Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2984185 A1 2016/12/22

(21) 2 984 185

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2016/06/08
(87) Date publication PCT/PCT Publication Date: 2016/12/22
(85) Entrée phase nationale/National Entry: 2017/10/26
(86) N° demande PCT/PCT Application No.: US 2016/036407
(87) N° publication PCT/PCT Publication No.: 2016/205037
(30) Priorité/Priority: 2015/06/17 (US62/180,905)

(51) Cl.Int./Int.Cl. *A61K 39/395* (2006.01), *A61P 25/06* (2006.01), *C07K 16/26* (2006.01)

(71) Demandeur/Applicant:
ELI LILLY AND COMPANY, US

(72) Inventeur/Inventor:
SHARMA, ANANT N., US

(74) Agent: GOWLING WLG (CANADA) LLP

(54) Titre : FORMULATION D'ANTICORPS ANTI-CGRP
(54) Title: ANTI-CGRP ANTIBODY FORMULATION

(57) Abrégé/Abstract:
Pharmaceutical formulations for anti-CGRP antibodies, and methods of using the same, are provided which are useful as treatment for migraines, episodic headaches, chronic headaches, chronic cluster headaches, and episodic cluster headaches.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 December 2016 (22.12.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/205037 A1

(51) International Patent Classification:
C07K 16/18 (2006.01) *A61K 39/00* (2006.01)
C07K 16/26 (2006.01)

(21) International Application Number:
PCT/US2016/036407

(22) International Filing Date:
8 June 2016 (08.06.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/180,905 17 June 2015 (17.06.2015) US

(71) Applicant: **ELI LILLY AND COMPANY** [US/US]; Lilly Corporate Center, Indianapolis, Indiana 46285 (US).

(72) Inventor: **SHARMA, Anant N.**; c/o Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

(74) Agents: **JIVRAJ, Sanjay M.** et al.; Eli Lilly and Company, P.O. Box 6288, Indianapolis, Indiana 46206-6288 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2016/205037 A1

(54) Title: ANTI-CGRP ANTIBODY FORMULATION

(57) Abstract: Pharmaceutical formulations for anti-CGRP antibodies, and methods of using the same, are provided which are useful as treatment for migraines, episodic headaches, chronic headaches, chronic cluster headaches, and episodic cluster headaches.

Anti-CGRP Antibody Formulation

The present invention is in the field of medicine. More specifically, the present invention relates to antibodies to calcitonin gene-related peptide (CGRP) and pharmaceutical formulations thereof. Additional aspects of the present invention relate to the use of such anti-CGRP antibodies and pharmaceutical formulations thereof for the treatment of patients suffering from CGRP-related disorders.

CGRP is a neuropeptide secreted by the nerves of the central and peripheral nervous systems and is implicated in pain pathways. The role of CGRP in headache and migraine has been established in the art and a number of clinical studies are currently evaluating the use of anti-CGRP antibodies for the treatment of headaches and migraine. (see, for example, Dodick et al. Lancet Neurol; 13(9): 885-892 (2014)).

Liquid pharmaceutical formulations for antibodies intended for human use require the chemical and physical stability of the antibody over its extended shelf life (e.g. WO06083689 and in WO06096491). Chemical instability of the antibody can result from a number of chemical reactions including deamidation, racemization, hydrolysis, oxidation, beta elimination and disulfide exchange. Physical instability can result from processes such as denaturation, aggregation, precipitation, and adsorption to surfaces. Instability of the antibody can result in the formation of a polypeptide by-product or derivatives having low activity, increased toxicity, and/or increased immunogenicity, which can pose concerns about the safety and efficacy of the antibody.

While the possible occurrence of protein instabilities is widely appreciated, it is difficult to predict particular instability issues for a particular protein. Applicants sought to formulate an anti-CGRP antibody (PCT/US2011/039381), wherein said antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), wherein the amino acid sequence of said LCVR is SEQ ID NO: 1 and the amino acid sequence of said HCVR is SEQ ID NO: 2. In formulating the anti-CGRP antibody for use in therapy, applicants discovered several factors that contributed to the instability of the antibody, such as photo degradation, polymer formation during freeze-thaw, and oxidation of polysorbate-80 (PS-80) in the formulation. Therefore, a stable pharmaceutical formulation was needed to overcome at least one or more of the observed issues.

Accordingly, the present invention provides a pharmaceutical formulation comprising an anti-CGRP antibody at a concentration of about 40 mg/mL to about 160 mg/mL, histidine buffer at a concentration of about 5 mM to about 20 mM, sodium chloride (NaCl) at a concentration of about 50 mM to about 200mM, PS-80 at a concentration of about 0.03% (w/v) to about 0.07% (w/v), and a pH at about 5.0 to about 6.5, wherein the anti-CGRP antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of LCVR given by SEQ ID NO: 1 and the amino acid sequence of HCVR given by SEQ ID NO: 2. Preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with a light chain (LC) and a heavy chain (HC), the amino acid sequence of LC given by SEQ ID NO: 3 and the amino acid sequence of HC given by SEQ ID NO: 4. More preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with two LCs and two HCs, the amino acid sequence of each LC given by SEQ ID NO: 3 and the amino acid sequence of each HC given by SEQ ID NO: 4.

In an alternative embodiment, the present invention provides a pharmaceutical formulation comprising an anti-CGRP antibody at a concentration of about 50 mg/mL to about 150 mg/mL, histidine buffer at a concentration of about 5 mM to about 20 mM, sodium chloride at a concentration of about 50 mM to about 200 mM, PS-80 at a concentration of about 0.03% (w/v) to about 0.07% (w/v), and a pH at about 5.0 to about 6.5, wherein the anti-CGRP antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of LCVR given by SEQ ID NO: 1 and the amino acid sequence of HCVR given by SEQ ID NO: 2. Preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with a light chain (LC) and a heavy chain (HC), the amino acid sequence of LC given by SEQ ID NO: 3 and the amino acid sequence of HC given by SEQ ID NO: 4. More preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with two LCs and two HCs, the amino acid sequence of each LC given by SEQ ID NO: 3 and the amino acid sequence of each HC given by SEQ ID NO: 4.

In an alternative embodiment, the present invention provides a pharmaceutical formulation comprising an anti-CGRP antibody at a concentration of about 100 mg/mL to about 160 mg/mL, histidine buffer at a concentration of about 5 mM to about 20 mM,

NaCl at a concentration of about 50 mM to about 200 mM, PS-80 at a concentration of about 0.03% (w/v) to about 0.07% (w/v), and a pH at about 5.0 to about 6.5, wherein the anti-CGRP antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of LCVR given by SEQ ID NO: 1 and the amino acid sequence of HCVR given by SEQ ID NO: 2. Preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with a light chain (LC) and a heavy chain (HC), the amino acid sequence of LC given by SEQ ID NO: 3 and the amino acid sequence of HC given by SEQ ID NO: 4. More preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with two LCs and two HCs, the amino acid sequence of each LC given by SEQ ID NO: 3 and the amino acid sequence of each HC given by SEQ ID NO: 4.

A further embodiment of the present invention also provides a pharmaceutical formulation comprising an anti-CGRP antibody in a histidine buffer, NaCl, and PS-80, wherein the concentration of anti-CGRP antibody is selected from the group consisting of about 50 mg/mL, about 100 mg/mL, about 120 mg/mL or about 150 mg/mL, histidine buffer at a concentration of about 5 mM to about 20 mM, NaCl at a concentration of about 50 mM to about 200mM, PS-80 at a concentration of about 0.03% (w/v) to about 0.07% (w/v), and a pH at about 5.0 to about 6.5, wherein the anti-CGRP antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of LCVR given by SEQ ID NO: 1 and the amino acid sequence of HCVR given by SEQ ID NO: 2. Preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with a light chain (LC) and a heavy chain (HC), the amino acid sequence of LC given by SEQ ID NO: 3 and the amino acid sequence of HC given by SEQ ID NO: 4. More preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with two LCs and two HCs, the amino acid sequence of each LC given by SEQ ID NO: 3 and the amino acid sequence of each HC given by SEQ ID NO: 4.

