmaceutical composition **according to any one of the previous claims**, wherein the pH is about 5.0, about 5.5, about 5.9, about 6.0, about 6.5 or about 6.8.
16. The pharmaceutical composition **according to any one of the previous claims**, which is suitable for intravenous administration or subcutaneous administration.
17. The pharmaceutical composition **according to any one of the previous claims**, comprising Eptinezumab and LuAG90222 in a ratio of about 2:1, about 1:1 or about 1:2 and comprises about 20-40 mM histidine buffer, about 90-180 mM of sorbitol, 0.0025-0.0120% w/v of Poloxamer P188, and 30-70 mM NaCl, and has a pH about 6, optionally about pH 5.9.
18. The pharmaceutical composition **according to any one of the previous claims**, comprising Eptinezumab and LuAG90222 in a ratio of 2:1 and further comprising about 25-35 mM histidine buffer, about 165-175 mM sorbitol, about 0.0025-0.010% w/v of Poloxamer P188, and about 25-35 mM NaCl, and has a pH about 6, optionally about pH 5.9.
19. The pharmaceutical composition **according to any one of the previous claims**, comprising Eptinezumab and LuAG90222 in a ratio of 1:1 and further comprising about 30-40 mM histidine buffer, about 130-140 mM sorbitol, about 0.005-0.010% w/v of Poloxamer P188, and about 45-55 mM NaCl, and has a pH about 6, optionally pH 5.9.
20. The pharmaceutical composition **according to any one of the previous claims**, Eptinezumab and LuAG90222 in a ratio of 1:2 and further comprising about 35-45 mM histidine buffer, about 90-100 mM sorbitol, about 0.010-0.0120 % w/v of Poloxamer

P188, and about 65-75 mM NaCl, and has a pH about 6, optionally pH 5.9.

21. The pharmaceutical composition **according to any one of the previous claims** for use as a medicament.
22. The pharmaceutical composition **according to any one of the previous claims** for use in treating or preventing headache, optionally chronic or episodic migraine or cluster headache, further optionally wherein the administration of said pharmaceutical composition comprising said antibody combination has an additive or synergistic effect on the inhibition, alleviation or prevention of the number of, duration, and/or the intensity of migraine episodes compared to the subcutaneous or intravenous administration of a pharmaceutical composition comprising the same dosage of Eptinezumab or LuAG09222 alone.
23. The pharmaceutical composition **according to any one of the previous claims** for use in treating or preventing pain, optionally any of acute pain, chronic pain, neuropathic pain, nociceptive pain, and/or radicular pain, further optionally wherein the administration of said pharmaceutical composition comprising said antibody combination has an additive or synergistic effect on the inhibition or alleviation of pain, compared to the subcutaneous or intravenous administration of a pharmaceutical composition comprising the same dosage of Eptinezumab or LuAG09222 alone.
24. The pharmaceutical composition **according to any one of the previous claims** for administration every month (every 4 weeks) or every 2 weeks.
25. The pharmaceutical composition **according to any one of the previous claims** wherein Eptinezumab comprises the heavy chain as defined in SEQ ID NO.: 5 or SEQ ID NO.: 6 and the light chain as defined in SEQ ID NO.: 11.
26. The pharmaceutical composition **according to any one of the previous claims** wherein LUAG09222 comprises the heavy chain as defined in SEQ ID NO.: 16 or SEQ ID NO.: 26 and the light chain as defined in SEQ ID NO.: 21.
27. A method of treating or preventing headache, optionally chronic or episodic migraine or cluster headache, comprising or consisting of the subcutaneous or intravenous administration of the combination of Eptinezumab and LuAG09222 antibodies, wherein Eptinezumab comprises the VH region as defined in SEQ ID NO.: 4 and the VL as defined in SEQ ID NO.: 10, and LU AG09222 comprises the VH region as defined in SEQ ID NO.: 15 and the and VL region as defined in SEQ ID NO.: 20, and optionally wherein the

administration of said antibody combination has an additive or synergistic effect on the inhibition, alleviation or prevention of the number of, duration, and/or the intensity of migraine episodes compared to the subcutaneous or intravenous administration of the same dosage Eptinezumab or LuAG09222 alone.

28. A method of treating or preventing pain, optionally any of acute pain, chronic pain, neuropathic pain, nociceptive pain, and/or radicular pain, comprising or consisting of the subcutaneous or intravenous administration of the combination of Eptinezumab and LuAG09222 antibodies, wherein Eptinezumab comprises the VH region as defined in SEQ ID NO.: 4 and the VL as defined in SEQ ID NO.: 10, and LU AG09222 comprises the VH region as defined in SEQ ID NO.: 15 and the and VL region as defined in SEQ ID NO.: 20, and optionally wherein the administration of said antibody combination has an additive or synergistic effect on the inhibition or alleviation of pain, compared to the subcutaneous or intravenous administration of the same dosage of Eptinezumab or LuAG09222 alone.
29. The method **of claim 27 or 28**, wherein the Eptinezumab and LuAG09222 antibodies are subcutaneously or intravenously by administration of a pharmaceutical composition **according to any one of claims 1-20**.