Another embodiment of the present invention also provides a pharmaceutical formulation comprising an anti-CGRP antibody in a histidine buffer, NaCl, and PS-80, wherein the concentration of anti-CGRP antibody is selected from the group consisting of about 50 mg/mL, about 100 mg/mL, about 120 mg/mL or about 150 mg/mL, histidine

buffer at a concentration of about 10 mM, NaCl at a concentration of about 50 mM to about 200mM, PS-80 at a concentration of about 0.03% (w/v) to about 0.07% (w/v), and a pH at about 5.0 to about 6.5, wherein the anti-CGRP antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of LCVR given by SEQ ID NO: 1 and the amino acid sequence of HCVR given by SEQ ID NO: 2. Preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with a light chain (LC) and a heavy chain (HC), the amino acid sequence of LC given by SEQ ID NO: 3 and the amino acid sequence of HC given by SEQ ID NO: 4. More preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with two LCs and two HCs, the amino acid sequence of each LC given by SEQ ID NO: 3 and the amino acid sequence of each HC given by SEQ ID NO: 4.

In another embodiment, the present invention also provides a pharmaceutical formulation comprising an anti-CGRP antibody in a histidine buffer, NaCl, and PS-80, wherein the concentration of anti-CGRP antibody is selected from the group consisting of about 50 mg/mL, about 100 mg/mL, about 120mg/ml or about 150 mg/mL, histidine buffer at a concentration of about 10 mM, NaCl at a concentration of about 150mM, PS-80 at a concentration of about 0.03% (w/v) to about 0.07% (w/v), and a pH at about 5.0 to about 6.5, wherein the anti-CGRP antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of LCVR given by SEQ ID NO: 1 and the amino acid sequence of HCVR given by SEQ ID NO: 2. Preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with a light chain (LC) and a heavy chain (HC), the amino acid sequence of LC given by SEQ ID NO: 3 and the amino acid sequence of HC given by SEQ ID NO: 4. More preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with two LCs and two HCs, the amino acid sequence of each LC given by SEQ ID NO: 3 and the amino acid sequence of each HC given by SEQ ID NO: 4.

In another embodiment, the present invention also provides a pharmaceutical formulation comprising an anti-CGRP antibody in a histidine buffer, NaCl, and PS-80, wherein the concentration of anti-CGRP antibody is selected from the group consisting of about 50 mg/mL, about 100 mg/mL, about 120mg/ml or about 150 mg/mL, histidine buffer at a concentration of about 10 mM, NaCl at a concentration of about 150mM, PS-

80 at a concentration of about 0.05% (w/v), and a pH at about 5.0 to about 6.5, wherein the anti-CGRP antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of LCVR given by SEQ ID NO: 1 and the amino acid sequence of HCVR given by SEQ ID NO: 2. Preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with a light chain (LC) and a heavy chain (HC), the amino acid sequence of LC given by SEQ ID NO: 3 and the amino acid sequence of HC given by SEQ ID NO: 4. More preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with two LCs and two HCs, the amino acid sequence of each LC given by SEQ ID NO: 3 and the amino acid sequence of each HC given by SEQ ID NO: 4.

More particularly, the present invention provides for a pharmaceutical formulation comprising an anti-CGRP antibody at a concentration of about 120 mg/mL, histidine buffer at a concentration of about 10 mM, NaCl at a concentration of about 150 mM, PS-80 at a concentration of about 0.05% (w/v), and pH of about 5.8, wherein the anti-CGRP antibody comprises a LCVR and a HCVR, the amino acid sequence of LCVR given by SEQ ID NO: 1 and the amino acid sequence of HCVR given by SEQ ID NO: 2. Preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with a light chain (LC) and a heavy chain (HC), the amino acid sequence of LC given by SEQ ID NO: 3 and the amino acid sequence of HC given by SEQ ID NO: 4. More preferably, the pharmaceutical formulation comprises an anti-CGRP antibody with two LCs and two HCs, the amino acid sequence of each LC given by SEQ ID NO: 3 and the amino acid sequence of each HC given by SEQ ID NO: 4.

In a further embodiment, the present invention provides a pharmaceutical formulation comprising an anti-CGRP antibody in a histidine buffer, wherein the concentration of the anti-CGRP antibody is about 40 mg/mL to about 160 mg/mL. Preferably, the concentration of the anti-CGRP antibody is about 50 mg/mL to about 150 mg/mL. More preferably, the concentration of the anti-CGRP antibody is about 50 mg/mL, about 100 mg/mL, about 120 mg/mL, or about 150 mg/mL. In particular embodiments the pharmaceutical formulation comprises an anti-CGRP antibody at a concentration of about 40 mg/mL to about 160 mg/mL in a histidine buffer, wherein the

histidine buffer is at a concentration of about 5 mM to about 20 mM. Preferably, the histidine buffer is at a concentration of about 10 mM.

In another embodiment, the present invention provides a pharmaceutical formulation comprising an anti-CGRP antibody and NaCl, wherein the concentration of NaCl is about 50 mM to about 200 mM. Preferably, the concentration of NaCl is about 125 to about 175mM. More preferably, the concentration of NaCl is about 150 mM. Even more preferably, the pharmaceutical formulation comprises an anti-CGRP antibody, histidine buffer at 10 mM, and NaCl, wherein the concentration of NaCl is about 50 mM to about 200 mM. Most preferably, the pharmaceutical formulation comprises an anti-CGRP antibody at a concentration in the range of about 40 mg/mL to about 160 mg/mL, histidine buffer at a concentration of about 10 mM, NaCl at a concentration of about 50 mM to about 200mM, and a pH of about 5.8. Preferably, the NaCl is at a concentration of about 150mM.

In another embodiment, the present invention provides a pharmaceutical formulation comprising an anti-CGRP antibody and PS-80, wherein the concentration of PS-80 is about 0.03% (w/v) to about 0.07% (w/v). Preferably the concentration of PS-80 in the pharmaceutical formulation is about 0.05% (w/v). In a preferred embodiment, the pharmaceutical formulation comprises an anti-CGRP antibody at a concentration in the range of about 40 mg/mL to about 160 mg/mL, and PS-80 at a concentration of about 0.03% (w/v) to about 0.07% (w/v). More preferably, the pharmaceutical formulation comprises an anti-CGRP antibody at a concentration in the range of about 40 mg/mL to about 160 mg/mL, histidine buffer at a concentration of about 5mM to 20mM, and of PS-80 is about 0.05% (w/v). Even more preferably, the pharmaceutical formulation comprises an anti-CGRP antibody at a concentration in the range of about 40 mg/mL to about 160 mg/mL, NaCl at a concentration of about 50 mM to about 200 mM, and PS-80 at a concentration of about 0.05% (w/v). Most preferably, the pharmaceutical formulation comprises an anti-CGRP antibody at a concentration in the range of about 100 mg/mL to about 150 mg/mL, histidine buffer at a concentration of about 125 mM to about 175mM, PS-80 at a concentration of about 0.05% (w/v) and a pH of about 5.8.

The present invention also provides a method of treating or preventing a condition related to elevated levels of CGRP, preferably headaches and/or migraines comprising

administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical formulation of the present invention. Some embodiments of the present invention provide a method of treating or preventing migraine, episodic headache, chronic headache, chronic cluster headaches, and/or episodic cluster headaches comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical formulation of the present invention. According to some embodiments, a method of treating or preventing chronic and episodic cluster headaches is provided comprising administering to a patient in need thereof a dose of 300 mg of an anti-CGRP antibody. Further embodiments provide a method of treating or preventing chronic and episodic cluster headaches administering to a patient in need thereof a dose of 360 mg of an anti-CGRP antibody. In other embodiments, the present invention provides a method of treating or preventing chronic and episodic migraines comprising administering to a patient in need thereof a dose of 120 mg of an anti-CGRP antibody. Further embodiments provide a method of treating or preventing chronic and episodic migraine comprising administering to a patient in need thereof a dose of 240 mg of an anti-CGRP antibody. Another embodiment provides a provide a method of treating or preventing chronic and episodic migraine comprising administering to a patient in need thereof an initial loading dose of 240 mg of an anti-CGRP antibody followed by a monthly maintenance dose of 120 mg of an anti-CGRP antibody. Preferably, the dose is administered at weekly, semi-monthly, monthly or quarterly intervals. More preferably, the administration is monthly.

In another embodiment, the present invention also provides a method to treat or prevent cluster headache in a patient in need by administering a monthly subcutaneous dose of 300mg of an anti-CGRP antibody, wherein the anti-CGRP antibody binds to an epitope comprising amino acids VTHRLAGLLSR of SEQ ID NO: 7. In a further embodiment, the present invention provides a method to treat or prevent episodic migraine in a patient in need by administering a monthly subcutaneous dose of 120mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LCVR given by the amino acid sequence of SEQ ID NO: 1 and a HCVR given by the amino acid of SEQ ID NO: 2. Preferably, the anti-CGRP antibody is in a pharmaceutical formulation comprising about 10mM histidine buffer, about 150mM NaCl, about 0.05% PS-80, and a

pH of about 5.8. In another embodiment, the present invention also provides a method to treat or prevent cluster headache in a patient in need by administering a monthly subcutaneous dose of 300mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LC given by the amino acid sequence of SEQ ID NO: 3 and a HC given by the amino acid of SEQ ID NO: 4. Preferably, the anti-CGRP antibody is in a pharmaceutical formulation comprising about 10mM histidine buffer, about 150mM NaCl, about 0.05% PS-80 and a pH of about 5.8.

In another embodiment, the present invention also provides a method to treat or prevent cluster headache in a patient in need thereof by administering a monthly dose of 300 mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LCVR given by the amino acid sequence of SEQ ID NO: 1 and a HCVR given by the amino acid of SEQ ID NO: 2, and wherein the anti-CGRP antibody is in a pharmaceutical composition comprising a histidine buffer. In a particular embodiment, the anti-CGRP antibody is in a pharmaceutical composition comprising a histidine buffer at a pH of about 5.5-6.1. In another particular embodiment, the anti-CGRP antibody is in a pharmaceutical composition comprising about 5 mM to about 20 mM histidine buffer. Preferably the pharmaceutical composition has a pH of about 5.7-6.0. More preferably, the pharmaceutical composition has a pH of about 5.8.

In another particular embodiment, the present invention also provides a method to treat or prevent cluster headache in a patient in need thereof by administering a monthly dose of 300mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LCVR given by the amino acid sequence of SEQ ID NO: 1 and a HCVR given by the amino acid of SEQ ID NO: 2, and wherein the anti-CGRP antibody is in a pharmaceutical composition comprising a buffer, NaCl, and a surfactant. Preferably the anti-CGRP antibody is in a pharmaceutical composition comprising a buffer, about 50mM to about 200mM of NaCl, and a surfactant. More preferably, the anti-CGRP antibody is in a pharmaceutical composition at a pH of about 5.7-6.0. Most preferably, the anti-CGRP antibody is in a pharmaceutical composition at a pH of about 5.8.

In another particular embodiment, the present invention also provides a method to treat or prevent cluster headache in a patient in need thereof by administering a monthly dose of 300mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a

LCVR given by the amino acid sequence of SEQ ID NO: 1 and a HCVR given by the amino acid of SEQ ID NO: 2, and wherein the anti-CGRP antibody is in a pharmaceutical composition comprising a buffer, salt, and PS-80 as a surfactant. Preferably the anti-CGRP antibody is in a pharmaceutical composition comprising a buffer, salt, and about 0.03% (w/v) to about 0.07% (w/v) PS-80. More preferably, the anti-CGRP antibody is in a pharmaceutical composition at a pH of about 5.7-6.0. Most preferably, the anti-CGRP antibody is in a pharmaceutical composition at a pH of about 5.8.

In a further embodiment, the present invention provides a method to treat or prevent episodic migraine in a patient in need by administering a monthly subcutaneous dose of 120mg of an anti-CGRP antibody, wherein the anti-CGRP antibody binds to an epitope comprising amino acids VTHRLAGLLSR of SEQ ID NO: 7. In a further embodiment, the present invention provides a method to treat or prevent episodic migraine in a patient in need by administering a monthly subcutaneous dose of 120mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LCVR given by the amino acid sequence of SEQ ID NO: 1 and a HCVR given by the amino acid of SEQ ID NO: 2. Preferably, the anti-CGRP antibody is in a pharmaceutical formulation comprising about 10mM histidine buffer, about 150mM NaCl, about 0.05% PS-80, and a pH of about 5.8. In a further embodiment, the present invention provides a method to treat or prevent episodic migraine in a patient in need by administering a monthly subcutaneous dose of 120mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LC given by the amino acid sequence of SEQ ID NO: 3 and a HC given by the amino acid of SEQ ID NO: 4. Preferably, the anti-CGRP antibody is in a pharmaceutical formulation comprising about 10mM histidine buffer, about 150mM NaCl, about 0.05% PS-80 and a pH of about 5.8.

In another embodiment the present invention provides a method to treat or prevent episodic migraine in a patient in need thereof by administering a monthly dose of 120 mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LCVR given by the amino acid sequence of SEQ ID NO: 1 and a HCVR given by the amino acid of SEQ ID NO: 2, and wherein the anti-CGRP antibody is in a pharmaceutical composition comprising a histidine buffer. In a particular embodiment, the anti-CGRP antibody is in a pharmaceutical composition comprising a histidine buffer at a pH of about 5.5-6.1. In

another particular embodiment, the anti-CGRP antibody is in a pharmaceutical composition comprising about 5 mM to about 20 mM histidine buffer. Preferably the pharmaceutical composition has a pH of about 5.7-6.0. More preferably, the pharmaceutical composition has a pH of about 5.8.

In another particular embodiment, the present invention provides a method to treat or prevent episodic migraine in a patient in need thereof by administering a monthly dose of 120 mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LCVR given by the amino acid sequence of SEQ ID NO: 1 and a HCVR given by the amino acid of SEQ ID NO: 2, and wherein the anti-CGRP antibody is in a pharmaceutical composition comprising a buffer, NaCl, and a surfactant. Preferably the anti-CGRP antibody is in a pharmaceutical composition comprising a buffer, about 50mM to about 200mM of NaCl, and a surfactant. More preferably, the anti-CGRP antibody is in a pharmaceutical composition at a pH of about 5.7-6.0. Most preferably, the anti-CGRP antibody is in a pharmaceutical composition at a pH of about 5.8.

In another particular embodiment the present invention provides a method to treat or prevent episodic migraine in a patient in need by administering a monthly dose of 120 mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LCVR given by the amino acid sequence of SEQ ID NO: 1 and a HCVR given by the amino acid of SEQ ID NO: 2, and wherein the anti-CGRP antibody is in a pharmaceutical composition comprising a buffer, salt and PS-80 as a surfactant. Preferably the anti-CGRP antibody is in a pharmaceutical composition comprising a buffer, salt, and about 0.03% (w/v) to about 0.07% (w/v) PS-80. More preferably, the anti-CGRP antibody is in a pharmaceutical composition at a pH of about 5.7-6.0. Most preferably, the anti-CGRP antibody is in a pharmaceutical composition at a pH of about 5.8.

In another embodiment the present invention provides a method to treat or prevent chronic migraine in a patient in need thereof by administering a monthly dose of 120 mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LCVR given by the amino acid sequence of SEQ ID NO: 1 and a HCVR given by the amino acid of SEQ ID NO: 2, and wherein the anti-CGRP antibody is in a pharmaceutical composition comprising a histidine buffer. In a particular embodiment, the anti-CGRP antibody is in a pharmaceutical composition comprising a histidine buffer at a pH of about 5.5-6.1. In

another particular embodiment, the anti-CGRP antibody is in a pharmaceutical composition comprising about 5 mM to about 20 mM histidine buffer. Preferably the pharmaceutical composition has a pH of about 5.7-6.0. More preferably, the pharmaceutical composition has a pH of about 5.8.

In another particular embodiment, the present invention provides a method to treat or prevent chronic migraine in a patient in need by administering a monthly dose of 120 mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LCVR given by the amino acid sequence of SEQ ID NO: 1 and a HCVR given by the amino acid of SEQ ID NO: 2, and wherein the anti-CGRP antibody is in a pharmaceutical composition comprising a buffer, NaCl, and a surfactant. Preferably the anti-CGRP antibody is in a pharmaceutical composition comprising a buffer, about 50mM to about 200mM of NaCl, and a surfactant. More preferably, the anti-CGRP antibody is in a pharmaceutical composition at a pH of about 5.7-6.0. Most preferably, the anti-CGRP antibody is in a pharmaceutical composition at a pH of about 5.8.

In another particular embodiment the present invention provides a method to treat or prevent chronic migraine in a patient in need by administering a monthly dose of 120 mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LCVR given by the amino acid sequence of SEQ ID NO: 1 and a HCVR given by the amino acid of SEQ ID NO: 2, and wherein the anti-CGRP antibody is in a pharmaceutical composition comprising a buffer, salt and PS-80 as a surfactant. Preferably the anti-CGRP antibody is in a pharmaceutical composition comprising a buffer, salt, and about 0.03% (w/v) to about 0.07% (w/v) PS-80. More preferably, the anti-CGRP antibody is in a pharmaceutical composition at a pH of about 5.7-6.0. Most preferably, the anti-CGRP antibody is in a pharmaceutical composition at a pH of about 5.8.The present invention also provides a pharmaceutical formulation for use in therapy, preferably for use in the treatment or prevention of migraines and/or headaches. In particular embodiments, the present invention provides a pharmaceutical formulation for use in the treatment or prevention of at least one or more of the following conditions: episodic migraine, chronic migraine, episodic headaches, chronic headaches, chronic cluster headaches, and/or episodic cluster headaches. Preferably, the dose of anti-CGRP antibody that is administered to a patient is 120 mg or 240 mg for episodic and/or chronic migraine and

300 mg or 360 mg for episodic and/or chronic cluster headaches. Moreover, the present invention provides for a use of a pharmaceutical formulation of the present invention in the manufacture of a medicament for the treatment or prevention of migraine and/or headache. In particular, the present invention provides for a use of a pharmaceutical formulation in the manufacture of a medicament for the treatment of at least one of more of the following conditions: episodic migraine, chronic migraine, episodic headache, chronic headache, chronic cluster headache, and / or episodic cluster headache.

As used herein, the term "patient" refers to a human. In some embodiments, a patient is a human who has been diagnosed as having a condition or disorder for which treatment or administration with a pharmaceutical formulation of the present invention is indicated. In some embodiments, a patient is a human that is characterized as being at risk of a condition or disorder for which treatment or administration with a pharmaceutical formulation of the present invention is indicated.

As used herein, the term "treating" (or "treat" or "treatment") refers to processes involving a slowing, interrupting, arresting, controlling, stopping, reducing, or reversing the progression or severity of a symptom, disorder, condition, or disease, but does not necessarily involve a total elimination of all disease-related symptoms, conditions, or disorders associated with CGRP activity. As used herein, the term "prevention" (or "prevent" or "preventing") refers to precluding, averting, obviating, forestalling, reducing the incidence of, stopping, or hindering the symptoms of a disease, disorder and/or condition. Prevention includes administration to a subject who does not exhibit symptoms of a disease, disorder, and/or condition at the time of administration.

As used herein, the term "therapeutically effective amount" refers to the amount or dose of an anti-CGRP antibody in a pharmaceutical formulation of the present invention, which upon single or multiple dose administration to the patient, provides the desired pharmacological effect in the patient. A dose can include a higher initial loading dose, followed by a lower dose. A "dose" refers to a predetermined quantity of a therapeutic drug calculated to produce the desired therapeutic effect in a patient. A therapeutically effective amount can be determined by the attending diagnostician, as one skilled in the art, by considering a number of factors such as the patient's size, age, and general health, the specific disease or surgical procedure involved, the degree or severity

of the disease or malady, the response of the individual patient, the mode of administration, the bioavailability characteristics of the preparation administered, the dose regimen selected, and the use of any concomitant medications.

As used herein, the term “month” or derivations thereof, refers to a time period that includes 28 to 31 consecutive days. The term "about" as used herein, means in reasonable vicinity of the stated numerical value, such as plus or minus 10% of the stated numerical value.

The general structure of an “antibody” is known in the art. Anti-CGRP antibodies are disclosed in WO2011/156324. As used herein, a “drug substance” (“DS”) is a formulation that comprises an antibody, buffer (e.g. histidine), excipient (e.g. NaCl), and surfactant (e.g. PS-80), and is within a certain pH range or at a specified pH. A “drug product” (“DP”) is a formulation comprising a buffer, excipient, surfactant, and antibody, wherein the antibody in the DP may be at a lower concentration than the antibody concentration in the DS.

The pharmaceutical formulations of the present invention are in the liquid dosage form of a solution. Administration of the pharmaceutical formulations of the present invention may be via parenteral administration. Parenteral administration, as used herein, may include injection of a dosage form into the body by a sterile syringe or some other mechanical device such as an infusion pump. Parenteral routes can include intravenous, intramuscular, subcutaneous, and intraperitoneal routes of administration. Subcutaneous administration is a preferred route. The pharmaceutical formulations of the present invention are intended for pharmaceutical use in a human.

The invention is further illustrated by the following examples which should not be construed as limiting.

Examples

Production of Antibodies

Antibodies of the invention can be made and purified as follows. An appropriate host cell, such as CHO, is either transiently or stably transfected with an expression system for secreting antibodies using an optimal predetermined HC:LC vector ratio or a single vector system encoding both LC and both HC, such as each LC being SEQ ID NO: 3 and each HC being SEQ ID NO: 4. Clarified media, into which the antibody has been

secreted, is purified using any of many commonly-used techniques. For example, the medium may be conveniently applied to a Protein A or G Sepharose FF column that has been equilibrated with a compatible buffer, such as phosphate buffered saline (pH 7.4). The column is washed to remove nonspecific binding components. The bound antibody is eluted, for example, by pH gradient. Antibody fractions are detected, such as by SDS-PAGE, and then are pooled. Further purification is optional, depending on the intended use. The antibody may be concentrated and/or sterile filtered using common techniques. Soluble aggregate and multimers may be effectively removed by common techniques, including size exclusion, hydrophobic interaction, ion exchange, or hydroxyapatite chromatography. The purity of the antibody after these chromatography steps is greater than 99%. The product may be immediately frozen at -70°C in the formulation matrix of the invention or may be lyophilized. The amino acid and nucleic acid sequences for the exemplified antibody are provided below.

Manufacture of an anti-CGRP Pharmaceutical Formulation

The manufacturing process for an anti-CGRP antibody pharmaceutical formulation of the present invention includes compounding of the buffer excipient composition, and adding the anti-CGRP antibody drug substance (DS).

The buffer excipient composition consists of L-Histidine, L-Histidine Hydrochloride Monohydrate, NaCl , PS-80, and water (Table 1). The anti-CGRP antibody comprises a light chain of SEQ ID NO: 3, and a heavy chain of SEQ ID NO: 4.

Table 1. Buffer excipient composition

Component	**Quantity (mg/mL)**	**Final Concentration**
L-Histidine	0.478	10 mM
L-Histidine Hydrochloride Monohydrate	1.45	
NaCl	8.76	150 mM
PS-80	0.50	0.05% (w/v)*
Water for Injection	*q.s.* to 1 mL	

* weight per volume

The buffer excipient composition is prepared and filtered. An appropriate quantity of water at a temperature not more than 25°C is weighed into a tared empty vessel of appropriate size. The appropriate quantities of L-Histidine, L-Histidine Hydrochloride Monohydrate and NaCl are added and mixed. PS-80 is weighed out in a glass container and an appropriate quantity of water is added into the glass container to give the indicated final concentration, and the solution is mixed. The PS-80 solution is added to the other excipients, the solution is mixed, and the solution is prepared to have a pH and osmolality adjusted to within 5.8 ± 0.3 and 254-344 mOsm/Kg, respectively. The buffer excipient composition is passed through a filter for bioburden reduction.

The anti-CGRP antibody DS is prepared by expressing the antibody in cells, purifying, concentrating, and freezing the antibody in solution in 10 mM histidine buffer, 150 mM NaC1, 0.05% PS-80, and pH of about 5.8. The DS solution is stored at -70°C. The frozen DS is equilibrated to a temperature of 20 ± 5°C and mixed with an appropriate amount of the buffer excipient solution to achieve the intermediate antibody DP concentration. The pH of the solution is checked to be within 5.8 ± 0.3.

The solution is mixed and a sample is taken for an in-process UV assay to determine the antibody DP concentration. An appropriate quantity of the buffer excipient solution is added to reach the final target batch weight. After mixing, the pH of the solution is checked to be within 5.8± 0.3. The antibody DP solution is passed through a filter for bioburden reduction prior to sterile filtration and filling into vials or syringes. The final concentration of the antibody DP can be between about 40 mg/mL to about 160 mg/mL.

Photo Stability

Light can influence the active molecule in a drug formulation, as well as the final product or package resulting in photodegradation that may result in the loss of potency of the product. The effect of light on anti-CGRP antibody formulated in citrate buffer or histidine buffer at pH 5.8 in glass prefilled syringes is evaluated by size exclusion chromatography (SEC). The light exposure levels are approximately 20% of ICH Q1B for visible light and 10% for the UV light.

Anti-CGRP antibody, at approximately 165 mg/mL (in 10 mM Histidine, 150 mM NaCl, pH 6.0), is divided into two aliquots. One aliquot is dialyzed into 10mM histidine, 150mM NaCl, pH 5.8 buffer, and the other aliquot is dialyzed into 10mM citrate, 150mM NaCl, pH 5.8 buffer. Following dialysis, the antibody is diluted with the appropriate buffer (histidine or citrate) to 50 mg/mL or to 120 mg/mL. PS-80 is added to each formulation to a final concentration of 0.05%. The formulations are filtered through a 0.22 μm sterilizing grade PVDF filter and filled into glass prefilled syringes. Eight syringes per formulation for size exclusion chromatography (SEC) analysis are utilized. Syringes are placed in light chambers for exposure to either ultraviolet (UV), visible or both UV and visible light. Syringes in an opaque box are also included as "dark" controls. The temperature is constant at 20°C. Total polymer is measured by SEC. The results are summarized in Table 2.

Table 2. Comparison of percent total polymer between histidine and citrate buffer

DP Concentration and Light Condition	Histidine Buffer Total Polymer (%)	Citrate Buffer Total Polymer (%)
50 mg/mL Dark	1.44	1.70
50 mg/mL UV	1.63	2.06
50 mg/mL VIS	1.88	2.60
50 mg/mL UV/ VIS	2.33	3.47
120 mg/mL Dark	1.54	1.98
120 mg/mL UV	2.18	2.89
120 mg/mL VIS	2.38	3.66
120 mg/mL UV/ VIS	2.86	4.20

Under conditions essentially as described above, the results provided in Table 2 demonstrate that the percent total polymer in histidine buffer were lower than that observed with citrate buffer. These data demonstrate that the formulations comprising the histidine buffer provide for better stability following exposure to light compared to formulations comprising citrate.

Excipient Compatibility Study

Stability of anti-CGRP antibody pharmaceutical formulations is evaluated in an excipient compatibility study. The formulations, at pH 6.0, comprise 120 mg/mL anti-CGRP antibody, 0.04% PS-80, either 10mM or 20mM histidine buffer, and either 150mM NaCl, 5% mannitol, or a combination of 100mM NaCl and 1.5% mannitol. Formulations are prepared by dialysis, and stored in HDPE containers at indicated temperatures, and are protected from light. Total polymer is determined by SEC at the beginning of the study, at 1 month, and at 2 months.

Table 3. Comparison of percent total polymer between mannitol, NaCl, and a combination of mannitol and NaCl.

Formulation	**Time points (months)**	**Total Polymer (%), 5°C**	**Total Polymer (%), 25°C**	**Total Polymer (%), 40°C**
10mM Histidine, 150mM NaCl	0	1.53	1.53	1.53
	1	1.68	2.02	2.43
	2	1.74	2.30	3.13
20mM Histidine, 5% Mannitol	0	1.98	1.98	1.98
	1	2.09	2.37	2.60
	2	2.17	2.71	3.22
10mM Histidine, 100mM NaCl, 1.5% Mannitol	0	1.44	1.44	1.44
	1	1.59	1.74	2.11
	2	1.56	2.09	2.84

Under conditions essentially as described above, the percent total polymer in the formulation comprising 5% mannitol was higher compared to the percent total polymer for the formulation comprising 150mM NaCl, or the formulation comprising 100mM NaCl and 1.5% mannitol. The addition of NaCl and/or a combination of NaCl and mannitol is shown to positively affect the stability of the protein.

Stability Following Freeze-Thaw

Freezing is a common processing step used to maintain stability and quality of a protein during development and production, and may allow for a longer shelf life. However, freezing can induce complex physical and chemical changes in the solvent/solute conditions, resulting in denaturation of proteins with the possibility of generation of aggregates over time. The stability of pharmaceutical formulations in

histidine buffer following freeze-thaw (FT) is determined by SEC. Eight different formulations are prepared and stored in HDPE containers. Each formulation is at pH 6.0, comprises 0.02% PS-80,10mM histidine, and either 150, 120, 100, or 20 mg/mL anti-CGRP antibody DP, and either 5% mannitol, 150mM NaCl, or 1.5% mannitol and 100mM NaCl.

Respective formulations in HDPE containers undergo three freeze-thaw cycles. For one cycle, each formulation is frozen at -70°C and thawed at room temperature. Respective formulations in HDPE containers undergo a slow freeze-thaw in a lyophilizer chamber. Controls are stored at 5°C for the duration of the study. Following the third cycle or following the slow freeze-thaw, percent total polymer is assessed by SEC.

Table 4. Comparison of percent total polymer between mannitol, NaCl, and a combination of mannitol and NaCl.

Total Polymer (%)	**5% Mannitol**		**150mM NaCl**			**1.5% Mannitol, 100mM NaCl**		
Stress	120 mg/ml DP	20 mg/ml DP	150 mg/mL DP	100 mg/mL DP	20 mg/mL DP	150 mg/mL DP	100 mg/mL DP	20 mg/mL DP
Control	1.7	2.2	1.64	1.65	1.19	1.45	1.6	1.2
FT cycle 1	1.8	2.8	1.58	1.65	1.71	1.57	1.51	1.28
FT cycle 2	N.D.	N.D.	1.62	1.66	2.32	1.54	1.51	1.33
FT cycle 3	1.8	5.1	1.6	1.61	3.15	1.51	1.5	1.29
Slow FT	1.9	11.6	1.72	1.71	1.91	1.52	1.48	N.D.

N.D.: Not determined

Under conditions described above, the percent total polymer in the formulation comprising 5% mannitol and 20 mg/mL DP was increased in FT cycle 3 and in the slow FT, compared to the percent total polymer in all other formulations. The percent polymer was also increased in the formulation comprising 20 mg/mL DP and 150mM NaCl. NaCl

and/or a combination of NaCl and mannitol, together with concentrations of antibody greater than 20mg/mL in the formulation are shown to have a stabilizing effect on the protein following freeze-thaw.

Capillary Shear Device

The capillary shear device (CSD) is a high shear force simulating stress device that uses a peristaltic pump and a capillary tube to study physical stress on a formulated DP. A CSD is used to evaluate shear force physical stress of pharmaceutical formulations of the present invention, wherein said formulations comprise 10mM histidine, 150 mM NaCl, anti-CGRP antibody at a concentration of 5 mg/mL, 40 mg/mL, or 120 mg/mL, varying concentrations of PS-80, and pH of 6.0.

Anti-CGRP antibody DP is pumped through a 0.5mm inner diameter stainless steel capillary tube, with or without air, at a rate of approximately 3.3 mL/sec using a peristaltic pump. This pump rate results in a shear value of approximately 105 sec^{-1}. Calculated energy dissipation is approximately 105 W/Kg. Controls do not undergo pumping.

Three different capillary shear device set-ups are utilized in this study. Stainless steel and PTFE capillary tubes are chosen because these materials are commonly used in manufacturing. Stainless steel capillary tubes without air in the system or PTFE capillary tubes without air in the system both represent a nominal stress condition. Nominal stress will be encountered when the solution is pumped using a peristaltic pump through a filling needle. Stainless steel capillary tubes with air entrapment in the system represent a high stress condition because the protein can unfold relatively easy in the air-liquid interface. Total polymer is determined by SEC, and particulate matter is determined by high accuracy particle counter (HIAC). SEC data are shown in Table 5, and HIAC data are shown in Table 6.

Table 5. Percent Total Polymer - SEC

% PS-80	**Control**	**Stainless Steel**	**Stainless Steel with Air**
5 mg/ml Antibody			

0	0.89	0.91	1.65
0.005	1.04	1.03	1.63
0.02	1.06	1.06	1.13
0.03	1.09	1.06	1.12
0.05	1.17	1.19	1.23
40 mg/ml Antibody			
0	1.23	1.23	2.49
0.005	1.24	1.24	1.35
0.02	1.30	1.25	1.47
0.03	1.31	1.30	1.52
0.05	1.31	1.38	1.50
120 mg/ml Antibody			
0	1.58	1.61	1.86
0.005	1.48	1.66	1.66
0.02	1.48	1.68	1.68
0.03	1.49	1.65	1.59
0.05	1.51	1.75	1.65

Table 6. Particulate Matter - HIAC

40 mg/mL anti-CGRP Antibody					
% PS-80	**Tubing Type**	**Particle Size (2 µm)**	**Particle Size (5 µm)**	**Particle Size (10 µm)**	**Particle Size (25 µm)**
0	Control	296	104	21	4
0.005	Control	53	26	11	6
0.02	Control	53	21	8	0
0.03	Control	57	19	6	1
0.05	Control	78	24	5	0
0	Stainless Steel	20284	1882	201	3
0.005	Stainless Steel	2612	501	94	4
0.02	Stainless Steel	1660	401	79	4
0.03	Stainless Steel	501	144	37	2
0.05	Stainless Steel	650	178	47	0
0	Stainless Steel w/ Air	62009	45330	24688	3683
0.005	Stainless Steel w/ Air	1225	344	162	2
0.02	Stainless Steel w/ Air	2993	803	178	4
0.03	Stainless Steel w/	3959	946	135	0

	Air				
0.05	Stainless Steel w/ Air	972	285	73	4

The SEC data in Table 5 show that under conditions essentially described above, the addition of PS-80 to the stainless steel with air groups (high stress conditions) led to a reduction in the total polymer.

Compared to formulations lacking PS-80, the addition of 0.005%, 0.02%, 0.03%, or 0.05% of PS-80 led to a reduction in particle formation in most of the groups as determined by HIAC (Table 6). These studies demonstrate that the addition of PS-80 to the solution reduces the particulate matter present in the anti-CGRP antibody formulation.

PS-80 Oxidation

Formulations at pH 6.0 comprising the anti-CGRP antibody (120 mg/ml), 10mM histidine, 150mM NaCl, and 0.05% PS-80 are used to determine PS-80 oxidation at various temperatures and time-points. Respective formulations are filled into vials or glass prefilled syringes and placed in chambers at room temperature (at the beginning of the study), 5°C, 25°C, or 40°C. The corresponding buffer (10mM histidine, 150mM NaCl, 0.05% PS-80, pH 6.0) without the antibody is used as a control. PS-80 hydrolysis method is used to determine percent PS-80. Amount of free oleic acid and amount of total oleic acid are determined. PS-80 hydrolysis results in total oleic acid (TOA), and TOA is measured by high-performance liquid chromatography (HPLC). To obtain the percent of intact PS-80, free oleic acid is subtracted from the total oleic acid.

Table 7. Percent PS-80 in formulations at various time-points and temperatures

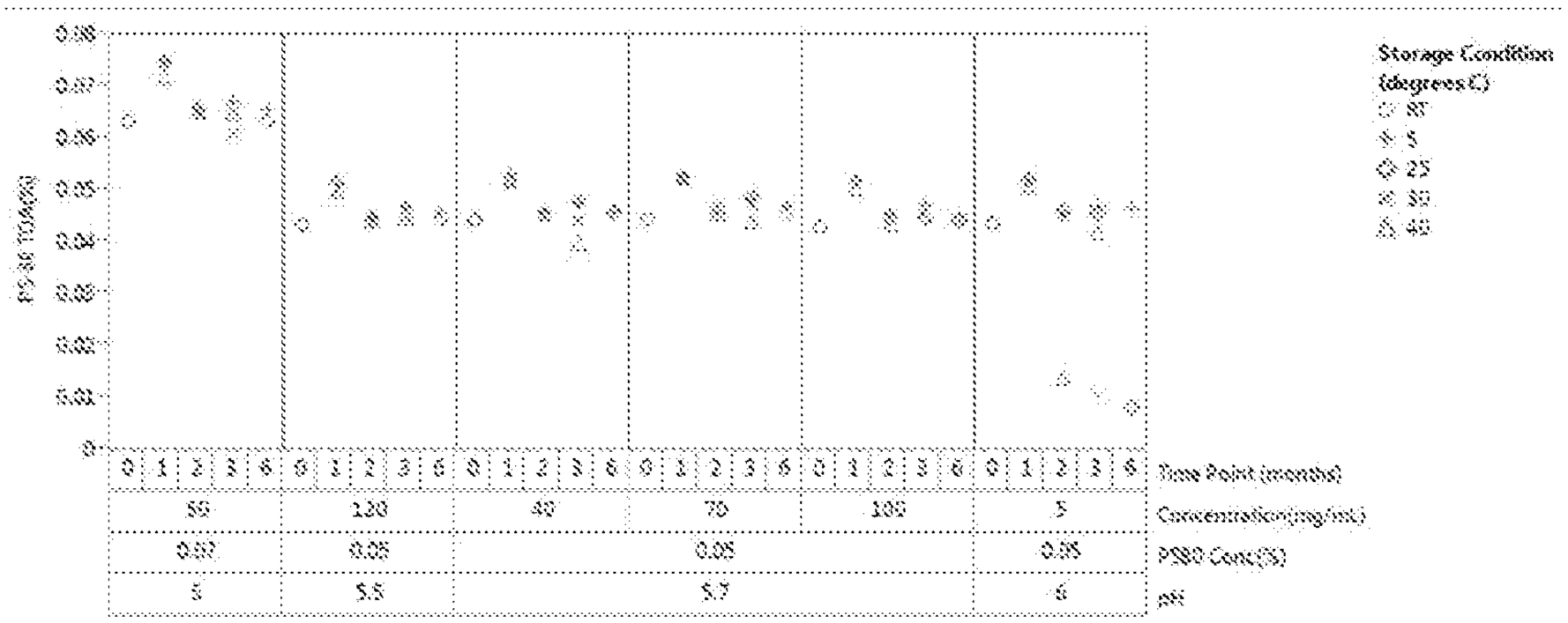
PS-80 %	Time (months)	Temperature	Control (%)	DP (%)
14 mL Vial	0	RT	0.051	0.052
	1	5°C	0.052	0.05
		25°C	0.054	0.051
		40°C	0.051	0.052
	3	5C	0.052	0.052
		25C	0.054	0.051
	6	5C	0.054	0.051

		25C	0.047	0.05
2.25 mL Syringe	1	5C	0.051	0.05
		25C	0.048	0.051
		40C	0.029	0.05
	3	5C	0.052	0.051
		25C	0.008	0.05
	6	5C	0.052	0.05
		25C	0.006	0.038

Following a procedure essentially as described above, oxidation of PS-80 was most pronounced in the 2.25 mL control groups at 25°C at 3 and 6 months (Table 7). Oxidation of PS-80 was confirmed by mass spectrometry (data not shown).

In a similar study, formulations are prepared as indicated in Figure 1. DS is dialyzed into the respective matrix and PS-80 is added or diluted to achieve the indicated final concentration. Respective formulations are filled into glass prefilled syringes and stored in chambers at room temperature, 5°C, 25°C, 30°C, or 40°C. The concentration of PS-80 is determined at the beginning of the study at room temperature, after 1, 2, or 3 months at 5°C, 25°C, or 30°C, and at 6 months at 5°C or 25°C. The results are shown in Figure 1.

Figure 1. Percent PS-80



Following a procedure as essentially described above, oxidation of PS-80 was observed in formulations comprising 5 mg/mL antibody. These data show that antibody at a concentration greater than 5 mg/mL prevents oxidation of PS-80.

Dose Ranging Clinical Trial for Migraine

A phase IIb, randomized, double-blind, placebo-controlled, dose-ranging study was conducted with 410 patients aged 18–65 years with 4 to 14 migraine headache days and at least 2 migraine attacks per month. The patients were randomly assigned (2:1:1:1:1) to placebo or 1 of 4 LY2951742 dose groups. Subcutaneous injections of LY2951742 doses of 5 mg, 50 mg, 120 mg, 300 mg or placebo were given once every 28 days for 12 weeks. The primary objective was to assess whether at least one dose of LY2951742 was superior to placebo in the prevention of migraine headache. Superiority was defined as a ≥95% posterior probability of greater improvement for any LY2951742 dose compared with placebo, as measured by the mean change from baseline in the number of migraine headache days in the last 28-day period of the 12-week treatment phase.

The results showed that all 4 dose arms were numerically superior to placebo on primary outcome measures at all-time points. One dose arm (120 mg) of LY2951742 met the primary objective ($p = 0.004$) with a significantly greater reduction compared to placebo in the number of migraine headache days in the last 28 day period of the 12 week treatment phase.

Clinical Trial for Episodic Cluster Headache

A Phase III, randomized, double blind clinical trial is being conducted with 162 patients aged 18-65 years with at least two cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥1 month. The patients are randomly assigned to either the placebo or treatment group. Subcutaneous injections of a pharmaceutical composition comprising LY2951742 at doses of 300 mg or placebo are given once every 30 days for 8 weeks. The primary objective is to assess whether 300 mg of LY2951742 was superior to placebo in the prevention of episodic cluster headaches. The primary outcome measured is the mean change from baseline in number of weekly cluster headache attacks after treatment.

Sequences

SEQ ID NO: 1 – Exemplified LCVR (of an anti-CGRP antibody of the present invention)

DIQMTQSPSSLSASVGDRVTITCRASKDISKYLNWYQQKPGKAPKLLIYYTSGYH
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGDALPPTFGGGTKVEIK

SEQ ID NO: 2 – Exemplified HCVR (of an anti-CGRP antibody of the present invention)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI
YEGTGKTVYIQKFADRVTITADKSTSTAYMELSSLRSEDTAVYYCARLSDYVSGF
GYWGQGTTVTVSS

SEQ ID NO: 3 – Exemplified LC (of an anti-CGRP antibody of the present invention)

DIQMTQSPSSLSASVGDRVTITCRASKDISKYLNWYQQKPGKAPKLLIYYTSGYH
SGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGDALPPTFGGGTKVEIKRTVA
APSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQ
DSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 4 – Exemplified HC (of an anti-CGRP antibody of the present invention)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFGNYWMQWVRQAPGQGLEWMGAI
YEGTGKTVYIQKFADRVTITADKSTSTAYMELSSLRSEDTAVYYCARLSDYVSGF
GYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWN
SGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKR
VESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEV
QFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSN
KGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNH
YTQKSLSLSLG

SEQ ID NO: 5 – Exemplified nucleotide sequence (encoding a LC of an anti-CGRP antibody of the present invention)

gacatccagatgacccagtctccatcctccctgtctgcatctgtaggagacagagtcaccatcacttgccgagcaagtaaagaca
tttctaagtatttaaactggtatcagcagaaaccagggaaagcccctaagctcctgatctattacacatcaggatatcactcaggag
tcccatcaaggttcagtggcagtggatctgggacagatttcactctcaccatcagcagtctgcaacctgaagattttgcaacttacta
ctgtcaacaaggtgatgcgcttcctccgacgttcggcggagggaccaaggtggagatcaaacggactgtggctgcaccatctgt
cttcatcttcccgccatctgatgagcagttgaaatctggaactgcctctgttgtgtgcctgctgaataacttctatcccagaggcc
aaagtacagtggaaggtggataacgccctccaatcgggtaactcccaggagagtgtcacagagcaggacagcaaggacagc
acctacagcctcagcagcaccctgacgctgagcaaagcagactacgagaaacacaaagtctacgcctgcgaagtcacccatca
gggcctgagctcgcccgtcacaaagagcttcaacaggggagagtgc

SEQ ID NO: 6 – Exemplified nucleotide sequence (encoding a HC of an anti-CGRP antibody of the present invention)

caggtgcagctggtgcagtctggggctgaggtgaagaagcctgggtcctcagtgaaggtttcctgcaaggcatctggctacacc
tttggtaattactggatgcagtgggtgcgacaggcccctggacaagggcttgagtggatgggagctatttatgagggaactggta
agactgtgtacattcagaagttcgccgacagagtcaccattaccgcggacaaatccacgagcacagcctacatggagctgagca
gcctgagatctgaggacacggccgtgtattactgtgcgagattaagtgattacgtctcgggatttggctactggggccaaggaac
cacggtcaccgtctcctcagcctccaccaagggcccatcggtcttcccgctagcgccctgctccaggagcacctccgagagca
cagccgccctgggctgcctggtcaaggactacttccccgaaccggtgacggtgtcgtggaactcaggcgccctgaccagcgg
cgtgcacaccttcccggctgtcctacagtcctcaggactctactccctcagcagcgtggtgaccgtgccctccagcagcttgggc
acgaagacctacacctgcaacgtagatcacaagcccagcaacaccaaggtggacaagagagttgagtccaaatatggtccccc
atgcccaccctgcccagcacctgaggccgccgggggaccatcagtcttcctgttcccccccaaaacccaaggacactctcatgat
ctcccggacccctgaggtcacgtgcgtggtggtggacgtgagccaggaagaccccgaggtccagttcaactggtacgtggatg
gcgtggaggtgcataatgccaagacaaagccgcgggaggagcagttcaacagcacgtaccgtgtggtcagcgtcctcaccgt
cctgcaccaggactggctgaacggcaaggagtacaagtgcaaggtctccaacaaaggcctcccgtcctccatcgagaaaacc
atctccaaagccaaagggcagccccgagagccacaggtgtacaccctgcccccatcccaggaggagatgaccaagaaccag
gtcagcctgacctgcctggtcaaaggcttctaccccagcgacatcgccgtggagtgggaaagcaatgggcagccggagaaca
actacaagaccacgcctcccgtgctggactccgacggctccttcttcctctacagcaggctaaccgtggacaagagcaggtggc
aggaggggaatgtcttctcatgctccgtgatgcatgaggctctgcacaaccactacacacagaagagcctctccctgtctctgggt
tga

SEQ ID NO: 7 – Human αCGRP Peptide

ACDTATCVTHRLAGLLSRSGGVVKNNFVPTNVGSKAF

WE CLAIM:

1. A pharmaceutical formulation comprising an anti-CGRP antibody at a concentration of about 40 mg/mL to about 160 mg/mL, histidine buffer at a concentration of about 5 mM to about 20 mM, NaCl at a concentration of about 50 mM to about 200mM, PS-80 at a concentration of about 0.03% (w/v) to about 0.07% (w/v), and a pH at about 5.0 to about 6.5, wherein the anti-CGRP antibody comprises a light chain variable region (LCVR) and a heavy chain variable region (HCVR), the amino acid sequence of LCVR given by SEQ ID NO: 1 and the amino acid sequence of HCVR given by SEQ ID NO: 2.

2. The formulation of claim 1, wherein the anti-CGRP antibody comprises a light chain (LC) and a heavy chain (HC), the amino acid sequence of LC given by SEQ ID NO: 3 and the amino acid sequence of HC given by SEQ ID NO: 4.

3. The formulation of claim 1, wherein the anti-CGRP antibody comprises two LCs and two HCs, the amino acid sequence of each LC given by SEQ ID NO: 3 and the amino acid sequence of each HC given by SEQ ID NO: 4.

4. The formulation of any one of claims 1 to 3, wherein the concentration of anti-CGRP antibody is about 50 mg/mL to about 150 mg/mL.

5. The formulation of any one of claims 1 to 3, wherein the concentration of anti-CGRP antibody is about 100 mg/mL to about 160 mg/mL.

6. The formulation of any one of claims 1 to 3, wherein the concentration of anti-CGRP antibody is selected from the group consisting of about 40 mg/mL, about 50 mg/mL, about 100 mg/mL, about 120 mg/mL, and about 150 mg/mL.

7. The formulation of any one of claims 1 to 3, wherein the concentration of anti-CGRP antibody is about 50 mg/mL.

8. The formulation of any one of claims 1 to 3, wherein the concentration of anti-CGRP antibody is about 100 mg/mL.

9. The formulation of any one of claims 1 to 3, wherein the concentration of anti-CGRP antibody is about 120 mg/mL.

10. The formulation of any one of claims 1 to 3, wherein the concentration of anti-CGRP antibody is about 150 mg/mL.

11. The formulation of any one of claims 1 to 10, wherein the concentration of histidine buffer is about 10 mM to about 15 mM.

12. The formulation of claim 11, wherein the concentration of histidine buffer is about 10 mM.

13. The formulation of any one of claims 1 to 12, wherein the concentration of NaCl is about 125 mM to about 175 mM.

14. The formulation of claim 13, wherein the concentration of NaCl is about 150 mM.

15. The formulation of any one of claims 1 to 14, wherein the concentration of PS-80 is about 0.05% (w/v).

16. The formulation of any one of claims 1 to 15, wherein the pH is about 5.8.

17. The formulation of any one of claims 1 to 3, wherein the concentration of anti-CGRP antibody is selected from the group consisting of about 50 mg/mL, about 100 mg/mL, about 120mg/mL, and about 150 mg/mL, the concentration of histidine buffer is about 10mM, the concentration of NaCl is about 150mM, and the concentration of PS-80 is about 0.05%, the pharmaceutical formulation having a pH between about 5.5 to about 6.0.

18. The formulation of claim 17, where in the concentration of anti-CGRP antibody is about 100 mg/mL.

19. The formulation of claim 17, where in the concentration of anti-CGRP antibody is about 120 mg/mL.

20. The formulation of claim 17, where in the concentration of anti-CGRP antibody is about 150 mg/mL.

21. The formulation of claim 17, wherein the said formulation is suitable for subcutaneous injection.

22. A method of treating or preventing migraines, episodic headaches, chronic headaches, chronic cluster headaches, or episodic cluster headaches

comprising administering to a patient a therapeutically effective amount of a pharmaceutical formulation of any one of claims 1-21.

23. The method of claim 22, wherein the dose of anti-CGRP antibody administered to a patient is about 300 mg.

24. The method of claim 22, wherein the dose of anti-CGRP antibody administered to a patient is about 240 mg.

25. The method of claim 22, wherein the dose of anti-CGRP antibody administered to a patient is about 120 mg.

26. The method according to claims 22-25, wherein the dose is administered at weekly, semi-monthly or monthly intervals.

27. A method to treat or prevent episodic migraine in a patient comprising administering a monthly subcutaneous dose of 120 mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LC given by the amino acid sequence of SEQ ID NO: 3 and a HC given by the amino acid of SEQ ID NO: 4.

28. A method to treat or prevent cluster headache in a patient comprising administering a monthly subcutaneous dose of 300 mg of an anti-CGRP antibody, wherein the anti-CGRP antibody comprises a LC given by the amino acid sequence of SEQ ID NO: 3 and a HC given by the amino acid of SEQ ID NO: 4.

29. The method according to claims 27-28, wherein the anti-CGRP antibody is in a pharmaceutical formulation comprising a histidine buffer.

30. The method according to claims 27-29, wherein the histidine buffer is at a concentration of about 10 mM to about 15 mM.

31. The method according to claims 27-30, wherein the anti-CGRP antibody is in a pharmaceutical formulation at a pH of about 5.7-6.0.

32. The method according to claim 31, wherein the pharmaceutical formulation has a pH of about 5.8.

33. The method according to claims 27-32, wherein the anti-CGRP antibody is in a pharmaceutical formulation comprising about 10mM histidine buffer, about 150mM NaCl, about 0.05% PS-80, and has a pH of about 5.8.

34. A pharmaceutical formulation of any of claims 1 to 21 for use in the treatment or prevention of at least one of migraine, episodic headache, chronic headache, chronic cluster headache, and episodic cluster headache.

35. The pharmaceutical formulation for use of claim 34, wherein the dose of the anti-CGRP antibody administered to a patient is 300 mg.

36. The pharmaceutical formulation for use of claim 34, wherein the dose of the anti-CGRP antibody administered to a patient is 240 mg.

37. The pharmaceutical formulation for use of claim 34, wherein the dose of the anti-CGRP antibody administered to a patient is 120 mg.

38. The pharmaceutical formulation for use of any one of claims 35-37, wherein dose is administered at monthly intervals.

39. Use of a pharmaceutical composition according to any one of claims 1 to 21 for the preparation of a medicament for the treatment or prevention of at least one of migraine, episodic headache, chronic headache, chronic cluster headache, and episodic cluster headache.

40. A pharmaceutical formulation comprising an anti-CGRP antibody at a concentration of about 120 mg/mL, histidine buffer at a concentration of about 10 mM, NaCl at a concentration of about 150 mM, and PS-80 at a concentration of about 0.05% (w/v), the pharmaceutical formulation having a pH between about 5.0 to about 6.5, wherein the anti-CGRP antibody comprises two LC and a two HC, the amino acid sequence of each LC given by SEQ ID NO: 3, and the amino acid sequence of each HC given by SEQ ID NO: 4.

41. The pharmaceutical formulation according to claim 40, wherein the pharmaceutical formulation has a pH of 5.8.